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ATP2B1 gene rs71454161, rs73196661 and rs73196675 polymorphisms in eclampsia

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Abstract. – OBJECTIVE: We aimed to explore the associations of the ATP2B1 gene polymorphisms with eclampsia.

PATIENTS AND METHODS: A total of 150 patients with eclampsia (disease group) and 150 healthy pregnant women (control group) were taken as the subjects of study. The peripheral blood of the two groups of subjects was collected to extract deoxyribonucleic acids (DNAs), and the ATP2B1 gene rs71454161, rs73196661 and rs73196675 polymorphisms were detected by sequencing the Polymerase Chain Reaction (PCR) products, and then, analyzed combined with gene expression determined via Reverse Transcription-quantitative Polymerase Chain Reaction (RT-qPCR) and clinical indicators, such as 24-h urine protein, platelets, and LDH.

RESULTS: A difference was observed in the allele distribution of ATP2B1 gene rs71454161 (p=0.000) and rs73196661 (p=0.011) between the disease group and control group. Disease group exhibited higher frequencies of allele G of rs71454161 and allele T of rs73196661 than control group. Besides, there was a difference in the genotype distribution of ATP2B1 gene rs71454161 (p=0.000), rs73196661 (p=0.000) and rs73196675 (p=0.000) between disease group and control group. Disease group exhibited higher frequencies of genotype GG of rs71454161, genotype TT of rs73196661 and genotype CG of rs73196675 than control group. Moreover, a difference in the distributions of ATP2B1 gene rs71454161 (p=0.000) and rs73196661 (p=0.014) was found between the two groups in the dominant model. Disease group exhibited lower frequencies of AA+AG of rs71454161 and CC+CT of rs73196661 than control group in the dominant model. Differences in the distributions of haplotypes ACC (p=0.000), ATC (p=0.047) and GTC (p=0.000) of ATP2B1 gene rs71454161, rs73196661 and rs73196675 were observed between disease group and control group. Furthermore, a high degree of linkage disequilibrium was detected between rs71454161 and rs73196661 (D'=0.329). The ATP2B1 gene rs73196675 polymorphism was evidently correlated with the gene expression of ATP2B1 (p<0.05), and the patients with genotype GG had a lower expression level of ATP2B1. The ATP2B1 gene rs71454161 was evidently correlated with the 24-h urinary protein in eclampsia patients (p=0.021), and the patients with genotype AG had a higher level of 24-h urinary proteins. The rs73196661 polymorphism was significantly correlated with LDH (p=0.000), and the patients with genotype CC had a higher level of LDH.

CONCLUSIONS: The ATP2B1 gene polymorphism was significantly correlated with the occurrence and progression of eclampsia.

Key Words:
ATP2B1, Gene polymorphism, Eclampsia.

Introduction

Eclampsia, a serious hypertensive disease during gestation period accompanied by convulsions and other neuropsychological symptoms, is developed from pre-eclampsia and severe pre-eclampsia, which is the most serious stage of hypertension during gestation period and has a great threat to the life of mother and fetus[1-4]. At present, the cause of eclampsia is still unclear. Studies[5,6] have shown that it may be related to obesity, advanced age, external environment and other factors. Besides, hereditary chronic hypertension may also be an important cause of the disease. It is of great help for the prevention and treatment of eclampsia to study its causes and progression factors. Gene polymorphism, a key factor affecting the susceptibility to diseases, has been proven to have a relationship with the occurrence of various diseases[7]. ATP2B1 is a membrane calcium ion transporter enzyme gene, which has a close relationship with the occurrence of hypertension[8]. Wang et al[9] reported that ATP2B1 mutation could increases the susceptibility to hypertension in Asian population. Sun et al proved association of ATP2B1 gene

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with incidence of eclampsia[10]. The ATP2B1 gene polymorphism may induce eclampsia. In this study, the ATP2B1 gene rs71454161, rs73196661 and rs73196675 polymorphisms of peripheral blood karyocytes in 150 patients with eclampsia and 150 normal pregnant women were detected, based on which the relationship between ATP2B1 gene and the onset of eclampsia was analyzed combined with haplotype analysis, gene expression and clinical indicators.

Patients and Methods

General Data

A total of 150 patients with eclampsia treated in our hospital (disease group) and 150 healthy pregnant women (control group) were enrolled as the subjects of study. The selection of patients was based on the guideline proposed by the National Institute for Health and Care Excellence (NICE) guidelines. The general data and clinical data of subjects, including name, age, marriage and childbearing history, family history, drug allergy history and menstrual history, were collected from both groups. The mean age of the disease group and control group was (32.12 ±3.84) years old and (31.25±3.16) years old, respectively, and there were no statistically significant differences in general materials, including age between the two groups. The inclusion criteria of eclampsia patients in the disease group were as follows: patients with systolic blood pressure >160 mmHg or diastolic blood pressure >110 mmHg, with the 24-h urine volume <400 mL, with increased serum creatinine, with retinal hemorrhage, papilledema or disturbances of visual acuity, and with convulsion, coma and other mental symptoms. This study was approved by the Ethics Committee of The First Affiliated Hospital of Zhengzhou University. Signed written informed consents were obtained from all participants before the study.

Specimen Collection

The peripheral blood samples of patients in the disease group were collected when patients were quiet with no mental symptoms, such as convulsion. 5 mL of venous blood of elbow collected from the disease group and control group was centrifuged at 3500 rpm for 5 min. Subsequently, the mid-layer nucleated cells were transferred into a 1.5 mL centrifuge tube for the extraction of genomic DNAs in the subsequent steps.

DNA Extraction from Nucleated Cells From the Peripheral Blood

Thermo Blood Genomic DNA Extraction Kits (Thermo Fisher Scientific, Waltham, MA, USA) were employed to extract DNAs from peripheral blood nucleated cells in both disease group and control group in strict accordance with kit instructions. Genomic DNAs were extracted from the peripheral blood of the subjects of study, whose purity was detected by a spectrophotometer to select qualified samples for the next analysis.

PCR Amplification and Polymorphism Detection

The regions of ATP2B1 gene polymorphisms rs71454161, rs73196661 and rs73196675 were amplified using a PCR instrument and a system (25 μL in total) composed of 1 μL of forward primers, 1 μL of reverse primers, 0.5 μL of DNA templates, 12.5 μL of Taq polymerase and 10 μL of dH_2O. The primer sequences are listed in Table I. Finally, the PCR products were sent to Hebei Biotechnology Co., Ltd. (Shijiazhuang, China) for polymorphism analysis.

Reverse Transcription-Quantitative Polymerase Chain Reaction (RT-qPCR)

The real-time fluorescent quantitative PCR was used to detect the expressions of ATP2B1 and the internal reference glyceraldehyde 3-phosphate dehydrogenase (GAPDH) in both control group and disease group. The total RNAs of peripheral blood nucleated cells in each group were extracted *via* TRIzol method (Invitrogen, Carlsbad, CA, USA), and then, reversely transcribed into complementary deoxyribose nucleic acids (cDNAs), followed by detection of gene expressions by qPCR. PCR reaction conditions were as follows: pre-denaturation at 95°C for 5 min, 35 cycles of denaturation at 95°C for 30 s, annealing at 55°C for 40 s and extension at 72°C for 30 s, then extension at 72°C for 5 min, and heat preservation at 4°C. The primers were designed, synthesized and verified by Sangon Biotech (Shanghai, China) Co., Ltd., whose sequences are shown in Table I.

Detection of Clinical Indicators

The Biochemical Room and Clinical Examination Room of the Clinical Laboratory in our hospital were responsible for the detection of 24-h urine protein, platelets, LDH and other clinical indexes of eclampsia patients, and all testing instruments needed routine quality control treatment every day before use.

Table I. PCR primer sequences.

	Forward/reverse primer	Primer sequence
rs71454161 locus	Forward	TGAAGGAGCTGCAATCCTCTT
	Reverse	TGACCACCCCTGATGACAGT
rs73196661 locus	Forward	AGATGGAGCTATTGAGAATCGCA
	Reverse	GCCAGTTTTGTAAGTTTCCCTTG
rs73196675 locus	Forward	AGATTGGCAAAGCAGGTCTGT
	Reverse	TAAGCCAGTGAGATCGTGACT
ATP2B1	Forward	CTCAGTTGCGTATAGCGGTGT
	Reverse	CAGCTCTGTAAGCGTAATTCCA
GAPDH	Forward	TGAAGGAGCTGCGATCCTCTT
	Reverse	CTGTTCCTGCTCAATTCGACT

Statistical Analysis

The Statistical Product and Service Solutions (SPSS) 22.0 (IBM, Armonk, NY, USA) was employed for statistical analysis. Measurement data were compared using χ^2-test and subjected to Hardy-Weinberg equilibrium test. Haplotypes were analyzed at the SHEsis website. $p<0.05$ indicated that the differences were statistically significant.

Results

The allele Distributions of ATP2B1 Gene rs71454161, rs73196661 and rs73196675 in Disease Group and Control Group

The allele distribution of ATP2B1 gene rs71454161, rs73196661 and rs73196675 in disease group and control group is shown in Table II. There was a difference in the allele distribution of ATP2B1 gene rs71454161 (p=0.000) and rs73196661 (p=0.011) between disease group and control group. Disease group exhibited higher frequencies of allele G of rs71454161 and allele T of rs73196661 than control group.

The Genotype Distribution of ATP2B1 Gene rs71454161, rs73196661 and rs73196675 in Disease Group and Control Group

The genotype distribution of ATP2B1 gene rs71454161, rs73196661 and rs73196675 in disease group and control group is shown in Table III. A difference in the genotype distribution of ATP2B1 gene rs71454161 (p=0.000), rs73196661 (p=0.000) and rs73196675 (p=0.000) was ob-

Table II. Allele distributions of ATP2B1 gene rs71454161, rs73196661 and rs73196675 in disease group and control group.

Locus	Allele	Control group	Disease group	OR	95% CI	χ^2	p
rs71454161	A	150 (0.500)	95 (0.317)	0.46	0.33-0.64	20.86	0.000
	G	150 (0.500)	205 (0.683)				
rs73196661	C	156 (0.520)	125 (0.417)	0.65	0.47-0.91	6.43	0.011
	T	144 (0.480)	175 (0.583)				
rs73196675	C	151 (0.503)	150 (0.500)	0.98	0.71-1.35	0.006	0.934
	G	149 (0.497)	150 (0.500)				

Table III. Genotype distribution of ATP2B1 gene rs71454161, rs73196661 and rs73196675 in disease group and control group.

Locus	Genotype	Control group	Disease group	χ^2	p
rs71454161	AA	38 (0.253)	20 (0.133)	20.49	0.000
	AG	74 (0.493)	55 (0.367)		
	GG	38 (0.253)	75 (0.500)		
rs73196661	CC	35 (0.233)	40 (0.267)	26.95	0.000
	CT	86 (0.573)	45 (0.300)		
	TT	29 (0.193)	65 (0.433)		
rs73196675	CC	55 (0.367)	35 (0.233)	21.07	0.000
	CG	41 (0.273)	80 (0.533)		
	GG	54 (0.360)	35 (0.233)		

served between disease group and control group. Disease group exhibited higher frequencies of genotype GG of rs71454161, genotype TT of rs73196661 and genotype CG of rs73196675 than control group.

The Polymorphism Analyses of ATP2B1 Gene rs71454161, rs73196661 and rs73196675 in Disease Group and Control Group

The polymorphism analyses of ATP2B1 gene rs71454161, rs73196661 and rs73196675 in disease group and control group (Table IV) showed that there was a difference in the distribution of ATP2B1 gene rs71454161 (p=0.000) and rs73196661 (p=0.014) between the two groups in the dominant model. Disease group exhibited lower frequencies of AA+AG of rs71454161 and CC+CT of rs73196661 than control group in the dominant model.

The Haplotype Analyses of ATP2B1 Gene in Disease Group and Control Group

The haplotype and linkage disequilibrium analyses of ATP2B1 gene in disease group and control group are shown in Table V and Table VI, respectively. Differences in the distributions of haplotypes ACC (p=0.000), ATC (p=0.047) and GTC (p=0.000) of ATP2B1 gene rs71454161, rs73196661 and rs73196675 were observed between disease group and control group. Moreover, a high degree of linkage disequilibrium was detected between rs71454161 and rs73196661 (D'=0.329).

The Relationships of Gene Expression of ATP2B1 with ATP2B1 gene rs71454161, rs73196661 and rs73196675 in Disease Group and Control Group

The relationships of gene expression of ATP2B1 with ATP2B1 gene rs71454161, rs73196661 and rs73196675 in disease group and control group are shown in Figures 1-3. The ATP2B1 gene rs73196675 polymorphism was evidently correlated with the gene expression of ATP2B1 (p<0.05), and the patients with genotype GG had a lower expression level of ATP2B1.

The Relationships of Clinical Indexes of Eclampsia Patients with ATP2B1 Gene rs71454161, rs73196661 and rs73196675 Polymorphisms

Based on Table VII, the ATP2B1 gene rs71454161 was evidently correlated with the 24-h urinary protein in eclampsia patients (p=0.021), and the patients with genotype AG had a higher

Table IV. Polymorphism analyses of ATP2B1 gene rs71454161, rs73196661 and rs73196675 in disease group and control group.

	Locus	Genotype	Control group	Disease group	χ^2	p
Dominant model	rs71454161	AA+AG	112 (0.747)	75 (0.500)	21.24	0.000
		GG	38 (0.253)	75 (0.500)		
	rs73196661	CC+CT	121 (0.807)	85 (0.567)	8.53	0.014
		TT	29 (0.193)	65 (0.433)		
	rs73196675	CC+CG	96 (0.640)	115 (0.767)	5.76	0.056
		GG	54 (0.360)	35 (0.233)		
Recessive model	rs71454161	AA	38 (0.253)	20 (0.133)	5.4	0.067
		AG+GG	112 (0.747)	130 (0.867)		
	rs73196661	CC	35 (0.233)	40 (0.267)	2.54	0.281
		CT+TT	115 (0.767)	110 (0.733)		
	rs73196675	CC	55 (0.367)	35 (0.233)	5.02	0.081
		CG+GG	95 (0.633)	115 (0.767)		
Heterozygous model	rs71454161	AA	38 (0.253)	20 (0.133)	3.61	0.164
		AG	74 (0.493)	55 (0.367)		
	rs73196661	CC	35 (0.233)	40 (0.267)	3.52	0.172
		CT	86 (0.573)	45 (0.300)		
	rs73196675	CC	55 (0.367)	35 (0.233)	2.15	0.341
		CG	41 (0.273)	80 (0.533)		
Homozygous model	rs71454161	AA	38 (0.253)	20 (0.133)	2.23	0.328
		GG	38 (0.253)	75 (0.500)		
	rs73196661	CC	35 (0.233)	40 (0.267)	2.59	0.274
		TT	29 (0.193)	65 (0.433)		
	rs73196675	CC	55 (0.367)	35 (0.233)	4.61	0.100
		GG	54 (0.360)	35 (0.233)		

Table V. The haplotype analyses of ATP2B1 gene in disease group and control group.

Haplotype	Control group	Disease group	OR	95% CI	χ^2	*p*
ACC	47.74 (0.159)	14.73 (0.049)	0.273	0.148-0.501	19.478	0.000
ACG	36.12 (0.120)	25.41 (0.085)	0.676	0.396-1.154	2.078	0.150
ATC	36.89 (0.123)	22.39 (0.075)	0.575	0.331-0.998	3.936	0.047
ATG	29.24 (0.097)	32.47 (0.108)	1.124	0.663-1.905	0.188	0.664
GCC	30.51 (0.102)	34.80 (0.116)	1.159	0.693-1.939	0.316	0.574
GCG	41.63 (0.139)	50.07 (0.167)	1.243	0.796-1.943	0.917	0.338
GTC	35.85 (0.120)	78.09 (0.260)	2.592	1.680-4.000	19.322	0.000
GTG	42.01 (0.140)	42.05 (0.140)	1.001	0.631-1.588	0	0.996

Table VI. Linkage disequilibrium analyses among ATP2B1 gene rs71454161, rs73196661, and rs73196675.

D′	rs71454161	rs73196661	rs73196675
rs71454161	–	0.329	0.002
rs73196661	0.329	–	0.007
rs73196675	0.002	0.007	–

level of 24-h urinary protein. The rs73196661 polymorphism was significantly correlated with LDH (p=0.000), and the patients with genotype CC had a higher level of LDH.

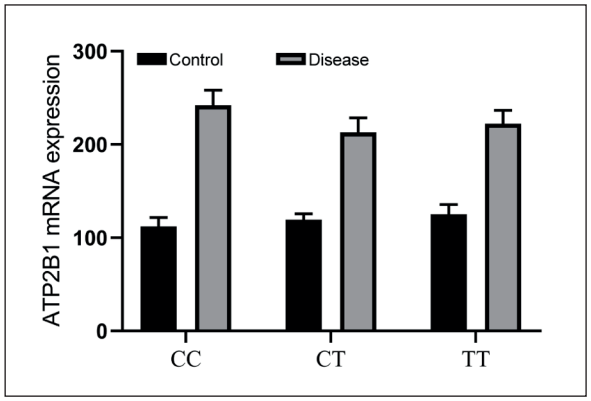

Figure 2. Relationship between gene expression of ATP2B1 and ATP2B1 gene rs73196661 in disease group and control group.

Discussion

Eclampsia, an important disease affecting the health of pregnant women, is related to the high blood pressure level in the patients[11,12]. At present, the pathogenesis and causes of the disease are not clear. Previous studies[13,14] have manifested that the disease is mainly relevant with age, basic diseases, metabolic level, multiple pregnancy and other factors. Moreover, the onset of eclampsia is also affected by genetic factors, of which gene polymorphism has been indicated to be closely related to the occurrence of the disease[15]. Some studies[16,17] have shown that the INSR gene rs2059806 and SOD2 Ala-

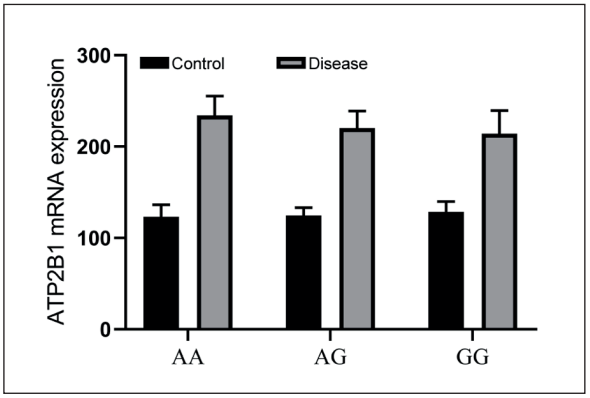

Figure 1. Relationship between gene expression of ATP2B1 and ATP2B1 gene rs71454161 in disease group and control group (*p<0.05).

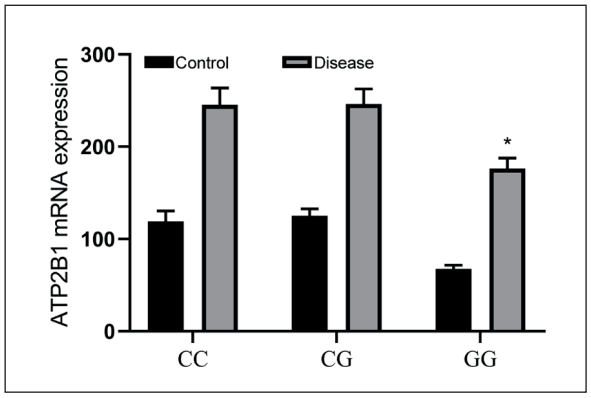

Figure 3. Relationship between gene expression of ATP2B1 and ATP2B1 gene rs73196675 in disease group and control group.

Table VII. Relationships of clinical indexes of eclampsia patients with ATP2B1 gene rs71454161, rs73196661 and rs73196675 polymorphisms.

		Urine protein (g/24 h)		Platelets (×10^9/L)		LDH (U/L)	
Locus	Genotype	Disease group	*p*	Disease group	*p*	Disease group	*p*
rs71454161	AA	3.51 ± 0.23	0.021	112 ± 21	0.212	614 ± 23	0.198
	AG	5.34 ± 0.52		108 ± 10		619 ± 12	
	GG	3.69 ± 0.41		118 ± 13		626 ± 35	
rs73196661	CC	3.85 ± 1.24	0.109	104 ± 7	0.074	728 ± 21	0.000
	CT	3.51 ± 0.29		113 ± 12		611 ± 28	
	TT	3.59 ± 0.49		114 ± 14		607 ± 18	
rs73196675	CC	3.37 ± 0.62	0.121	107 ± 15	0.123	624 ± 27	0.153
	CG	3.87 ± 0.46		111 ± 8		635 ± 25	
	GG	3.92 ± 0.22		112 ± 15		624 ± 26	

16Val polymorphisms are related to the onset of eclampsia. Therefore, it is very important to find more genes with high correlations with the occurrence of eclampsia.

Hypertension is an important cause of the onset of eclampsia, and the ATP2B1 gene has been conformed to be one of the genes closely interrelated with hypertension[18]. ATP2B1 can transport calcium ions out of cells in inverse concentration gradient, which plays a vital role in maintaining intracellular calcium homeostasis. Moreover, ATP2B1 is also related to the relaxation and contraction of vascular smooth muscle[18]. It is reported that ATP2B1 polymorphisms are closely related to the susceptibility and occurrence of various diseases, including hypertension[19,20] and colorectal cancer[21]. In this study, the ATP2B1 gene rs71454161, rs73196661 and rs73196675 polymorphisms in peripheral blood nucleated cells were compared between 150 eclampsia patients and 150 normal pregnant women. A difference in the allele distribution of ATP2B1 gene rs71454161 (p=0.000) and rs73196661 (p=0.011) was observed between disease group and control group. Disease group exhibited higher frequencies of allele G of rs71454161 and allele T of rs73196661 than control group. In addition, there was a difference in the genotype distribution of ATP2B1 gene rs71454161 (p=0.000), rs73196661 (p=0.000) and rs73196675 (p=0.000) between disease group and control group. The frequencies of genotype GG of rs71454161, genotype TT of rs73196661 and genotype CG of rs73196675 were higher in disease group than those in control group. These results indicated that the onset of eclampsia is significantly related to ATP2B1 gene rs71454161, rs73196661 and rs73196675 polymorphisms. The gene polymorphisms are likely to be one of the important predisposing factors for the onset of eclampsia. Gene testing can facilitate the screening of high-risk populations to early intervene in the prevention and treatment of eclampsia, which is of great significance to increase the survival rate of puerperae of appropriate age or old age.

Polymorphism analysis showed that there was a difference in the distribution of ATP2B1 gene rs71454161 (p=0.000) and rs73196661 (p=0.014) between the two groups in the dominant model. Disease group exhibited lower frequencies of AA+AG of rs71454161 and CC+CT of rs73196675 than control group in the dominant model. Differences in the distributions of haplotypes ACC (p=0.000), ATC (p=0.047) and GTC (p=0.000) of ATP2B1 gene rs71454161, rs73196661 and rs73196675 were observed between disease group and control group. Moreover, a high degree of linkage disequilibrium was detected between rs71454161 and rs73196661 (D'=0.329). It can be inferred from these results that the onset of eclampsia may be affected by not only a single gene polymorphism, but also multiple genotypes at multiple sites. These findings will help researchers understand the impact of gene polymorphisms on the onset of the disease.

The ATP2B1 gene rs71454161, rs73196661 and rs73196675 polymorphisms were analyzed combined with gene expression of ATP2B1. It was found that the ATP2B1 gene rs73196675 polymorphism was evidently correlated with the gene expression of ATP2B1 (p<0.05), and the patients with genotype GG had a lower expression level of ATP2B1. These results indicate that the gene polymorphisms can affect the onset of eclampsia by influencing the gene expression.

Finally, the clinical data of eclampsia patients were analyzed combined with the ATP2B1 gene rs71454161, rs73196661 and rs73196675 polymorphisms. It was revealed that the ATP2B1 gene rs71454161 was evidently correlated with the 24-h urinary protein in eclampsia patients (p=0.021), and the patients with genotype AG had a higher level of 24-h urinary protein. The rs73196661 polymorphism was significantly correlated with LDH (p=0.000), and the patients with genotype CC had a higher level of LDH. Moreover, 24-h urinary protein was related with disease progression in patients with eclampsia, and LDH level was associated with microvascular hemolysis.

Conclusions

Therefore, the above results revealed that the ATP2B1 gene rs71454161, rs73196661 and rs73196675 polymorphisms are not only associated to the susceptibility to eclampsia, but also may be related to the progression of the disease. The novelty of this study was that our findings could provide a potential strategy for the treatment and prevention of eclampsia.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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