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# Relationship between onset of eclampsia and AGTR1 gene polymorphisms

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**Abstract. – OBJECTIVE: We aimed to study the correlations of angiotensin II receptor type 1 (AGTR1) gene polymorphisms with the occurrence and development of eclampsia.**

**PATIENTS AND METHODS: A total of 200 pregnant women with eclampsia admitted to our hospital from January 1, 2017 to September 30, 2019 were collected as observation group and 200 normal pregnant women during the same period were recruited in the control group. Genome sequencing was performed to detect the AGTR1 gene polymorphisms in the two groups. Expression level of AGTR1 in both groups was detected. The influences of AGTR1 on clinical data of pregnant women with eclampsia were analyzed.**

**RESULTS: There were no significant differences in age ($p$=0.545), height ($p$=0.738), weight ($p$=0.695) and hypertension ($p$=0.372) between observation group and control group. However, significant differences were found in the distributions of alleles at AGTR1 rs1799870 ($p$=0.002) and AGTR1 rs52936049 ($p$=0.047) between groups. The frequencies of T allele at rs1799870 and rs52936044 in observation group were higher than those in the control group. In addition, the distributions of AGTR1 gene genotypes at rs1799870 ($p$=0.012), rs144520513 ($p$=0.008) and rs529360494 (p $p$ =0.036) in observation group differed from those in control group. Observation group had higher frequencies of TT genotype at rs1799870, GG genotype at rs144520513 and TG genotype at rs529360494 than those in control group. Besides, the frequency of CGG haplotype ($p$=0.008) of AGTR1 gene in observation group was notably lower than that in the control group, while the frequency of TGT haplotype ($p$=0.012) of AGTR1 gene in the former was remarkably higher than that in the latter. Moreover, the linkage disequilibrium between rs529360494 and rs144520513 of AGTR1 gene was relatively high (D'=0.623). AGTR1 gene polymorphism rs529360494 showed an evident relationship with the expression of AGTR1 gene, and the expression of AGTR1 in pregnant women with eclampsia who carried TG genotype was markedly reduced ($p$<0.05). Furthermore, AGTR1 gene polymorphism rs1799870 was associated with prothrombin time (PT) in pregnant women with eclampsia ($p$=0.046), and PT in those carrying genotype TC was shorter. Rs144520513 was related to the levels of triglyceride (TG) ($p$<0.001) and low-density lipoprotein (LDL) ($p$<0.001) in pregnant women with eclampsia, and TG and LDL levels were significantly lower.**

**CONCLUSIONS: AGTR1 gene polymorphisms are closely associated with the onset and progression of eclampsia.**

*Key Words:*
AGTR1, Eclampsia, Gene polymorphism.

## Introduction

Gestational hypertension is a disease affecting the health of pregnant women and fetuses, and eclampsia caused by this disease is also a vital cause of death of pregnant women[1,2]. In Western countries, pre-eclampsia and eclampsia-induced deaths of pregnant women represented the 10-20% of the total. Eclampsia greatly threatens the life of both mothers and fetuses[3]. Eclampsia may result from the family history of hypertension, changes in psychological state during pregnancy, imbalance of nutritional structure, etc., but its specific cause remains unclear[4]. The pathogenesis of the disease may be related to the abnormal expressions and secretion of vasodilator/contractive vasoactive substances *in vivo* caused by the special physiological state, hormone level, immune environment, and gene expression after pregnancy. Eventually, the continuous increase in blood pressure, dysfunction of multiple organs and the

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nerve system lead to symptoms of eclampsia[5]. During the occurrence and development of eclampsia, the renin-angiotensin system may exert greater impacts because it can regulate blood pressure and the balance between water and electrolyte[6]. Angiotensin II type I receptor (AGTR1) has been proven to play an important role in the blood pressure regulation system of the body. Some gene polymorphisms can affect the susceptibilities of arterial hypertension[7], lung cancer[8] and chronic obstructive pulmonary disease[9], indicating that gene polymorphisms may influence the onset of diseases. In this study, therefore, we explored the influences of AGTR1 gene polymorphisms rs1799870, rs144520513 and rs529360494 on the onset of eclampsia. In the meantime, in-depth polymorphism analysis and relevant clinical data were adopted to find out the internal relationship between AGTR1 gene and eclampsia.

## Patients and Methods

### General Data

A total of 200 pregnant women with eclampsia admitted to our hospital from January 1, 2017 to September 30, 2019 were collected as observation group and 200 normal pregnant women during the same period were recruited in control group. According to International Guidelines[10], inclusion criteria for pregnant women in observation group: 1) pregnant women aging 23-38 years with a history of hypertension or eclampsia family history; 2) pregnant women with systolic pressure ≥160 mmHg or diastolic pressure ≥110 mmHg; 3) pregnant women with urine protein ≥5 g/24 h and oliguria; 4) pregnant women with pulmonary edema, thrombocytopenia, and 5) pregnant women with neuropsychiatric symptoms and brain or visual disorders. In addition, pregnant women with serious diseases, such as coronary heart disease and acute hepatic and renal dysfunction, were excluded. No statistically significant differences in general data were found between observation group and control group. All subjects signed the informed consent. This study was approved by the Ethics Committee of People's Hospital of Dongying District.

### Sample Collection and Pretreatment

Peripheral blood samples were collected from observation group and control group using anticoagulant tubes, with 3-5 mL per tube. After vital signs of pregnant women in observation group were stable following rescue treatment on eclampsia onset, the elbow vein blood was collected. Then, the collected peripheral blood samples were centrifuged at 300 rpm for 5 min and temporarily stored in a refrigerator at 4°C. After that, deoxyribonucleic acids (DNAs) were extracted within 7 days.

### DNA Extraction

Peripheral blood genomic DNA extraction kit (Invitrogen, Carlsbad, CA, USA) was applied to extract genomic DNAs in peripheral blood samples collected in observation group and control group. Afterwards, 200 μL of samples in the intermediate nucleated cell layer of peripheral blood centrifuged at 3000 rpm were taken. 20 μL of proteinase K (20 mg/mL) was mixed well in a vortex. Then, 200 μL of buffer solution was added. After fully mixing upside down, it was let stand at 65°C for 15 min. Subsequently, 400 μL of absolute ethyl alcohol was added, shaken and mixed for 30 s, after which flocculent precipitates were poured into an adsorption column, centrifuged at 12000 rpm/min for 30 s. Then, liquid waste was discarded, and the adsorption column was put back into the collection tube. Next, 500 μL of deproteinized liquid was added and centrifuged, followed by rinsing twice with 700 μL of rinsing solution and centrifugation. Ultimately, preheated elution buffer was added to the adsorption column, placed for 2 min and centrifuged, and the obtained solution was genomic DNAs.

### Polymerase Chain Reaction (PCR) Amplification and Gene Polymorphism Analysis

Primers of AGTR1 gene polymorphic loci rs1799870, rs144520513 and rs529360494 were designed and amplified *via* PCR. Next, Primer Premier 5.0 was utilized to design primers, which were shown as follows: rs1799870 polymorphic region: forward: (5'→3')'ATTTAGCACTGGCTGACTTATGC' and reverse (5'→3')'CAGCGGTATTCCATACTGTG', rs144520513 polymorphic region: forward: (5'→3')'GCCCTTTGGCAATTACCTATGT' and reverse: (5'→3')'CGTGAGTAGAAACACACTAGCGT', rs529360494 polymorphic region: forward: (5'→3')'GGCTATTGTTCACCCAATGAAGT' and reverse: (5'→3')'TGGGACTCAAAGCAC'. Finally, the mixture was denatured, annealed and extended to obtain the product, and PCR products were sent to Shanghai Biological Co., Ltd. (Shanghai, China) for sequencing and analysis of polymorphism.

### AGTR1 Gene Detection

Reverse Transcription-quantitative Polymerase Chain Reaction (RT-qPCR) assay was carried out to detect AGTR1 gene. TRIzol method (Invitrogen, Carlsbad, CA, USA) was adopted for the extraction of total RNA from nucleated cells in peripheral blood according to conventional operation procedures. Next, cDNAs were obtained after RT and detected by Real-Time fluorescence qPCR. PCR conditions: 95°C for 5 min, (96°C for 35 s, 56°C for 45 s and 72°C for 40 s) × 40 cycles and 72°C for 5 min. Primers of AGTR1 gene: forward: (5'→3')'TGAGCGAGTTCGACTCCTTG' and reverse: (5'→3')'GTGGGTCGGACTTGGAAAACA'. Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) was used as the internal reference in the quantitative analysis of AGTR1 expression. GAPDH: (5'→3')'CGCTCTCTGCTCCTCCTGTTC' and reverse: (5'→3')' ATCCGTTGACTCCGACCTTCAC'.

### Analysis of Related Clinical Indexes

Clinical indexes of pregnant women with eclampsia in observation group were analyzed in the Clinical Laboratory of our hospital, during which all instruments were used after routine daily quality control. Prothrombin time (PT) and activated thromboplastin time (APTT) were analyzed using an automatic coagulation analyzer, while triglyceride (TG) and low-density lipoprotein (LDL) were examined *via* an automatic biochemical analyzer.

### Statistical Analysis

Statistical Product and Service Solutions (SPSS) 22.0 (IBM Corp., Armonk, NY, USA) was employed for statistical analysis. Measurement data were compared *via* the *t*-test, and chi-square test was performed for count data comparison. Besides, online polymorphism analysis was carried out using SHEsis website (http://analysis.bio-x.cn/myAnalysis.php). $p<0.05$ represented that the difference was statistically significant.

## Results

### General Data of Research Objects

The general data of the research objects were shown in Table I. There were no significant differences in age ($p=0.545$), height ($p=0.738$), weight ($p=0.695$) and the number of hypertension cases ($p=0.372$) between observation group and control group.

### Distributions of Polymorphic Alleles and Genotypes at rs1799870, rs144520513, and rs529360494 of AGTR1 Gene

The distributions of polymorphic alleles at rs1799870, rs144520513 and rs529360494 of AGTR1 gene were shown in Table II, and those of genotypes were displayed in Table III. Significant differences were found in the distributions of alleles at rs1799870 ($p=0.002$) and rs52936049 ($p=0.047$) of AGTR1 gene between observation group and control group. The frequencies of T allele

**Table I.** General data of pregnant women in control group and observation group (x±s).

| Group | No. | Age (years old) | Height (cm) | Weight (kg) | History of hypertension (n) |
|---|---|---|---|---|---|
| Control group | 200 | 29.87±3.14 | 167.12±20.24 | 58.27±3.15 | 23 |
| Observation group | 200 | 30.24±4.12 | 169.24±16.27 | 60.16±2.84 | 35 |
| $t/\chi^2$ | | 0.382 | 0.103 | 0.273 | 1.241 |
| *p* | | 0.545 | 0.738 | 0.695 | 0.372 |

**Table II.** Allele analysis at rs1799870, rs144520513 and rs529360494 of AGTR1 gene.

| Locus | Allele | Control group | Observation group | Odds ratio (OR) | 95% confidence interval (CI) | $\chi^2$ | *p* |
|---|---|---|---|---|---|---|---|
| rs1799870 | C | 199 (0.497) | 156 (0.390) | 0.64 | 0.48-0.85 | 9.36 | 0.002 |
| | T | 201 (0.502) | 244 (0.610) | | | | |
| rs144520513 | G | 193 (0.482) | 194 (0.485) | 0.99 | 0.75-1.30 | 0.005 | 0.943 |
| | A | 207 (0.517) | 206 (0.515) | | | | |
| rs529360494 | T | 182 (0.455) | 210 (0.525) | 0.75 | 0.57-0.99 | 3.92 | 0.047 |
| | G | 218 (0.545) | 190 (0.475) | | | | |

**Table III.** Genotype analysis at rs1799870, rs144520513 and rs529360494 of AGTR1 gene.

| Locus | Genotype | Control group | Observation group | $\chi^2$ | *p* |
|---|---|---|---|---|---|
| rs1799870 | TT | 55 (0.275) | 83 (0.415) | 9.11 | 0.012 |
| | TC | 91 (0.455) | 78 (0.390) | | |
| | CC | 54 (0.270) | 39 (0.195) | | |
| rs144520513 | GG | 39 (0.195) | 55 (0.275) | 9.65 | 0.008 |
| | GA | 115 (0.575) | 84 (0.420) | | |
| | AA | 46 (0.230) | 61 (0.305) | | |
| rs529360494 | TT | 41 (0.205) | 47 (0.235) | 6.63 | 0.036 |
| | TG | 100 (0.500) | 116 (0.580) | | |
| | GG | 59 (0.295) | 37 (0.185) | | |

**Table IV.** Haplotype analysis of AGTR1 gene.

| Haplotype | Control group | Observation group | OR | 95% CI | $\chi^2$ | *p* |
|---|---|---|---|---|---|---|
| CAG | 53.10 (0.133) | 39.04 (0.098) | 0.707 | 0.456-1.096 | 2.425 | 0.119 |
| CAT | 44.93 (0.112) | 43.20 (0.108) | 0.957 | 0.615-1.490 | 0.038 | 0.846 |
| CGG | 56.37 (0.141) | 32.91 (0.082) | 0.547 | 0.347-0.861 | 6.938 | 0.008 |
| CGT | 44.60 (0.112) | 40.84 (0.102) | 0.906 | 0.578-1.420 | 0.185 | 0.667 |
| TAG | 59.20 (0.148) | 65.09 (0.163) | 1.119 | 0.763-1.641 | 0.331 | 0.565 |
| TAT | 49.78 (0.124) | 58.67 (0.147) | 1.209 | 0.806-1.815 | 0.843 | 0.358 |
| TGG | 49.33 (0.123) | 52.96 (0.132) | 1.085 | 0.716-1.643 | 0.147 | 0.701 |
| TGT | 42.69 (0.107) | 67.28 (0.168) | 1.692 | 1.121-2.554 | 6.374 | 0.012 |

at rs1799870 and rs52936044 in observation group were higher than those in the control group. In addition, the distributions of AGTR1 gene genotypes at rs1799870 ($p$=0.012), rs144520513 ($p$=0.008) and rs529360494 ($p$=0.036) in observation group differed from those in control group. Observation group had higher frequencies of TT genotype at rs1799870, GG genotype at rs144520513 and TG genotype at rs529360494 than control group.

### Analyses of Haplotypes and Linkage Disequilibrium of AGTR1 Gene

The analysis results of haplotypes and linkage disequilibrium of AGTR1 gene were shown in Table IV and V, respectively. It was discovered that the frequency of CGG haplotype ($p$=0.008) of AGTR1 gene in observation group was notably lower than that in control group, while the frequency of TGT haplotype ($p$=0.012) of AGTR1 gene in the former was remarkably higher than that in the latter. Moreover, the linkage disequilibrium between rs529360494 and rs144520513 of AGTR1 gene was relatively high (D'=0.623).

### Relationship Between AGTR1 Gene Polymorphisms and Gene Expressions

The relationship between AGTR1 gene polymorphisms and gene expressions was displayed in Figure 1. AGTR1 gene polymorphism rs529360494 showed an evident relationship with the expression of AGTR1 gene, and the expression of AGTR1 gene in pregnant women with eclampsia carrying TG genotype was markedly reduced ($p$<0.05).

### Association Between AGTR1 Gene Polymorphisms and Clinical Indexes of Eclampsia

AGTR1 gene polymorphisms were demonstrated to be associated with clinical indexes of coagulation and lipid metabolism in pregnant women with eclampsia (Table VI). AGTR1 gene

**Table V.** Linkage disequilibrium analysis at each locus of AGTR1 gene.

| D' | rs1799870 | rs144520513 | rs529360494 |
|---|---|---|---|
| rs1799870 | - | 0.024 | 0.005 |
| rs144520513 | 0.024 | - | 0.632 |
| rs529360494 | 0.005 | 0.632 | - |

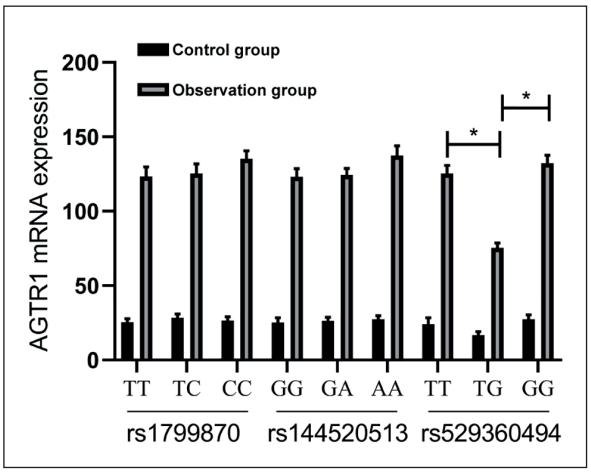


**Figure 1.** Relationship between AGTR1 gene polymorphisms and gene expressions (*$p$<0.05, $t$-test).

polymorphism rs1799870 was correlated with PT in pregnant women with eclampsia ($p$=0.046), and PT in those carrying genotype TC was shorter. Besides, rs144520513 was related to the levels of TG ($p$<0.001) and LDL ($p$<0.001) in pregnant women with eclampsia, and TG and LDL levels in those carrying GG genotype were significantly lower.

## Discussion

Eclampsia, a result of severe hypertension during pregnancy, greatly jeopardizes the nervous system and multiple organ functions of the whole body of pregnant women, and also threatens the life of the fetuses[11]. With the incidence rate of about 7% and a higher death rate, eclampsia has been highlighted in maternal and child health care[12]. Its promoting factors include multiple pregnancy, family history of related diseases and immune diseases (antiphospholipid antibody syndrome)[13]. Due to the close correlation with hypertension, the special hypercoagulable state of blood and physiological increased blood volume in pregnant women, eclampsia is dramatically affected by the regulation system of body blood pressure, and blood viscosity[14].

Genetic abnormality in the renin-angiotensin system exerts a relatively enormous impact on the systemic vascular system, so it may be a genetic predisposing factor for eclampsia[15]. AGTR1 gene, located at 3q21-25, has been observed to strongly influence the vasoconstriction function in the body and is a vital substance for modulating blood pressure[16]. This gene can facilitate lymph node invasion and metastasis of breast cancer by upregulating CXCR4/SDF-1α, and it is related to vascular system activity[17]. AGTR1 gene can also affect the progression of epithelial ovarian cancer[17]. In the meantime, it has been reported that AGTR1 gene polymorphisms are related to the susceptibility of hypertension, which are predisposing factors for hypertension[18]. Besides, they are also able to affect the formation of alcoholic fatty liver[19]. The above findings indicate that AGTR1 gene polymorphisms may be related to disease susceptibility and pathogenesis by regulating expressions of relevant vasoconstrictor active substances. In this research, significant differences were discovered in the distribution of alleles at rs1799870 ($p$=0.002) and rs52936049 ($p$=0.047) of AGTR1 gene between the observation group and control group. The frequencies of T allele at rs1799870 and rs52936044 in the observation group were higher than those in the control group. In addition, the distributions of AGTR1 gene genotypes at rs1799870 ($p$=0.012),

**Table VI.** Associations ofAGTR1 gene polymorphisms with indexes of coagulation and lipid metabolism in eclampsia patients.

| | Genotype | PT (s) | | APTT (s) | | TG (mmol/L) | | LDL (mmol/L) | |
|---|---|---|---|---|---|---|---|---|---|
| | | Observation group | $p$ | Observation group | $p$ | Observation group | $p$ | Observation group | $p$ |
| rs1799870 | TT | 11.23±0.73 | 0.046 | 26.64±2.14 | 0.423 | 3.23±1.01 | 0.421 | 3.24±0.64 | 0.174 |
| | TC | 10.21±0.64 | | 27.02±3.12 | | 3.53±0.74 | | 3.25±1.02 | |
| | CC | 11.27±0.32 | | 26.93±3.12 | | 3.11±0.97 | | 3.64±0.85 | |
| rs144520513 | GG | 10.26±0.55 | 0.164 | 26.84±2.18 | 0.221 | 2.22±0.13 | <0.001 | 1.74±0.21 | <0.001 |
| | GA | 10.47±0.27 | | 27.18±3.01 | | 3.25±0.42 | | 3.54±0.65 | |
| | AA | 10.73±0.64 | | 27.05±2.94 | | 3.64±0.74 | | 4.22±1.05 | |
| rs529360494 | TT | 10.11±0.14 | 0.201 | 27.21±3.22 | 0.174 | 3.23±0.94 | 0.265 | 3.74±0.35 | 0.154 |
| | TG | 10.29±0.23 | | 27.87±2.34 | | 3.75±0.82 | | 3.43±0.76 | |
| | GG | 10.24±0.41 | | 27.34±2.32 | | 3.44±0.53 | | 3.34±0.62 | |

rs144520513 ($p$=0.008) and rs529360494 ($p$=0.036) in observation group differed from those in control group. Observation group had higher frequencies of TT genotype at rs1799870, GG genotype at rs144520513 and TG genotype at rs529360494 than those in control group. The above results verified the importance of AGTR1 gene polymorphisms rs1799870, rs144520513 and rs529360494 in the pathogenesis of eclampsia, suggesting that the gene polymorphisms are one of the predisposing factors for eclampsia. Alleles with higher frequencies, such as T allele at rs1799870 and rs529360494, represented the risk of eclampsia. Meanwhile, the risk of eclampsia in pregnant women carrying specific genotypes, such as TT genotype at rs1799870, GG genotype at rs144520513 and TG genotype at rs529360494, was remarkably higher than those carrying other genotypes. Hence, blood pressure and specific genotypes at these loci should be continuously monitored during pregnancy. Prevention of preeclampsia and eclampsia is of great significance to raise the survival rate of the mother and the fetus.

Haplotype analysis was carried out based on the genetic linkage of each polymorphic locus of genes. It was found that the frequency of CGG haplotype ($p$=0.008) of AGTR1 gene in observation group was notably lower than that in control group, while the frequency of TGT haplotype ($p$=0.012) of AGTR1 gene in the former was remarkably higher than that in the latter. Moreover, the linkage disequilibrium between rs529360494 and rs144520513 of AGTR1 gene was relatively high (D'=0.623). The above results illustrated that the loci of AGTR1 gene may have high linkage in the genetic process, which can affect the occurrence of eclampsia. In addition, pregnant women carrying CGG haplotype of AGTR1 gene had a lower incidence rate of eclampsia than normal pregnant women, while pregnant women with TGT haplotype exhibited the opposite result.

At last, AGTR1 gene polymorphism rs1799870 was demonstrated to be correlated with PT in pregnant women with eclampsia ($p$=0.046), and PT in those carrying genotype TC was shorter. Besides, rs144520513 was related to the levels of TG ($p$<0.001) and LDL ($p$<0.001) in pregnant women with eclampsia, and TG and LDL levels in those carrying GG genotype were significantly lower. It is suggested that AGTR1 gene polymorphisms are able to affect coagulation function and lipid metabolism in eclampsia pregnancies and may be crucial factors influencing disease progression.

## Conclusions

In summary, these results proved that AGTR1 gene polymorphisms are closely associated with the onset and progression of eclampsia.

### Conflict of Interests

The authors declare that they have no conflict of interests.

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