European Review for Medical and Pharmacological Sciences 2019; 23: 10609-10616

Association of ATP2B1 gene polymorphism with incidence of eclampsia

X.-M. SUN[1], M. YANG[1], C.-X. JIANG[2]

[1]Department of Obstetrics, the Affiliated Hospital of Southwest Medical University, Luzhou, China
[2]Department of Clinical Laboratory, Jining No. 1 People's Hospital, Jining, China

Abstract. – OBJECTIVE: The aim of this study was to analyze the association of ATPase plasma membrane Ca^{2+} transporting 1 (ATP2B1) gene polymorphism with the incidence of eclampsia, and to investigate the possible underlying mechanism.

PATIENTS AND METHODS: ATP2B1 genotype and allele distributions in umbilical venous blood cells were analyzed in 50 control subjects and 117 eclampsia patients *via* Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and TaqMan genotyping technique. Meanwhile, the differences in the single nucleotide polymorphisms at rs2681472 and rs17249754 in the case group and control group were analyzed using the χ^2-test. The risk factors for eclampsia were analyzed *via* univariate, multivariate, and Logistic regression analyses. Furthermore, the associations of rs2681472 gene polymorphism with risk factors for eclampsia (hypertension and lower extremity edema) were verified *via* χ^2-test.

RESULTS: The statistically significant differences were observed in the gestational week, body mass index, blood pressure, and incidence rates of proteinuria and lower extremity edema of pregnant women between the case group and the control group ($p<0.05$). Meanwhile, the genotype and allele distributions at rs2681472 in the case group were remarkably different from those of the control group ($p<0.05$). However, no evident differences were observed at rs17249754 between the two groups ($p>0.05$). According to univariate, multivariate, and logistic regression analyses, hypertension, and lower extremity edema were significantly associated with the incidence of eclampsia ($p<0.05$). In addition, the gene polymorphism at rs2681472 showed significant differences among subjects with and without hypertension and lower extremity edema ($p<0.05$).

CONCLUSIONS: ATP2B1 gene polymorphism at rs2681472 shows significant differences between eclampsia patients and normal controls. Moreover, its gene polymorphism is closely related to the occurrence of hypertension and lower extremity edema.

Key Words:
ATP2B1, Gene polymorphism, Eclampsia, Risk factors, Hypertension, Lower extremity edema

Introduction

Eclampsia is a multi-system pregnancy-specific disease that affects 5-8% of pregnancy[1]. Meanwhile, it is also the major cause of perinatal morbidity and mortality in the world. The risks of eclampsia in women with cardiovascular events, as well as metabolic and mental disorders in descendants, are extremely high[2]. Currently, the etiology and pathogenesis of eclampsia remain unclear, with no effective prevention and treatment methods. The genetic susceptibility is considered as an important etiology. In recent years, the single nucleotide polymorphism (SNP) of genes has been widely discussed. It has been found that multiple genes are associated with an increased risk of eclampsia[3]. Meanwhile, multiple susceptibility gene mutations or SNPs may contribute to the development of eclampsia[4]. To fully clarify the role of the genetic factors in the pathogenesis of preeclampsia, more genetic studies are needed. Eclampsia is usually characterized by proteinuria, edema, and vasoconstriction in the late trimester of pregnancy. This may result in a decline in uterine placental blood flow and maternal characteristic hypertension[5]. Xu et al[6] have demonstrated that the susceptibility to hypertension and arteriosclerosis in the Chinese population is closely related to ATP2B1 gene polymorphism. However, whether ATP2B1 gene polymorphism is associated with susceptibility to eclampsia has not been fully elucidated.

ATPase plasma membrane Ca^{2+} transporting 1 (ATP2B1) gene plays a key role in intracellular calcium homeostasis[7]. Levy et al[8] have

Corresponding Author: Chunxiao Jiang, BM; e-mail: jiangchunxiao7126@163.com

found that the ATP2B1 gene is closely related to systolic blood pressure (SBP), diastolic blood pressure (DBP), and hypertension. In fact, ATP2B1 mutation increases the susceptibility to hypertension in Asians[9]. ATP2B1 gene polymorphism is a marker for hypertension, which is also closely related to the incidence of hypertension and eclampsia. Therefore, the association of ATP2B1 gene polymorphism with the incidence of eclampsia has been widely explored. ATP2B1 has SNPs at such loci as rs2070759, rs10858911, rs2681472, rs17249754, rs2854371, and rs1401982. According to previous investigations, the gene polymorphisms at rs2681472 and rs17249754 are associated with the susceptibility to hypertension. Therefore, the associations of ATP2B1 rs2681472 and rs17249754 SNPs with the incidence of eclampsia were analyzed in this study. Our findings might help to determine whether the ATP2B1 gene polymorphism promoted the incidence of eclampsia.

Patients and Methods

Patients

A total of 117 eclampsia patients and 50 normal control pregnant women aged 24-34 years old were enrolled in this study. The following information was collected, including age, gestational week, height, body mass index (BMI), blood pressure, proteinuria, and lower extremity edema. The exclusion criteria were as follows: those with chronic hypertension, multiple pregnancies, history of kidney, autoimmune, metabolic, or cardiovascular disease. This study was approved by the Ethics Committee of the Affiliated Hospital of Southwest Medical University. The signed written informed consents were obtained from all participants before the study.

Main Reagents

The main reagents were: protein extraction lysis buffer TRIzol (Sigma-Aldrich, St. Louis, MO, USA), peripheral blood lymphocyte extract (Haoyang, Tianjin, China), reverse transcription kit (Sigma-Aldrich, St. Louis, MO, USA), dNTP reagent (Promega, Madison, WI, USA), DNA polymerase and amplification primers forward and reverse primers of glyceraldehyde 3-phosphate dehydrogenase (GAPDH), rs2681472 and rs17249754 (SBS Genetech Co. Ldt., Shanghai, China).

Total RNA Extraction and Reverse Transcription (RT)

A total of 5 mL of maternal venous whole blood was collected into ethylenediaminetetraacetic acid (EDTA)-containing tubes. The middle buffy coat was obtained *via* density-gradient centrifugation. The cells were washed, centrifuged, and lysed with TRIzol on ice for 30 min, followed by centrifugation with chloroform and precipitation of the total RNA. Subsequently, the concentration of the total RNA was measured using a spectrophotometer. RT system (20 μL) was constructed according to relevant instructions. Briefly, 1000 ng of RNA was loaded, and the kit reagents were added successively. Then, the diethyl pyrocarbonate (DEPC)-treated water (Beyotime, Shanghai, China) was added until the total volume was 20 μL. The specific RT conditions were as follows: reaction at 37°C for 15 min, and 85°C for 5 min. Finally, RT products were taken out after cooling to 4°C, and the complementary deoxyribose nucleic acid (cDNA) was stored at -80°C for use.

PCR Amplification

According to the instructions of the amplification kit, a 25 μL amplification system was prepared, including 1 μL of amplification template, 1 μL of forward primers, 1 μL of reverse primers, 12 μL of 2× TapMaster Mix, and 10 μL of DEPC-treated water. The mixture was vibrated and mixed evenly, followed by centrifugation and precipitation. PCR amplification was as follows: preheating at 94°C for 2 min, 94°C for 40 s, 55°C for 30 s, and 72°C for 30 s, for a total of 40 cycles. After electrophoresis at 72°C and 120 V for 30 min, the images were analyzed using a gel imager (Bio-Rad, Hercules, CA, USA). The primer sequences used in this study were as follows: rs2681472, F: 5'-CAAGCACCACGGCTCTAC-3', R: 5'-CGTCGTATAGGCGTGTCCAGGA-3'; rs17249754, F: 5'-ATCTGCCGTGGACACATGCCGACTG-3', R: 5'-GCGACACGAGTCGTGTGCG-3'; GAPDH: F: 5'-CGCTCTCTGCTCCTCCTGTTC-3', R: 5'-ATCCGTTGACTCCGACCTTCAC-3'.

Statistical Analysis

The Statistical Product and Service Solutions (SPSS) 22.0 software (IBM Corp., Armonk, NY, USA) was used for all statistical analysis. The χ^2-test was performed for the enumeration data of patients' features, and the independent-samples *t*-test was applied for the measurement data. Har-

Table I. Clinical features of subjects.

	Case group	Control group	F/χ^2	*p*
Age of pregnant women	28.34 ± 4.42	27.93 ± 3.65	1.73	0.74
Gestational week	36.79 ± 4.27	38.62 ± 2.78	6.33	0.016
Height (cm)	159.36 ± 11.61	157.97 ± 13.39	2.07	0.67
BMI (kg/m^2)	27.43 ± 4.35	24.17 ± 3.64	7.65	0.014
Blood pressure				
SBP	153.75 ± 24.26	118.16 ± 13.94	23.21	< 0.001
DBP	98.36 ± 15.89	72.62 ± 8.97	10.73	< 0.01
Proteinuria (+/-)	53/64	13/37	5.549	0.019
Lower extremity edema (+/-)	67/50	12/38	15.55	< 0.01

dy-Weinberg genetic equilibrium test was conducted for the enrolled subjects. The χ^2-test was adopted for the comparison of the genotype and allele frequency distributions. The risk factors for eclampsia were statistically analyzed using multivariate logistic regression analysis. The associations of the risk factors and clinical features of patients with gene polymorphism were detected using univariate and multivariate regression analyses. The correlations between the related risk factors (hypertension and lower extremity edema) and rs2681472 gene polymorphism were analyzed *via* χ^2-test. $p \leq 0.05$ was considered statistically significant.

Results

Clinical Features of Subjects

As shown in Table I, there were no statistically significant differences in age and height of pregnant women between the case group and control group (p>0.05). However, the case group showed significantly longer means of the gestational week, higher BMI, and mean blood pressure (p<0.05). Furthermore, the occurrence rates of proteinuria and lower extremity edema were higher than the control group (p<0.05).

Hardy-Weinberg Genetic Equilibrium Test of Subjects

To verify the ATP2B1 genetic equilibrium in subjects, the χ^2-test was performed for rs2681472/rs17249754 genotype frequency. The results found that the subjects in the case group and the control group met the rs2681472/rs17249754 genetic equilibrium (p>0.05) (Table II).

Rs2681472/rs17249754 Genotype and Allele Distributions

After RT-PCR and gel electrophoresis, the genotype results of all subjects were analyzed. The χ^2-test results demonstrated that the statistically significant differences were observed in rs2681472 genotypes and alleles between the two groups (p<0.05). However, there were no evident differences in rs17249754 genotypes and alleles between the two groups (p>0.05). This indicated that the gene distributions were remarkably different at rs2681472, whereas were not different at rs17249754 between the two groups (Table III).

Logistic Regression Analysis of Risk Factors for Eclampsia

According to the clinical features of patients and normal controls, the age of pregnant women, gestational week, height, BMI, blood pressure,

Table II. Hardy-Weinberg genetic equilibrium test.

Gene	Genotype	Case group			Control group		
		No. = 117	χ^2	*p*	No. = 50	χ^2	*p*
rs2681472	AA	38	0.004	0.95	18	1.01	0.315
	AG	61			20		
	GG	18			12		
rs17249754	GG	31	1.89	0.169	16	0.16	0.689
	GA	49			23		
	AA	37			11		

Table III. Rs2681472/rs17249754 genotype and allele distributions.

Gene	Genotype	Case group		Control group		χ^2	*p*	Allele	Case group		Control group		χ^2	*p*
		No.	%	No.	%				No.	%	No.	%		
rs2681472	AA	38	32.48	12	24	8.811	0.012	A	137	58.55	44	44	5.972	0.015
	AG	61	52.14	20	40			G	97	41.45	56	56		
	GG	18	15.38	18	36									
rs17249754	GG	31	26.50	11	22	0.421	0.810	G	111	47.44	45	45	0.167	0.683
	GA	49	41.88	23	46			A	123	52.56	55	55		
	AA	37	31.62	16	32									

proteinuria, and lower extremity edema in case group and control group were analyzed (Table IV). Subsequently, the influences of the age of the pregnant women, gestational week, height, BMI, blood pressure, proteinuria, and lower extremity edema on the incidence of eclampsia were detected *via* multivariate logistic regression analysis. The results showed that blood pressure, proteinuria, and lower extremity edema were the major risk factors for eclampsia [OR (95% CI) = 9.33 (1.67-16.18), 4.64 (1.22-6.86), and 4.97 (1.34-7.31), $p<0.05$] (Table V).

Table IV. Logistic regression analysis and variable assignment.

Variable	Assignment
Age of pregnant women	< 30 = 1, ≥ 30 = 0
Gestational week	< 36 = 1, ≥ 36 = 0
Height (cm)	< 160 = 1, ≥ 160 = 0
BMI (kg/m^2)	< 24 = 1, ≥ 24 = 0
Blood pressure (SBP/DBP, mmHg)	< 135/< 85 = 1, ≥ 135/85 = 0
Proteinuria	Yes = 1, No = 0
Lower extremity edema	Yes = 1, No = 0

Correlations Between rs2681472 Gene Polymorphism and Risk Factors for Eclampsia Patients

The above analysis indicated that rs2681472 gene polymorphism was significantly associated with the incidence of eclampsia. Therefore, the degree of the correlation between rs2681472 gene polymorphism and clinical features of patients was analyzed. As shown in Table VI, rs2681472 gene polymorphism showed remarkable associations with BMI ($p=0.001$), blood pressure ($p=0.0248$), and proteinuria ($p=0.028$). All these results indicated that, combined with Logistic regression analysis results, the blood pressure and proteinuria were high-risk factors for eclampsia.

Correlation Analysis of rs2681472 Gene Polymorphism with Hypertension and Lower Extremity Edema

The genotype and gene frequency of rs2681472 were detected *via* χ^2-test in subjects with and without hypertension and lower extremity edema. The results revealed that the genotype and gene frequency of rs2681472 exhibited evident differences among the subjects with and without hypertension and lower extremity edema ($p<0.05$) (Table VII). Combined with logistic regression analysis and univariate and multivariate regression analyses, it could be concluded that hypertension and lower extremity edema were risk factors for eclampsia, which could also affect rs2681472 gene polymorphism.

Table V. Logistic regression analysis of risk factors.

Independent variable	β	S*	OR	95% CI	p
Blood pressure	3.11	0.79	9.33	1.67-16.18	0.0029
Proteinuria	1.82	0.41	4.64	1.22-6.86	0.032
Lower extremity edema	2.18	0.51	4.97	1.34-7.31	0.027

Table VI. Univariate and multivariate regression analyses.

Variable/Univariate analysis (n = 117)	Type	OR (95% CI)	p
rrs2681472 gene polymorphism	GA	0.978 (0.536-1.94)	0.031
Age of pregnant women	< 30 = 1, ≥ 30 = 0	0.046 (0.021-0.67)	0.355
Gestational week	< 36 = 1, ≥36 = 0	0.64 (0.41-0.72)	0.0391
Height (cm)	< 160 = 1, ≥160 = 0	0.076 (0.012-0.194)	0.413
Blood pressure (SBP/DBP, mmHg)	< 135/< 85 = 1, ≥ 135/85 = 0	1.984 (0.819-4.341)	0.0013
Proteinuria	Yes = 1, No = 0	1.358 (0.323-3.291)	0.022
Lower extremity edema	Yes = 1, No = 0	1.657 (0.531-4.710)	0.017
Multivariate analysis (n = 117)			
rs2681472 gene polymorphism	GA	1.162 (0.661-2.109)	0.0345
BMI (kg/m^2)	< 24 = 1, ≥ 24 = 0	2.157 (1.274-3.653)	0.0023
Blood pressure (SBP/DBP, mmHg)	< 135/< 85 = 1, ≥ 135/85 = 0	1.634 (0.518-4.736)	0.0248
Proteinuria	Yes = 1, No = 0	1.158 (0.313-3.824)	0.028

Table VII. Correlation analysis of rs2681472 gene polymorphism with hypertension and lower extremity edema.

Gene	Genotype	Hypertension		No hypertension		χ^2	*p*	Lower extremity edema		No lower extremity edema		χ^2	*p*
		No.	%	No.	%			No.	%	No.	%		
rs2681472	AA	17	24.64	33	33.67			22		31			
	AG	29	42.03	52	53.06	9.685	0.008	32		42		6.096	0.047
	GG	23	33.33	13	13.27			25		15			

Discussion

The association between ATP2B1 gene polymorphism and susceptibility to hypertension was first reported in the European population[8,10]. This has been confirmed in 2 independent cohort studies involving 4,818 subjects in China that the ATP2B1 gene is significantly correlated with hypertension[11]. The pathological feature of eclampsia is calcium metabolic disorder. Current studies have found that Ca^{2+} concentration in plasma declines, while that in cytoplasm increases in eclampsia patients. This may lead to dysfunction of vascular smooth muscles closely related to Ca^{2+} concentration. Moreover, it can interfere in the regulation of blood pressure by smooth muscles[12-14] and result in characteristic hypertension and other clinical phenomena in eclampsia. According to other studies, ATP2B1 gene polymorphism is also closely correlated with the incidence of asymptomatic atherosclerosis in hypertension patients. This is helpful for early identification of patients with asymptomatic atherosclerosis[15]. In this paper, considering that ATP2B1 gene polymorphism and eclampsia are associated with elevated blood pressure, ATP2B1 gene polymorphism was analyzed in the case group and control group, respectively. The results manifested that although rs2681472 and rs17249754 polymorphisms were related to blood pressure, rs2681472 polymorphism was closely related to eclampsia. These results demonstrated that the genes associated with hypertension were not necessarily the same ones leading to eclampsia. The above findings suggested that in the research on the pathogenesis of eclampsia and treatment of the related symptoms, it was necessary to study the functions of the genes and the related proteins. In addition, it is important to control the blood pressure, such as the alteration of the genetic background of the ATP2B1 gene and the regulation of the expression of Ca^{2+} transport-associated proteins.

According to Hernandez-Diaz et al[16], preeclampsia is a syndrome rather than a definite disease. Its incidence is closely related to heredity and environment. In one sequencing analysis of 124 candidate genes for susceptibility to eclampsia in the Finnish population, it has been found that rs13406336 and rs4556933 SNPs are closely related to patients with a history of eclampsia[17]. Therefore, the blood pressure-related gene ATP2B1 was analyzed in this paper. ATP2B1 gene located on 12q21.3 encodes the plasma membrane Ca^{2+} transport-associated protein, which is involved in the regulation of the intracellular free calcium concentration. Meanwhile, it also affects the intracellular signal transduction[18] and contraction or relaxation of vascular smooth muscles, thereby participating in the blood pressure regulation[19]. Currently, the pathophysiological significance of the ATP2B1 gene product in the development of hypertension remains uncertain. Kobayashi et al[20] has proved that the genetic mutations caused by changes in ATP2B1 SNP can be stably inherited in hypertension patients. This may result in genetic hypertension in descendants. In mice with specific knockout of the ATP2B1 gene, it has been proved that ATP2B1 in vascular smooth muscle cells is associated with hypertension. The mRNA and protein levels of ATP2B1 in the aorta are significantly declined when compared with those in the wild-type control mice. However, Ca^{2+} concentration in smooth muscle cells and SBP are remarkably elevated in the gene knockout mice[20]. Based on the association between the incidence of eclampsia and ATP2B1 gene polymorphism, whether the risk factors for eclampsia are related to ATP2B1 gene polymorphism was explored in this study. Univariate, multivariate, and Logistic regression analyses illustrated that blood pressure and proteinuria were important risk factors for the incidence of eclampsia. Further analysis showed that hypertension and proteinuria were associated with ATP2B1 gene polymorphism. The elevated blood pressure might be due to the fact that Ca^{2+} pathway dysfunction regulated by ATP2B1 affects Ca^{2+} transport and blood pressure regulation. However, the proteinuria might be associated with the decline in the protein reabsorption function in the kidney. The specific mechanism still needs further research. Eclampsia is a maternal-fetal disease. Therefore, only the maternal genotypes were detected in this paper. In the future, more attention should be paid to the role of fetal or paternal genes in the development of eclampsia.

Conclusions

This study demonstrated that the ATP2B1 gene polymorphism at rs2681472 shows significant differences between eclampsia patients and normal controls. Furthermore, its gene polymorphism is closely related to the occurrence of hypertension and lower extremity edema.

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1) Gathiram P, Moodley J. Pre-eclampsia: its pathogenesis and pathophysiolgy. Cardiovasc J Afr 2016; 27: 71-78.
2) Jiao S, Wang SY, Huang Y. LncRNA PRNCR1 promoted the progression of eclampsia by regulating the MAPK signal pathway. Eur Rev Med Pharmacol Sci 2018; 22: 3635-3642.
3) Giannakou K, Evangelou E, Papatheodorou SI. Genetic and non-genetic risk factors for pre-eclampsia: umbrella review of systematic reviews and meta-analyses of observational studies. Ultrasound Obstet Gynecol 2018; 51: 720-730.
4) Giannakou A, Sicko RJ, Kay DM, Zhang W, Romitti PA, Caggana M, Shaw GM, Jelliffe-Pawlowski LL, Mills JL. Copy number variants in hypoplastic right heart syndrome. Am J Med Genet A 2018; 176: 2760-2767.
5) Sircar M, Thadhani R, Karumanchi SA. Pathogenesis of preeclampsia. Curr Opin Nephrol Hypertens 2015; 24: 131-138.
6) Xu J, Qian HX, Hu SP, Liu LY, Zhou M, Feng M, Su J, Ji LD. Gender-specific association of ATP2B1 variants with susceptibility to essential hypertension in the Han Chinese population. Biomed Res Int 2016; 2016: 1910565.
7) Little R, Cartwright EJ, Neyses L, Austin C. Plasma membrane calcium ATPases (PMCAs) as potential targets for the treatment of essential hypertension. Pharmacol Ther 2016; 159: 23-34.
8) Levy D, Ehret GB, Rice K, Verwoert GC, Launer LJ, Dehghan A, Glazer NL, Morrison AC, Johnson AD, Aspelund T, Aulchenko Y, Lumley T, Kottgen A, Vasan RS, Rivadeneira F, Eiriksdottir G, Guo X, Arking DE, Mitchell GF, Mattace-Raso FU, Smith AV, Taylor K, Scharpf RB, Hwang SJ, Sijbrands EJ, Bis J, Harris TB, Ganesh SK, O'Donnell CJ, Hofman A, Rotter JI, Coresh J, Benjamin EJ, Uitterlinden AG, Heiss G, Fox CS, Witteman JC, Boerwinkle E, Wang TJ, Gudnason V, Larson MG, Chakravarti A, Psaty BM, van Duijn CM. Genome-wide association study of blood pressure and hypertension. Nat Genet 2009; 41: 677-687.
9) Wang Y, Zhang Y, Li Y, Zhou X, Wang X, Gao P, Jin L, Zhang X, Zhu D. Common variants in the ATP2B1 gene are associated with hypertension and arterial stiffness in Chinese population. Mol Biol Rep 2013; 40: 1867-1873.
10) Kohara K, Tabara Y, Nakura J, Imai Y, Ohkubo T, Hata A, Soma M, Nakayama T, Umemura S, Hirawa N, Ueshima H, Kita Y, Ogihara T, Katsuya T, Takahashi N, Tokunaga K, Miki T. Identification of hypertension-susceptibility genes and pathways by a systemic multiple candidate gene approach: the millennium genome project for hypertension. Hypertens Res 2008; 31: 203-212.
11) Liu C, Li H, Qi Q, Lu L, Gan W, Loos RJ, Lin X. Common variants in or near FGF5, CYP17A1 and MTHFR genes are associated with blood pressure and hypertension in Chinese Hans. J Hypertens 2011; 29: 70-75.
12) Kisters K, Barenbrock M, Louwen F, Hausberg M, Rahn KH, Kosch M. Membrane, intracellular, and plasma magnesium and calcium concentrations in preeclampsia. Am J Hypertens 2000; 13: 765-769.
13) Kisters K, Körner J, Louwen F, Witteler R, Jackisch C, Zidek W, Ott S, Westermann G, Barenbrock M, Rahn KH. Plasma and membrane Ca^{2+} and Mg^{2+} concentrations in normal pregnancy and in preeclampsia. Gynecol Obstet Invest 1998; 46: 158-163.
14) Idogun ES, Imarengiaye CO, Momoh SM. Extracellular calcium and magnesium in preeclampsia and eclampsia. Afr J Reprod Health 2007; 11: 89-94.
15) An D, Zhang J, Tang X, Gao P, Li Y, Wang Y, Zhu D. Association of ATP2B1 common variants with asymptomatic intracranial and extracranial large artery stenosis in hypertension patients. Clin Exp Hypertens 2019; 41: 323-329.
16) Hernandez-Diaz S, Toh S, Cnattingius S. Risk of pre-eclampsia in first and subsequent pregnancies: prospective cohort study. BMJ 2009; 338: b2255.
17) Lokki AI, Daly E, Triebwasser M, Kurki MI, Roberson E, Happola P, Auro K, Perola M, Heinonen S, Kajantie E, Kere J, Kivinen K, Pouta A, Salmon JE, Meri S, Daly M, Atkinson JP, Laivuori H. Protective low-frequency variants for preeclampsia in the Fms related tyrosine kinase 1 gene in the Finnish population. Hypertension 2017; 70: 365-371.
18) Long Y, Xia JY, Chen SW, Gao CL, Liang GN, He XM, Wu J, Jiang CX, Liu X, Huang W, Wan Q, Xu Y. ATP2B1 gene Silencing increases insulin sensitivity through facilitating Akt activation via the Ca^{2+}/calmodulin signaling pathway and Ca^{2+}-associated eNOS activation in endothelial cells. Int J Biol Sci 2017; 13: 1203-1212.
19) Tabara Y, Kohara K, Miki T; Millennium Genome Project for Hypertension. Hunting for genes for hypertension: the millennium genome project for hypertension. Hypertens Res 2012; 35: 567-573.
20) Kobayashi Y, Hirawa N, Tabara Y, Muraoka H, Fujita M, Miyazaki N, Fujiwara A, Ichikawa Y, Yamamoto Y, Ichihara N, Saka S, Wakui H, Yoshida S, Yatsu K, Toya Y, Yasuda G, Kohara K, Kita Y, Takei K, Goshima Y, Ishikawa Y, Ueshima H, Miki T, Umemura S. Mice lacking hypertension candidate gene ATP2B1 in vascular smooth muscle cells show significant blood pressure elevation. Hypertension 2012; 59: 854-860.