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Polymorphisms in the PPARγ gene and their association with metabolic syndrome in Uyghurs and Kazakhs from Xinjiang, China

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ABSTRACT. We investigated the association between polymorphisms rs1801282 and rs3856806 of the PPARγ gene and metabolic syndrome (MS) among Uyghurs and Kazakhs. Mass spectrometry techniques were used to detect the PPARγ genotypes rs1801282 and rs3856806 in 987 subjects, CC genotype and C allele frequencies were 83.6 and 91.7%, respectively, at rs1801282 in Kazakhs, which were higher than those in Uyghurs (72.3 and 85.0%, respectively; $P < 0.05$). CC genotype and C allele frequencies were 73.6 and 85.3%, respectively, at the rs3856806 loci in Kazakhs, which were higher than those in Uyghurs (60.7 and 77.9%, respectively; $P < 0.05$). For the rs3856806 polymorphism in Kazakhs, CT/TT genotype and T allele frequencies were 21.2 and 12.4% for MS subjects, which were lower than those for the control group (31.6 and 17.0%, respectively; $P < 0.05$). Risk analysis of Kazakhs revealed that individuals with the CT and TT genotypes at rs3856806 had an increased risk, 0.524- and 0.770-fold, respectively, of developing MS than those possessing the CC genotype. Individuals with the T allele also had an increase in risk, by 0.699-fold, of developing MS than those with the C allele. For Uyghurs, those with the CC genotype at rs1801282 had higher systolic blood pressure than those with the CG/GG genotype.

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Among Kazakhs, those with the CC genotype at rs3856806 had higher triglyceride and waist-hip ratio levels but lower high-density lipoprotein cholesterol levels than those with the CT/TT genotype. The rs1801282 and rs3856806 PPARγ polymorphisms differ between Uyghurs and Kazakhs from Xinjiang Province, China.

Key words: Uyghur; Kazakh; Metabolic syndrome; PPARγ; Gene polymorphism

INTRODUCTION

Metabolic syndrome (MS) is a cluster of conditions that severely affect the health of human individuals. It is characterized by insulin resistance, but can be diagnosed by the co-occurrence of various metabolic diseases, such as diabetes, impaired glucose regulation, hypertension, dyslipidemia, or central obesity (Bjorntorp, 1992; Kobayashi et al., 2011). As the standard of living has improved across populations, MS has become a global public health problem resulting in death and disability. The prevalence of MS is reported to be between 20 and 25% (Sun et al., 2012). Among Kazakhs, the prevalence of MS is 26.6% (Guo et al., 2011), while that in Uyghurs is 21.2% (Li et al., 2012). The prevalence of MS among these two nationalities is significantly higher than that in adults 35-74 years old (16.5%), across eight cities and provinces in mainland China (Gu et al., 2005).

It is generally accepted that MS is a complex disease caused by genetic, environmental, and other unknown factors (Pousada et al., 2006; Zhang et al., 2014). Common environmental factors include a high fat diet, reduced participation in sporting activities, and a generally unhealthy lifestyle. Genetic susceptibility is also a major cause of MS. Recent reports have shown a correlation between polymorphisms in peroxisome proliferator activated receptor γ (PPARγ) and components of MS, such as hypertension, diabetes and obesity; however, the conclusions from these studies are inconsistent (Tellechea et al., 2009; Huguenin and Rosa, 2010; Bego et al., 2011). Whether polymorphisms at multiple loci of the PPARγ gene are related to the occurrence of MS in Uyghurs and Kazakhs remains unclear. Investigations into this issue are required to clarify the key risk factors of MS in Uyghurs and Kazakhs. We used a case-control study to investigate the association between mutations in the PPARγ gene and MS among Uyghurs and Kazakhs from Xinjiang Province, China.

MATERIAL AND METHODS

Study population

This study was conducted from 2009 to 2010, with stratified cluster sampling used for the investigation of MS status among research subjects. We included 3049 subjects who were Uyghurs (Jiangbazi, Jiashi County, Kashgar Prefecture) and 5692 subjects who were Kazakhs (Xinyuan County, Yili Prefecture); all subjects were from the Xinjiang Autonomous Region of mainland China. The age of the subjects was 18 years or more. According to the definition of MS proposed by the International Diabetes Federation in 2005 (Alberti et al., 2005), 250 Uyghur patients with MS were randomly selected (case group), along with 248 randomly selected cases of non-MS patients (control group). Similarly, 245 Kazakh patients with MS were

randomly selected (case group), along with 244 cases of non-MS patients randomly selected using a group-matching method from the same population as the control group.

All selected subjects were given a questionnaire to survey demographic data, personal medical history, diet, and exercise. Laboratory tests were conducted to measure levels of fasting triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), serum total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and fasting plasma glucose (FPG). These tests were conducted on an automatic biochemical analyzer (Olympus AU400).

This study was conducted in accordance with the Declaration of Helsinki, with the approval of the Ethics Committee of Medical College of Shihezi University. All participants signed informed consent forms.

DNA extraction

Fasting venous blood (200 μL) was obtained from subjects, and a blood genomic DNA isolation kit (Spin Column; BioTeke, Beijing, China) was used to extract genomic DNA from whole blood. All extracted DNA was verified by 0.7% agarose (w/v) gel electrophoresis. A NanoDrop (NanoDrop Technologies, Inc, Wilmington, DE, USA) spectrophotometer was used to quantify the concentration and purity of DNA. The optical density (OD) at 260 nm (OD_{260}) and 280 nm (OD_{280}) of samples was measured and the $OD_{260/280}$ ratio determined. Samples with an $OD_{260/280}$ ratio of 1.7-2.0 and concentration greater than or equal to 30 ng/μL were used. The DNA samples that met these criteria were diluted in double-distilled water to adjust the concentration to 10-30 ng/μL and stored at -80°C.

Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF-MS)

Polymerase chain reaction (PCR) assays

Oligonucleotide primers were designed using the MySequenom website (https://www.mysequenom.com/Home) and Assay Designer 3.0. All PCRs were conducted in a 5-μL volume and the reaction mixture comprised 0.1 μL dNTPs, 0.7 μL DNA, 0.15 μL Taq DNA polymerase, 1.35 μL water, 0.4 μL $MgCl_2$, 0.5 μL 10X PCR buffer, and 1.8 μL primer mixture. Thermal cycling conditions involved an initial denaturation step at 94°C for 4 min, followed by 45 amplification cycles (94°C for 20 s, 56°C for 30 s, and 72°C for 1 min), and a final extension step at 72°C for 3 min. Reactions were then incubated at 4°C. All reactions were conducted in a thermal cycler in conjunction with parallel negative controls.

Purification of amplicons

Shrimp alkaline phosphatase (SAP) was used to remove dNTP overhangs from PCR amplicons. The final volume of each SAP reaction was 2.0 μL and comprised 0.17 μL 10X SAP buffer, 1.53 μL double-distilled water, and 0.3 μL SAP. Reactions were incubated at 37°C for 40 min and then at 85°C for 5 min before storage at 4°C.

Single-base extension

The final volume of single-base extension reactions was 2.0 μL and comprised 0.2 μL

5X iPlex Buffer, 0.94 µL primer mix, 0.2 µL iPlex terminator, 0.619 µL water, and 0.041 µL iPlex enzymes. Reactions were incubated at 94°C for 30 s; 40 cycles of 94°C for 5 s, 52°C for 5 s and 80°C for 1 min; five cycles of 52°C for 5 s; and 80°C for 1 min. Finally, reactions were subject to extension at 72°C for 3 min and stored at 4°C.

MALDI-TOF-MS analysis

After samples were purified using resin, a MassARRAY Nanod-ispenser (Sequenom, San Diego, CA, USA) was used to transfer the purified products to a SpectroCHIP (Sequenom) chip and MALDI-TOF-MS was used for analysis. We used TYPER 4.0 (Sequenom) to complete the classification and obtain the results.

Statistical analysis

Epidata 3.02 was used to establish a database, and a double entry method was used for data entry and logical error detection. To confirm the group representation of the sample, we used the Hardy-Weinberg equilibrium. SPSS17.0 was used for statistical analysis. A gene counting method was used to calculate the genotype and allele frequencies. For comparison between groups, the chi-square test was used. To compare clinical variables between groups, the Student *t*-test was used. Logistic regression analysis was used for risk factors. Odds ratio (OR) and 95% confidence interval (CI) were calculated.

RESULTS

Clinical characteristics

General clinical data for subjects in the MS and control groups are shown (Table 1), with no significant difference observed for gender and age between Uyghurs and Kazakhs ($P > 0.05$).

Table 1. Comparison of the clinical biochemical indicators between MS and control groups in Uyghur and Kazakh (means ± SD).

Clinical and biochemical indexes	Uyghur		Kazakh	
	MS group	Control group	MS group	Control group
N (male/female)	250 (86/164)	248 (85/163)	245 (85/160)	244 (83/161)
Age (year)	41.34 ± 13.39	40.89 ± 12.21	42.51 ± 9.61	41.49 ± 8.80
Height# (cm)	159.00 ± 8.15	157.40 ± 7.68*	163.58 ± 8.10	161.82 ± 7.69*
Weight# (kg)	64.36 ± 11.69	52.64 ± 8.61*	74.30 ± 13.47	57.53 ± 8.85*
WC (cm)	92.88 ± 8.96	76.22 ± 5.78*	93.87 ± 9.35	76.07 ± 7.07*
HC# (cm)	99.46 ± 7.65	90.65 ± 5.85*	102.32 ± 6.70	91.50 ± 5.89*
TG (mM)	1.77 ± 0.93	0.85 ± 0.33*	1.76 ± 1.57	0.86 ± 0.36*
TC (mM)	4.75 ± 1.11	4.20 ± 1.00*	4.69 ± 1.10	4.30 ± 0.95*
LDL-C (mM)	2.66 ± 0.74	2.23 ± 0.69*	2.61 ± 0.90	2.16 ± 0.61*
HDL-C (mM)	1.09 ± 0.25	1.32 ± 0.27*	1.27 ± 0.40	1.57 ± 0.41*
SBP# (mmHg)	130.12 ± 20.89	112.14 ± 11.2*	140.03 ± 22.25	123.40 ± 19.3*
DBP# (mmHg)	82.93 ± 13.31	70.65 ± 9.38*	90.77 ± 13.63	79.37 ± 11.41*
FPG# (mM)	4.50 ± 0.92	4.30 ± 0.55*	5.23 ± 1.90	4.54 ± 0.81*
WHR	0.93 ± 0.06	0.83 ± 0.06*	0.92 ± 0.07	0.83 ± 0.05*
BMI# (kg/m^2)	25.34 ± 3.65	21.18 ± 2.64*	27.70 ± 4.19	21.91 ± 2.58*

MS = metabolic syndrome; WC = waist circumference; HC = hip circumference; BMI = body mass index; WHR = waist-to-hip ratio; SBP = systolic blood pressure; DBP = diastolic blood pressure; TC = total cholesterol; TG = triglyceride; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; FPG = fasting plasma glucose; MS group *vs* control group in the same nationality. *$P < 0.05$; comparison of biochemical indicators between Uyghurs and Kazakhs, #$P < 0.05$.

In the Uyghur and Kazakh MS groups, the results for a number of parameters were higher [height, weight, waist circumference, hip circumference (HC), TG, TC, LDL-C, systolic blood pressure (SBP), diastolic blood pressure (DBP), FPG, waist-hip ratio (WHR), and body mass index (BMI)] than those in controls ($P < 0.05$). In addition, HDL-C levels in the Uyghur and Kazakh MS groups were lower compared with those in controls ($P < 0.05$). In general, height, weight, HC, SBP, DBP, FPG, and BMI were higher in Kazakhs than in Uyghurs ($P < 0.05$).

Hardy-Weinberg equilibrium test

For the MS and control groups of Uyghurs and Kazakhs, genotype frequencies of the rs1801282 and rs3856806 loci were in Hardy-Weinberg equilibrium ($P > 0.05$). These results for the PPARγ gene in both nationalities indicated a genetic equilibrium with adequate representation of the population for subsequent analysis.

Comparison of rs1801282 and rs3856806 polymorphisms

The distribution frequencies of the rs1801282 CC genotype in Uyghurs and Kazakhs were 72.3 and 83.6%, respectively. The distribution frequencies of the rs1801282 CG/GC genotype in Uyghurs and Kazakhs were 27.7 and 16.4%, respectively. The distribution frequencies of the C alleles in Uyghurs and Kazakhs were 85.0 and 91.7%, respectively, while the distribution frequencies of the G alleles in Uyghurs and Kazakhs were 15.0 and 8.3%, respectively. There were significant differences in distribution frequencies of the three genotypes and alleles of the rs1801282 loci between Uyghurs ($\chi^2 = 18.477$, $P = 0.000$) and Kazakhs ($\chi^2 = 21.423$, $P = 0.000$).

Distribution frequencies of the rs3856806 CC genotype in Uyghurs and Kazakhs were 60.7 and 73.6%, respectively. The distribution frequencies of the rs3856806 CT/TT genotype in Uyghurs and Kazakhs were 39.3 and 26.4%, respectively. Distribution frequencies of C alleles were 77.9 and 85.3% for Uyghurs and Kazakhs, respectively. Distribution frequencies of T alleles were 22.1 and 14.7% for Uyghurs and Kazakhs, respectively. There were significant differences in the distribution frequencies of the three genotypes and alleles of the rs3856806 loci between Uyghurs ($\chi^2 = 18.510$, $P = 0.000$) and Kazakhs ($\chi^2 = 17.630$, $P = 0.000$) (Table 2).

Table 2. Comparison of frequencies of rs1801282 and rs3856806 genotypes and alleles of PPARγ gene (%).

SNP	Nationality	All subjects	Genotype		χ^2	P	Allele frequencies		χ^2	P
			CC	CG/GG			C	G		
rs1801282	Uyghur	498	357 (72.3)	126/11 (27.7)	18.477	0.000	840 (85.0)	148 (15.0)	21.423	0.000
	Kazakh	489	409 (83.6)	79/1 (16.4)			897 (91.7)	81 (8.3)		
			CC	CT/TT			C	T		
rs3856806	Uyghur	498	300 (60.7)	170/24 (39.3)	18.510	0.000	770 (77.9)	218 (22.1)	17.630	0.000
	Kazakh	489	360 (73.6)	114/15 (26.4)			834 (85.3)	144 (14.7)		

Association between rs1801282 and rs3856806 polymorphisms of PPARγ and MS

In Uyghurs, no significant difference was observed in the distribution frequencies of

genotypes and alleles of the rs1801282 and rs3856806 polymorphisms of PPARγ between the MS and control groups (P > 0.05). In Kazakhs, no significant difference was observed in the distribution frequencies of genotypes and alleles of the rs1801282 polymorphism of PPARγ between MS and control groups (P > 0.05). Frequencies of rs3856806 CT/TT genotypes and the T allele were lower in the MS group (21.2 and 12.4%, respectively) than in controls (31.6 and 17.0%, respectively); the differences were statistically significant (MS group: $\chi^2 = 9.353$, P = 0.009; control group: $\chi^2 = 4.048$, P = 0.044) (Tables 3 and 4).

Table 3. Comparison of frequencies of rs1801282 genotypes and alleles between MS groups and controls of Uyghurs and Kazakhs (%).

Nationality	Group	All subject	Genotype		χ^2	P	Allele frequencies		χ^2	P
			CC	CG/GG			C	G		
Uyghur	MS group	250	179 (72.2)	67/2 (27.8)	4.957	0.084	425 (85.7)	71 (14.3)	0.346	0.556
	Control group	248	178 (72.8)	59/9 (27.2)			415 (84.3)	77 (15.7)		
Kazakh	MS group	245	204 (73.1)	40/1 (26.9)	1.399	0.497	448 (91.4)	42 (8.6)	0.108	0.742
	Control group	244	205 (73.4)	39/0 (26.6)			449 (92.0)	39 (8.0)		

Table 4. Comparison of frequencies of rs3856806 genotypes and alleles between MS groups and controls of Uyghurs and Kazakhs (%).

Nationality	Group	All subject	Genotype		χ^2	P	Allele frequencies		χ^2	P
			CC	CT/TT			C	T		
Uyghur	MS group	250	150 (60.5)	90/8 (39.5)	3.247	0.197	390 (78.6)	106 (21.4)	0.279	0.597
	Control group	248	150 (61.0)	80/16 (39.0)			380 (77.2)	112 (22.8)		
Kazakh	MS group	245	193 (78.8)	43/9 (21.2)	9.353	0.009	429 (87.6)	61 (12.4)	4.048	0.044
	Control group	244	167 (68.4)	71/6 (31.6)			405 (83.0)	83 (17.0)		

Risk analysis of the PPARγ rs3856806 polymorphism and MS in Kazakhs

Univariate logistic regression analysis of the PPARγ rs3856806 polymorphism in Kazakhs was conducted. Risk assessment was conducted with the CC genotype and C allele as controls, with 95%CIs and ORs calculated. The risk of MS in individuals with rs3856806 CT and TT genotypes were 0.524- and 0.770-fold greater compared with those with the CC genotype. The risk of MS in individuals with the T allele was 0.699-fold greater compared with those with the C allele (Table 5).

Table 5. Risk analysis of rs3856806 polymorphism of PPARγ gene in Kazakhs.

Nationality	Genotype	MS group	Control group	χ^2	P	OR	95%CI for OR
	Allele frequencies	N = 245	N = 244				
Kazakh	CC	193	167			1.000	
	CT	43	71	8.747	0.003	0.524	0.340-0.807
	TT	9	6	0.237	0.627	0.770	0.269-2.210
	T	61	83	3.891	0.049	0.699	0.489-0.999
	C	426	405				

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Analysis of PPARγ polymorphisms and clinical biochemical indexes in Uyghurs and Kazakhs

In Uyghurs, individuals with the rs1801282 CC genotype had higher SBP than those with the CG/GG genotype ($P < 0.05$). There was no significant difference observed between other indexes. In Kazakhs, no significant difference was noted in clinical biochemical indexes among the different genotypes at the rs1801282 locus. For Kazakhs, individuals with the rs3856806 CC genotype had higher TG and WHR than those with the CT/TT genotype ($P < 0.05$). Furthermore, Kazakh individuals with the rs3856806 CC genotype had lower HDL-C levels than those with the CT/TT genotype ($P < 0.05$), with no significant difference noted between other indexes. In Uyghurs, no significant difference was noted in clinical biochemical indexes between the different genotypes at the rs3856806 locus ($P < 0.05$) (data not shown).

DISCUSSION

The PPARs are types of nuclear transcription factors activated by ligands and are members of the type II nuclear receptor superfamily (Meirhaeghe and Amouyel, 2004). The PPARs can be divided into three subtypes according to their biological structure: PPARα, PPARβ (PPARδ), and PPARγ (Holness et al., 2009). PPARγ is by far the most widely studied PPAR subtype. It was first identified in 1990 on chromosome 3p-2-5 with an approximate length of 146 kb (Issemann and Greenbaum, 1990; Fajas et al., 1997). Because of different promoters and alternative splicing, four mRNA isomers can be produced, with nine exons. The rs1801282 locus is located at exon 2, while rs3856806 is located at exon 6 of the PPARγ gene. PPARγ is associated with nearly all components of MS, including diabetes and obesity (Kota et al., 2005), hyperlipidemia (Wahli and Michalik, 2012), atherosclerosis (Huang et al., 2012), and hypertension.

In the present study, we showed that there was no statistically significant difference between MS and control groups of Uyghurs and Kazakhs with respect to age or gender. Genotype frequency was also consistent with the Hardy-Weinberg equilibrium. Frequency distribution of single nucleotide polymorphisms varied among the different groups. We showed that C and G allele frequencies were 85.0 and 15.0%, respectively, at the rs1801282 locus in Uyghurs. The rate of gene mutation was between 5.9 and 21.6% for Caucasians and higher than that in central Asian populations (1.7-9.3%) (Gouda et al., 2010). Frequencies of the C and T alleles were 77.9 and 22.1%, respectively, at the rs3856806 locus. The allele mutation rate was similar to those previously reported in non-Asian races (Bego et al., 2011), but lower than that in the Chinese Han population (29.2%) (Ding et al., 2012). C and G allele frequencies were 91.7 and 8.3%, respectively, at the rs1801282 locus in Kazakhs. The C and T allele frequencies were 85.3 and 14.7%, respectively, at the rs3856806 locus. We found that polymorphism distributions of rs1801282 and rs3856806 were significantly different between Uyghurs and Kazakhs. The CG/GG genotype and G allele frequencies at the rs1801282 locus, along with CT/TT genotype and T allele frequencies at the rs3856806 locus, in Uyghurs were all higher than those in Kazakhs. Our findings suggest that even though Uyghurs and Kazakhs live in close proximity in the Xinjiang region, distribution of PPARγ polymorphisms are influenced by different ethnic genetic factors.

Previous studies investigating the association between polymorphisms at the PPARγ locus and MS have resulted in inconsistent conclusions. Genotype and allele frequency dis-

tributions at the rs1801282 and rs3856806 loci in the MS and control groups were not significantly different in Uyghurs. This suggests that polymorphisms at the two loci are not related to the occurrence of MS in Uyghurs. In Kazakhs, frequencies of the CT/TT genotype and T allele at the rs3856806 locus were lower compared with those in the control group. Following risk analysis on Kazakhs, individuals with the CT genotype at the rs3856806 locus had a 0.524-fold greater risk of developing MS than those with the CC genotype. Individuals with the T allele had 0.699-fold greater risk of develop MS than those with the C allele. These results suggested that polymorphisms at the rs3856806 locus were associated with the occurrence of MS in Kazakhs, and the C allele was a risk factor for MS. In contrast, Tellechea et al. (2009) studied 572 Argentinean people and found that polymorphisms at the rs1801282 locus were associated with the incidence of MS. They also found that smoking increased the likelihood of developing MS. Huguenin and Rosa (2010) conducted a meta-analysis and found that rs1801282 polymorphisms were associated with diabetes. The G allele can significantly reduce the incidence of diabetes among Caucasian populations. Haseeb et al. (2009) found that the rs1801282 and rs3856806 polymorphisms were not correlated to the development of MS in Indian populations. Cao et al. (2010) found that polymorphisms at the rs1801282 locus were not associated with the incidence of type 2 diabetes mellitus in Han Chinese from Jiangsu Province. Carriers of the rs3856806CT/TT genotype exhibited a lower risk of developing type 2 diabetes mellitus compared with CC genotype carriers. The different conclusions drawn from these previous studies could be due to different experimental designs, sample content, and differing ethnic and regional factors, highlighting that multi-ethnic and multi-area research studies should be performed.

We found that Uyghurs with the CC genotype at rs1801282 had higher SBP than those with the CG/GG genotype. Among Kazakhs, people with the CC genotype at the rs3856806 locus had higher TG and WHR but lower HDL-C levels than those with the CT/TT genotype. These results suggest that polymorphisms at rs1801282 and rs3856806 could be related to hypertension in Uyghurs and to MS components such as blood lipids and obesity in Kazakhs. Gu et al. (2013) studied 820 people in Jiangsu Province and found that the rs1801282 CG/GG genotype might reduce the risk of hypertension (OR = 0.70), and conferred beneficial effects with respect to the onset of hypertension. Ylihärsilä et al. (2004) found that hypertension patients with the rs1801282 C genotype tended to have higher SBP. It is possible that this genotype results in increased insulin resistance, thus activating the renin-angiotensin system and causing increased blood pressure. In coronary atherosclerotic heart disease patients, Zhou et al. (2012) found that the rs3856806 polymorphism was associated with higher HDL levels and lower blood glucose levels, leading to a decrease in the risk of chronic heart disease. Chehaibi et al. (2014) found that the T allele carriers had lower prevalence rates of diabetes mellitus and TG levels than C allele carriers (OR = 0.575). These research results correspond to our findings; however, Passaro et al. (2011) could not discern an obvious correlation between PPARγ polymorphisms and MS.

The etiological mechanisms of MS are complicated and influenced by geography, racial differences, and other environmental factors. The role of other genes that are yet to be identified cannot be ruled out in MS etiology. We have examined the association between PPARγ polymorphisms and incidence of MS in Uyghurs and Kazakhs. We explored the possible pathogenesis of MS in these ethnic groups from a genetic perspective with the hope that our results could provide new insights for the diagnosis, prevention, and treatment of MS.

Conflicts of interest

The authors declare no conflict of interest.

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