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Original Research

Association between AGTR1 (c.1166 A>C) Polymorphisms and Kidney Injury in Hypertension

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Abstract

Background: High blood pressure is the main cause of cardiovascular diseases. Kidney damage is one of the most common organ secondary damage to hypertension. The study of hypertension gene polymorphisms is an important means of precision treatment of primary hypertension. **Objectives**: The objective of this study was to explore the relationship between *AGTR1* (c.1166 A>C) gene polymorphisms and hypertension combined with kidney damage, while exploring the relationship between codominant, dominant and recessive gene model and hypertension with kidney injury and the susceptibility of different genotypes to hypertension with kidney injury. **Methods**: The distribution of AGTR1 polymorphism in the AGTR1 in hypertensive patients (hypertension group, 292 patients) and hypertension with kidney injury patients (44 patients) were detected and compared by PCR-melting curve method. **Results**: The genotype distribution of hypertension and combined groups met Hardy-Weinberg equilibrium ($p > 0.05$); the distribution difference between the three genotypes was statistically significant ($p < 0.05$), the codominant, dominant and recessive distribution frequency of genotypes ($p < 0.05$), and no difference between A allele and C allele ($p > 0.05$). **Conclusions**: Our study identified the relationship of AGTRA (c.1166 A>C) with hypertension combined with renal injury, and compared the susceptibility of different genetic models, which may provide novel targets for precision gene therapy of hypertension. Clinical Trial Registration: URL: https://www.chictr.org.cn/indexEN.html; Unique identifier: ChiCTR2100051472.

Keywords: hypertension; renal injury; AGTR1; genetic polymorphism 24

1. Introduction

Hypertension is one of the leading causes of all-cause mortality worldwide, and poorly controlled blood pressure is the leading cause of cardiovascular disease (CVD) and cerebrovascular disease. It includes hemorrhagic (58%) and ischemic (50%) stroke, ischemic heart disease (55%), and other forms of CVD (58%), including heart failure and peripheral artery disease [1,2]. In addition, hypertension is a major cause of dementia caused by chronic kidney disease, renal disease progression, end-stage renal disease, and cerebral microvascular disease [3–5]. Hypertension includes both essential hypertension and secondary hypertension. Among them, essential hypertension accounts for 90%, and the causes of essential hypertension include genetic factors, living factors, and environmental factors. Living and environmental factors include a high-salt diet, smoking, obesity, and lack of exercise [6,7]. Recently, studies have shown that genetic factors play a key role in the generation and development of hypertension [8–10]. Therefore, the study of hypertension gene polymorphisms is of great significance and clinical value.

The renin-angiotensin system (RAS) is one of the most relevant hormone systems for regulating blood volume and blood pressure homeostasis, and is also important in the pathogenesis of cardiovascular and renal diseases. In general, RAS functions as a series of proteolytic enzymes, which successively cleaves the circulating prohormones in the blood to generate the octapeptide angiotensin II (Ang II). Angiotensin II (Ang II) regulates its activity by activating the G protein-coupled angiotensin receptor type 1 (AGTR1) [11].

At the same time, the metabolism of renal energy and substrate may interfere with the regulatory mechanisms of homeostasis, leading to the dysregulation of renal tubular transport and hemodynamics, thus leading to increased blood pressure [12]. The kidney is not only an organ closely related to blood pressure (BP) regulation and the development of hypertension, but also a tissue mediator of the genetic predisposition to hypertension [13]. Chronic kidney disease (CKD) is associated with cardiovascular disease, including hypertension, vascular remodeling, endothelial dysfunction, etc., while angiotensin II (Ang II) is a known channel factor because it may cause pathological changes in blood vessels by mediating structural and functional pathologies, such as abnormal proliferation of vascular smooth muscle and changes in vascular elastin and

Table 1. Demographic characteristics of the combined and hypertensive groups.

	Consolidation group (N = 44)	Hypertension group (N = 292)	*p*-value
Age	53.30 ± 17.519	48.72 ± 14.471	0.198
Age-range	27~91	16~86	
Gender (male), n (%)	30 (68.2)	184 (63.0)	0.506
Hyperlipemia, n (%)	31 (70.5)	153 (52.4)	0.025
Hyperglycemia, n (%)	11 (25.0)	22 (7.5)	0.001

collagen content [14]. In addition, there have been studies showing that angiotensin II (Ang II) may also mediate vascular effects through inflammation and proteolysis pathways [15], further exacerbating kidney damage. Therefore, angiotensin II (Ang II) is an important factor in the study of the mechanism of action of hypertension complicated by kidney damage, and a series of effects of angiotensin II (Ang II) are mostly produced under the action of angiotensin II receptor 1. Therefore, in the study of hypertension, the *AGTR1* gene has been the focus of research. In this paper, the distribution characteristics of the gene polymorphisms of AGTR1 (c.1166 A>C) in people with hypertension and hypertension with kidney injury were studied to determine the correlation between *AGTR1* gene and hypertension with kidney injury.

2. Methods

2.1 Study Population and Sample Collection

This hospital-based case-control study was conducted at Dushu Lake Hospital from September 2021 to September 2022 in Suzhou City, Jiangsu Province, China. Forty-four patients with hypertension and renal injury were selected as the combined group, and 292 hypertensive patients with normal renal function were selected as the hypertensive group during the same period. The inclusion criteria for the consolidation group were: (1) the patient had a systolic BP of 140 mmHg and/or a diastolic BP of 90 mmHg; (2) the glomerular filtration rate was lower than <60 mL/(min · 1.73 m^2); (3) the patient has no mental disorders; (4) the patient is voluntarily enrolled. Exclusion criteria: (1) secondary hypertension; (2) mental disorders. All the enrolled patients were admitted to the Department of Cardiology of Suzhou Dushu Lake Hospital, and had no history of renal history before the visit, and had not undergone renal biopsy. This study was approved by the hospital ethics committee, and all patients gave informed consent and signed the informed consent form.

The age and sex of the combined group or hypertension group were not significant ($p > 0.05$). The occurrence of hyperglycemia and hyperlipidemia in the combined group and the hypertensive group was statistically significant ($p < 0.05$) (Table 1).

2.2 AGTR1 Genotyping

We used ethylenediaminetetraacetic acid (EDTA) anticoagulant tube to extract 2 mL of peripheral venous blood. Human genomic DNA was extracted by ROTEX 96 automatic nucleic acid extraction instrument (Xi'an Tianlong Technology Co., LTD., Xi'an, Shaanxi, China) and Ex-DNA whole blood genomic nucleic acid extraction reagent (Xi'an Tianlong Technology Co., LTD., Xi'an, Shaanxi, China). The obtained DNA was tested by AGTR1 (c.1166 A>C) detection kit (PCR-melting curve method) (Wuxi Ruiqi Gene Biotechnology Co., LTD., Wuxi, Jiangsu, China), and the experimental operation and results interpretation were conducted in strict accordance with the operating instructions.

2.3 Statistical Analysis

The SPSS 26.0 software is used for statistical analysis (SPSS Inc., Chicago, IL, USA). The Hardy Weinberg equilibrium was used to determine the consistency of the genotype distributions. Differences in genotype frequencies for each polymorphism between the combined and hypertensive groups were tested using a degree-of-freedom chi-square (χ^2) test. Logistic regression was used to analyze the association of genotype and other CVD risk factors. A *p*-value of <0.05 was considered statistically significant.

3. Results

The genotype distribution of the combined and hypertensive groups complied with Hardy-Weinberg equilibrium ($p > 0.05$). Three groups of A GTR1 (c.1166 A>C) were distributed statistically significantly ($p < 0.05$), suggesting that hypertension combined with kidney injury and *AGTR1* (c.1166 A>C) Gene polymorphism is related. The distribution of the A or C allele was not statistically significant ($p > 0.05$) (Table 2).

The Logistic regression analysis showed that under the co-dominant gene model (AA vs. AC vs. AA), the risk of hypertension with kidney injury was lower than those with AA (OR = 0.877, 95% CI = 0.840–0.915, $p = 0.014$); those with CC had the greater risk of hypertension with AA (OR = 1.023, 95% CI = 0.978–1.070, $p = 0.016$). Under the dominant gene model (AA vs. AC + CC), the risk of hypertension combined with kidney injury in those carrying the AA genotype was 5.425-fold higher than in those carrying the AC and CC genotypes (OR = 5.425, 95% CI = 0.767–38.51, $p = 0.047$). Under the recessive gene model (CC vs. AA + AC), those with CC genotype had a higher risk of hypertension with kidney injury than AA and AC genotypes (OR =

Table 2. Distribution of genotypes and alleles frequency in consolidation group and hypertension groups.

Genotype/allele of the gene set		Consolidation group, N (%)	Hypertension group, N (%)	χ^2	*p*-value
Genotype	AA	43 (97.7)	256 (87.7)	12.496	0.002
	AC	0 (0)	36 (12.3)		
	CC	1 (2.3)	0 (0)		
Allele	A	86 (97.7)	548 (93.8)	2.171	0.141
	C	2 (2.3)	36 (6.2)		

Table 3. Analysis of the susceptibility of different genotypes and alleles of AGTR1 to hypertension combined with kidney injury.

Genotype/allele of the gene set		χ^2	*p*-value	OR	95% CI
Codominance	AA				
	AC	5.940	0.015	0.877	0.8400~0.915
	CC	5.838	0.016	1.023	0.9780~1.070
Dominance	AA				
	AC + CC	3.946	0.047	5.425	0.7630~38.51
Covert gender	CC				
	AA + AC	6.656	0.01	1.023	0.9780~1.00
Allele	A				
	C	2.171	0.141	2.712	0.6650~1167.0

Table 4. Association of the *AGTR1* gene polymorphism distribution with other risk factors for cardiovascular disease.

AGTR1	Genotype			χ^2	*p*-value
	AA	AC	CC		
	N (%)	N (%)	N (%)		
Blood fat				1.712	0.423
Normal	133 (87.5)	19 (12.5)	0 (0)		
Dyslipidemia	166 (90.2)	17 (9.3)	1 (0.5)		
Diabetes mellitus				11.299	0.004
No	268 (88.4)	35 (11.6)	0 (0)		
Yes	31 (93.9)	1 (3.03)	1 (3.03)		

1.023, 95% CI = 0.665–11.067, $p = 0.01$). The allele type model distribution was not significant ($p > 0.05$) (Table 3).

Meanwhile, we assessed the relationship between the AGTR1 genotype distribution and other risk factors for cardiovascular disease, for example, hyperlipidemia and diabetes. Among them, defined triglycerides >1.7 mmol/L, total cholesterol >5.2 mmol/L, HDL cholesterol >1.04 mmol/L, LDL cholesterol <3.37 mmol/L were dyslipidemia, and fasting blood glucose higher than 7 mmol/L was diabetes. The results showed that the gene distribution of AGTR1 was not statistically significant ($p > 0.05$), but was significant with the prevalence of diabetes ($p < 0.05$) (Table 4).

4. Discussion

The renin-angiotensin-aldosterone system (RAAS) is a key system for regulating blood volume and blood pressure, and has important implications in the pathogenesis of cardiovascular and renal diseases. Angiotensin is the main active substance of RAAS, which can contract and relax the small systemic blood vessels, which is closely related to the occurrence of hypertension in patients. Secondly, in addition to systemic RAS, there are local renin-angiotensin systems, such as in the kidney, local renin-angiotensin system is different from systemic RAS, the local system through the production of reactive oxygen species, inflammatory factors, vascular response, tissue hypertrophy and fibrosis, which may lead to an increased probability of kidney injury under the pathological state of hypertension. Meanwhile, it was shown that enhanced intracellular angiotensin expression in the high-glucose state led to RAS-induced diabetes development [16], which coincided with the resulting link between *AGTR1* gene polymorphism and diabetes development.

The human *AGTR1* gene is located at 3 q 21~25, contains only one exon structure, and A1166C is located in the non-coding region at end 3, which does not encode a protein, but may play a role for regulating transcription and translation of genes [17]. From a biological perspective, angiotensin is mainly mediated by A GTR1 and distributed in important tissues and organs such as blood vessels, heart, kidney and other important adults, which has a close impact

on hemodynamics [18]. Therefore, the polymorphism expression of the blood, angiotensin receptor 1 gene may be an important factor leading to the range of responses studied above.

Studies have shown that Ang II-induced AT1 receptor signaling (AGTR1) is clinically relevant and diverse in cardiovascular and renal pathology, among which, pharmacological inhibition of RAS, especially inhibition of Ang II formation or Ang II-mediated AT1 activation, has proven to be a very successful strategy for the treatment of multiple cardiovascular and renal diseases [18]. This is consistent with our conclusion that *AGTR1* (c.1166 A>C) Gene polymorphisms have a certain relationship with the occurrence of kidney injury. At the same time, some scholars have found that the *AGTR1* gene is an important predictor of blood pressure response to potassium intake [19]. some scholars have also found that the genetic diversity of AGTR1 is related to hypertension combined with myocardial infarction [20]. Therefore, we believe that AGTR1 plays a crucial role in the occurrence and development of hypertension and kidney injury in hypertension. Therefore, we recommend that hypertensive patients undergo genetic testing to determine the cause and adjust treatment methods when conditions permit. This may avoid damage to other target organs, especially the kidneys, caused by high blood pressure.

Hypertension is already recognized as one of the most important risk factors for cardiovascular disease, and the number of patients with hypertension is very large, however, less than 50% of patients know their hypertension condition, and the rest of the patients who know the condition are not treated or have poor treatment results [21]. Genetic factors play a crucial role in the occurrence and development of hypertension, and multiple genes and susceptibility sites associated with high blood pressure have been found worldwide [22]. In recent years, gene research has provided new ideas and possibilities for the precise treatment of hypertension, and with the completion of the Human Genome Project, the further exploration and development of gene polymorphisms research has brought new hope for the comprehensive treatment of hypertension. This study has some limitations. First, this study was conducted in a relatively small sample, and further validation requires a larger sample size. Secondly, all the patients in this study were from Suzhou Dushu Lake Hospital, so there were certain regional clustering and ethnic unity. Third, despite our rigorous experimental design to reduce possible errors in the study, the inherent bias in the study cannot be excluded from the study.

5. Conclusions

In conclusion, by exploring the relationship between AGTR1 and hypertension combined with renal injury, we found that *AGTR1* (c.1166 A>C) Gene polymorphisms have a certain relationship with the occurrence of kidney injury, which is of certain significance for the screening for kidney injury susceptibility in hypertensive patients. At the same time, the collection of data found that the genetic polymorphism of AGTR1 has some relationship to the incidence of diabetes, but the study of the genetic role has some complexity, and the relationship between AGTR1 and hypertension combined with kidney injury needs further exploration.

Availability of Data and Materials

All data generated or analysed during this study are included in this published article. The datasets used and/or analysed during the article are available from the corresponding author on reasonable request.

Author Contributions

YiyZ and YJ designed the study, performed the research, analyse the data, and wrote the paper. ZH and KL helped analyse the data. YafZ participated in the design of the article, participated in and directed the analysis of the data, and helped write the final version. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

This study was approved by the Dushu Lake Hospital ethics committee, approval number 220017. All patients gave informed consent and signed the informed consent form.

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Conflict of Interest

The authors declare no conflict of interest.

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