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MicroRNA-155-5p rs767649 Polymorphism is Associated with Susceptibility to Essential Hypertension in the Chinese Tibetan Population in the Gannan Area

Wen Yan[1], Ruidi Chen[1], Yufei Zhao[1], Xiaozhen Zhang[1] and Xingjie Li[1*]

Abstract

Background The latest evidence has demonstrated the aberrant expression and diagnostic meaning of microRNA-155-5p in hypertension. Rs767649 is a common polymorphism in miR-155-5p and can mediate its expression.

Objective A case–control study based on a Chinese Tibetan population was constructed to evaluate the genetic association between miR-155-5p rs767649 polymorphism and essential hypertension (EH) susceptibility.

Methods Two hundred and fifty subjects with hypertension and 250 participants without hypertension were enrolled. miR-155-5p levels in the serum of participants were detected by qRT-PCR. Allele and genotype distributions of rs767649 were compared based on Sanger sequencing results. The association of rs767649 with EH susceptibility was estimated via logistic regression analysis.

Results The genotypes of rs767649 in miR-155-5p revealed a marked difference between EH and control groups, and the TA genotype of rs767649 may depress the risk of developing EH. qRT-PCR results verified up-regulated expression of miR-155-5p in patients with EH, and cases carrying rs767649 TT genotype had higher serum miR-155-5p levels and concentration of lipids than TA/AA genotype carriers. After adjusting for other clinical indicators, rs767649 polymorphism was still independently related to EH susceptibility.

Conclusion The findings revealed the genetic association of rs767649 polymorphism in miR-155-5p with EH susceptibility in the Chinese Tibetan population in the Gannan area. Rs767649 TT genotype was a risk factor for EH, which might be interrelated to increased miR-155-5p levels and lipid disorders.

Keywords MicroRNA-155-5p, Polymorphism, Hypertension, Genetic predisposition

1 Introduction

Hypertension (HTN) is a multifactorial-induced disease that can cause cardiovascular disease. Stroke (ischemic and hemorrhagic) and coronary artery disease are chiefly caused by HTN [1]· HTN is typically classified into essential hypertension (EH) and secondary hypertension (SH) and EH accounts for about 90% of the cases [2]. The number of people with EH has increased from about 700 million in 1990 to 1.28 billion in 2021 [3]. Current treatments rely on healthy lifestyle modifications and medication to lower blood pressure. Tibetans are a unique indigenous people in China, living chiefly on the Tibetan Plateau. The high-altitude geography and the Tibetan people's long-term dietary habits of high salt intake can bring about the

*Correspondence:
Xingjie Li
lixinjie2369@163.com
[1] Lanzhou University Second Hospital Health Management Center, No. 981, Nanbinhe Road, Chengguan District, Lanzhou 730000, Gansu, China

development of EH in the Tibetan population. Statistics demonstrate that the prevalence of EH in the Tibetan population is notably higher (31.4%) than the Chinese average (27.5%) [4]. However, the underlying pathogenesis is indistinct.

In addition to factors such as geography and lifestyle, genetics are also pivotal factors influencing the pathogenesis of EH [5]. Conservative small non-coding RNAs (miRNAs) are approximately 21–23 bp in length and restrain post-transcriptional translation or gene expression by specifically combining with the 3′ untranslated region (3′UTR) of the mRNA [6, 7]. Some miRNAs are momentous in the process of functional regulation of blood vessels and are referred to in almost all aspects of cardiovascular disease, such as miR-126, which regulates thrombosis, cell proliferation, and apoptosis processes based on in vitro or in vivo studies [8].

Multiple evidence reveals that abnormal expression of miRNAs causes the development of EH. miR-29b and miR-128 are markedly up-regulated in patients with HTN [9, 10], and miR-200b expression is down-regulated in patients with HTN [11]. miR-155, a pivotal circulating cytokine, can mediate the development of HTN [12]. It has been demonstrated that the expression level of miR-155 in hypertensive patients was markedly higher than that in healthy controls [13], whereas miR-155 expression levels in the aorta of pregnant hypertensive rats and adult SH rats were abated and negatively correlated with blood pressure [14, 15]. Further studies have discovered that miR-155 can regulate blood pressure by modulating the transforming growth factor-β1 (TGF-β1) signaling pathway [16]. Recent discussions have demonstrated that miR- 155-5p can play a pivotal faction in pulmonary arterial hypertension (PAH) and its expression is up-regulated in PAH [17, 18].

Single nucleotide polymorphisms (SNPs) are variants in the genome that occur with a frequency of at least 1% in the general population and largely affect the stability and function of miRNAs and thereby lead to the development of disease [19]. Different genotypes of the miR-155 rs767649 polymorphism play a basilic role in susceptibility to rheumatoid arthritis, systemic lupus erythematosus, and hepatocellular carcinoma [20–22]. There is much evidence that polymorphisms in miRNAs may be interrelated to genetic susceptibility to EH. miR-495 A>C (rs2281611) and miR-200b T>C (rs7549819) polymorphic variants have been interrelated to susceptibility to HTN [23]. Research on polymorphisms of miRNAs has contributed to our understanding of the pathogenic mechanism of EH and is conducive to the therapeutic development of HTN-related diseases.

Based on these findings, the present study investigated the potential association of miR-155-5p (rs767649) polymorphism with EH susceptibility in the Tibetan population in the Gannan region, China.

2 Methods

2.1 Study Population

Five hundred Tibetan subjects including 250 healthy controls (HC) and 250 EH patients were enrolled from January 2022 to June 2023 at Lanzhou University Second Hospital. Patients diagnosed with HTN who have a systolic blood pressure ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg measured repeatedly without taking any medication. Both patients with a history of antihypertensive therapy and newly diagnosed EH were included. Collectively, 28 EH patients had a history of antihypertensive therapy with valsartan, Irbesartan and/or nifedipine, and 222 EH patients were newly diagnosed. Among all EH patients, 27 type 2 diabetes (T2DM) cases were identified. Patients with the presence of other chronic diseases were not included in this study. Body mass index (BMI) is computed by height and weight formulas. Waist circumference (WC) was measured using the same tape measure. Systolic blood pressure (SBP), DBP, fasting blood glucose (FBG), total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein-cholesterol (LDL-C) levels were measured by enzyme colorimetric autoanalyzer. All patients were aware of the purpose of this study and subscribed to informed consent forms. This study was approved by the Ethnic Committee of Lanzhou University Second Hospital.

2.2 Genotype Analysis

Genomic DNA was extracted from the blood samples following the instructions of the DNA isolation kit (Thermo, Shanghai, China). The miR-155-5p rs767649 locus sequence was amplified by PCR and the sample was sent to Sino Geno Max Company (Beijing, China) for Sanger sequencing. Statistics of different genotypes and frequencies according to the results.

2.3 Quantitative Reverse Transcription Polymerase Chain Reaction (qRT-PCR)

Total RNA was extracted according to the instructions of the TRizol method and reverse transcribed into cDNA by a reverse transcription kit (Thermo, USA). The expression level of the objective genes was then determined in accordance with the instructions of the SYBR GREEN Quantification Kit (Merck, Germany). U6 was used as an internal reference gene, and $2^{-\Delta\Delta Ct}$ method was used to analyze the relative expression of miR-155-5p, calculated relative to the control group. The samples were taken in triplicate and the results were obtained from three independent experiments.

2.4 Statistical Analysis

All data were statistically analyzed by GraphPad Prism version 4.0 and IBM SPSS Statistics version 19.0. The Chi-square goodness-of-fit χ^2 test was used to evaluate whether the genetic distribution of genes deviated from the Hardy–Weinberg equilibrium (HWE) and conspicuous differences in genetic variants between patients and controls. Categorical variables are represented as absolute values and percentages. Continuous variables are represented as mean ± standard deviation (normal/parametric distribution) or median. Multifactor regression analysis was performed to assess the Odds ratios (OR) and 95% confidence intervals (95% CI) for several indicators. One-way ANOVA was applied to analyze the association between rs767649 genotype and EH lipids.

Table 1 Baseline characteristics of the study population

Characteristics	Control ($n=250$)	Essential hypertension ($n=250$)	*P* value
Age, year	51.52 ± 10.23	50.16 ± 9.89	0.130
Gender, male/female	129/121	133/117	0.720
BMI, kg/m^2	23.67 ± 3.06	26.21 ± 3.03	< 0.001
WC, cm	81.03 ± 8.05	87.30 ± 8.22	< 0.001
SBP, mmHg	115.01 ± 13.88	139.61 ± 12.69	< 0.001
DBP, mmHg	70.84 ± 7.98	87.77 ± 8.23	< 0.001
FBG, mmol/L	4.90 ± 1.41	5.42 ± 1.91	0.001
TC, mmol/L	5.02 ± 1.00	5.32 ± 0.95	0.001
TG, mmol/L	1.56 ± 0.93	1.67 ± 0.95	0.173
HDL-C, mmol/L	1.49 ± 0.41	1.26 ± 0.37	< 0.001
LDL-C, mmol/L	2.70 ± 0.81	2.86 ± 0.78	0.025

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; WC: waist circumference; FBG, fasting blood glucose; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol

3 Results

3.1 Comparison of Basic Characteristics of Research Subjects

Firstly, this experiment analyzes the baseline characteristics of healthy control subjects and hypertensive patients. According to the results, there were no significant differences in age, gender, and TG level of the two groups of patients which were not statistically insignificant (all $P > 0.05$, Table 1). There were remarkable differences in BMI, WC, SBP, DBP, FBG, TC, HDL-C, and LDL-C indicators between the two groups (all $P < 0.05$, Table 1), indicating that elevation of the patient's blood pressure might be caused by the above factors.

3.2 Comparison of Genotypes and Allelic Polymorphisms of the miR-155-5p Gene rs767649

Analysis of results of genotype frequencies and allelic polymorphisms of rs767649 in the healthy control group and the EH group were shown in Table 2. Genetic inheritance in the healthy control population was consistent with Hardy–Weinberg equilibrium (pHWE > 0.05) through analysis of results by χ2 test and data from the same Mundell group. There was a high percentage of TT genotype carriers (126, 50.40%) and a low percentage of TA genotype carriers (87, 34.80%) in the EH group. The frequency of the TA genotype in the control group was observably higher than that in the EH group ($P = 0.005$, OR = 0.579), indicating that the rs767649 TA genotype was a protective genotype for EH. The dominant model data showed a high frequency of TT genotype in the EH

Table 2 The genotype and allele frequencies of miR-155-5p gene rs767649 polymorphisms in patients with essential hypertension

Genotype/allele	HC ($n=250$)	Hypertension ($n=250$)	OR (95% CI)	*P* value
TT	99 (39.60)	126 (50.40)	1	–
TA	118 (47.20)	87 (34.80)	0.579 (0.395–0.849)	0.005
AA	33 (13.20)	37 (14.80)	0.881 (0.514–1.509)	0.644
Dominant model				
TT	99 (39.60)	126(50.40)	1	
TA + AA	151 (60.40)	124 (49.60)	0.645 (0.453–0.920)	0.015
Recessive model				
TT + TA	217 (86.80)	213 (85.20)	1	
AA	33 (13.20)	37 (14.80)	1.142 (0.689–1.894)	0.606
Additive model				0.126
T	316 (63.20)	339 (67.80)	1	-
C	184 (36.80)	161 (32.20)	0.816 (0.628–1.059)	0.126
p^{HWE}	0.816			

HC, healthy control; OR, Odds ratio; CI, confidence interval; HWE, Hardy–Weinberg equilibrium

group (126, 50.40), and the results indicated that the TT genotype was the causative genotype for EH.

Indicators with remarkable differences in Table 1 were subjected to multifactorial regression to analyze their correlation with the development of EH. According to the results, rs767649 polymorphism was independently associated with the development of EH (all $P<0.05$, Table 3). The remaining indicators were not remarkably associated with the development of EH (Table 3).

3.3 Association of miR-155-5p rs767649 Genotype with miR-155-5p Levels and Lipid Levels

Detection of miR-155-5p expression levels by qRT-PCR on the serum of two groups of study subjects. Compared with normotensive controls, the miR-155-5p expression level was markedly higher in EH patients (Fig. 1A, $P<0.001$). The expression level of miR-155-5p was markedly lower in carriers of the rs767649 TA/AA genotype than in carriers of the TT genotype in the control group (Fig. 1B, $P<0.001$). Similarly, the expression level of miR-155-5p was dramatically higher in EH patients who were carriers of the rs767649 TT genotype (Fig. 1B, $P<0.001$). The expression levels of miR-155-5p in EH patients were all higher than those in healthy controls (Fig. 1B, $P<0.001$).

Previous studies have found that the development of EH might be associated with rs767649 polymorphic and abnormal lipid levels. One-way ANOVA analysis of the four lipid levels showed marked differences in TC, TG, HDL-C, and LDL-C levels in carriers of different genotypes of rs767649 ($P<0.001$). Compared to TA/AA genotype carriers, the rs767649 TT genotype carriers had high serum lipid concentrations (Table 4). The above results demonstrate that miR-155-5p levels and lipid concentrations are up-regulated in carriers of the rs767649 TT genotype.

Table 3 Logistic regression analysis of factors related to the onset of essential hypertension

Items	OR	95% CI	*P* value
BMI	1.233	0.847–1.795	0.274
WC	1.283	0.884–1.861	0.190
FBG	1.306	0.904–1.885	0.155
TC	1.464	1.012–2.119	0.043
HDL-C	0.799	0.552–1.157	0.235
LDL-C	1.430	0.989–2.068	0.057
rs767649	2.496	1.726–3.609	< 0.001

BMI, body mass index; WC: waist circumference; FBG, fasting blood glucose; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; OR, Odds ratio; CI, confidence interval

4 Discussion

Numerous studies have discovered genetic heterogeneity at HTN susceptibility loci in different ethnic groups. The risk of HTN in Tibetan populations is supremely high, with a multiformity of intrinsic influences. This is the first study to investigate the relativity between EH

Table 4 Association of different miR-155-5p gene rs767649 genotypes with lipids in essential hypertension population

Variables	Rs767649 genotype			*F*	*P* value
	TT	TA	AA		
TC, mmol/L	5.63 ± 0.89	4.98 ± 0.95	5.02 ± 0.77	16.02	< 0.001
TG, mmol/L	1.98 ± 0.86	1.22 ± 0.83	1.72 ± 1.12	18.64	< 0.001
HDL-C, mmol/L	1.15 ± 0.37	1.41 ± 0.28	1.27 ± 0.42	14.53	< 0.001
LDL-C, mmol/L	3.12 ± 0.61	2.47 ± 0.88	2.89 ± 0.70	20.63	< 0.001

TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol

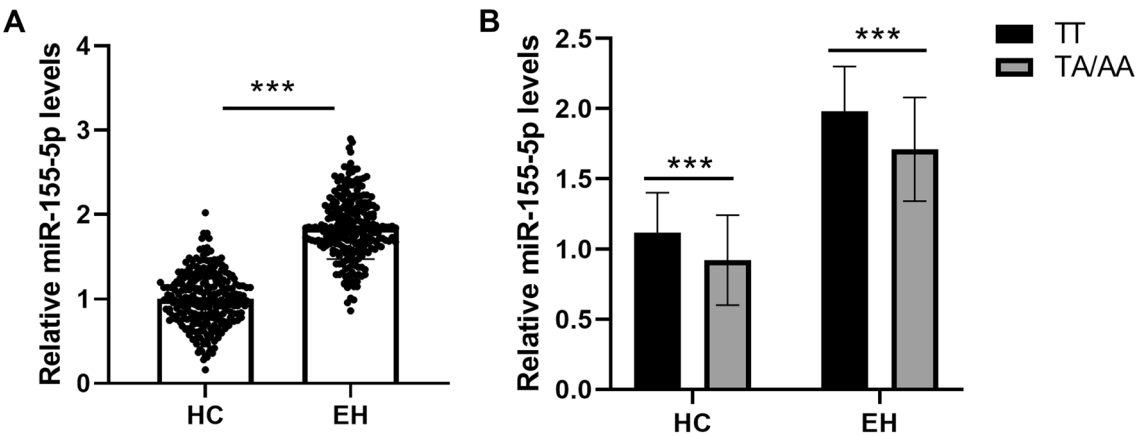

Fig. 1 Relative expression levels of miR-155-5p. **A** Relative expression levels of miR-155-5p in EH patients and HC group. **B** Relative expression levels of miR-155-5p in carriers of diverse genotypes of rs767649. ***$P<0.001$

susceptibility and miR-155-5p rs767649 polymorphism in Tibetan people in Gannan, China. We discovered the genetic association of rs767649 polymorphism in miR-155-5p with EH susceptibility. The rs767649 TT genotype raised the risk of EH in the Gannan Tibetan populations. Notably, based on the clinical data, a higher level of HDL was detected in control group without HTN, which may be related to their more active lifestyle, such as reasonable diet structure, good exercise habits, etc. And those factors may have an impact on not only the co-morbid risk factors, but also the principal disease state of HTN. However, in this study, we did not collect relevant indicators, which may be a limitation of our research. In future studies, these factors need to be taken into account to further verify the genetic association of rs767649 polymorphism and EH.

EH is a critical threat to human health and safety and its occurrence is influenced by numerous factors. It has been reported that the rs767649 T>A polymorphism located in the promoter region of miR-155-5p enhances the transcriptional activity and expression of this miRNA and correlates with susceptibility to EH [24]. Meng et al. certificate that the frequency of genetic polymorphisms varies between regions and even races [25]. The frequency of HOTAIR rs920778 polymorphism TT variant genotypes is distinctly higher in PTC patients than in CC and C allele genotypes [26]. Our research discovered that the rs767649 polymorphic locus was independently related to the development of EH. The frequency of carriers of the miR-155-5p rs767649 polymorphism TT genotype in hypertensive patients was notably higher than that of the TA + AA genotype, manifesting that the causative genotype of EH is the miR-155-5p rs767649 TT genotype. Recently, Kim et al. have examined the genotype distributions of miR-155-5p rs767649 polymorphism in HTN patients in a Korean population, but no significant genetic association is detected, which is inconsistent with our findings [27]. We considered that racial differences may be the reason. So the genetic association of miR-155-5p rs767649 polymorphism with EH should be verified in other different ethnic groups.

Some studies have demonstrated notable dysregulation of miR-155-5p expression in EN patients [12, 28], illustrating that there is an influence of miR-155-5p on the development of EN. In this study, we found that the miR-155-5p expression level in the serum of rs767649 TT genotype carriers was notably higher than that of TA/AA genotype carriers, and the miR-155-5p expression level of all EN patients was higher than that of the healthy population. The above results authenticate that the miR-155-5p rs767649 polymorphism is interrelated with genetic susceptibility to EH, which might be related to elevated miR-155-5p expression. In hypertensive rat models, highly expressed miR-155-5p is detected, it is involved in vascular endothelial dysfunction in HTN [29]. In carotid atherosclerosis, elevated miR-155-5p contributes to the permeable and angiogenic activity of carotid endothelial cells, thereby promoting the occurrence of carotid atherosclerosis [30]. HTN leads to vascular endothelial dysfunction, which in turn aggravates HTN, and this interaction plays a key role in the occurrence and development of HTN and its complications [31]. Based on the previous evidence, the underlying mechanism of miR-155-5p in EH might be related to vascular endothelial dysfunction. Interestingly, another study has reported the dynamic change of miR-155-5p expression in the aortae of adult spontaneous hypertensive rats, and a significant decrease of miR-155-5p is detected in the aortae of hypertensive rats compared to normal rats at 16 weeks of age, that is inconsistent with our present findings and previous evidence [15]. We think that the dynamic change of miR-155-5p levels in hypertensive rats is still to be studied, and its level is also clearly related to the age of rats, which also needs to be considered in future research.

The expression level of miR-155-5p is also up-regulated in diabetic patients with prominently elevated blood glucose and lipid levels, and it is demonstrated that the up-regulation of miR-155-5p promoted the accumulation of lipids [32]. Gu et al. discovered that miR-155-5p promotes lipids metabolism by inhibiting the cAMP/PKA signaling pathway validating this mechanism [33]. To investigate whether a similar mechanism exists in EH patients, the clinical characteristics of 500 Tibetan hypertensive patients and healthy control subjects were enumerated in this study. By comparing the results of the measurements, it was found that the levels of indicators such as body weight and blood glucose/lipids in hypertensive patients differed substantially compared to the healthy group. It elucidated that changes in the above indicators might be the pivotal factors influencing the elevation of blood pressure in the Tibetan population. The significant indicators were further validated by including them in the multifactorial regression analysis, which showed that TC was independently interrelated with the development of EH. Serum levels of lipids such as TC, TG, and LDL-C were markedly up-regulated in carriers of the rs767649 TT genotype compared with other genotypes, revealing that the miR-155-5p rs767649 TT genotype promoted lipids accumulation in patients. The above results indicate that the rs767649 TT genotype promotes the up-regulation of miR-155-5p expression levels in patients thereby promoting lipids accumulation.

However, several limitations are presented in the current study. First, only a single SNP of miR-155-5p was examined in the current study, its interaction with other

SNPs should be explored in future studies. Besides, due to the relatively small sample size, the present findings should be verified in other larger cohorts. Moreover, the pathologies and mechanism study were not included in the current study, which should be taken into account in future studies.

To conclude, the relationship rs767649 polymorphism of miR-155-5p might be related to EN susceptibility in the Tibetan population in the Gannan region, where TT genotype and T allele increase the risk of developing EH, demonstrating that it could probably become a novel marker for EH risk. This study also revealed the possible relevance of rs767649 polymorphism with miR-155-5p expression and lipids accumulation. More well-designed research, however, is required to validate the current study's conclusions.

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Author contributions
Conceptualization, W.Y. and X.L.; data curation, W.Y., R.C. and Y.Z.; formal analysis, Y.Z. and X.Z.; funding acquisition, X.L.; investigation, Y.Z. and X.Z.; methodology, W.Y. and R.C.; project administration, X.L.; resources, Y.Z. and X.Z.; software, W.Y. and R.C.; supervision, X.L.; validation, W.Y. and R.C.; visualization, W.Y. and R.C.; roles/writing—original draft, W.Y.; writing—review and editing, X.L.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest
The authors declare that they have no competing interests.

Ethics approval and consent to participate
The study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Lanzhou University Second Hospital before the study began. The participants' right to be informed about the study was ensured and agreed to participate in the study.

Consent for publication
Not applicable.

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