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Original Research

Association of polymorphisms in endothelial dysfunction-related genes with susceptibility to essential hypertension in elderly Han population in Liaoning province, China

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Hypertension is a complex disease which is mainly influenced by genetic factors. Recently, genome-wide association study (GWAS) found three novel endothelial dysfunction-related sites: Vascular endothelial growth factor A (*VEGFA*) rs9472135, Faciogenital dysplasia 5 (*FGD5*) rs11128722, Zinc Finger C3HC-type Containing 1 (*ZC3HC1*) rs11556924. Endothelial dysfunction is one of the early events in pathophysiology of essential hypertension. To investigate the association of endothelial dysfunction-related genes with essential hypertension, we conducted a case-control study of 431 patients with hypertension and 345 controls. The polymorphisms were detected using Taqman Probe. The alleles and genotypes of *ZC3HC1* rs11556924 and *VEGFA* rs9472135 were not statistically different between the two groups, while the allele of *FGD5* rs11128722 was different [$P = 0.045$, OR = 1.265, 95% CI = (1.009–1.586)], especially in the male [$P = 0.035$, OR = 1.496, 95% CI = (1.037–2.158)]. Analyzing the different of genotype distribution of 3 SNPs in the two groups under different genetic models, the genotypes of *FGD5* rs11128722 showed difference in male under dominant model [$P = 0.049$, OR = 1.610, 95% CI = (1.018–2.544)]. The polymorphism of *FGD5* rs11128722 had a significant difference in Body Mass Index (BMI) among different genotypes; In the additive genetic model, BMI of GA genotype was higher than that of GG ($P = 0.038$); GA + AA was higher than GG in the dominant genetic model ($P = 0.011$). In our study, we found that the polymorphisms of *VEGFA* rs9472135 and *ZC3HC1* rs11556924 may not significantly associated with the risk of essential hypertension, and *FGD5* rs11128722 may increase the risk of it, especially in elderly men.

Keywords

Essential hypertension; Polymorphism; Vascular endothelial dysfunction

1. Introduction

Hypertension is one of the main diseases endangering human health. It is estimated that the number of untreated patients with hypertension will increase to 1.56 billion by 2025 in the world's adult population [1, 2], more than 90% of which are primary (essential) hypertension. Hypertension is a complex multifactorial disease, which is influenced by genetic, environmental and demographic factors. The diagnosis of essential hypertension is made when no other cause for increased blood pressure is found. Previous study has shown that the influence of genetic factors on the change of blood pressure reaches 30% to 50%. Therefore, identifying the susceptibility gene loci of hypertension will help to understand the pathological and physiological characteristics of the disease [3].

In recent genome-wide association study (GWAS) studies in European population, three novel sites related to endothelial dysfunction were found [4, 5]: Vascular endothelial growth factor A (*VEGFA*) rs9472135, Faciogenital dysplasia 5 (*FGD5*) rs11128722, Zinc Finger C3HC-type Containing 1 (*ZC3HC1*) rs11556924. Endothelial dysfunction is one of the early events in pathophysiology of essential hypertension, which is considered to promote subclinical target organ damage and promote the progress of atherosclerosis [6]. *VEGFA* is produced by vascular endothelial cells (EC), which is usually called *VEGF* [7]. Previous studies have shown that the imbalance of *VEGF* signaling pathway is regarded as the key mediator of tumor angiogenesis, and hypertension is the most common adverse reaction of cancer patients based on *VEGF* pathway inhibitor treatment. The relationship between *VEGF* polymorphisms and essential hypertension has been studied in different regions and nationalities. However, the conclusions reported at home and abroad are not consistent. *FGD5* is a member of the *FGD* family of guanine nucleotide exchange factor. The *FGD* family consists of *FGD1-6* and *Cdc42-GEF* (*FRG*) related to *FGD1*. Some studies have shown that *FGD5* is expressed by endothelial cells to maintain *VEGFA* signal transduction and endothelial chemotaxis by inhibiting the proteasome dependent degradation of *VEGFR2*, and activate *Cdc42* [8]. Abnormal activation of *Cdc42* may lead to the occurrence of certain diseases, such as tumor, car-

diovascular disease, diabetes mellitus and neurodegenerative disease. *ZC3HC1* is a mammalian E3 ligase that regulates mitotic entry time [9, 10]. At present, only two studies have verified the relationship between *ZC3HC1* and hypertension [11, 12]. Kunnas T *et al.* believe that *ZC3HC1* rs1556924 is associated with 50-year-old patients with essential hypertension.

Due to the influence of different ethnicity and environment, it is necessary to conduct this study to confirm whether *VEGFA* rs9472135, *FGD5* rs11128722 and *ZC3HC1* rs11556924 are the susceptible sites of essential hypertension in Chinese Han population.

2. Materials and methods

2.1 Study population

A total of 431 patients with hypertension and 345 controls were enrolled from Fushun and Panjin city in Liaoning province, China. There were 302 (38.9%) male and 474 (61.1%) female in our study. In summary, participants with hypertension who met the following criteria were recruited: (1) systolic blood pressure (SBP) of at least 140 mmHg or diastolic blood pressure (DBP) of at least 90mmHg, or treatment with antihypertensive medication; (2) aged 60 years and above; (3) all patients were free from severe liver, kidney and acute or chronic infectious diseases, hyperthyroidism or hypothyroidism, systemic arteriopathy, various tumors and other cardio-cerebrovascular diseases and metabolic diseases.

2.2 Data collection and clinical evaluation

Clinical data including gender, age, height, weight, waist circumference, Body Mass Index (BMI), SBP, DBP were recorded in heath datasheet. Ten milliliters of peripheral blood of each fasting study individual was collected in EDTA vacutainers. Biochemical profiles, including fasting blood glucose (FBG), total cholesterol (TC) and triglyceride (TG) were done on automated biochemical analyzer (Murray, BS-820).

2.3 DNA isolation and genotyping

Genomic DNA was extracted from blood samples using a Blood Genetic DNA Mini Kit (CWBIO, Beijing, China). The concentration of the DNA was tested by NanoDrop 2000 (Thermo Fisher Scientific, Waltham, MA, USA), then stored at –80 °C for future use. Genotyping of 3 SNPs in all participants was conducted using Taqman^{TM} Probe (Taqman^{TM} SNP Genotyping Assays; Applied Biosystems, Foster City, CA, USA) and a QuantStudio^{TM} 6 Flex Real-Time PCR (Applied Biosystems, Foster City, CA, USA). The experiment was carried out strictly according to the method of Wang's report [13]. Total system was 5 μL, as following: 2.0 μL of purified genomic DNA, 2.5 μL of TaqPath^{TM} ProAmp^{TM} Master Mixes (Applied Biosystems, Foster City, CA, USA), 0.1 μL of 40 $\times$ SNP Genotyping Assay, and 0.4 μL of deoxyribonuclease-free water. The appropriate PCR thermal cycling conditions was set: maintained 5 minutes for initial denature/enzyme activation, followed by 40 cycles of 5 seconds at 95 °C for denaturation, and 1 minutes at 60 °C for annealing and extension. After PCR amplification, an endpoint plate read was conducted using QuantStudio^{TM} 6 Flex Real-Time PCR System. The genotype of each sample can be determined based on the fluorescence signal. Basic information of 3 SNPs are shown in Table 1.

Table 1. Basic information of three SNPs.

Gene	SNPs	Chromosome position	Risk allele	Function
ZC3HC1	rs11556924	7 : 130023656	C>T	missense mutation
FGD5	rs11128722	3 : 14916619	G>A	intronic mutation
VEGFA	rs9472135	6 : 43842065	T>C	intronic mutation

SNPs, single nucleotide polymorphisms.

2.4 Statistical analysis

The Epidata 3.1 software package was used for database design, data entry, and data check. Statistical analysis was performed with SPSS 21.0 software (IBM, ASiaAnalytics Shanghai, Shanghai, China). Quantitative variables were expressed as mean $\pm$ standard deviation. Qualitative variables were expressed as counts and proportions. Independent-samples *t*-test and one-way analysis of variance (ANOVA) were used to compare the mean differences for continuous variables across levels of a categorical variable, and two-two comparison between groups using SNK-q. Univariate and multivariate logistic regression analysis was used to test the genetic susceptibility of each SNP to hypertension in genetic models. A value of $P < 0.05$ was considered as statistically significant.

2.5 Data availability statement

With the permission of the corresponding authors and their institutions, combined with the relevant documents, all data used for analysis will be shared after ethics approval if requested by other investigators for reasonable purposes of replicating procedures and results.

3. Results

3.1 Comparison of general clinical indicators between essential hypertension and healthy people

The clinical and demographic characteristics of 431 patients and 345 controls were reported in Table 2. The patients and controls had no significant difference in age, gender and TG. However, the patients had significantly higher levels of BMI, waist circumference, SBP, DBP, FBG, TC ($P < 0.05$). The proportion of overweight and obesity in the case group was higher than that in the control group.

3.2 Distribution of alleles and genotypes of 3 SNPs in the two groups

It revealed that there was a strong association between alleles of *FGD5* rs11128722 with hypertension risk [$P = 0.045$, OR = 1.265, 95% CI = (1.009–1.586)], while the genotype carrying rate did not; After stratification by gender, only the alleles distribution of male patients had a statistically significant

Table 2. Clinical and epidemiological characteristics of the subjects.

Variable	Patients (n = 431, 55.4%)	Controls (n = 345, 44.6%)	*P* value
Gender [n (%)]			
Male	167 (38.70)	135 (39.10)	0.941
Female	264 (61.30)	210 (60.90)	
Age (year, $\bar{x} \pm s$)	68.20 ± 9.69	66.64 ± 14.98	0.094
BMI (kg/m^2)	24.05 ± 3.21	22.89 ± 2.81	<0.001
Normal (18.5–24 kg/m^2)	222 (51.51)	233 (67.53)	
Overweight (24–28 kg/m^2)	163 (37.82)	99 (28.70)	<0.001
Obesity (≥28 kg/m^2)	46 (10.67)	13 (3.77)	
Waist circumference (cm)	80.48 ± 16.89	76.95 ± 16.73	0.004
SBP (mmHg)	151.23 ± 16.40	124.27 ± 10.44	<0.001
DBP (mmHg)	91.27 ± 9.80	78.60 ± 5.98	<0.001
FBG (mmol/L, $\bar{x} \pm s$)	5.44 ± 2.49	4.80 ± 2.33	<0.001
TG (mmol/L, $\bar{x} \pm s$)	2.25 ± 7.03	2.17 ± 12.31	0.917
TC (mmol/L, $\bar{x} \pm s$)	5.24 ± 3.24	4.57 ± 2.15	0.001

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; TG, triglyceride; TC, total cholesterol.

difference [*P* = 0.035, OR = 1.496, 95% CI = (1.037–2.158)] (Table 3). In contrast, there was no significant difference in the alleles and genotypes of *VEGFA* rs9472135, *ZC3HC1* rs115556924 between the two groups; Even after stratification by gender, no significant difference had been found (Table 3).

3.3 Genotype distribution of 3 SNPs in the two groups under different genetic models

Besides the genotypes of *FGD5* rs11128722 was different in male under dominant model [*P* = 0.049, OR = 1.610, 95% CI = (1.018–2.544)], there was no significant difference between genotype distribution of 3 SNPs in the two groups under different genetic models (Table 4).

3.4 Analysis of blood pressure difference in SNP loci of 3 genes under three genetic models

There was no significant difference in SBP and DBP among different genotypes of *VEGFA* rs9472135, *FGD5* rs11128722 and *ZC3HC1* rs115556924 (Table 5).

3.5 Analysis of differences of BMI among SNP loci of 3 genes under three genetic models

There was no significant difference in BMI of *VEGFA* rs94721352 and *ZC3HC1* rs111556924 among different genotypes under different genetic models; In *FGD5* rs11128722, the BMI of genotype GA was higher than that of GG genotype in additive model (*P* = 0.038), and GA + AA genotype was higher than that of GG genotype in the dominant model (*P* = 0.011) (Table 6).

Table 3. Distribution of *ZC3HC1* rs11556924, *FGD5* rs11128722, *VEGFA* rs9472135 alleles and genotypes in two groups.

Alleles and genotypes	Patients (%)	Controls (%)	OR (95% CI)	*P* value
rs11556924				
C	818 (94.9)	660 (95.7)	1.183 (0.735–1.903)	0.549
T	44 (5.1)	30 (4.3)		
CC	388 (90.1)	315 (91.3)		0.487
CT	42 (9.7)	30 (8.7)		
TT	1 (0.2)	0 (0.0)		
Female				
C	502 (95.1)	404 (96.2)	1.308 (0.692–2.471)	0.432
T	26 (4.9)	16 (3.8)		
CC	238 (90.2)	194 (92.4)		0.421
CT	26 (9.8)	16 (7.6)		
TT	0 (0.0)	0 (0.0)		
Male				
C	316 (94.6)	256 (94.8)	1.042 (0.508–2.135)	1
T	18 (5.4)	14 (5.2)		
CC	150 (89.8)	121 (89.6)		0.54
CT	16 (9.6)	14 (10.4)		
TT	1 (0.6)	0 (0.0)		
rs11128722				
G	607 (70.4)	518 (75.1)	1.265 (1.009–1.586)	0.045
A	255 (29.6)	172 (24.9)		
GG	208 (48.3)	190 (55.1)		0.107
GA	191 (44.3)	138 (40)		
AA	32 (7.4)	17 (4.9)		
Female				
G	376 (71.2)	310 (73.8)	1.139 (0.854–1.519)	0.381
A	152 (28.8)	110 (26.2)		
GG	130 (49.2)	111 (52.9)		0.641
GA	116 (43.9)	88 (41.9)		
AA	18 (6.8)	11 (5.2)		
Male				
G	231 (69.2)	208 (77.0)	1.496 (1.037–2.158)	0.035
A	103 (30.8)	62 (23.0)		
GG	78 (46.7)	79 (58.5)		0.088
GA	75 (44.9)	50 (37.0)		
AA	14 (8.4)	6 (4.4)		
rs9472135				
T	767 (89.0)	622 (90.1)	1.133 (0.815–1.574)	0.505
C	95 (11.0)	68 (9.9)		
TT	338 (78.4)	281 (81.4)		0.247
TC	91 (2.1)	60 (17.4)		
CC	2 (0.5)	4 (1.2)		
Female				
T	473 (89.6)	383 (91.2)	1.204 (0.777–1.865)	0.44
C	55 (10.4)	37 (8.8)		
TT	209 (79.2)	175 (83.3)		0.075
TC	55 (20.8)	33 (15.7)		
CC	0 (0.0)	2 (1.0)		
Male				
T	294 (88.0)	239 (88.5)	1.049 (0.637–1.728)	0.899
C	40 (12.0)	31 (11.5)		
TT	129 (77.2)	106 (78.5)		0.929
TC	36 (21.6)	27 (20.0)		
CC	2 (1.2)	2 (1.5)		

4. Discussion

Hypertension is a complex disease that comes about as a result of the interaction between genetic and environmental factors. Endothelial dysfunction is one of the early events in pathophysiology of essential hypertension. It's reported that endothelial dysfunction seems to promote microvascular dysfunction and may be an early alteration in ischemic heart

Table 4. Distribution of *ZC3HC1* rs11556924, *FGD5* rs11128722, *VEGFA* rs9472135 genotypes in different gene models.

SPNs	Genetic model		OR (95% CI)	*P* value
rs11556924	Additive model	TT VS. CC	NA	NA
		CT VS. CC	1.305 (0.797, 2.136)	0.321
	Dominant model	CT + TT VS. CC	1.336 (0.818, 2.182)	0.268
	Recessive model	TT VS. CT + CC	NA	NA
Female	Additive model	TT VS. CC	NA	NA
		CT VS. CC	1.325 (0.691, 2.540)	0.421
	Dominant model	CT + TT VS. CC	1.325 (0.691, 2.540)	0.421
	Recessive model	TT VS. CT + CC	NA	NA
Male	Additive model	TT VS. CC	NA	NA
		CT VS. CC	0.922 (0.433, 1.964)	0.849
	Dominant model	CT + TT VS. CC	0.980(0.464, 2.067)	1
	Recessive model	TT VS. CT + CC	NA	NA
rs11128722	Additive model	AA VS. GG	1.719 (0.925, 3.197)	0.096
		GA VS. GG	1.264 (0.942, 1.697)	0.134
	Dominant model	GA + AA VS. GG	1.314 (0.989, 1.746)	0.061
	Recessive model	AA VS. GA + GG	1.547 (0.844, 2.837)	0.182
Female	Additive model	AA VS. GG	1.397 (0.633, 3.084)	0.436
		GA VS. GG	1.126 (0.773, 1.638)	0.567
	Dominant model	GA + AA VS. GG	1.156 (0.804, 1.661)	0.46
	Recessive model	AA VS. GA + GG	1.324 (0.611, 2.868)	0.565
Male	Additive model	AA VS. GG	2.363 (0.864, 6.464)	0.1
		GA VS. GG	1.519 (0.944, 2.444)	0.093
	Dominant model	GA + AA VS. GG	1.610 (1.018, 2.544)	0.049
	Recessive model	AA VS. GA + GG	1.967 (0.735, 5.266)	0.244
rs9472135	Additive model	CC VS. TT	0.416 (0.076, 2.286)	0.419
		TC VS. TT	1.261 (0.878, 1.811)	0.235
	Dominant model	TC + CC VS. TT	1.208 (0.847, 1.724)	0.323
	Recessive model	CC VS. TC + TT	0.397 (0.072, 2.183)	0.415
Female	Additive model	CC VS. TT	NA	NA
		TC VS. TT	1.396 (0.867, 2.246)	0.191
	Dominant model	TC + CC VS. TT	1.316 (0.823, 2.103)	0.289
	Recessive model	CC VS. TC + TT	NA	NA
Male	Additive model	CC VS. TT	0.822 (0.114, 5.932)	1
		TC VS. TT	1.096 (0.625, 1.920)	0.777
	Dominant model	TC + CC VS. TT	1.077 (0.623, 1.861)	0.889
	Recessive model	CC VS. TC + TT	0.806 (0.112, 5.799)	1

SNPs, single nucleotide polymorphisms; NA, not available.

disease and the atherosclerosis process [14]. Genetic factors play a very important role in cardiovascular disease. Previous studies have shown that some SNPs may be protective factors for myocardial ischemia and microvascular dysfunction [15, 16]. Further research is needed to determine the relationship between endothelial dysfunction-related sites and hypertension. The present study was designed to investigate the association of three endothelial dysfunction-SNPs (*VEGFA* rs9472135, *FGD5* rs11128722, and *ZC3HC1* rs11556924) with essential hypertension in elderly Han populations in Liaoning province. In our study, we found that *FGD5* rs1128722 may be a risk factor for the pathogenesis of essential hypertension in Han population in Liaoning Province, especially in the elderly male population. *ZC3HC1* rs111556924 and *VEGFA* rs9472135 genes were not associated with hypertension.

FGD5 rs11128722 may be associated with hypertension, and allele A may be a risk factor for essential hypertension, especially in male population. It is necessary to further study the mechanism of *FGD5* in regulating blood pressure, or whether *FGD5* rs11128722 can change the gene and protein expression of *FGD5*. The results showed that the polymorphism of *FGD5* rs11128722 was statistically significant in comparing BMI among different genotypes. In the additive model, the BMI of genotype GA was higher than that of GG genotype; and in the dominant model, the BMI of genotype GA + AA was higher than that of GG genotype. As obesity is a risk factor for hypertension, it is suggested that *FGD5* rs11128722 may be associated with the risk of hypertension.

ZC3HC1 is a mammalian E3 ligase, which can regulate mitotic entry time [9], and may promote the development of

Table 5. Comparison of blood pressure values among different genotypes of three gene polymorphisms.

SNPs	Genetic model		Number of cases	SBP	*P* value	DBP	*P* value
rs11556924	Additive model	CC	703	139.20 ± 18.96	0.624	85.59 ± 10.28	0.921
		CT	72	139.46 ± 23.66		86.11 ± 11.98	
		TT	1	158		85	
	Dominant model	CT + TT	703	139.71 ± 23.60	0.857	86.10 ± 11.90	0.695
		CC	73	139.20 ± 18.96		85.59 ± 10.28	
	Recessive model	TT	1	158	0.334	85	0.951
		CT + CC	775	139.22 ± 19.43		85.64 ± 10.44	
rs11128722	Additive model	GG	398	138.39 ± 19.98	0.224	85.03 ± 10.63	0.102
		GA	329	139.68 ± 18.14		86.00 ± 9.77	
		AA	49	143.22 ± 22.79		88.14 ± 12.65	
	Dominant model	GA + AA	378	140.14 ± 18.81	0.21	86.28 ± 10.20	0.097
		GG	398	138.39 ± 19.98		85.03 ± 10.63	
	Recessive model	AA	49	143.22 ± 22.79	0.139	88.14 ± 12.65	0.083
		GA + GG	727	138.98 ± 19.17		85.47 ± 10.25	
rs9472135	Additive model	TT	619	139.00 ± 19.22	0.269	85.67 ± 10.31	0.822
		TC	151	140.66 ± 20.33		85.60 ± 11.05	
	Dominant model	CC	6	128.83 ± 15.21	0.486	83.00 ± 7.10	0.855
		TC + CC	157	140.21 ± 20.25		85.50 ± 10.92	
		TT	619	139.00 ± 19.22		85.67 ± 10.31	
	Recessive model	CC	6	18.83 ± 15.21	0.188	83.00 ± 7.10	0.534
		TC + TT	770	139.33 ± 19.44		85.66 ± 10.46	

SNPs, single nucleotide polymorphisms; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table 6. Comparison of BMI among different genotypes of three gene polymorphisms.

SNPs	Genetic model		Number of cases	BMI	*P* value
rs11556924	Additive model	CC	703	23.53 ± 3.05	0.449
		CT	72	23.64 ± 3.53	
		TT	1	19.72	
	Dominant model	CT + TT	703	23.53 ± 3.05	0.902
		CC	73	23.58 ± 3.54	
	Recessive model	TT	1	19.72	0.217
		CT + CC	775	23.54 ± 3.09	
rs11128722	Additive model	GG	398	23.26 ± 3.10	0.038
		GA	329	23.85 ± 3.08[a]	
		AA	49	23.68 ± 2.94[a]	
	Dominant model	GA + AA	378	23.82 ± 3.06	0.011
		GG	398	23.26 ± 3.10	
	Recessive model	AA	49	23.68 ± 2.94	0.737
		GA + GG	727	23.53 ± 3.10	
rs9472135	Additive model	TT	619	23.54 ± 3.11	0.828
		TC	151	23.54 ± 3.04	
		CC	6	22.76 ± 3.15	
	Dominant model	TC + CC	157	23.51 ± 3.04	0.895
		TT	619	23.54 ± 3.11	
	Recessive model	CC	6	22.76 ± 3.15	0.539
		TC + TT	770	23.54 ± 3.09	

SNPs, single nucleotide polymorphisms; BMI, body mass index.

[a] Comparison with the additive model GG of rs11128722.

carcinogenesis together with established active carcinogenic proteins [17]. *ZC3H31* may be closely related to essential hypertension through endothelial dysfunction. The mutant *ZC3HC1* rs115556924 (C>T) is located in 7q32.2 and encodes a non-synonymous substitution in *ZC3HC1* gene. A recent study by López-Mejías *et al.* [18] showed that carotid intima-media thickness (CIMT) value of patients with rheumatoid arthritis carrying *ZC3HC1* rs115556924 TT genotype was

significantly higher than that of CC genotype. CIMT is a marker of subclinical atherosclerosis. Their hypothesis is that changes in the stability and functional properties of *ZC3HC1* protein may cause endothelial dysfunction.

Studies have shown that *FGD5* maintains *VEGFA* signal transduction and endothelial cell chemotaxis by inhibiting the proteasome dependent degradation of *VEGFR2* [19]. *VEGFA* signal transduction mediated by *VEGFR2* can maintain vascular homeostasis and ensure the survival of endothelial cells, and it is also necessary for vascular remodeling [20]. There are three ways for *VEGFA* to regulate blood pressure. The most important one is that *VEGF* activates *VEGFR2* receptor and releases no through phosphatidylinositol 3 kinase (PI3K)/protein kinase B (Akt)/eNOS pathway, thus regulating blood pressure [21]. If the content of *VEGF* in serum is too high, it will lead to excessive mitosis of endothelial cells in local microcirculation, and eventually the endothelial function will be damaged. The imbalance of *VEGF* signal transduction pathway is regarded as the key mediator of tumor angiogenesis. Therefore, a variety of drugs targeting *VEGF* and its receptor have been developed for the treatment of different types of tumors, and with the wide application of these drugs in clinical practice, they will lead to obvious cardiovascular side effects. Hypertension is the most common adverse reaction based on *VEGF* pathway inhibitors in cancer patients. The relationship between *VEGF* polymorphism and essential hypertension has been studied in different regions and nationalities. In Korean population, *VEGF*-2578C>A and -1154G>A polymorphisms have a protective effect on hypertension susceptibility [22]. *VEGFA* 2549 (18) I/D and *VCAM1* rs3917010 were associated with SBP and DBP in Russian Tatars [23]. Observational data from a large number of participants showed that *VEGF*-1154G/A polymorphism can prevent hypertension [22, 24]. In another study, the -1154G/A polymorphism was described as a risk factor for hypertensive nephropathy [25].

There are some limitations in this study. (1) The sample size of this study is small, only two areas of Liaoning Province are selected for physical examination, and there is no sampling survey with larger population base, so the results of this study need to be further confirmed; (2) Hypertension is a multifactorial disease affected by both environmental and genetic factors. This study only explored the relationship between different gene loci and hypertension from the genetic aspect. In the future, the interaction between genetic factors such as *ZC3HC1*, *VEGFA*, *FGD5* and other environmental factors will provide an important theoretical basis for the etiology and pathogenesis of essential hypertension; (3) Although some studies have discussed the other loci of the three genes, the loci selected in this study are the first time to be verified in Chinese population, and there are problems such as difference in ethnicity. It is expected that further studies with larger sample size will confirm the results of this study.

In a word, the polymorphisms of *VEGFA* rs9472135 and *ZC3HC1* rs11556924 may not significantly associated with the risk of essential hypertension, and *FGD5* rs11128722 may increase the risk of it, especially in elderly men.

Author contributions

NT, MWL, YW, WYL, XPL designed the research study. NT, MWL, YW, FXZ, FFN, MKS, XTW, YTY, ML, LW, LXO, ZBY, WYL, XPL collected the data. FXZ, FFN, MKS, XTW, YTY, ML, LW, LXO, ZBY provided help and advice on the data analysis. NT, MWL analyzed the data and drafted the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

All subjects have written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by Ethics Committee of China Medical University.

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Conflict of interest

The authors declare no conflict of interest.

References

[1] Ferdinand KC, Nasser SA. Management of Essential Hypertension. Cardiology Clinics. 2017; 35: 231–246.

[2] Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. Lancet. 2005; 365: 217–223.

[3] Tanira MOM, Al Balushi KA. Genetic variations related to hypertension: a review. Journal of Human Hypertension. 2005; 19: 7–19.

[4] Ehret GB, Ferreira T, Chasman DI, Jackson AU, Schmidt EM, Johnson T, *et al.* The genetics of blood pressure regulation and its target organs from association studies in 342,415 individuals. Nature Genetics. 2016; 48: 1171–1184.

[5] Evangelou E, Warren HR, Mosen-Ansorena D, Mifsud B, Pazoki R, Gao H, *et al.* Genetic analysis of over 1 million people identifies 535 new loci associated with blood pressure traits. Nature Genetics. 2018; 50: 1412–1425.

[6] Dharmashankar K, Widlansky ME. Vascular Endothelial Function and Hypertension: Insights and Directions. Current Hypertension Reports. 2010; 12: 448–455.

[7] Ferrara N, Gerber H, LeCouter J. The biology of VEGF and its receptors. Nature Medicine. 2003; 9: 669–676.

[8] Ando K, Fukuhara S, Moriya T, Obara Y, Nakahata N, Mochizuki N. Rap1 potentiates endothelial cell junctions by spatially controlling myosin II activity and actin organization. Journal of Cell Biology. 2013; 202: 901–916.

[9] Bassermann F, von Klitzing C, Münch S, Bai R, Kawaguchi H, Morris SW, *et al.* NIPA defines an SCF-type mammalian E3 ligase that regulates mitotic entry. Cell. 2005; 122: 45–57.

[10] Jones PD, Kaiser MA, Ghaderi Najafabadi M, McVey DG, Beveridge AJ, Schofield CL, *et al.* The Coronary Artery Disease-associated Coding Variant in Zinc Finger C3HC-type Containing

1 (ZC3HC1) Affects Cell Cycle Regulation. Journal of Biological Chemistry. 2016; 291: 16318–16327.
[11] Kunnas T, Nikkari ST. Association of Zinc Finger, C3HC-Type Containing 1 (ZC3HC1) rs11556924 Genetic Variant with Hypertension in a Finnish Population, the TAMRISK Study. Medicine. 2015; 94: e1221.
[12] Ma H, He Y, Bai M, Zhu L, He X, Wang L, *et al.* The genetic polymorphisms of ZC3HC1 and SMARCA4 are associated with hypertension risk. Molecular Genetics & Genomic Medicine. 2019; 7: e942.
[13] Wang Y, Zhang Z, Wei L, Zhang Q, Zou Z, Yang L, *et al.* Predictive role of heterozygous p.R4810K of RNF213 in the phenotype of Chinese moyamoya disease. Neurology. 2020; 94: e678–e686.
[14] Severino P, D'Amato A, Pucci M, Infusino F, Adamo F, Birtolo LI, *et al.* Ischemic Heart Disease Pathophysiology Paradigms Overview: From Plaque Activation to Microvascular Dysfunction. International Journal of Molecular Sciences. 2020; 21: 8118.
[15] Severino P, D'Amato A, Netti L, Pucci M, Mariani MV, Cimino S, *et al.* Susceptibility to ischaemic heart disease: Focusing on genetic variants for ATP-sensitive potassium channel beyond traditional risk factors. European Journal of Preventive Cardiology. 2020. (in press)
[16] Fedele F, Mancone M, Chilian WM, Severino P, Canali E, Logan S, *et al.* Role of genetic polymorphisms of ion channels in the pathophysiology of coronary microvascular dysfunction and ischemic heart disease. Basic Research in Cardiology. 2013; 108: 387.
[17] Li R, Morris SW. Development of anaplastic lymphoma kinase (ALK) small-molecule inhibitors for cancer therapy. Medicinal Research Reviews. 2008; 28: 372–412.
[18] López-Mejías R, Genre F, García-Bermúdez M, Corrales A, González-Juanatey C, Llorca J, *et al.* The ZC3HC1 rs11556924 polymorphism is associated with increased carotid intima-media thickness in patients with rheumatoid arthritis. Arthritis Research & Therapy. 2013; 15: R152.
[19] Heldin J, O'Callaghan P, Hernández Vera R, Fuchs PF, Gerwins P, Kreuger J. FGD5 sustains vascular endothelial growth factor a (VEGFA) signaling through inhibition of proteasome-mediated VEGF receptor 2 degradation. Cellular Signalling. 2017; 40: 125–132.
[20] Lee S, Chen TT, Barber CL, Jordan MC, Murdock J, Desai S, *et al.* Autocrine VEGF signaling is required for vascular homeostasis. Cell. 2007; 130: 691–703.
[21] Kruzliak P, Novák J, Novák M. Vascular endothelial growth factor inhibitor-induced hypertension: from pathophysiology to prevention and treatment based on long-acting nitric oxide donors. American Journal of Hypertension. 2014; 27: 3–13.
[22] Kim YR, Hong SH. The Protective Effects of the VEGF -2578C>A and -1154G>A Polymorphisms against Hypertension Susceptibility. Genetic Testing and Molecular Biomarkers. 2015; 19: 476–480.
[23] Timasheva Y, Nasibullin T, Imaeva E, Erdman V, Tuktarova I, Mustafina O. Genetic determinants of essential hypertension in the population of Tatars from Russia. Journal of Hypertension. 2017; 35: S16–S23.
[24] Małkiewicz A, Słomiński B, Skrzypkowska M, Siebert J, Gutknecht P, Myśliwska J. The GA genotype of the -1154 G/A (rs1570360) vascular endothelial growth factor (VEGF) is protective against hypertension-related chronic kidney disease incidence. Molecular and Cellular Biochemistry. 2016; 418: 159–165.
[25] Yang JW, Hutchinson IV, Shah T, Fang J, Min DI. Gene polymorphism of vascular endothelial growth factor -1154 G>A is associated with hypertensive nephropathy in a Hispanic population. Molecular Biology Reports. 2011; 38: 2417–2425.