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Original Article

The relationship between HNF1A variations and type 2 diabetes mellitus risk factors in the Uyghur population in Urumqi

Rebiya Nuli[1], Jureti Azati[3], Zulifeiya Shawuti[4], Jiaoyu Shan[1], Aizatiguli Kadeer[2], Azierguli Abudukerimu[1], Patamu Mohemaiti[2]

[1]College of Basic Medical Science, [2]School of Public Health, Xinjiang Medical University, Urumqi 830011, Xinjiang, China; [3]The People's Hospital of Xinjiang Uyghur Autonomous Region, Xinjiang, China; [4]Department of Endocrinology, The Fifth Affiliated Hospital of Xinjiang Medical University, Xinjiang, China

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Abstract: Type 2 diabetes (T2DM) is a main threaten health problem in Uyghur minority population in China. This study investigated the relationship between the common variations of hepatocyte nuclear factor 1A (HNF1A) of rs2464196, rs1169288, and rs1169289, and T2DM in a Uyghur population. A case-control study was conducted on 202 Uyghur subjects, and the relationship between HNF1A variants and the risk of T2DM was assessed. For rs2464196, subjects with AG genotype who smoked or had a high LDL-C level had an increased risk of T2DM (OR=2.284, 95% CI=1.034-5.046 and OR=4.157, 95% CI=1.539-11.225, respectively). In conjunction with the GG genotype of this variant, higher triglycerides (TG), high-density lipoprotein (HDL-C), and lower low-density lipoprotein (LDL-C) were associated with increased risk of T2DM (OR=2.908, 3.058 and 5.619). For rs1169288, TG genotype with higher TC, TG, LDL-C and lower HDL-C was associated with increased risk for T2DM (OR=2.793, OR=4.076, OR=5.043 and OR=4.649, respectively). Meanwhile, those with GG genotype and higher TG, LDL-C, and lower HDL-C got increased risk for T2DM (OR=2.461, OR=3.042 and OR=3.638). For rs1169289, smoking or a high LDL-C in conjunction with the CG genotype was associated with increased risk for T2DM (OR=5.370 and OR=4.575), while higher TC, TG, LDL-C, and lower HDL-C with GG genotype was associated with increased risk of T2DM (OR=2.25, OR=2.17, OR=2.999, and OR=4.217). The HNF1A variants of rs2464196, rs1169288 and rs1169289 may interact with persistent smoking and/or blood lipids to influence the risk of T2DM in the Uyghur population in Urumqi.

Keywords: Type 2 diabetes, hepatocyte nuclear factor 1A gene, blood lipid, Uyghur

Introduction

Based on data from the International Diabetes Federation (IDF), 415 million people suffer from diabetes, and this number will increase to 642 million internationally by 2040. Of these diabetics, 90% worldwide have type 2 diabetes mellitus (T2DM), a disease that is closely correlated with patient genetics and an unhealthy lifestyle. The three countries with the most individuals with T2DM are China (109.6 million in 2015 and an estimated 150.7 million by 2040), India (69.2 million in 2015 and an estimated 123.5 million by 2040), and the USA (29.3 million in 2015 and an estimated 35.1 million by 2040). Notably, China stands for the country with the most cases of T2DM. In China, the Uyghurs are a minority population living in Xinjiang, which is located in Northwest China. According to one study [1], the prevalence of diabetes is higher in the Uyghur population (10.47%) than in the other kind of population (7.36%) in Xinjiang. Within Xinjiang, Urumqi is the most important city.

Zhang reported that T2DM is a multifaceted condition caused by a number of factors and their interactions, including genetics, such as certain polymorphisms, and lifestyle related factors, such as an exercise, medications, smoking, and intake of alcohol [2]. Recently, single nucleotide polymorphisms (SNPs) in the Hepatocyte nuclear factor 1A (HNF1A) gene has been reported to contribute to the susceptibility to becoming a type 2 diabetes [3]. Heterozygous mutations in HNF1A are respon-

Table 1. Characteristics of study participants

Characteristics	Case (n=78)	Controls (n=124)	*P*
Sex			
Male	38	46	0.103
Female	40	78	
Age	52.9±12.0	43.4±11.1	< 0.001
BMI (kg/m^2)	25.8±4.0	24.2±3.3	0.03
Smoking			
Non-smoking	26	62	0.02
Smoking	52	62	
Drinking			
Non-drinking	45	90	0.029
Drinking	33	34	
HDL-C			
Low HDL-C	44	28	< 0.001
Normal HDL-C	34	96	
LDL-C			
High LDL-C	46	26	< 0.001
Normal LDL-C	32	98	
Triglyceride			
High TG	40	26	< 0.001
Normal TG	38	98	
CHOL			
High TC	32	26	0.002
Normal TC	46	98	

sible for a monogenic form of diabetes called maturity onset diabetes of the young (MODY), and common variants of HNF1A are associated with certain metabolic phenotypes. Currently, there are no adequate data concerning HNF1A polymorphisms and the risk of acquiring T2DM in the Uyghur population. In order to assess the relationship between HNF1A gene polymorphisms as risk factors for T2DM in the Uyghur population, a case control study was carried out. In addition, potential relationships between these polymorphisms and other risk factors associated with T2DM in the Uyghur were identified.

Material and methods

Subjects

A total of 202 inhabitants of Urumqi city of Xinjiang participated in and contributed blood samples to this study, where 124 served as controls and 78 had T2DM. Each participant gave written informed consent following a full description of the study, which was approved by the Ethics Committee of the first affiliated hospital of Xinjiang Medical University (Study No. 20151126-07). T2DM patients and non-diabetic controls were recruited by the endocrinology department and the Health Examination Center of the first affiliated hospital of Xinjiang Medical University, respectively. Patients in this study with T2DM were diagnosed based on the criteria set in 1999 by the World Health Organization (WHO), where a patient is considered diabetes when the fasting blood glucose (FPG) ≥ 7.00 mmol/L or the 2 h oral glucose tolerance test (OGTT) ≥ 11.0 mmol/L. Non-T2DM patients were excluded based on clinical data.

Clinical measurements and laboratory methods

For each participant, body weight and height were measured using standard methods, and then body mass index (BMI) was calculated as weight/height^2 (kg/m^2). Additional data were collected via questionnaire from all subjects and included age, gender, and use of tobacco and alcohol. Fasting plasma TG, TC, HDL-C and LDL-C levels were measured using an automatic biochemical analyzer (Olympus, Tokyo, Japan) according to standard methods. Abnormal lipid profiles were defined based on the Chinese Guidelines on Prevention and Treatment of Dyslipidemia in Adult (2007), where abnormal lipid levels were considered TG > 1.7 mmol/l, TC > 5.18 mmol/l, HDL-C < 1.04 mmol/l and LDL-C > 3.37 mmol/l. Participants were categorized into smokers and non-smokers based on tobacco use, where those who were smokers at the time of the study and had smoked at least 100 cigarettes during their lifetime were classified as smokers. Alcohol intake was self-reported using a standard questionnaire and participants were defined as drinking and non-drinking. Subjects were divided into three groups based on their genotypes for each variant. For example, when assessing rs2464196, subjects were divided into three groups of the AA, AG and GG genotypes.

Primer design

Primers were designed by Beijing Biomed Co. The forward primer of rs1169288 was 5'-TTCCCCAGCTCCAATGTAAACAGA-3', and the reverse primer was 5'-GCGTGAAGTCTTCCCCATCGTC-3'. The forward primer of rs1169289 was 5'-TTCCCCAGCTCCAATGTAAACAGA-3', and the rev-

Table 2. Genotype and alle distribution of the SNPs (rs2464196, rs1169288, rs1169289) of *HNF1A* gene among Uyghur population

Genotype/allele	Cases (n=78)	Controls (n=124)	χ^2	*P*
rs2464196				
AA	14 (17.95)	36 (29.03)	3.163	> 0.05
AG	36 (46.15)	50 (40.32)		
GG	28 (35.90)	38 (30.65)		
A	64 (41.03)	122 (49.19)	2.572	> 0.05
G	92 (58.97)	126 (50.81)		
rs1169288				
TT	22 (28.21)	44 (35.48)	1.172	> 0.05
TG	40 (51.28)	58 (46.77)		
GG	16 (20.51)	22 (17.74)		
T	84 (53.84)	146 (58.87)	0.986	> 0.05
G	72 (46.15)	102 (41.13)		
rs1169289				
CC	22 (28.21)	36 (29.03)	0.617	> 0.05
CG	36 (46.15)	62 (50)		
GG	20 (25.64)	26 (20.97)		
C	80 (51.28)	134 (54.03)	0.291	> 0.05
G	76 (48.72)	114 (45.97)		

erse primer was 5'-GCGTGAAGTCTTCCCCATCGTC-3'. The forward primer of rs2464196 was 5'-CAGAGTGTGCCGGTCATCAACAGC-3', and the reverse primer was 5'-TACACACCCAGACACGCACTAGGGA-3'.

Single nucleotide polymorphism (SNP) selection and genotyping

To reach a power of > 80%, which is considered adequate for confidence in the data, SNPs were selected from the HapMap database only if they had minor allele frequencies (MAF) > 15%. Using this methodology resulted in the identification of the variants rs2464196, rs1169288, and rs1169289. Using a blood genomic DNA (gDNA) extraction kit, gDNA was isolated from the peripheral blood of the participants and used as a template for PCR amplification of polymorphic regions. The resulting PCR products were sequenced using an ABI PRISM 3100 DNA sequenator.

Statistical analysis

Data were analyzed by splitting it into categorical and continuous variables, where categorical variables are presented numerically and were analyzed by chi-square (χ^2) test, and continuous variables are presented as mean ± standard deviation. To assess Hardy-Weinberg equilibrium (HWE) for allele frequencies was examined by the χ^2 testusingSAS9.4software(SASInstitute Inc., Cary, NC, USA). Associations between SNPs and T2DM were assessed using logistic regression models following adjustments for participant gender, BMI, and age. The risk for T2DM was evaluated by calculating the 95% confidence intervals (95% CIs) and odds ratios (ORs) and their corresponding *P* values. Potential correlations between different SNPs and use of tobacco and alcohol by the patients, or TG, TC, HDL-C, and LDL-C lipid levels were assessed using logistic regression multiplicative interaction models. Differences were considered statistically significant when $P < 0.05$.

Results

Characteristics of the participants

The mean age of the study participants was significantly higher in those with T2DM than the healthy controls ($P < 0.001$). In addition, TG, LDL-C and HDL-C were more likely to be present at abnormal levels in the diabetic participants than in the healthy controls ($P < 0.001$) (**Table 1**).

Genotype frequencies

It was determined that the SNPs of interest, rs2464196, rs1169288, and rs1169289, were in Hardy-Weinberg equilibrium in both T2DM and healthy cohorts ($P > 0.1$). In addition, there were no significant differences between the genotypes of T2DM and control cohorts (**Table 2**). The rs2464196, rs1169288 and rs1169289 genotypes were not associated with susceptibility to T2DM ($P > 0.05$), even after adjustments were made for participant gender, BMI and age (**Table 3**).

HNF1A variants and risk of T2DM

For rs2464196, smoking combined with the AG genotype was associated with an increased risk for developing T2DM compared to not smoking and having the AA genotype (OR= 2.284, 95% CI=1.034-5.046) (**Table 4**). In addition, high TG and low HDL-C levels with the AA

Table 3. Association of genotypes of SNPs (rs2464196, rs1169288, rs1169289) of *HNF1A* gene and the risk of T2DM in Uyghur population

Genotype/allele	Unadjusted OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
rs2464196				
AA	Reference		Reference	
AG	1.895 (0.862-4.162)	0.111	1.851 (0.698-4.909)	0.216
GG	1.023 (0.535-1.959)	0.944	1.784 (0.771-4.129)	0.176
rs1169288				
TT	Reference		Reference	
TG	1.455 (0.639-3.311)	0.372	1.238 (0.446-3.439)	0.682
GG	1.055 (0.493-2.254)	0.891	1.305 (0.504-3.375)	0.583
rs1169289				
CC	Reference		Reference	
CG	1.259 (0.572-2.768)	0.567	1.425 (0.523-3.878)	0.489
GG	1.325 (0.649-2.703)	0.439	2.056 (0.833-5.077)	0.118

OR, odds ratio; CI, confidence interval.

genotype compared to with the GG genotype were correlated with an increased risk of T2DM (OR=2.908, 95% CI=1.327-6.373 and OR=3.058, 95% CI=1.339-6.983, respectively). As presented in **Table 5**, a high LDL-C with an AG or GG genotype was also associated with an increased risk for T2DM (OR=4.157, 95% CI=1.539-11.225 and OR=5.619, 95% CI=2.316-13.632, respectively).

For rs1169288, compared to being a non-smoker and having the TT genotype, being a smoker in conjunction with having the TG genotype was associated with an increased risk for T2DM (OR=0.081, 95% CI=0.007-0.933) (**Table 4**). Meanwhile, the presence of high TC, TG and LDL-C and low HDL-C levels with the TT genotype increased the patient risk of being T2DM compared to having high TC and TG levels with the TG genotype (OR=2.793, 95% CI=1.155-6.752 and OR=4.076, 95% CI=1.623-10.237, respectively). High TG levels in conjunction with the GG genotype also correlated with a higher risk of developing T2DM (OR=2.461, 95% CI=1.162-5.212). Both the TG and GG genotype when paired with low HDL-C levels were associated with T2DM (OR=5.043, 95% CI=1.981-12.840 and OR=3.042, 95% CI=1.400-6.609, respectively). High LDL-C levels paired with either the TG or GG genotype was linked to a higher chance of having T2DM (OR=4.649, 95% CI=1.874-11.532 and OR=3.638, 95% CI=1.640-8.068, respectively) (**Table 5**).

For rs116289, smokers with the CG genotype were more likely to have T2DM than non-smokers with the CC genotype (OR=5.37, 95% CI=1.446-19.952) (**Table 4**). In addition, when there were high TC and TG levels, the CC genotype conferred an increased risk of T2DM compared to the GG genotype (OR=2.25, 95% CI=1.037-4.880 and OR=2.17, 95% CI=1.039-4.532, respectively). Low HDL-C or high LDL-C levels in conjunction with the GG genotype were also associated with an increased risk of T2DM (OR=2.999, 95% CI=1.367-6.579 and OR=4.217, 95% CI=1.881-9.457, respectively). Finally, those with a CG genotype with low LDL-C levels were more likely to have T2DM (OR=4.575, 95% CI=1.708-12.253) (**Table 5**).

Interestingly, consumption of alcohol in conjunction with any of the variants of interest (rs2464196, rs1169288, and rs1169289) failed to have any effect on the risk of having T2DM (**Table 4**).

Discussion

This article presents a case-control study on 202 inhabitants of Uyghur assessing the relationships between 3 HNF1A SNPs, environmental factors and the risk of having T2DM. It was found in the allelic frequencies of the HNF1A variants of interest, rs2464196, rs1169288, and rs1169289, were approximately equal between both the T2DM patient and healthy control populations. Interestingly, smoking and abnormal blood lipid levels were found to independently interact with the certain genotype of rs2464196, rs1169288, and rs1169289 to increase the risk for T2DM. This research is the first time study to examine and identify these relationships in the Uyghur population.

It has previously been demonstrated that rare mutations in the HNF1A gene can cause monogenic diabetes (MODY3). In addition,

Table 4. Interaction of SNPs of HNF1A and risk factors associated with the risk of T2DM

Genotype	Status	Cases/Controls	Adjusted P	Adjusted OR	95% CI
rs2464196					
AA	Smoking	9/16	Reference		
	Non-Smoking	5/20			
AG	Smoking	27/26	0.041	2.284	1.034-5.046
	Non-Smoking	9/24			
GG	Smoking	16/20	0.44	5.032	1.044-24.245
	Non-Smoking	12/18			
AA	Drinking	6/15	Reference		
	Non-drinking	8/21			
AG	Drinking	15/9	0.134	2.013	0.805-5.033
	Non-drinking	21/41			
GG	Drinking	12/10	0.17	1.668	0.804-3.462
	Non-drinking	16/28			
rs1169288					
TT	Smoking	16/24	Reference		
	Non-Smoking	6/20			
TG	Smoking	26/25	0.044	0.081	0.007-0.933
	Non-Smoking	14/33			
GG	Smoking	10/13	0.201	0.191	0.015-2.421
	Non-Smoking	6/9			
TT	Drinking	13/10	Reference		
	Non-drinking	9/34			
TG	Drinking	15/16	0.752	0.727	0.101-5.242
	Non-drinking	25/42			
GG	Drinking	5/8	0.337	0.402	0.062-2.581
	Non-drinking	11/14			
rs1169289					
CC	Smoking	16/24	Reference		
	Non-Smoking	6/12			
CG	Smoking	24/26	0.012	5.37	1.446-19.952
	Non-Smoking	12/36			
GG	Smoking	12/12	0.18	1.733	0.775-3.875
	Non-Smoking	8/14			
CC	Drinking	15/12			
	Non-drinking	7/24			
CG	Drinking	10/16	0.153	1.891	0.790-4.526
	Non-drinking	26/46			
GG	Drinking	8/6	0.184	1.647	0.789-3.438
	Non-drinking	12/20			

OR, odds ratio; CI, confidence interval.

HNF1A was also recently identified in a large study recently published as a T2DM genetic risk factor.

Previous GWAS have shown that variations in the HNF1A gene may affect a number of metabolic traits and increase the risk of developing T2DM, as well as lead to higher TC and LDL-C levels [4].

T2DM is considered a polygenic disease, and previous research has noted that certain variants of the HNF1A gene are contributors [5]. In particular, the rs2464196, rs1169288, and

Table 5. Interaction of SNPs of HNF1A and blood lipid level associated with the risk of T2DM in Uyghur population

Genotype	Status	Cases/Controls	*Adjusted P*	Adjusted OR	95% CI
rs2464196					
AA	High TC	8/10	Reference		
	Normal TC	6/26			
AG	High TC	12/6	0.139	1.972	0.803-4.843
	Normal TC	24/44			
GG	High TC	12/10	0.075	1.999	0.933-4.282
	Normal TC	16/28			
AA	High TG	8/8	Reference		
	Normal TG	6/28			
AG	High TG	18/10	0.102	2.102	0.862-5.129
	Normal TG	18/40			
GG	High TG	14/8	0.008	2.908	1.327-6.373
	Normal TG	14/30			
AA	Low HDL-C	8/6	Reference		
	Normal HDL-C	6/30			
AG	Low HDL-C	20/16	0.068	2.276	0.941-5.503
	Normal HDL-C	16/34			
GG	Low HDL-C	16/6	0.008	3.058	1.339-6.983
	Normal HDL-C	12/32			
AA	High LDL-C	6/7	Reference		
	Normal LDL-C	8/29			
AG	High LDL-C	22/12	0.005	4.157	1.539-11.225
	Normal LDL-C	14/38			
GG	High LDL-C	18/7	0	5.619	2.316-13.632
	Normal LDL-C	10/31			
rs1169288					
TT	High TC	16/10	Reference		
	Normal TC	6/34			
TG	High TC	10/18	0.023	2.793	1.155-6.752
	Normal TC	30/40			
GG	High TC	6/5	0.094	1.89	0.898-3.979
	Normal TC	10/17			
TT	High TG	12/10	Reference		
	Normal TG	10/34			
TG	High TG	23/11	0.003	4.076	1.623-10.237
	Normal TG	17/47			
GG	High TG	5/5	0.019	2.461	1.162-5.212
	Normal TG	11/17			
TT	Low HDL-C	14/11	Reference		
	Normal HDL-C	8/33			
TG	Low HDL-C	23/10	0.001	5.043	1.981-12.840
	Normal HDL-C	17/48			
GG	Low HDL-C	7/7	0.005	3.042	1.400-6.609
	Normal HDL-C	9/15			
TT	High LDL-C	15/12	Reference		
	Normal LDL-C	7/32			
TG	High LDL-C	22/8	0.001	4.649	1.874-11.532

	Normal LDL-C	18/40			
GG	High LDL-C	9/6	0.001	3.638	1.640-8.068
	Normal LDL-C	7/16			
rs1169289					
CC	High TC	12/10	Reference		
	Normal TC	10/26			
CG	High TC	13/5	0.273	1.604	0.689-3.735
	Normal TC	23/57			
GG	High TC	7/11	0.04	2.25	1.037-4.880
	Normal TC	13/15			
CC	High TG	15/12	Reference		
	Normal TG	7/24			
CG	High TG	17/8	0.093	2.128	0.882-5.134
	Normal TG	19/54			
GG	High TG	8/6	0.039	2.17	1.039-4.532
	Normal TG	12/20			
CC	Low HDL-C	15/12	Reference		
	Normal HDL-C	7/24			
CG	Low HDL-C	16/10	0.079	2.157	0.916-5.080
	Normal HDL-C	20/52			
GG	Low HDL-C	13/8	0.006	2.999	1.367-6.579
	Normal HDL-C	7/18			
CC	High LDL-C	14/12	Reference		
	Normal LDL-C	8/24			
CG	High LDL-C	21/6	0.002	4.575	1.708-12.253
	Normal LDL-C	15/56			
GG	High LDL-C	11/8	0	4.217	1.881-9.457
	Normal LDL-C	9/18			

OR, odds ratio; CI, confidence interval.

rs1169289 polymorphisms are associated with an increased risk of T2DM, but few studies have investigated this association between variants of HNF1A and the risk of developing T2DM in China [6, 7]. One of these studies was a functional analysis of the HNF1A variants rs2464196, rs1169288 and rs1169289 and their relationship with the development of early-onset inherited T2DM. This research found that for Japanese subjects with a healthy weight, the rs1169288 variants increased the risk of T2DM [8]. By contrast, case control studies on common HNF1A variants on the risk of developing T2DM in European and North American populations have yielded conflicting results [9]. In an-other study, we sequence HNF1A in a family with early-onset T2DM and noted the presence of HNF1A variants [10]. Overall, this data point to the importance and influence of both genetics and the environment on the relationship between HNF1A variants and T2DM in Uyghur population.

This present research is a case control study that focused on how interactions between genetics and the environment can affect the risk of developing T2DM in the Uyghur population.

Specifically, the presence of the rs2464196 AG genotype, rs1169288 TG genotype or rs1169-289 CG genotype was associated with an increased risk of developing T2DM when the subject also smoked. A number of studies have shown that the risk of T2DM increases from smoking in general. HNF1A G319S variant was associated with incident type 2 diabetes in Aboriginal Canadians and cigarette smoking may influence the development of the diabetes phenotype in the HNF1A G319S carriers [11]. HNF1A variants interact with smoking and increase the risk of T2DM. The results of this study agreed with these results, as they covered that the interactions between HNF1A variants and smoking are risk factors for T2DM.

The role of alcohol consumption on the risk of T2DM has not been well-characterized. In this study, no significant association was observed between alcohol intake and the presence of HNF1A variants on T2DM in the Uyghur population.

It has been well-established independent that abnormal plasma lipid levels amplify the risk for T2DM. HNF1A gene translates into hepatocyte nuclear factor1A, which functions as a transcriptional regulator of a number of genes that have been implicated in metabolism and lipid transport [12]. One study found SNPs in rs1169288 were significantly correlated with lipid levels in China [13]. In addition, the presence of the SNP rs1169288 C allele increased the risk for a higher severity of coronary atherosclerosis. A large-scale GWAS demonstrated that certain HNF1A alleles were associated with increased plasma LDL-C levels [14]. In this study, it was found in the levels of LDL-C, HDL-C and TGs were higher in subjects with T2DM compared to healthy subjects ($P < 0.01$). These findings agree with a study on T2DM that noted a higher frequency of obesity, hypertension, dyslipidemia and coronary heart disease in Uyghurs [15, 16].

The Uyghur's genetic background and eating habits may allow for mapping of complex interactions between genes and potential T2DM risk factor. In this study, we demonstrated that 3 HNF1A SNPs were linked to abnormal blood lipid levels in T2DM in this population. For the rs2464196 variant, the GG genotype in conjunction with high TG and low HDL-C levels was associated with an increased risk of developing T2DM, as were high LDL-C levels paired the rs246196 AG genotype. Therefore, the concurrent presence of both HNF1A gene variants and abnormal blood lipid levels is a risk factor for T2DM in this population.

In conclusion, this research evaluated the potential interactions between HNF1A SNPs and risk factors of T2DM and whether they are associated with T2DM in the Uyghur population in Xinjiang. This work suggests that HNF1A potentially interacts with the use of tobacco and/or blood lipids, and, thus, influences the risk of developing T2DM in our population. One caveat of this study is that the sample size was relatively small. Therefore, it is important that future work includes replicating this study in a larger population, as well as performing functional studies to delineate the mechanisms governing these effects.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Patamu Mohemaiti, School of Public Health, Xinjiang Medical University, 393 Xinyi Road, Urumqi 830011, Xinjiang, China. Tel: +8613565988794; +8613579956237; Fax: 09914361763; E-mail: patam0616@aliyun.com; rabux@xjmu.edu.cn

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