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Original Article

Genetic Variations in Thiamin Transferase *SLC35F3* and the Risk of Hypertension in Koreans

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

ABSTRACT

Hypertension is a major health issues globally. Multiple genetic and environmental factors are involved in hypertension etiology. Solute carrier family 35 member F3 (SLC35F3) is a type of transporter uptakes thiamin across the cellular and mitochondrial membrane. Recent studies suggested that variations in *SLC35F3* are associated with the risk of hypertension; however, studies are limited in Koreans. This study examined the association of the genetic variations in *SLC35F3* and the risk of hypertension in Koreans using the Korean Genome Epidemiology Study (Ansan/Ansung study). A total of 8,298 Koreans (males 3,983, females 4,315) were analyzed for their general characteristics, dietary intake, and blood pressure. Twenty-four tagging variations in *SLC35F3* were selected and investigated for their association with the risk of hypertension using a sex-stratified approach. Findings suggested that, in males, rs12135117 A allele carriers were at the lower risk for hypertension (adjusted odds ratio, 0.859; 95% confidence interval [CI], 0.740–0.998). In females, rs10910387 TC genotype tended to increase the risk 1.172-fold for hypertension (95% CI, 1.002–1.370). Multiple linear regression models exhibited that rs12135117 A allele was negatively associated with blood pressure in males, and rs10910387 TC genotype had a positive association with blood pressure in females. However, statistical significance for these genetically modified effects was in lacked (Bonferroni's corrected $p > 0.002$). In conclusion, genetic variation in *SLC35F3* is not a decisive prediction marker for hypertension risk in Koreans. Given the rarity of data, more studies are required to evaluate the role of *SLC35F3* and thiamin in the hypertension etiology.

Keywords: Genetic variation; Hypertension; Koreans; Thiamin transferase

INTRODUCTION

A growing prevalence of hypertension is a global health issue [1]. Hypertension is one of the major causes of death in Koreans along with cancer, cardiac diseases, pneumonia, and cerebrovascular diseases, and is also an important risk factor for cerebrovascular diseases. According to the 2018 Death Statistics by Statistics Korea, the mortality rate of hypertensive diseases increased by 23.6% in the last decade and has been increasing by 4.9% every year [2].

Hypertension is grouped into primary and secondary hypertension depending on its cause. Primary hypertension refers to elevated blood pressure that is presented without a

clear cause and accounts for approximately 90%–95% of all hypertension case, whereas secondary hypertension refers to the symptoms caused by another condition [3,4]. Primary hypertension is reported to result from various and complex combinations of genetic and environmental factors, including food and dietary intake of nutrients [5].

Thiamin is a water-soluble vitamin, also known as vitamin B1. Thiamin is mainly found in the form of thiamin pyrophosphate (TPP) in the body, which is a coenzyme necessary for energy metabolism and promotes energy production. Hence, thiamin intake and requirements are associated with energy consumption and metabolism [6,7]. A reduction in thiamin levels in the body has been reported to be associated with the accumulation of the intermediates in glucose metabolism, including pyruvic acid and lactic acid [8,9]. Thiamin has been reported to be involved in cardiovascular diseases etiology, because it promotes dilation of peripheral arteries and increased cardiac output and blood pressure [10,11]. A study using induced hypertension rat models proved that supplementation with thiamin reduced the symptoms of hypertension through the regulation of messenger RNA expression associated with the renin-angiotensin system [12]. It has also been reported that systolic blood pressure (SBP) decreases with body TPP levels [11]. Additionally, thiamin supplementation improves endothelial cell-dependent vascular dilation and delays the progression of atherosclerosis [13]. These reports suggest that thiamin is associated with mechanism of blood pressure control.

Dietary thiamin is hydrolyzed into thiamin monophosphate (TMP) and is absorbed in the jejunum and ileum [14]. TMP is transported across the epithelial membrane into the cytoplasm by the solute carrier family proteins (SLC19A1, SLC19A2, SLC44A4, and SLC22A1) [14]. Solute carrier family 35 member F3 (SLC35F3) is a protein that mediates the intracellular transport of thiamin. The *SLC35F3* gene is located on chromosome 1q42.2 and includes nine exons (419 kb) encoding a 421-amino acid (46,817 Da) protein [15]. A Chinese study reported that a rs34032258 C > G single nucleotide polymorphism (SNP) in the *SLC35F3* thiamin transporter gene is associated with the risk of hypertension [16]. This variant is associated with the levels of diastolic blood pressure (DBP) and blood urea nitrogen and creatinine; subjects with CG and GG genotypes have a higher DBP than those with CC genotype [16]. A study conducted in the United States reported that genetic variants including rs17514104 and rs16842784 in the *SLC35F3* gene were associated with blood pressure [10]. These studies suggested the association between the *SLC35F3* and hypertension, yet only limited number of data were reported on such association in a Korean population.

Hypertension is one of the common cardiovascular risk factors as well as critical disease itself. Although efforts are being made to prevent and treat hypertension in Koreans, it is necessary to continuously discover nutritional and genetic factors associated with hypertension. This study investigated the association between hypertension and variation in thiamin transporter *SLC35F3* gene in Koreans. The incidence of hypertension and the subsequent health behaviors differ between males and females [17,18]. Therefore, in this study, analyses were conducted in males and females, respectively.

MATERIALS AND METHODS

Cohort description

This study was conducted using the Ansan and Ansung study, a part of the Korean Genome Epidemiology Study (KoGES). The KoGES is a cohort project initiated by the Korea Centers

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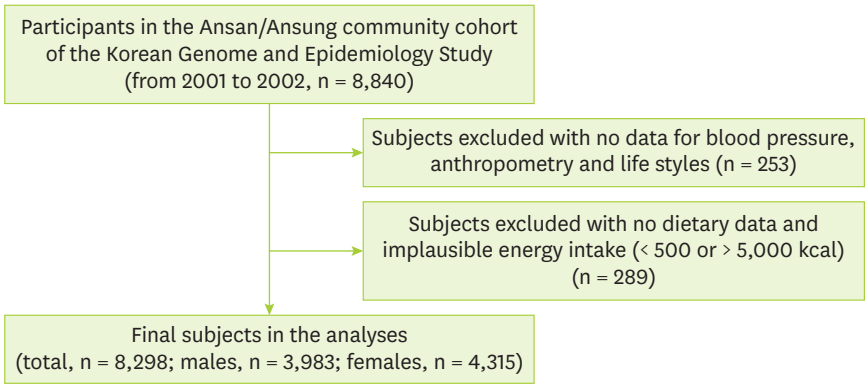

Figure 1. Simplified flow chart of study subject selection.

for Disease Control and Prevention to identify the risk factors of chronic diseases including diabetes, hypertension, and cardiovascular diseases that commonly affect Koreans. Data was collected in Ansan (urban) and Ansung (rural area) in 2001 and 2002. More detailed information of KoGES was described in elsewhere [19]. The subject inclusion criteria for this study were as follows. Of the total 8,840 subjects whose genomic and epidemiological information was available, subjects having no data on blood pressure (n = 8), body weight (n = 4), alcohol consumption and smoking status were excluded (n = 144). Subjects having no data on exercise (n = 50), and the education level (n = 47) were also excluded. Additionally, subjects having no data on energy (n = 218) intake and data with unusual energy intake amounts (< 500 kcal or > 5,000 kcal) were excluded (n = 71). Finally, a total of 3,983 males and 4,315 females, i.e., 8,298 subjects were finally selected for analysis (**Figure 1**). This study was approved by the Institutional Review Board (40525-201905-BR-017-01) of Keimyung University, Korea.

Data collection

All study data including general, dietary and genotype information were obtained from the KoGES under the permission of the Korea Centers for Disease Control and Prevention. General epidemiological information about the subjects including age, sex, and education level were collected through questionnaires. SBP, DBP, and anthropometric measurements were also collected and analyzed [19]. The level of physical activity was calculated in metabolic equivalents of task [20]. Smoking and alcohol drinking status of the subjects was categorized as "Ever (past or current)" and "Never". The level of education was grouped as follows: "Low" for elementary school graduate or less, "middle" for middle and high school graduate, and "high" for college graduate or more.

Diagnosis for hypertension

Following the 2018 Korean Society of Hypertension Guidelines, subjects were defined a case with hypertension if their SBP was ≥ 140 mmHg or DBP was ≥ 90 mmHg [21], and/or taking any type of treatment for hypertension [16].

Dietary data collection and analyses

Data about the energy and nutritional intake of the subjects in the KoGES were collected as follows. Data on nutritional intake were collected using a semi-quantitative food frequency questionnaire (semi-FFQ) [22]. Frequency of intake ("Almost never," "Once a month," "2–3 times a month," "1–2 times a week," "3–4 times a week," "once a day," "twice a day," and "3 times a day") and the average portion ("small," "medium," and "large") of 103 different foods

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consumed for the last 12 months were recorded by the subjects in the FFQs. From the dietary intake, nutritional consumption was estimated using the database of the Korean Nutrition Society [22,23].

Genetic data analyses and selection of *SLC35F3* genetic markers

Fasting blood samples were collected from the subjects and were used for genotyping. The detailed procedure for genotyping, quality control and imputation were described earlier [24]. The genotype data was analyzed using 500 ng of genomic DNA and Affymetrix Genome-Wide Human SNP array 5.0 (Affymetrix Inc., Santa Clara, CA, USA). The quality control steps of genotype and imputation were conducted following criteria: If samples with high missing genotype call rate > 4%, high heterozygosity (> 30%) and sex, ethnic mismatch or cryptic relatedness were excluded. Additionally, SNPs with high missing gene call rate (> 5%), minor allele frequency (MAF) of < 0.01, and those not in Hardy-Weinberg equilibrium (HWE, $p < 1 \times 10^{-6}$) were also excluded. Imputation of genotype data was conducted by IMPUTE software referencing Asian (JPT and CHB) genotype data in HapMap (release 22/NCBI, build 36, and dbSNP build 126) [25,26]. After the imputation process, SNPs with genotype information content (info < 0.5), a posterior probability score < 0.90, MAF < 0.01 and HWE $p < 1 \times 10^{-7}$ were removed from the dataset [27].

According to the 1000 Genome Project, there are approximately 27,700 genetic variations in the *SLC35F3* gene [28]. Among them, a total of 336 genetic variations were found and extracted in the genomic data by PLINK (v1.07) [29]. Using Haploview software (v 4.2), a linkage disequilibrium block (LD block, frequency > 0.1) analysis was performed on 235 of the 336 genetic variations with a MAF ≥ 0.1. A total of 24 tagging loci were found from the analysis [30]. Therefore 24 taggers were finally selected as genetic markers and used to analyze the correlations between the genetic variations and risk of hypertension. The LD blocks and list of all the markers analyzed in the study are shown in **Supplementary Figure 1** and **Supplementary Table 1**.

Statistical analyses

General characteristics of the subjects were analyzed using the χ^2 tests or Student's t-tests taking account of the data type. Logistic regression was used to analyze the correlation between *SLC35F3* genotypes and the risk of hypertension. Crude model examined the risk of hypertension caused by a genetic variation without the covariates, and adjusted model examined the risk of hypertension with the covariates including residence area, age, body mass index (BMI, kg/m^2), smoking and alcohol use, educational and physical activity level, and total energy, sodium, potassium, and thiamin intake. The association between genotypes and hypertension were addressed in odds ratios and 95% CIs. To provide the more information of the influence of genetic variants on blood pressure, multiple linear regression analyses were performed with the variants showed an association with risk for hypertension additionally. The multicollinearity among the covariates were examined with the condition index (all variables < 55). The Bonferroni method was used to address the multiple comparison problem at the statistical significance level of $p < 0.002$ (0.05/24 is the number of genetic variations analyzed). SAS version 9.3 (SAS Institute Inc., Cary, NC, USA) were used for all statistical analyses.

RESULTS

Table 1 shows the general characteristics of the hypertension and control groups. In males and females, hypertension cases were 1,451 (36.43%) and 1,405 (32.56%), respectively. Both the

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Table 1. General characteristics of the study population taking into account the sex and hypertension phenotypes

Variables	Males (n = 3,983, 100%)			Females (n = 4,315, 100%)		
	Normal	Hypertension	p value	Normal	Hypertension	p value
No. of subjects	2,352 (63.57)	1,451 (36.43)		2,910 (67.44)	1,405 (32.56)	
Residence area			< 0.001			< 0.001
Ansan (urban)	922 (36.41)	714 (49.21)		1,214 (41.72)	908 (64.35)	
Ansung (rural)	1,610 (63.59)	737 (50.79)		1,696 (58.28)	503 (35.65)	
Age (yr)	50.29 ± 8.42	53.93 ± 8.82	< 0.001	50.29 ± 8.47	57.22 ± 8.22	< 0.001
Body mass index (kg/m^2)	23.88 ± 2.83	24.97 ± 2.96	< 0.001	24.39 ± 3.08	25.98 ± 3.33	< 0.001
Physical activity (MET-h)	23.30 ± 14.45	24.93 ± 15.63	0.021	21.95 ± 13.62	24.21 ± 15.68	0.045
Alcohol drinking			< 0.001			< 0.001
Never drinker	498 (19.67)	222 (15.30)		2,013 (69.18)	1,076 (76.58)	
Ever drinker	2,034 (80.33)	1,229 (84.70)		897 (30.82)	329 (23.42)	
Tobacco smoking			0.274			0.957
Never smoker	477 (18.84)	294 (20.26)		2,771 (95.22)	1,336 (95.09)	
Ever smoker	2,055 (81.16)	1,157 (79.74)		139 (4.78)	69 (4.91)	
Education			< 0.001			< 0.001
High	598 (23.62)	272 (18.75)		233 (7.66)	39 (2.78)	
Middle	1,498 (59.16)	834 (57.48)		1,636 (56.22)	490 (34.88)	
Low	436 (17.22)	345 (23.78)		1,051 (36.12)	876 (62.35)	
Nutrient consumption						
Total energy (kcal/day)	2,007.3 ± 578.5	2,023.7 ± 597.2	0.534	1,891.1 ± 621.8	1,805.9 ± 631.3	< 0.001
Potassium (mg/day)	2,529.1 ± 1,058.2	2,574.2 ± 1,058.9	0.210	2,544.5 ± 1,146.5	2,394.9 ± 1,149.1	< 0.001
Sodium (mg/day)	3,339.3 ± 1,627.6	3,423.5 ± 1,568.6	0.066	3,014.7 ± 1,523.7	2,937.6 ± 1,546.8	0.039
Thiamin (mg/day)	1.30 ± 0.52	1.33 ± 0.54	0.189	1.20 ± 0.52	1.12 ± 0.52	< 0.001

Data are presented as mean ± standard deviation or numbers of subjects (%).
MET-h, metabolic equivalent hours.

male and female hypertension subjects had a higher mean age and BMI (all $p < 0.001$). Male and female normal subjects were more likely living in the rural area (both $p < 0.001$). Male cases were more likely to be a drinker ($p < 0.001$), yet the ratio of smokers did not differ between phenotype. The hypertensive group also tended to have higher level of physical activity than the control group. In both males and females, subjects with lower level of education were more likely have a hypertension (both $p < 0.001$). The dietary nutrients consumption differed by hypertension phenotype in males and females. The total calorie intake and dietary intake of potassium, sodium and thiamin did not differ between hypertensive and non-hypertensive males. In contrast, females with hypertension had a significantly lower level of intake for total energy ($p < 0.001$) and potassium ($p < 0.001$) than those without hypertension. Female hypertension group consumed significantly lower level of thiamin ($p < 0.001$), although the level of consumption satisfied the recommended nutrient intake (RNI, 1.1 mg/day) [31].
As these various demographic, lifestyle, and dietary factors may be associated with the risk of hypertension, those were considered as covariates in statistical models analyzing the association between *SLC35F3* variants and the risk of hypertension.

Table 2 shows the association between *SLC35F3* variants and the risk of hypertension predicted by logistic regression analyses (refer to **Supplementary Tables 2** and **3** for all analyses results). Among the examined total 24 genetic variants, a genetic variation rs12135117 T > A found to be associated with the risk of hypertension in males. Although crude statistical model did not show the significant association, having of rs12135117 variant allele A decreased the risk for hypertension by approximately 14% (95% CI, 0.740–0.998, $p = 0.047$) in the adjusted model with various demographic, lifestyle, and dietary characteristics of the subjects. In females, the genetic variation rs10910387 T > C in *SLC35F3* showed an association with risk for hypertension. Adjusted statistical model revealed that having of variant TC genotype elevated the risk for disease 1.17 folds (95% CI, 1.002–1.370, $p = 0.061$). Those genetic variants which have shown

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Table 2. The association between selected *SLC35F3* genetic variations and the risk of hypertension

Variation	Control	Case	OR_crude (95% CI)*	OR_adjusted (95% CI)†	p_adjusted‡
Males					
rs12135117					
TT	1,811 (71.52)	1,076 (74.16)	Reference	Reference	-
AT	641 (25.32)	350 (24.12)	0.919 (0.791–1.068)	0.902 (0.773–1.053)	0.092
AA	80 (3.16)	25 (1.72)	NA	NA	-
AT + AA	721 (28.48)	375 (25.84)	0.875 (0.757–1.013)	0.859 (0.740–0.998)	0.047
Females					
rs7552485					
TT	1,093 (41.40)	495 (38.70)	Reference	Reference	
TC	1,172 (44.39)	607 (47.46)	1.144 (0.990–1.321)	1.172 (1.002–1.370)	0.061
CC	375 (14.20)	177 (13.84)	1.042 (0.847–1.283)	1.022 (0.816–1.280)	0.588

Values are presented as number (%).
OR, odds ratio; CI, confidence interval; NA, not applicable due to the rarity.
*OR_crude, OR from crude logistic regression model; †OR_adjusted, OR from logistic regression model adjusted with residence area, age, body mass index, alcohol drinking and tobacco smoking status, educational level, physical activity and total energy, sodium, potassium and thiamin intake; ‡Bonferroni-corrected $p > 0.002$.

Table 3. The association between selected *SLC35F3* genetic variations and blood pressure

Variation		Standardized beta coefficient	Standard error	Adjusted r^{2*}	95% confidence limit	p value†
Males						
rs12135117	SBP	−1.730	0.576	0.138	−2.860, −0.600	0.003
A allele	DBP	−0.785	0.383	0.074	−1.538, −0.033	0.041
Females						
rs10910387	SBP	1.287	0.601	0.245	0.108, 2.466	0.032
TC	DBP	0.962	0.374	0.183	0.228, 1.697	0.010
CC	SBP	0.625	0.860	0.245	−1.062, 2.313	0.468
	DBP	0.930	0.536	0.183	−0.120, 1.981	0.083

DBP, diastolic blood pressure; SBP, systolic blood pressure.
*Multiple linear regression models were adjusted with residence area, age, body mass index, alcohol drinking and tobacco smoking status, educational level, physical activity and total energy, sodium, potassium and thiamin intake; †Bonferroni-corrected $p > 0.002$.

the association with blood pressure (**Table 3**) were applied for further regression analyses. In males, the presence of rs12135117 A allele was negatively associated with the SBP ($\beta = -1.730$, adjusted $r^2 = 0.138$, $p = 0.003$) and DBP ($\beta = -0.785$, adjusted $r^2 = 0.074$, $p = 0.041$). In females, having of TC rs10910387 genotype was positively associated with SBP ($\beta = 1.287$, adjusted $r^2 = 0.245$, $p = 0.032$) and DBP ($\beta = 0.962$, adjusted $r^2 = 0.183$, $p = 0.01$). However, significance of modified risk of the genetic variants on risk for hypertension and blood pressure were moderate after correction by Bonferroni's rule ($p > 0.002$).

DISCUSSION

This study examined the whether the variations in the *SLC35F3* thiamin transporter gene were associated with the risk of hypertension using the KoGES data—Ansan/Ansung study. Findings suggested that *SLF35F3* genetic variations did have the significant modifying effect on the risk of hypertension in Koreans.

Beriberi, Wernicke-Korsakoff syndrome, and subacute cerebellar degenerative diseases are well known for severe disorders of thiamin deficiency. Recently, a growing volume of studies suggested that inadequate thiamin intake also acted as a risk factor for other diseases [31-33]. Thiamin deficiency leads to reduced adenosine triphosphate synthesis and transketolase reactions, resulting in reduced synthesis of nicotinamide adenine dinucleotide phosphates and pentose. This deficiency, therefore, impairs fatty and nucleic acid synthesis,

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neurotransmission, and regulatory functions [32,33], and leads to the clinical symptoms including psychological issues, such as loss of appetite, weight loss, numbness, short-term memory loss, and confusion. Cardiovascular symptoms, including hypersensitivity, muscle weakness, and cardiac hypertrophy are also common types of the vitamin deficiency [32,33].

Absorbed thiamin in the jejunum and ileum is transported across the cell membrane by *SLC35F3*, a thiamin transporter, into the cytoplasm [7,15]. It has thus been hypothesized that genetic variations in *SLC35F3* may result in the functional changes of protein, hence modify thiamin levels and diseases risk. A few earlier studies support this idea, as described above: A study with approximately 2,500 Chinese hypertensive patients and normal controls reported that GG genotype carriers of the rs34032258 C > G variant have higher DBP compared to that in CC genotype carriers [16]. Having the TT genotype of the rs17514104 C > T variant was also associated with an increased risk of hypertension [10]. It has also been reported that possessing of such altered allele was associated with a risk for decreased vascular tolerance, which has been reported to be a symptom of thiamin deficiency that increases cardiac stroke volume and blood pressure in response to temperature-induced stress [10].

In this study, the rs12135117 and rs7552485 variants in *SLC35F3* were associated with the risk of hypertension and the level of blood pressure in males and females, although the statistical significance were minimal. This limited association may be resulted from the type of variation investigated. A total of 24 tagging loci were examined in this study, however, they were all genic/upstream transcript and intronic variants. Such type of mutation may contribute to the putative association between variants of *SLC35F3* and the risk of hypertension in this study. Additionally, the level of thiamin intake may contribute to the minimal association between genetic variation and the hypertension in this study population. A nutrient-wide approach study with meta-data from INTERnational Collaborative Study on Macro-/Micronutrients and Blood Pressure and United States National Health and Nutrition Examination Survey reported that dietary thiamin intake was inversely associated with SBP [34]. A Korean study also suggested that the risk for hypertension was decreased in the individuals with the nutrition adequacy ratio for thiamin ≥ 1.2 [35]. In current study, males' levels of thiamin consumption were higher than RNI (1.2 mg/day) and there was no difference in the mean thiamin intake between hypertensive and non-hypertensive groups. In females, although hypertension group consumed lower level of thiamin, compared to normal, both phenotypes' thiamin intake satisfied RNI. Such favorable thiamin intake may result in the minimal effect of genetic variation on the risk for hypertension and blood pressure regulation. However, again, the statistical significance of the genetically modified risk for hypertension by *SLC35F3* variation was modest. These hypotheses are required to be examined with further study.

Hypertension is a common type of disorder in a Korean population. More than 60% Koreans above 70 years old have hypertension and it is a risk factor for other cardiovascular diseases [36]. To the best of our knowledge, this is the first study analyzed the association between variations in thiamin transporter gene, *SLC35F3*, and hypertension in Koreans. However, the study may harbor few limitations: First, this study used the Ansung/Ansan study data of KoGES data. The examined genetic data did not fully cover the subjects' *SLC35F3* variations and was found to be intronic variations mostly. Furthermore, this study was a cross-sectional design. Although the statistical models used in the analysis accounted for several covariates, not all factors associated with hypertension could be considered. Thus, the results of this study should be interpreted with caution.

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This study examined the association between genetic variations of *SLC35F3* in thiamin metabolism and hypertension in Koreans, although the statistical significance for findings was limited. Further research is needed to ascertain the effect of the thiamin and related *SLC35F3* variants to explore new approach to prevent and treat the hypertension.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Description of the examined genetic variations of *SLC35F3* and their minor allele frequencies in multiple ethnicities

Click here to view

Supplementary Table 2

Distribution of genotypes in the studied *SLC35F3* genetic variations and their association with hypertension in males

Click here to view

Supplementary Table 3

Distribution of genotypes in studied *SLC35F3* genetic variations and the association with hypertension in females

Click here to view

Supplementary Figure 1

Pairwise linkage disequilibrium blocks among 235 significant single nucleotide polymorphisms in *SLC35F3*.

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