

Original Article

Angiotensin receptor type 1 polymorphism A1166C is associated with left ventricular remodeling in severe preeclampsia patients and their fetuses

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Abstract: Objective: To study the correlation of the AT1R gene A1166C polymorphism and left ventricular remodeling in severe preeclampsia patients and their fetuses. Methods: We collected blood from case and control groups and genotyped the samples with the PCR-RFLP technique. We measured the interventricular septum thickness (IVST) in the end diastolic period and posterior wall thickness (PWT), relative wall thickness (RWT) and left ventricular mass index (LVMI) using ultrasound. Results: The frequencies of the AT1R gene 1166 site variant (genotypes AC and CC) and C allele in the case group for both mothers and fetuses were higher than in the control group. The IVST and PWT of mothers and fetuses and LVMI and RWT of mothers in the case group were higher than in the control group. The LVMI and RWT of mothers and IVST and RWT of fetuses with the AC or CC genotype were higher than those with the AA genotype in the case group. Conclusions: There is an association between the AT1R gene 1166 site variation and severe preeclampsia in both mothers and their fetuses. The C allele may be a predisposing factor. Remodeling of the left ventricle of severe preeclampsia has a close correlation with the AT1R gene A1166 C variation.

Keywords: Angiotensin II type 1 receptor (AT1R), gene polymorphism, A1166C, preeclampsia, ventricular remodeling

Introduction

Preeclampsia is a potentially serious condition of pregnancy that occurs in nearly 10% of pregnancies in China [1]. It has a severe morbidity and mortality risk for both the mother and fetus. The etiology of the disease is not completely understood, but it has a genetic correlation. Preeclampsia belongs to a monogenic group of inherited diseases that occur in the gestational period. Target organs that are damaged, include the heart, brain, liver, kidney and placenta. Preeclampsia heart disease accounts for up to 5% of the total heart diseases during pregnancy; it has a morbidity of 0.34% and is the second leading cause of maternal death [2]. Its syndrome is characterized by myocardial damage, in which both cardiac function and cardiac muscles are damaged. Clinically, left heart failure and pulmonary edema are found; however, their diagnoses are easily delayed because they are hazardous and insidious.

Therefore, the study of hereditary factors is a focal point in the field of obstetrics [3-5].

Substantial research has shown a genetic association with multifactorial polygenic inheritance in the development of preeclampsia [6-8]. Some reports indicate that the risk of suffering from the disease is increased during pregnancy if the father or mother has hypertension (relative risks of 4.34 and 2.33, respectively) [9]. According to reports on the inheritance of preeclampsia, the probability is higher from a preeclamptic mother than from a normal pregnant woman [10]. Several studies have tried to demonstrate or refute the role of the renin-angiotensin system (RAS) genes as candidates for developing preeclampsia [11-14]. The circulating RAS is an important pathway that regulates blood pressure, and angiotensin II (Ang II) is the most important. Ang II acts on the angiotensin receptor (ATR), which plays an important role in regulating the electrical stabil-

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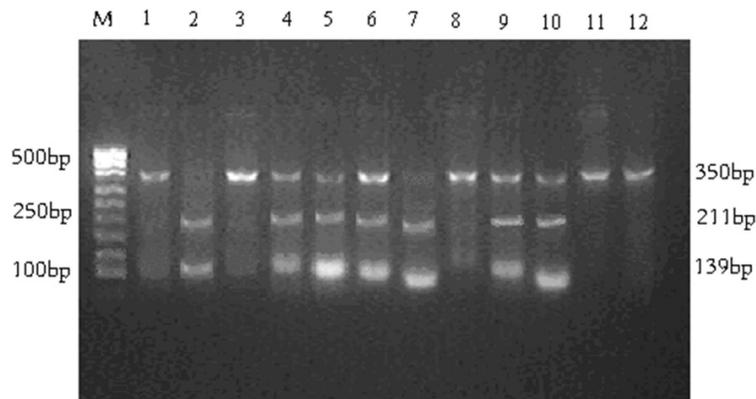


Figure 1. The Electrophoretogram of AT1R gene 1166 situs polymorphism subtypes. M: Marker; 1, 3, 8, 11, 12. AA: homozygote wild type. 2, 7: CC: homozygote variation typ; e 4, 5, 6, 9, 10: AC: heterozygote variation type.

ity of the atrium [15]. The ATR type 1 (AT1R) gene is mapped to 3q21-25 and is approximately 2.2 kb in length with an exon and no intron [16]. The SNPs of the AT1R gene include A1166C, A1166G, T537C, G1517T and A1878G. Of these SNPs, A1166C is closely associated with some diseases including hypertension [17]. It was reported that variations in the nucleotides in the AT1R gene A1166 site are significantly correlated with preeclampsia [13]. The frequency of polymorphism variation at the AT1R gene A1166 site and the frequency of allele C are significantly increased in preeclamptic patients. The frequencies of genotypes AC and CC are apparently higher than in a normal pregnancy group, indicating that the polymorphism of the AT1R gene A1166C site plays an important role in preeclampsia. Furthermore, the variation in the AT1R gene A1166C increases risk factor in those suffering from preeclampsia [12, 14].

Several studies indicate that the polymorphic A1166C site of AT1R may result in an increase in the AT1R density, leading to an increased risk of cardiovascular disease [18-19]. Cardiac muscle pachynsis and remodeling might occur when there is AT1R over-expression. Some researchers believe that the A1166C polymorphism might play a role in the formation of left ventricular hypertrophy in hypertension [20-21]. Patients suffering from hypertension, especially those who carry the C allele are more likely to have left chamber remodeling [21]. In recent years, studies indicate that left ventricular pachynsis in preeclampsia has familial ten-

dencies [22]. Therefore, hereditary factors may play a central role in left chamber remodeling in preeclampsia patients. However, many questions remain unanswered, i.e., whether the AT1R gene polymorphism is found in the fetus and, if present, whether it affects the fetus' heart and what, if any, is the relative effect on the mother and her fetus. The purpose of our study was to investigate any possible relationship between the AT1R gene A1166C polymorphism and the variation in the heart structure and

function in patients and their fetuses. In other words, the aim was to better understand the etiopathogenesis of preeclampsia heart disease.

Materials and methods

Patients

A total of 2228 unrelated, young pregnant women (150 preeclamptic participants and 2,078 healthy pregnant controls) were recruited from the Department of Obstetrics in the 1st Affiliated Hospital of Xinjiang Medical University at the time of delivery. A prospective case-control study was conducted on 60 women, including a case group (n=30) and control group (n=30). The average age and pregnancy period of the case group were 28 ± 4 years and 36 ± 3 weeks, respectively. A case was defined as a severe preeclampsia according to *Williams Obstetrics*. The average age and pregnancy period of the control group were 29 ± 5 years and 38 ± 2 weeks, respectively.

Written informed consent was obtained from all participants recruited for the study. The study was conducted in accordance with the guidelines of the Helsinki Declaration. An approval of the Ethics Committee of the First Affiliated Hospital of Xinjiang Medical University was obtained prior to the study.

Sample collection and PCR-RFLP

Five milliliter (5 ml) of peripheral venous blood from all the patients, as well as the umbilical

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Table 1. Comparison of AT1R genotype and allele frequency between the two groups of pregnant women

Group	Genotype frequency		Allele frequency	
	AA cases (n, %)	AC+CC cases (n, %)	A (%)	C (%)
Case group	19 (63.3)	11 (36.7)	80	20
Control group	27 (90.0)	3 (10.0)	95	5
χ^2	4.565		4.876	
<i>P</i>	0.033		0.027	

Note: AA-homozygote wild type; AC-heterozygote variation type; CC-homozygote variation type.

Table 2. A comparison of the AT1R genotype and allele frequency between two groups of fetuses

Group	Genotype frequency		Gene frequency	
	AA cases (n, %)	AC+CC cases (n, %)	A (%)	C (%)
Case group	22 (73.33)	8 (26.67)	83.33	16.67
Control group	28 (93.33)	2 (6.67)	96.67	3.33
χ^2	4.32		9.88	
<i>P</i>	0.0378		0.002	

Note: AA-homozygote wild type; AC-heterozygote variation type; CC-homozygote variation type.

artery of fetuses, was collected in an ethylene diamine-tetra acetic acid (EDTA) vial after 12 hours of fasting. Samples were immediately stored at -70°C for DNA extraction.

Genomic DNA was extracted using the DNA blood mini-kit (Baitaite Biotechnology LTD. Company, China) according to the manufacturer's instructions. AT1R gene was amplified by polymerase chain reaction (PCR) using the following primer pair, forward: 5'ATA ATG TAA GCT CATCCA CC-3', and reverse: 5'GAG ATT GCA TTT CTGTCA GT-3', which were synthesized by the Shanghai Shengggong Biotechnology Company. The total volume of the reaction was 30 μL , including 2.0 μL of DNA template, 15 μL of PCR Master, 1.5 μL of primer (each kind of primer), 1.0 μL of MgCl_2 and 9 μL of normal saline. The PCR conditions were as follows: the initial denaturation was performed for 5 min at 95°C , which was followed by 35 cycles of denaturation for 30 seconds at 94°C , annealing for 30 seconds at 72°C , and a final extension at 72°C for 5 minutes. The total system contained 30 μL and 35 cycles. For restrictive enzymolysis methodology, the final volume of each sample tube was a 15 μL mixture containing 6 μL of PCR amplification product, 5 units of Ddel endoenzyme, 1.5 μL of 10-time Buffer fluid, 0.1 mL of 1% BSA and 6.9 μL of ddH_2O .

The restriction was enzymatically performed for 4 hours at 37°C . For electrophoresis typing, the restricted product was mixed with 3 μL of bromophenol blue. Visualization of the products was performed using a 2.5% agarose gel with 0.5 $\mu\text{g}/\text{ml}$ ethidium bromide staining and in the 1-time TBE fluid in which the level of hydrogen ion exponent was at 8.0 in a common temperature. Gel images were observed using a UV-image analyzer. The genotyping results were confirmed by a secondary observer. Any sample in which a genotype could not be accurately called was discarded from the analysis.

Echocardiography

Echocardiography was performed with the subjects lying in the dorsal decubitus position, using a portable color ultrasound machine (USA, Philips SONOS 5500) and a 2.0 to 4.0 MHz multiphase-array probe by two experienced cardiologists blinded to all clinical details of the subjects. Echocardiograph measurements of the interventricular septal thickness were performed at the end diastole. Records were made of the: (IVSTd), posterior wall thickness (PWTd); left ventricular end-diastolic diameters (LVEDd); and end systolic period diameter (LVSD).

The LV mass (LVM) was calculated using the regression equation described by Devereux and Reichek [23]: $\text{LVM}=1.04 [(\text{LVEDd}+\text{PWTd}+\text{IVSTd})^3-\text{LVEDd}^3]-13.6$. The left chamber cardiac muscle weight index (LVMI) was calculated with the equation: $\text{LVMI}=\text{LVM}/\text{surface area}$, and the relative locular wall thickness (RWT) was calculated by the equation $\text{RWT}=(\text{IVSTd}+\text{PWTd})/\text{LVIDd}$. At least three cardiac cycles were performed every time and the indexes were averaged. The same methods were performed on the mothers and fetuses. The LVMI of the fetuses could not be detected.

Statistical analyses

For each polymorphism, Hardy-Weinberg equilibrium (HWE) was calculated using an online calculator (<http://www.had2know.com/academics/hardy-weinbergequilibrium-calculator>

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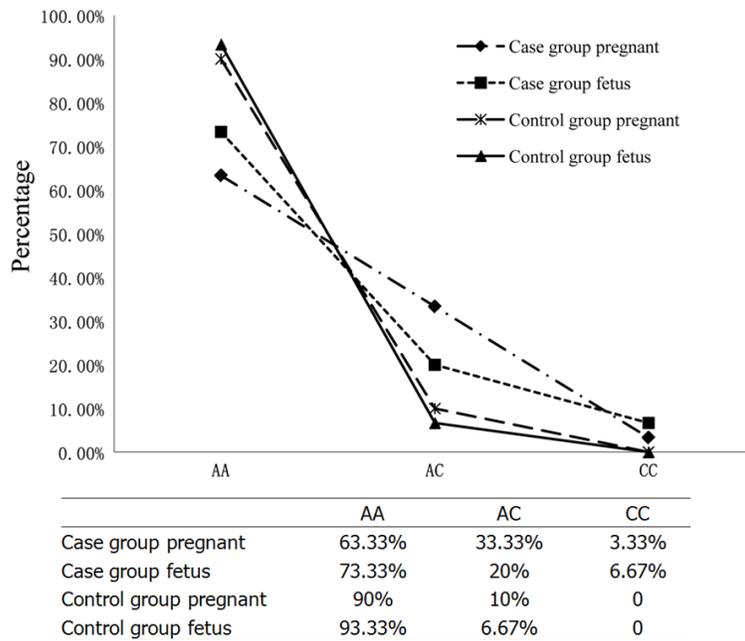


Figure 2. A comparison of the AT1R genotype frequency between pregnant women and their fetuses. AA-homozygote wild type; AC-heterozygote variation type; CC-homozygote variation type.

Table 3. Comparison of left ventricle structure indexes in two groups of pregnant women ($\bar{x} \pm s$)

Index	Case group	Control group	t	P
IVST (cm)	1.08±0.15	0.84±0.13	6.53	0.0001
LVDD (cm)	4.93±0.63	4.50±0.38	3.22	0.0023
LVSD (cm)	3.66±1.01	2.9±0.34	3.89	0.0004
PWT (cm)	1.28± 0.17	1.17±0.14	2.72	0.0086
RWT	0.45±0.01	0.37±0.04	10.50	0.0001
LVM (g)	212.15±20.41	169.49±17.31	8.73	0.0001
LVMI (g/m ²)	116.4±12.96	92.41±12.05	7.43	0.0001

Note: IVST: interventricular septal thickness, LVDD: left ventricular end diastolic period diameter, LVSD: end systolic period diameter, PWT: post wall thickness, RWT: relative wall thickness, LVM: left ventricular mass, LVMI: left ventricular mass index.

2-alleles. html). The measurement data are presented as the mean and the enumeration data are presented as the frequency. Statistical analyses were performed using SPSS software (version 23.0; IBM). The methods used are as follows: general statistical description; goodness of fit chi-square test comparing AT1R genotype and distribution of alleles between two groups; fourfold table chi-square test when it conformed to the Hardy-Weinberg genetic equilibrium law; t test between two groups that compared ventricular sinister structure index; and t test between two independent samples when analyzing the difference of indexes be-

tween two genotypes with AC and CC as a single genotype. $P < 0.05$ indicates that the difference is statistically significant.

Results

The clinical features of the patients

The age and week of pregnancy between the two groups were not significantly different ($P > 0.05$, data not shown).

The AT1R genotype and allele distribution in patients

The product after PCR amplification was a 350-bp fragment. If the fragment had a 1166 polymorphic site substitution with site C instead of site A, it could produce two fragments after cutting with a restriction enzyme, one is 139 bp and the other is 211 bp. If there is no such substitution, the generation of two fragments would not occur. Therefore, three genotypes may be produced (Figure 1). They are Type AA (homozygote wild type) with a 350-bp band, type AC (heterozygote variation type) with three bands (350 bp, 211 bp and 139 bp) and type CC (homozygote variation type) with two bands (211 bp and 139 bp).

The AT1R genotype and allele distribution fit the Hardy-Weinberg genetic equilibrium law via the chi-square test for goodness of fit. The genotype distributions in the control and case groups were not significantly different (Pearson chi-square $P > 0.05$). Therefore, the distribution frequency of the AT1R1166C genotype is genetically balanced and has general representation.

A comparison of the AT1R genotype and allele frequency between the two groups of pregnant women is shown in Table 1. The frequency of the AT1R genotype AC+CC and C allele in severe preeclampsia patients was much higher

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Table 4. Comparison of left ventricle structure index in two groups of fetus ($\bar{x} \pm s$)

Index	Case group	Control group	t	P
IVST (cm)	0.45±0.08	0.39±0.07	2.81	0.01
LVDD (cm)	2.55±0.41	2.40±0.52	1.28	0.21
PWT (cm)	0.44±0.28	0.33±0.07	1.99	0.05
RWT	0.33±0.06	0.32±0.07	0.63	0.53

Note: IVST: interventricular septal thickness, LVDD: left ventricular end diastolic period diameter, PWT: post wall thickness, RWT: relative wall thickness.

Table 5. Data showing left ventricle structure index between the AT1R genotype in case group of pregnant woman ($\bar{x} \pm s$)

Index	Genotype		Difference between genotypes	
	AA (n=19)	AC+CC (n=11)	t	P
IVST (cm)	1.11±0.14	1.03±0.17	1.29	0.2071
LVDD (cm)	4.83±0.56	5.11±0.74	1.17	0.2530
LVSD (cm)	3.68±1.17	3.62±0.71	0.16	0.8771
PWT (cm)	1.3±0.18	1.24±0.14	1.02	0.3184
RWT	0.44±0.01	0.46±0.01	4.43	0.0001
LVM (g)	206.19±20.87	222.45±15.46	2.25	0.0328
LVMI (g/m ²)	111.4±10.30	125.05±12.90	3.19	0.0035

Note: IVST: interventricular septal thickness, LVDD: left ventricular end diastolic period diameter, LVSD: end systolic period diameter, PWT: post wall thickness, RWT: relative wall thickness, LVM: left ventricular mass, LVMI: left ventricular mass index.

Table 6. Data showing fetus left ventricle structure index and genotype in the case group fetus ($\bar{x} \pm s$)

Index	Genotype		Difference between genotypes	
	AA (n=22)	AC+CC (n=8)	t	P
IVST (cm)	0.38±0.06	0.44±0.07	-2.25	0.03
LVDD (cm)	2.45±0.54	2.28±0.47	0.79	0.43
PWT (cm)	0.32±0.07	0.36±0.07	-1.38	0.18
RWT	0.30±0.06	0.38±0.07	-2.73	0.01

Note: IVST: interventricular septal thickness, LVDD: left ventricular end diastolic period diameter, PWT: post wall thickness, RWT: relative wall thickness.

than in normal pregnant women. The comparison of the AT1R genotype and allele frequency between the two groups of fetuses is shown in **Table 2**. The frequencies of the AT1R genotype AC+CC and the C allele are much higher in the case group than in the control group. The difference in the AT1R genotype frequency between pregnant women and fetuses was not significant different ($P > 0.05$), which indicates that the variation in the AT1R genetic polymorphism

in a fetus is the same as in pregnant women (**Figure 2**).

The relation of AT1R polymorphism A1166C and left ventricular remodeling

The indexes of pregnant women's left ventricle structure in the case group were much higher than in the control group (**Table 3**). Indexes (IVST and PWT) of the fetus's left ventricle structure in the case group were much higher than in the control group (**Table 4**). The differences in the blood pressures between AT1R genotypes AA and AC+CC in the case group of pregnant women were not significant but, the differences of the LVMI and RWT between the AT1R AC+CC and AA genotypes were significant (see **Table 5**). The fetus' IVST and RWT were higher in the AT1R AC+CC genotype than in the AA genotype in the case group (**Table 6**).

Discussion

Benedetto compared patients with a normal pregnancy to those with chronic hypertension, gestational hypertension and eclampsia. The analysis and evaluation of ACEI/D, the AT1R gene A1166C and AG-TM235T indicated that the frequency of ACEI/D and the AT1R gene A1166C were much higher in eclampsia patients than in the control group [24]. In our research, we learned about the function of the AT1R gene A1166C polymorphism in pregnant women with severe preeclampsia and their fetuses. The frequency of genotypes AC and CC at the AT1R gene A1166 site in pregnant women in the case group is apparently higher than in the control group. Additionally, allele C in pregnant women in the case group is apparently higher than in the control group, which supports that the polymorphism of the AT1R gene A1166C site is related to preeclampsia. This indicates that it may be a risk factor in the pathogenesis of severe preeclampsia. In addition, the variation of polymorphisms in the fetus is the same as in pregnant women. The frequency of fetuses' variation at the AT1R

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gene 1166 site and allele C in the case group is higher than in the control group, indicating that the variation of the AT1R gene 1166 site is hereditary and is expressed the same way in the severe preeclampsia patients and their fetuses.

Several studies concluded that the A1166C polymorphism of the AT1R gene might play a role in the formation of left ventricular remodeling in general hypertension patients, especially in those who have the C allele [25-27]. In our research, we found a relationship between the variation of the AT1R gene 1166 site and cardiac damage in preeclampsia patients. We also found that the difference in pregnant women's blood pressure between the AT1R genotype AC+CC and type AA in the case group was not significant, but with VMI and RWT, the former was much greater than the latter, indicating that the genotypes AC+CC and allele C at the AT1R gene 1166 site might be related to the left chamber restructure of pregnant women with severe preeclampsia. The polymorphism of the AT1R gene A1166C might take part in the formation of left chamber remodeling in pregnant women with preeclampsia, especially those who have the C allele. Meanwhile, similar results show that IVST and PWT in a fetus with the AT1R genotype AC+CC are much greater than the fetuses in the control group as well as fetuses with the AT1R genotype AA, indicating that the AT1R gene 1166 polymorphic site AC/CC-type and C allele are related to left ventricle remodeling in severe preeclampsia patients. This further supports that hereditary factors may play a central role in left ventricle pathogenesis due to severe preeclampsia.

In conclusion, this study has identified a strong relationship between the AT1R gene 1166 site variation and severe preeclampsia. Our findings show a possible role of the C allele as an important predisposing factor to severe preeclampsia. AT1R gene 1166 site variations are expressed the same way in mothers and their fetuses. Remodeling of the left ventricle is found in severe preeclampsia patients and their fetuses have a close correlation with the A1166C variation in the AT1R gene.

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Disclosure of conflict of interest

None.

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