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Correlations of CYP11B2 gene polymorphisms with eclampsia

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Abstract. – OBJECTIVE: The aim of this study was to explore the relationship between CYP11B2 gene polymorphisms and eclampsia.

PATIENTS AND METHODS: A total of 400 pregnant women treated in our hospital were enrolled in this study, including 200 normal pregnant women (pregnancy group) and 200 pregnant women with eclampsia (eclampsia group). Peripheral blood was collected from subjects of the two groups. Subsequently, genomic deoxyribonucleic acids (DNAs) were extracted and amplified *via* polymerase chain reaction (PCR) for detection of CYP11B2 rs4543, rs3802228 and rs104894072 polymorphisms. The expression level of CYP11B2 gene was measured as well. Additionally, the correlations of CYP11B2 gene polymorphisms with blood pressure and coagulation and renal function indexes were analyzed.

RESULTS: The distribution of alleles of rs4543 locus in CYP11B2 gene was significantly different between eclampsia group and pregnancy group (p=0.027). The frequency of the allele C was significantly lower in eclampsia group than that of pregnancy group (p<0.05). There was a statistically significant difference in the genotype distribution of CYP11B2 rs3802228 (p=0.000) and rs104894072 (p=0.000) between eclampsia group and pregnancy group (p<0.05). Meanwhile, the frequency of AA genotype of rs3802228 and TG genotype of rs104894072 was remarkably higher in eclampsia group than that in pregnancy group (p<0.05). The distribution of the locus rs104894072 (p=0.044) in dominant model and rs3802228 (p=0.002) in recessive model in eclampsia group was different from that in pregnancy group (p<0.05). Eclampsia group showed remarkably elevated frequency of TT + TG of the locus rs104894072 in dominant model and lowered frequency of AG + GG of the locus rs3802228 in recessive model (p<0.05). Similarly, a significant difference was observed in the distribution of the haplotypes CGG (p=0.001) and TGT (p=0.048) in CYP11B2 gene between eclampsia group and pregnancy group (p<0.05). The linkage disequilibrium of the loci rs3802228 and rs104894072 was relatively high (D'=0.382). The polymorphism of the locus rs104894072 in CYP11B2 gene had an evident relation to CYP11B2 gene expression (p<0.05). Meanwhile, the expression of CYP11B2 gene was markedly higher in patients with GG genotype in eclampsia group (p<0.05). The polymorphism of CYP11B2 rs4543 was notably associated with PT level of patients in eclampsia group (p=0.000). Conversely, rs3802228 polymorphism was correlated with 24 h urine protein level (p=0.000). Besides, the proportion of patients with CGG haplotype was significantly larger among patients with systolic blood pressure of 140-160 mmHg (p<0.05). In addition, the proportion of patients with TGT haplotype was evidently greater among patients with systolic blood pressure >180 mmHg in eclampsia group (p<0.05).

CONCLUSIONS: CYP11B2 gene polymorphisms are significantly correlated with the development and progression of eclampsia.

Key Words:
Gene polymorphism, Eclampsia, CYP11B2.

Introduction

Eclampsia, a severe hypertension occurring during the pregnancy of women, seriously threatens the life of the mother and the fetus[1,2]. Currently, the development of eclampsia has been found associated with many factors, including physiological conditions of mothers (such as primiparae), pathological factors (like long-term hypertension) and family factors (including a family history of hypertension)[3,4]. Eclampsia mainly leads to sys-

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temic small blood vessel spasm and insufficient blood supply to local tissues, accompanied by severe hypertension and proteinuria, as well as convulsion or coma. All these complications endanger the life of the mother[5]. As a result, discovering the pathogenesis and progression pattern of eclampsia is of great significance to reduce maternal mortality rate. The renin-angiotensin-aldosterone system plays an important role in the pathogenesis of hypertension[6,7]. Aldosterone functions as the most powerful mineralocorticoid, which is able to directly act on endothelial cells and collagens, thereby increasing the risk of hypertension[8,9]. Previous studies have demonstrated that CYP11B2 gene can encode aldosterone synthase. However, the correlations of CYP11B2 gene polymorphisms with eclampsia have not been fully investigated. In this study, 200 normal pregnant women and 200 pregnant women with eclampsia were enrolled as research objects. Peripheral blood was collected from those subjects for extraction of deoxyribonucleic acids (DNAs) in nucleated cells. The polymorphisms of CYP11B2 rs4543, rs3802228 and rs104894072 were detected, and the distribution of alleles, genotypes and haplotypes was analyzed. Meanwhile, conjoint analysis was performed by combining CYP11B2 gene expression and blood pressure and coagulation and renal function indicators of patients. In addition, the association between CYP11B2 gene polymorphisms and eclampsia was explored.

Patients and Methods

General Data

A total of 400 pregnant women treated in our hospital in the past 4 years were selected as study subjects, including 200 women without any diseases during pregnancy (pregnancy group) and 200 women with eclampsia during pregnancy (eclampsia group). The selection of patients was based on the guideline proposed by the National Institute for Health and Care Excellence (NICE). The mean age of subjects in pregnancy group and eclampsia group was (32.35±2.41) and (33.15±3.16) years old, respectively. Their general data and clinical information (including name, age, blood pressure, respiratory rate, heart rate, menstrual history, obstetrical history and drug allergy history) were collected. No statistically significant differences were observed in general data such as age between pregnancy group and eclampsia group (p>0.05). Inclusion criteria for patients in eclampsia group were as follows: patients with continually increased blood pressure, urinary protein ++, liver, renal and coagulation function abnormalities, and convulsion that could not be caused by other factors except preeclampsia. This investigation was approved by the Ethics Committee of The Second Children & Women's Healthcare of Jinan City. Signed written informed consents were obtained from all participants before the study.

Collection and Treatment of Samples

Peripheral blood (8 mL) was collected from all patients in both pregnancy group and eclampsia group into purple-cover anticoagulation tubes by specialized persons in the clinical lab. Subsequently, blood samples were mixed *via* perversion and centrifuged at 3000 rpm for 5 min within 30 min. Thereafter, the middle karyocytes were carefully collected into Eppendorf (EP; Hamburg, Germany) tubes using a tip for DNA extraction.

Extraction of Genomic DNAs from Peripheral Blood Karyocytes

Genomic DNAs were extracted from peripheral blood karyocytes in eclampsia group and pregnancy group in strict accordance with the instructions of Promega kit (Madison, WI, USA). Briefly, the samples were mixed with proteinase K and buffer, followed by still standing at 65°C. After that, the samples were added with anhydrous alcohol and mixed *via* oscillation. Then, the sediments were transferred to an adsorption column and centrifuged for 30 s. Next, the waste solution was removed, and the adsorption column was put back to collection tubes. Afterwards, the column was added with deproteinized solution, centrifuged and rinsed with washing solution twice, followed by centrifugation again. Next, pre-heating elution buffer was added to the adsorption column, followed by standing for 5 min and centrifugation. Finally, the resulting solution was genomic DNAs.

Polymerase Chain Reaction (PCR) Amplification and Polymorphism Detection

Primers for polymorphisms of the loci rs4543, rs3802228 and rs104894072 in CYP11B2 gene were designed using Primer Premier 5.0 and subjected to PCR. The primers for polymorphic loci were: polymorphic region of rs4543: forward primer (5'→3') 'ACCTGGAGATGCACCAGAC', and reverse primer (5'→3') 'GGCCCATTCAACAAGAACACG', rs3802228: forward primer

(5'→3') 'TTCAACCGCCCTCAACACTAC', and reverse primer (5'→3') 'GGAAACGCTGTCGTGTCCA', and rs104894072: forward primer (5'→3') 'CTGAACCGAAATGTGCTGTCA', and reverse primer (5'→3') 'CCTAGCCGTTCCCCAAAAAG'. Next, products obtained after denaturation, annealing and extension of premixed mixture were sent to Jiangsu Biotechnology Co., Ltd. (Nanjing, China) for sequencing and polymorphism analysis.

Measurement of CYP11B2 Gene Expression

Reverse transcription-quantitative PCR (RT-qPCR) assay was performed to detect the expression level of CYP11B2 gene. Total RNAs were extracted from peripheral blood karyocytes in pregnancy group and eclampsia group using TRIzol method (Invitrogen, Carlsbad, CA, USA). Subsequently, extracted RNA was reversely transcribed into complementary DNAs (cDNAs). QPCR was then performed under the conditions of 95°C for 5 min, 35 cycles of 95°C for 30 s, 58°C for 40 s and 72°C for 40 s, and 72°C for 5 min. The experiment was repeated for 3 times. The relative expression of miRNAs was calculated using $2^{-\Delta\Delta CT}$. Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) was used as the internal reference. Primer sequences used in this study were as follows: CYP11B2, forward: (5'→3') 'TATCCATGCCCTGCATTCTATGT', and reverse: (5'→3') 'GTCCAGCGAGTCAAGCTCTT'. GAPDH, forward: (5'→3') 'CGCTCTCTGCTCCTCCTGTTC', and reverse: (5'→3') 'ATCCGTTGACTCCGACCTTCAC'.

Examination of Coagulation and Renal Function Indicators

In the clinical laboratory of our hospital, the examination of coagulation function indexes activated partial thromboplastin time (APTT) and prothrombin time (PT) and renal function indicator 24-h urinary protein was carried out using a fully automatic coagulometer and a urine analyzer in pregnancy group and eclampsia group, respectively.

Statistical Analysis

Statistical Product and Service Solutions (SPSS) 22.0 software (IBM Corp., Armonk, NY, USA) was used for all statistical analysis. The differences between two groups were analyzed by using the Student's *t*-test. One-way ANOVA was applied to compare the differences among different groups, followed by post-hoc test (Least Significant Difference). Polymorphism analysis was conducted using the online website SHEsis. To test the population homogeneity of the study subjects, the allele frequencies were tested against Hardy-Weinberg equilibrium by the χ^2-test. $p<0.05$ was considered statistically significant.

Results

Distribution of Alleles of the Loci rs4543, rs3802228 and rs104894072 in CYP11B2 Gene in Eclampsia Group and Pregnancy Group

All allele frequencies did not deviate from Hardy-Weinberg equilibrium. The distribution of alleles of CYP11B2 rs4543, rs3802228 and rs104894072 was shown in Table I. The results showed that the distribution of alleles of CYP11B2 rs4543 in eclampsia group was different from that in pregnancy group ($p=0.027$). The frequency of C allele was significantly lower in eclampsia group than that in pregnancy group ($p<0.05$).

Distribution of Genotypes of CYP11B2 rs4543, rs3802228 and rs104894072 in Eclampsia Group and Pregnancy Group

The results of genotype distribution of the loci rs4543, rs3802228 and rs104894072 in CYP11B2

Table I. Distribution of alleles of CYP11B2 rs4543, rs3802228 and rs104894072.

Locus	Allele	Pregnancy group	Eclampsia group	OR	95% CI	χ^2	p
rs4543	C	192 (0.480)	161 (0.403)	0.72	0.55-0.96	4.87	0.027
	T	208 (0.520)	239 (0.598)				
rs3802228	A	205 (0.512)	229 (0.573)	1.27	0.96-1.68	2.95	0.088
	G	195 (0.487)	171 (0.427)				
rs104894072	T	169 (0.422)	193 (0.482)	0.78	0.59-1.03	2.92	0.084
	G	231 (0.578)	207 (0.517)				

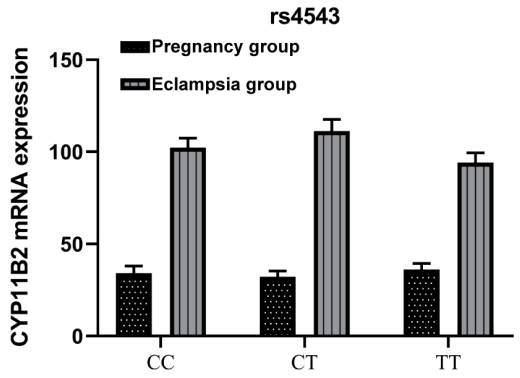

Figure 1. Correlation between CYP11B2 rs4543 polymorphism and gene expression.

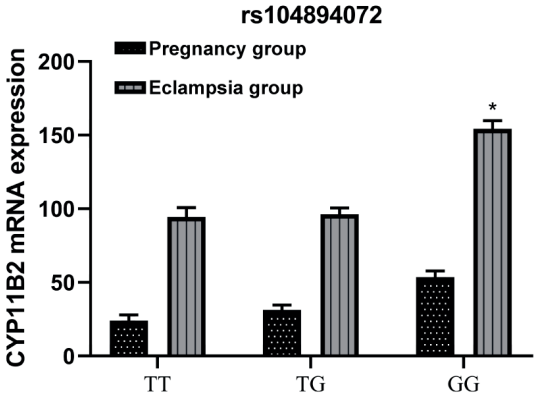

Figure 3. Relationship between CYP11B2 rs104894072 polymorphism and gene expression (*p<0.05).

gene (Table II) showed that there was a statistically significant difference in the distribution of genotypes of CYP11B2 rs3802228 (p=0.000) and rs104894072 (p=0.000) between eclampsia group and pregnancy group (p<0.05). The frequency of AA genotype of rs3802228 and TG genotype of rs104894072 was obviously higher in eclampsia group than that in pregnancy group (p<0.05).

Model Analysis of rs4543, rs3802228 and rs104894072 Loci in CYP11B2 Gene in Eclampsia Group and Pregnancy Group

As shown in Table III, the distribution of the loci rs104894072 (p=0.044) in dominant model and rs3802228 (p=0.002) in recessive model in eclampsia group was different from that in pregnancy group. Eclampsia group showed remarkably elevated frequency of TT + TG of the locus rs104894072 in dominant model and lowered frequency of AG + GG of the locus rs3802228 in recessive model (p<0.05).

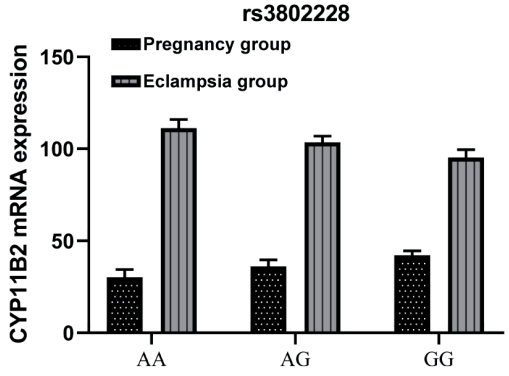

Figure 2. Association between CYP11B2 rs3802228 polymorphism and gene expression.

Haplotype Analysis of CYP11B2 rs4543, rs3802228 and rs104894072 in Eclampsia Group and Pregnancy Group

Based on haplotype analysis (Table IV) and linkage disequilibrium analysis (Table V), there was a statistically significant difference in the distribution of the haplotypes CGG (p=0.001) and TGT (p=0.048) in CYP11B2 gene between eclampsia group and pregnancy group (p<0.05). Meanwhile, the linkage disequilibrium of the loci rs3802228 and rs104894072 was relatively high (D'=0.382).

Correlations of the Polymorphisms of the Loci rs4543, rs3802228 and rs104894072 in CYP11B2 Gene with Gene Expression in Eclampsia Group and Pregnancy Group

The relationships of CYP11B2 rs4543, rs3802228, and rs104894072 polymorphisms with gene expression were shown in Figures 1-3. The results uncovered that the polymorphism of the locus rs104894072 in CYP11B2 gene was correlated with CYP11B2 gene expression (p<0.05). Moreover, the expression of CYP11B2 gene was markedly higher in patients with genotype GG in eclampsia group (p<0.05).

Relations of CYP11B2 rs4543, rs3802228 and rs104894072 Polymorphisms with Coagulation Function and Renal Function in Patients

The polymorphism of CYP11B2 rs4543 was notably associated with PT of patients in eclamp-

Table II. Distribution of genotypes of CYP11B2 rs4543, rs3802228 and rs104894072.

Locus	Genotype	Pregnancy group	Eclampsia group	χ^2	*p*
rs4543	CC	51 (0.255)	40 (0.200)	4.72	0.095
	CT	90 (0.450)	81 (0.405)		
	TT	59 (0.295)	79 (0.395)		
rs3802228	AA	35 (0.175)	85 (0.425)	58.46	0.000
	AG	135 (0.675)	59 (0.295)		
	GG	30 (0.150)	56 (0.280)		
rs104894072	TT	45 (0.225)	38 (0.190)	15.89	0.000
	TG	79 (0.395)	117 (0.585)		
	GG	76 (0.380)	45 (0.225)		

Table III. Model analysis of CYP11B2 rs4543, rs3802228, and rs104894072.

	Locus	Genotype	Pregnancy group	Eclampsia group	χ^2	*p*
Dominant model	rs4543	CC + CT	149 (0.705)	121 (0.605)	4.78	0.092
		TT	59 (0.295)	79 (0.395)		
	rs3802228	AA + AG	170 (0.850)	144 (0.720)	5.03	0.081
		GG	30 (0.150)	56 (0.280)		
	rs104894072	TT + TG	124 (0.620)	155 (0.775)	6.26	0.044
		GG	76 (0.380)	45 (0.225)		
Recessive model	rs4543	CC	51 (0.255)	40 (0.200)	1.45	0.484
		CT + TT	149 (0.745)	160 (0.800)		
	rs3802228	AA	35 (0.175)	85 (0.425)	12.41	0.002
		AG + GG	165 (0.825)	115 (0.575)		
	rs104894072	TT	45 (0.225)	38 (0.190)	1.36	0.507
		TG + GG	155 (0.775)	162 (0.810)		
Heterozygous model	rs4543	CC	51 (0.255)	40 (0.200)	2.81	0.245
		CT	90 (0.450)	81 (0.405)		
	rs3802228	AA	35 (0.175)	85 (0.425)	2.74	0.254
		AG	135 (0.675)	59 (0.295)		
	rs104894072	TT	45 (0.225)	38 (0.190)	3.3	0.192
		TG	79 (0.395)	117 (0.585)		
Homozygous model	rs4543	CC	51 (0.255)	40 (0.200)	2.3	0.317
		TT	59 (0.295)	79 (0.395)		
	rs3802228	AA	35 (0.175)	85 (0.425)	3.27	0.195
		GG	30 (0.150)	56 (0.280)		
	rs104894072	TT	45 (0.225)	38 (0.190)	3.72	0.156
		GG	76 (0.380)	45 (0.225)		

sia group (p=0.000). Furthermore, rs3802228 polymorphism was correlated with 24 h urine protein level (p=0.000) (Table VI).

Associations of CYP11B2 Gene Polymorphisms with Blood Pressure in Patients of Eclampsia Group

According to Figure 4, in eclampsia group, the proportion of patients with haplotype CGG was significantly larger among patients with systolic blood pressure of 140-160 mmHg (p<0.05). Similarly, the proportion of patients with haplotype TGT was evidently greater among patients with systolic blood pressure >180 mmHg (p<0.05).

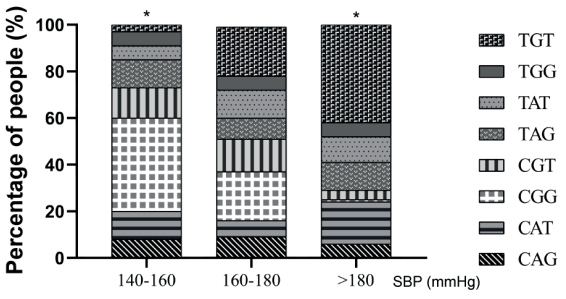

Figure 4. Correlations of CYP11B2 gene haplotypes with systolic blood pressure in patients of eclampsia group (*p<0.05).

Table IV. Haplotype analysis of CYP11B2 rs4543, rs3802228, and rs104894072.

Haplotype	Pregnancy group	Eclampsia group	OR	95% CI	χ^2	p
CAG	55.46 (0.139)	54.80 (0.137)	0.986	0.660-1.474	0.005	0.946
CAT	41.03 (0.103)	52.04 (0.130)	1.309	0.847-2.022	1.475	0.225
CGG	62.32 (0.156)	32.01 (0.080)	0.471	0.300-0.740	11.042	0.001
CGT	33.19 (0.083)	22.14 (0.055)	0.648	0.371-1.130	2.368	0.124
TAG	57.70 (0.144)	65.48 (0.164)	1.161	0.791-1.706	0.582	0.446
TAT	50.81 (0.127)	56.67 (0.142)	1.134	0.755-1.704	0.369	0.544
TGG	55.52 (0.139)	54.70 (0.137)	0.983	0.657-1.469	0.007	0.933
TGT	43.97 (0.110)	62.14 (0.155)	1.489	0.984-2.253	3.588	0.048

Table V. Linkage disequilibrium analysis of CYP11B2 rs4543, rs3802228 and rs104894072.

D′	rs4543	rs3802228	rs104894072
rs4543	-	0.004	0.019
rs3802228	0.004	-	0.382
rs104894072	0.019	0.382	-

Table VI. Relationships of CYP11B2 rs4543, rs3802228 and rs104894072 polymorphisms with coagulation function and renal function in patients.

		APTT (s)		PT (s)		Urine protein (g/24 h)	
Locus	Genotype	Eclampsia group	p	Eclampsia group	p	Eclampsia group	p
rs4543	CC	25.61±1.75	0.134	12.52±0.84	0.000	3.21±0.13	0.064
	CT	26.26±1.65		10.35±0.65		3.02±0.17	
	TT	25.35±1.21		12.11±0.92		2.98±0.35	
rs3802228	AA	25.85±1.74	0.175	11.95±0.75	0.243	3.15±0.23	0.000
	AG	25.13±1.14		12.04±0.83		2.54±0.09	
	GG	25.12±1.61		12.12±0.79		3.08±0.26	
rs104894072	TT	26.02±1.01	0.245	12.74±0.88	0.083	3.95±0.11	0.112
	TG	25.94±1.13		12.21±0.91		3.97±0.16	
	GG	25.74±1.36		11.87±0.94		4.01±0.24	

Discussion

Eclampsia is a disease that preeclampsia develops into a severe stage, which poses a great threat to the life of the mother and fetus. It is manifested as severe symptoms, such as headache, convulsion, vomiting, mydriasis and apnea[10,11]. Most eclampsia occurs during term delivery or within 2 d after delivery and can recover from self-limiting convulsions on their own within a short time[12]. It has been proved that the development of eclampsia is certainly related to genetics, including gene point mutation, frameshift mutation, deletion mutation and chromosomal variation[13]. Among them, gene polymorphisms have been observed to play an important role in the development and progression of eclampsia, including VEGF[14] and ACE[15]. Hence, exploration of the associations of gene polymorphisms with the susceptibility to and the progression of eclampsia is of great significance for illuminating the pathogenesis of the disease.

Cholesterol is catalyzed by a series of enzymes including CYP11A, 3β-HSD, CYP21 and CYP11B2 in the adrenal gland to produce aldosterone[16]. CYP11B2 gene encodes aldosterone synthase catalyzing deoxycorticosterone to produce aldosterone through a multi-step reaction, which is a crucial gene affecting aldosterone synthesis[17,18]. CYP11B2 gene, a core gene that impacts on aldosterone content, has been denoted to participate in the development of various diseases[19]. Moreover, diabetic nephropathy[20] and coronary heart disease[21] have been found correlated with CYP11B2 gene polymorphisms. These findings imply that CYP11B2 gene may be an important factor affecting the changes in blood pressure in the body. Mean-

while, the changes in its gene polymorphisms may alter the susceptibility to the disease. In this study, differences in the polymorphisms of CYP11B2 rs4543, rs3802228 and rs104894072 were detected between pregnancy group and eclampsia group. The results revealed that the distribution of alleles of CYP11B2 rs4543 in eclampsia group was significantly different from that in pregnancy group (p=0.027). The frequency of C allele was markedly lower in eclampsia group than that in pregnancy group (p<0.05). Besides, there was a difference in the distribution of genotypes of CYP11B2 rs3802228 (p=0.000) and rs104894072 (p=0.000) between eclampsia group and pregnancy group. The frequency of AA genotype of rs3802228 and TG genotype of rs104894072 was higher in eclampsia group than that in pregnancy group (p<0.05). The above results proved that the polymorphisms of the loci rs4543, rs3802228 and rs104894072 in CYP11B2 gene were able to affect the development of eclampsia, serving as important risk factors.

The influence of CYP11B2 gene on the development of eclampsia may not be caused by a single genotype. Therefore, conjoint analysis was conducted in this study. The results discovered that the distribution of the loci rs104894072 (p=0.044) in dominant model and rs3802228 (p=0.002) in recessive model in eclampsia group was different from that in pregnancy group. Eclampsia group had raised frequency of TT + TG of the locus rs104894072 in dominant model and lowered frequency of AG + GG of the locus rs3802228 in recessive model (p<0.05). In addition, the development of eclampsia may also be affected by the combination of multiple sites. Our results demonstrated that statistically significant difference was found in the distribution of the haplotypes CGG (p=0.001) and TGT (p=0.048) in CYP11B2 gene between eclampsia group and pregnancy group (p<0.05). Moreover, the linkage disequilibrium of the loci rs3802228 and rs104894072 was relatively high (D'=0.382). These results denoted that the probability of eclampsia was high in pregnant women carrying specific genotypes like TGT. In addition, eclampsia should be prevented in advance and paid close attention to in such pregnant women.

CYP11B2 gene polymorphisms may have an influence on the expression of CYP11B2, thus affecting the changes and phenotypes of downstream genes. The results of this study revealed that the polymorphism of the locus rs104894072 in CYP11B2 gene had an evident relation to CYP11B2 gene expression (p<0.05). The expression of CYP11B2 gene was markedly higher in patients with genotype GG in eclampsia group (p<0.05). This suggested that CYP11B2 gene polymorphism was capable of indeed affecting the expression of CYP11B2. However, whether CYP11B2 gene polymorphisms affected the expression of other genes related to aldosterone synthesis needed to be further analyzed.

In this study, the correlations of clinical information with CYP11B2 gene polymorphisms were finally analyzed. The results showed that the polymorphism of rs4543 locus in CYP11B2 gene was remarkably associated with the PT level of patients in eclampsia group (p=0.000). Meanwhile, rs3802228 polymorphism was correlated with 24 h urine protein level (p=0.000). In eclampsia group, the proportion of patients with CGG haplotype was significantly larger among patients with the systolic blood pressure of 140-160 mmHg (p<0.05). Besides, the proportion of patients with TGT haplotype was evidently greater among patients with systolic blood pressure >180 mmHg (p<0.05).

Conclusions

In summary, CYP11B2 gene polymorphisms are correlated with many clinical indicators in patients with eclampsia, which can be used as one of the vital indicators to determine the development of eclampsia.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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