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 (\(P = 0.043,\) \(\text{OR} = 1.265, 95\% \text{CI} = (1.009–1.586)\)), especially in the male (\(P = 0.035,\) \(\text{OR} = 1.496, 95\% \text{CI} = (1.037–2.158)\)). Analyzing the different of genotypes 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, \text{OR} = 1.610, 95\% \text{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 rs11556924 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 NanoDrop2000 (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™ Probe (Taqman™ SNP Genotyping Assays; Applied Biosystems, Foster City, CA, USA) and a QuantStudio™ 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, rs11128722 | 7: 130023656 C>T | misense 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 ± 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
difference \( P = 0.035, \text{OR} = 1.496, 95\% \text{CI} = (1.037–2.158) \) (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 \( P = 0.049, \text{OR} = 1.610, 95\% \text{CI} = (1.018–2.544) \), 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 different of BMI among SNP loci of 3 genes under three genetic models

There was no significant difference in BMI of VEGFA rs94721352 and ZC3HC1 rs115556924 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).

### 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 |
| | Additive model | TT VS. CC | NA | NA |
| | Dominant model | CT + TT VS. CC | 1.325 (0.691, 2.540) | 0.421 |
| | Recessive model | TT VS. CT + CC | NA | NA |
| Female | Additive model | 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 |
| Male | Additive model | AA VS. GG | 1.719 (0.925, 3.197) | 0.096 |
| | Dominant model | GA VS. GG | 1.264 (0.942, 1.697) | 0.134 |
| | Recessive model | AA VS. GG | 1.397 (0.633, 3.084) | 0.436 |
| rs11128722 | Additive model | AAVS.GG | 1.719 (0.925, 3.197) | 0.096 |
| | | GAVS.GG | 1.264 (0.942, 1.697) | 0.134 |
| | Dominant model | GA + AAVS.GG | 1.314 (0.989, 1.746) | 0.061 |
| | Recessive model | AAVS.GA + GG | 1.547 (0.844, 2.837) | 0.182 |
| Female | Additive model | GA VS. GG | 1.126 (0.773, 1.638) | 0.567 |
| | Dominant model | GA + AAVS.GG | 1.156 (0.804, 1.661) | 0.46 |
| | Recessive model | AAVS.GA + GG | 1.324 (0.611, 2.868) | 0.565 |
| Male | Additive model | AAVS.GG | 2.363 (0.864, 6.464) | 0.1 |
| | Dominant model | GA VS. GG | 1.519 (0.944, 2.444) | 0.093 |
| | Recessive model | GA + AAVS.GG | 1.610 (1.018, 2.544) | 0.049 |
| rs9472135 | Additive model | CCVS.TT | 0.416 (0.076, 2.286) | 0.419 |
| | | TCVS.TT | 1.261 (0.878, 1.811) | 0.235 |
| | Dominant model | TC + CCVS.TT | 1.208 (0.847, 1.724) | 0.323 |
| | Recessive model | CCVS.TC + TT | 0.397 (0.072, 2.183) | 0.415 |
| Female | Additive model | CCVS.TT | NA | NA |
| | | TCVS.TT | 1.396 (0.867, 2.246) | 0.191 |
| | Dominant model | TC + CCVS.TT | 1.316 (0.823, 2.103) | 0.289 |
| | Recessive model | CCVS.TC + TT | NA | NA |
| Male | Additive model | CCVS.TT | 0.822 (0.114, 5.932) | 1 |
| | | TCVS.TT | 1.096 (0.625, 1.920) | 0.777 |
| | Dominant model | TC + CCVS.TT | 1.077 (0.623, 1.861) | 0.889 |
| | Recessive model | CCVS.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 |
|--------|-------------------|-----------------|-----------|---------|-----------|---------|
|        | CC                | 703             | 139.20 ± 18.96 | 85.59 ± 10.28 |
|        | CT                | 72              | 139.46 ± 23.66 | 0.624   | 86.11 ± 11.98 | 0.921   |
|        | TT                | 1               | 158       | 85      |
| rs11556924 | 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 |
|        | TT                | 1               | 158       | 85      |
| Recessive model | CT + CC | 775             | 139.22 ± 19.43 | 0.334   | 85.64 ± 10.44 | 0.951   |
|        | GG                | 398             | 138.39 ± 19.98 | 85.03 ± 10.63 |
| Additive model | GA     | 329             | 139.68 ± 18.14 | 0.224   | 86.00 ± 9.77  | 0.102   |
|        | AA                | 49              | 143.22 ± 22.79 | 88.14 ± 12.65 |
| rs11128722 | 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 |
|        | AA                | 49              | 143.22 ± 22.79 | 88.14 ± 12.65 |
| Recessive model | GA + GG      | 727             | 138.98 ± 19.17 | 0.139   | 85.47 ± 10.25 | 0.083   |
|        | TT                | 619             | 139.00 ± 19.22 | 85.67 ± 10.31 |
| Additive model | TC     | 151             | 140.66 ± 20.33 | 0.269   | 85.60 ± 11.05 | 0.822   |
|        | CC                | 6               | 128.83 ± 15.21 | 83.00 ± 7.10   |
| rs9472135 | TC + CC      | 157             | 140.21 ± 20.25 | 0.486   | 85.50 ± 10.92 | 0.855   |
|        | 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 |
|--------|-------------------|-----------------|-----------|---------|
|        | CC                | 703             | 23.53 ± 3.05 |        |
|        | CT                | 72              | 23.64 ± 3.53 | 0.449   |
|        | TT                | 1               | 19.72     |        |
| rs11556924 | CT + TT       | 703             | 23.53 ± 3.05 | 0.902   |
|        | CC                | 73              | 23.58 ± 3.54 |        |
|        | TT                | 1               | 19.72     |        |
|        | CT + CC           | 775             | 23.54 ± 3.09 | 0.217   |
|        | GG                | 398             | 23.26 ± 3.10 |        |
| Additive model | GA     | 329             | 23.85 ± 3.08<sup>a</sup> | 0.038   |
|        | AA                | 49              | 23.68 ± 2.94<sup>a</sup> |        |
| rs11128722 | GA + AA      | 378             | 23.82 ± 3.06 | 0.011   |
|        | GG                | 398             | 23.26 ± 3.10 |        |
|        | AA                | 49              | 23.68 ± 2.94 |        |
|        | GA + GG           | 727             | 23.53 ± 3.10 | 0.737   |
|        | TT                | 619             | 23.54 ± 3.11 |        |
| Additive model | TC     | 151             | 23.54 ± 3.04 | 0.828   |
|        | CC                | 6               | 22.76 ± 3.15 |        |
| rs9472135 | 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.

<sup>a</sup>Comparison with the additive model GG of rs11128722.

carcinogenesis together with established active carcinogenic proteins [17]. ZC3H1 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 ZC3H1 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
significant 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 FGDS maintains VEGFA signal transduction and endothelial cell chemotaxis by inhibiting the protosome 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, FGDS 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 rs11128722 may not significantly associated with the risk of essential hypertension, and FGDS 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 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.

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