European Review for Medical and Pharmacological Sciences 2020; 24: 2674-2682

Correlation analysis between ADAMTS-13 gene polymorphism and hypertension-induced atrial fibrillation

H.-J. WANG[1], M. XIAO[2], Z. ZENG[3], D. BAO[4], L.-L. FAN[2]

[1]Heart Center & Beijing Key Laboratory of Hypertension, Beijing Chaoyang Hospital Affiliated to Capital Medical University, Beijing, China
[2]Department of Cardiology, Shandong Provincial Third Hospital, Shandong University, Jinan, China
[3]Department of Geriatric, Chui Yang Liu Hospital affiliated to Tsinghua University, Beijing, China
[4]Department of Obstetrics and Gynecology, PLA Rocket Force Characteristic Medical Center, Beijing, China

Hongjiang Wang and *Ming Xiao* contributed equally to this work

Abstract. – OBJECTIVE: The aim of this study was to explore the relationships between ADAMTS-13 gene polymorphisms and hypertension-induced atrial fibrillation (AF).

PATIENTS AND METHODS: A total of 200 hypertensive patients without AF (hypertension group) and 200 hypertensive patients with AF (AF group) treated in our hospital were enrolled. Then, peripheral blood was drawn from these subjects enrolled, and the genomic deoxyribonucleic acids (DNAs) were extracted for analysis of ADAMTS-13 gene polymorphism. Next, Reverse Transcription-quantitative Polymerase Chain Reaction (RT-qPCR) was employed to determine the expression of ADAMTS-13 gene, and the correlations of ADAMTS-13 gene polymorphism with ADAMTS-13 gene expression and clinical indicators were analyzed.

RESULTS: Results revealed that there was a difference in the distribution of alleles of ADSMTS-13 rs3094374 (p=0.046) and rs34054981 (p=0.039) between AF group and hypertension group. The frequency of T allele of the locus rs3094374 and that of the locus rs34054981 in ADSMTS-13 gene was higher in AF group than that in hypertension group. The distribution of genotypes of ADSMTS-13 rs28503257 (p=0.047) and rs34054981 (p=0.013) in AF group were different from those in hypertension group, and AF group had lower frequency of GA genotype of ADAMTS-13 rs28503257 and higher frequency of CT genotype of ADAMTS-13 rs34054981 than hypertension group. Besides, a difference was found in the distribution of ADSMTS-13 rs3094374 between AF group and hypertension group in recessive model (p=0.043), and the frequency of TC + CC was higher in the recessive model. Moreover, the distribution of the haplotypes CAT (p=0.012) and CGT (p=0.031) in ADAMTS-13 gene showed a difference between AF group and hypertension group. The linkage disequilibrium of the loci rs3094374 and rs28503257 in ADAMTS-13 gene was relatively great (D'=0.293). In addition, the polymorphism of the locus rs34054981 in ADAMTS-13 gene had an association with ADAMTS-13 gene expression (p<0.05). The expression of ADAMTS-13 gene was lower in patients carrying genotype TT in AF group. Furthermore, the ADAMTS-13 rs3094374 polymorphism was related to international normalized ratio (INR) (p=0.034), and the ADAMTS-13 rs28503257 polymorphism was correlated with the levels of brain natriuretic peptide (BNP) (p=0.047) and D-dimer (p=0.033).

CONCLUSIONS: ADAMTS-13 gene polymorphism is correlated with the susceptibility and procession of hypertension-induced AF.

Key Words:
Gene polymorphism, Hypertension-induced AF, ADAMTS-13.

Introduction

As the living standards of modern people have been improved, and the diet structure and living habits have changed, the incidence rate of hypertension has dramatically risen[1,2],

Corresponding Authors: Leilei Fan, MM; e-mail: fanleilei10@163.com
Hongjiang Wang, MD; e-mail: wanghongjiang@126.com

threatening the health of hundreds of millions of people around the world. The incidence rate of hypertension is significantly higher in China than the average in the world due to large population base and difficulties in health management[3]. Hypertensive population is prone to some cardiovascular diseases of which atrial fibrillation (AF) is one of the most common cardiovascular complications of hypertension[4]. Long-term high pressure in the compartments of the heart results in myocardial cell hypertrophy, myocardial fibrosis, electrophysiological disorders and also atrial ventricular dilatation, thereby inducing AF[5,6]. The development process of hypertension-induced AF is complex, and the specific molecular biological mechanism is not fully elucidated. Therefore, studying the mechanism by which this complication develops is meaningful.

Gene polymorphism, one of the most important factors affecting the physiological process of the body and the pathological process of diseases, greatly influences the susceptibility of many diseases including malaria[7] and asthma[8]. Besides, the development and procession of hypertension are associated with some gene polymorphisms, such as CYP4F2 rs2108622 polymorphism[9], PPAR-γ2 Pro12Ala polymorphism[10], and ACE2 gene polymorphism[11]. ADAMTS-13, an important gene influencing coagulation function and thrombosis, may affect the development of hypertension-induced AF.

In this study, we investigated the polymorphisms of the loci rs3094374, rs28503257, and rs34054981 in ADAMTS-13 gene based on data from 200 hypertensive patients without AF and 200 hypertensive patients with AF. Combined with ADAMTS-13 gene expression level, clinical international normalized ratio (INR), brain natriuretic peptide (BNP) and D-dimer, we then attempted to explore the association of ADAMTS-13 gene polymorphisms with hypertension-induced atrial fibrillation.

Patients and Methods

General Data

This study was approved by the Ethics Committee of Chaoyang Hospital affiliated to Capital Medical University. Signed written informed consents were obtained from all participants before the study. A total of 400 hypertensive patients treated in our hospital from 2017 to the present were collected, including 200 patients with AF as AF group and 200 patients without AF as hypertension group. General data, like age, gender, hospital ID number, disease history, family history, and clinical information of these patients were collected, and systolic blood pressure and diastolic blood pressure were measured at regular intervals. There were 117 males and 83 females with an average age of (58.42±2.18) years old in AF group and 126 males and 74 females with a mean age of (56.27±3.88) years old in hypertension group. The general data showed no statistically significant differences between the two groups.

Diagnostic criteria for hypertension-induced AF: patients meeting the diagnostic criteria for hypertension (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg), those with such risk factors as smoking, dyslipidemia and obesity, and those with persistent or transient AF detected *via* electrocardiogram.

Collection and Processing of Samples

Peripheral blood was collected from patients in hypertension group and AF group, and then, (within 1 h) centrifuged at 3000 rpm for 10 min in a centrifuge. Thereafter, the upper serum and the middle-nucleated cells were severally separated and collected into new centrifuge tubes. The upper serum was stored in liquid nitrogen for detection, while the middle-nucleated cells were used to extract genomic deoxyribonucleic acids (DNAs) for detection of ADAMTS-13 gene polymorphism.

Extraction of Genomic DNAs

Genomic DNAs were extracted from peripheral blood in hypertension group and AF group using a blood genome extraction kit (TIANGEN, Beijing, China) in strict accordance with the instructions of the kit. Specifically, 200 μL of proteinase K solution, peripheral blood samples from hypertension group and AF group and buffer were added to new centrifuge tubes, mixed on a vortex shaker and incubated at 65°C for 8 min. After that, the samples were added with 3 mL of alcohol, mixed, and transferred to adsorption columns. Next, 2 mL of buffer was added to the adsorption columns, followed by centrifugation at 3000 rpm for 1 min. Afterwards, buffer was added to the adsorption columns and centrifuged. Then, 200 μL of elution buffer was added to the adsorption columns, and the resulting solution was the genomic DNAs of subjects.

Polymerase Chain Reaction (PCR) Amplification and Analysis of Polymorphisms of rs3094374, rs28503257 and rs34054981 Loci in ADAMTS-13 Gene

The polymorphic regions of ADSMTS-13 rs3094374, rs28503257, and rs34054981 were amplified in a PCR instrument using a 25 μL of reaction system containing 1 μL of forward primer, 1 μL of reverse primer, 1 μL of template DNA in total, 12.5 μL of Taq enzyme, and 9.5 μL of distilled H_2O (dH_2O) under the conditions of 93°C for 5 min, 40 cycles of 95°C for 30 s, 56°C for 40 s, 72°C for 35 s, and 72°C for 5 min. The primers for polymorphic loci polymorphic region of ADAMTS-13 rs30943741: forward primer (5'→3') 'ACAGGCCGTGTCTTCTTACTT', and reverse primer (5'→3') 'GGGTCCCGAAGCAGTTCTG', rs28503257: forward primer (5'→3') 'GGGTGCCCCAAATATCACAG', and reverse primer (5'→3') 'CATCAGGCAACTCCAGGTCA', and rs34054981: forward primer (5'→3') 'CAGCAGGTATGGGACAGGTG', and reverse primer (5'→3') 'TGGCAATGTAGACACTGGTCA'. GAPDH: forward primer (5'→3') 'CTGGGCTACACTGAGCACC', and reverse primer (5'→3') 'AAGTGGTCGTTGAGGGCAATG'. The products of PCR were sent to Shenzhen Biotechnology Co., Ltd. (Shenzhen, China) for sequencing. The polymorphisms of loci in ADAMTS-13 gene in hypertension group and AF group were obtained after analysis.

Determination of ADAMTS-13 Gene Expression

Reverse Transcription-quantitative PCR (RT-qPCR) assay was performed to detect the expression of ADAMTS-13 gene in hypertension group and AF group. The RNAs were extracted from samples by TRIzol method (Invitrogen, Carlsbad, CA, USA) and reversely transcribed into complementary DNAs (cDNAs). Gene primers were designed using Primer Premier 5.0 and synthesized by Shanghai Bioengineering Co., Ltd. (Shanghai, China) ADAMTS-13 gene forward primer: (5'→3') 'TCCTCAGTGATAAGGCAACTCC', and reverse primer: (5'→3') 'GAGCCAGACGATCAACCCC'. PCR conditions were: 94°C for 2 min, 35 cycles of 94°C for 35 s, 57°C for 40 s and 72°C for 35 s, and 72°C for 5 min using a 25 μL of reaction system, consisting of 1 μL of forward and 1 μL of reverse primers, 0.5 μL of template cDNAs, 12.5 μL of SYBR premix Taq (TaKaRa, Otsu, Shiga, Japan), and 10 μL of dH_2O.

Detection of Relevant Clinical Indicators

The relevant clinical indicators INR, BNP, and D-dimer in hypertension group and AF group were tested in the laboratory medicine of our hospital according to the standard operating procedure (SOP) document.

Statistical Analysis

Statistical Product and Service Solutions (SPSS) 23.0 software (IBM Corp., Armonk, NY, USA) was used for statistical analysis. The comparison of enumeration data was carried out using χ^2-test, and Hardy-Weinberg equilibrium test was performed. Haplotype analysis was conducted using the online SHEsis website. $p<0.05$ suggested that the difference was statistically significant.

Results

Distribution of Alleles of the Loci rs3094374, rs28503257 and rs34054981 in ADAMTS-13 Gene

The distribution of alleles of ADAMTS-13 rs3094374, rs28503257, and rs34054981 is shown in Table I. It was found that the distribution of alleles of ADSMTS-13 rs3094374 (p=0.046) and rs34054981 (p=0.039) in AF group was different from that in the hypertension group. The frequency of T allele of rs3094374 locus and T allele of

Table I. Distribution of alleles of ADAMTS-13 rs3094374, rs28503257, and rs34054981.

Locus	Allele	Hypertension group	AF group	OR	95% CI	χ^2	p
rs3094374	T	199 (0.497)	224 (0.560)	0.77	0.58-1.02	3.33	0.046
	C	201 (0.502)	176 (0.440)				
rs28503257	G	192 (0.480)	195 (0.487)	0.97	0.73-1.28	0.04	0.831
	A	208 (0.520)	205 (0.512)				
rs34054981	C	215 (0.537)	191 (0.477)	0.78	0.59-1.03	4.88	0.039
	T	185 (0.463)	209 (0.522)				

Table II. Distribution of genotypes of ADAMTS-13 rs3094374, rs28503257, and rs34054981.

Locus	Genotype	Hypertension group	AF group	OR	95% CI	χ^2	*p*
rs3094374	TT	55 (0.275)	73 (0.365)	0.33	0.21-0.56	3.72	0.155
	TC	89 (0.445)	78 (0.390)				
	CC	56 (0.280)	49 (0.245)				
rs28503257	GG	42 (0.210)	55 (0.275)	1.22	0.96-1.44	5.39	0.047
	GA	108 (0.540)	85 (0.425)				
	AA	50 (0.250)	60 (0.300)				
rs34054981	CC	61 (0.305)	37 (0.185)	1.03	0.78-1.25	8.62	0.013
	CT	93 (0.465)	117 (0.585)				
	TT	46 (0.230)	46 (0.230)				

rs34054981 locus in ADSMTS-13 gene in AF group was higher than that in the hypertension group.

Distribution of Genotypes of rs3094374, rs28503257 and rs34054981 Loci in ADAMTS-13 Gene

The results of distribution of genotypes of ADAMTS-13 rs3094374, rs28503257, and rs34054981 (Table II) showed that there was a difference in the distribution of genotypes of ADSMTS-13 rs28503257 (p=0.047) and rs34054981 (p=0.013) between AF group and hypertension group. Besides, the frequency of the genotype GA of rs28503257 locus in ADAMTS-13 gene was lower in the AF group, while that of the genotype CT of rs34054981 locus was higher in the AF group.

Analysis of ADAMTS-13 rs3094374, rs28503257 and rs34054981 Polymorphisms

The polymorphism analysis and model constructed of the loci rs3094374, rs28503257, and rs34054981 in ADAMTS-13 gene are shown in Table III. The results manifested that the distri-

Table III. Analysis of ADAMTS-13 rs3094374, rs28503257, and rs34054981 polymorphisms.

	Locus	Genotype	Hypertension group	AF group	χ^2	*p*
Dominant model	rs3094374	TT + TC	144 (0.720)	151 (0.755)	3.53	0.171
		CC	56 (0.280)	49 (0.245)		
	rs28503257	GG + GA	150 (0.750)	140 (0.700)	3.54	0.170
		AA	50 (0.250)	60 (0.300)		
	rs34054981	CC + CT	154 (0.770)	154 (0.770)	3.85	0.146
		TT	46 (0.230)	46 (0.230)		
Recessive model	rs3094374	TT	55 (0.275)	73 (0.365)	5.31	0.043
		TC + CC	145 (0.725)	127 (0.635)		
	rs28503257	GG	42 (0.210)	55 (0.275)	3	0.223
		GA + AA	158 (0.790)	145 (0.725)		
	rs34054981	CC	61 (0.305)	37 (0.185)	3.24	0.198
		CT + TT	139 (0.695)	163 (0.815)		
Heterozygous model	rs3094374	TT	55 (0.275)	73 (0.365)	3.91	0.142
		TC	89 (0.445)	78 (0.390)		
	rs28503257	GG	42 (0.210)	55 (0.275)	1.74	0.419
		GA	108 (0.540)	85 (0.425)		
	rs34054981	CC	61 (0.305)	37 (0.185)	1.77	0.413
		CT	93 (0.465)	117 (0.585)		
Homozygous model	rs3094374	TT	55 (0.275)	73 (0.365)	2.06	0.357
		CC	56 (0.280)	49 (0.245)		
	rs28503257	GG	42 (0.210)	55 (0.275)	2.66	0.264
		AA	50 (0.250)	60 (0.300)		
	rs34054981	CC	61 (0.305)	37 (0.185)	3.3	0.192
		TT	46 (0.230)	46 (0.230)		

Table IV. Haplotype analysis of ADAMTS-13 rs3094374, rs28503257, and rs34054981.

Haplotype	Hypertension group	AF group	OR	95% CI	χ^2	*p*
CAC	57.66 (0.144)	50.65 (0.127)	0.861	0.574-1.292	14.574	0.524
CAT	51.86 (0.130)	50.83 (0.127)	0.977	0.646-1.479	0.497	0.012
CGC	55.92 (0.140)	40.36 (0.101)	0.691	0.449-1.063	13.952	2.857
CGT	35.57 (0.089)	34.16 (0.085)	0.957	0.585-1.564	0.428	0.031
TAC	58.44 (0.146)	49.22 (0.123)	0.82	0.546-1.233	3.843	0.912
TAT	40.05 (0.100)	54.30 (0.136)	1.412	0.915-2.179	0.711	2.441
TGC	42.99 (0.107)	50.76 (0.127)	1.207	0.784-1.860	1.717	0.731
TGT	57.53 (0.144)	69.71 (0.174)	1.257	0.859-1.838	6.501	1.388

Table V. Linkage disequilibrium analysis of ADAMTS-13 rs3094374, rs28503257, and rs34054981.

D′	rs3094374	rs28503257	rs34054981
rs3094374	–	0.293	0.034
rs28503257	0.193	–	0.084
rs34054981	0.034	0.084	–

bution of ADSMTS-13 rs3094374 in the recessive model of AF group was different from that in the hypertension group (p=0.043), and the frequency of TC + CC in the recessive model was higher in the hypertension group than that in the AF group.

Haplotype Analysis of the Loci rs3094374, rs28503257 and rs34054981 in ADAMTS-13 Gene

Haplotype analysis (Table IV) and linkage disequilibrium analysis (Table V) of ADAMTS-13 rs3094374, rs28503257, and rs34054981 revealed that a difference was detected in the distribution of the haplotypes CAT (p=0.012) and CGT (p=0.031) in ADSMTS-13 gene between AF group and hypertension group, and the linkage disequilibrium of ADAMTS-13 rs3094374 and rs28503257 was relatively great (D'=0.293).

Correlations of Polymorphisms of the Loci rs3094374, rs28503257 and rs34054981 in ADAMTS-13 Gene with Gene Expression

The relationships of ADAMTS-13 rs3094374, rs28503257, and rs34054981 polymorphisms with gene expression shown in Figures 1-3 uncovered that the polymorphism of rs34054981 locus in ADAMTS-13 gene was related to ADAMTS-13 gene expression (p<0.05), and the expression of ADAMTS-13 gene was lower in patients with genotype TT in AF group.

Associations of Polymorphisms of rs3094374, rs28503257 and rs34054981 Loci in ADAMTS-13 Gene with Clinical Indexes of Patients

The relationships of ADAMTS-13 rs3094374, rs28503257, and rs34054981 polymorphisms with clinical indexes of patients are shown in Table VI. It was discovered that the polymorphism of ADAMTS-13 rs3094374 had a correlation with INR (p=0.034), and that of rs28503257 was related to BNP (p=0.047) and D-dimer (p=0.033) levels.

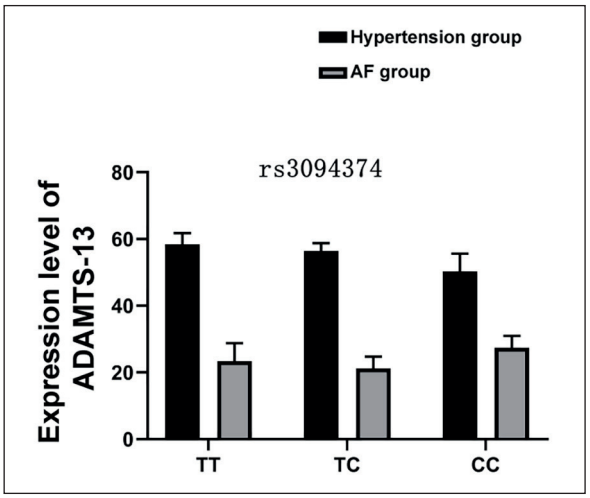

Figure 1. Association between ADAMTS-13 rs3094374 polymorphism and gene expression.

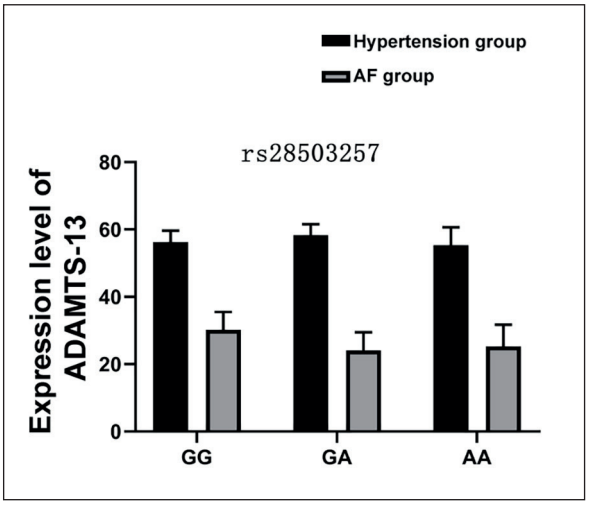

Figure 2. Relation between ADAMTS-13 rs28503257 polymorphism and gene expression.

Discussion

As a main disease affecting human health in modern society, hypertension is mainly caused by such factors as diet, lifestyle, environmental factors, genetic characteristics, and immune homeostasis[12]. AF, one of the major complications of hypertension, has not been fully elucidated. The development of hypertension-induced AF leads to persistent arrhythmia and insufficient cardiac ejection, resulting in severe consequences, such as stroke[13,14]. In addition, hypertension-induced AF may be associated with microvascular disease, clotting system dysregulation, and vascular permeability alteration due to an increase in blood pressure, but the specific mechanism of such a complication is not fully understood[15,16]. Studying the causes and predisposing factors of hypertension-induced AF is important for the treatment and prevention of this complication.

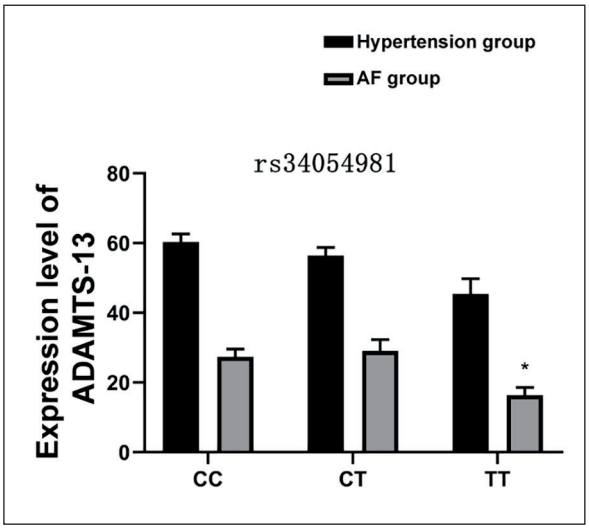

Figure 3. Correlation between ADAMTS-13 rs34054981 polymorphism and gene expression (*p<0.05 *vs.* patients carrying other genotypes).

ADAMTS-13 is a member of the thrombospondin integrin metallopeptidase family and vWF-CP synthesized by stellate cells, which has a relation to thrombotic microangiopathy, disseminated intravascular coagulation, and inflammatory diseases[17,18]. Moreover, it is reported that ADAMTS-13 can affect the development of cardiovascular diseases, like myocardial infarction and unstable angina pectoris[19]. It follows that ADAMTS-13 may be an important participant in the regulation on cardiovascular diseases. Besides, ADAMTS-13 gene polymorphism has been reported to affect the pathological process of various diseases, including cerebral aneurysm[20]. In this study, the polymorphisms of ADAMTS-13 rs3094374, rs28503257, and rs34054981 in hypertensive patients with and without AF were studied, and it was found that the distribution of alleles of rs3094374 locus (p=0.046) and rs34054981 locus (p=0.039) in ADSMTS-13 gene was different between AF group and hypertension group. The frequency of T allele of rs3094374 locus and T allele of rs34054981 locus in ADSMTS-13 gene in AF group was higher than that in the hypertension group. In addition, there was a difference in the genotype distribution of ADSMTS-13 rs28503257 (p=0.047) and rs34054981 (p=0.013) between AF group and hypertension group. AF group exhibited lower frequency of GA genotype of rs28503257 locus and higher frequency of CT genotype of rs34054981 locus in ADAMTS-13 gene. The above results suggest that there is a correlation between the development of hypertension-induced AF and ADAMTS-13 gene polymorphism, and hypertensive patients with T allele of rs3094374 locus, T allele of rs34054981 locus, and the genotype CT of rs34054981 are more prone to AF, while those with rs28503257 GA genotype are less likely to suffer AF.

Further studies manifested that the distribution of ADSMTS-13 rs3094374 in recessive model was different between AF group and hypertension group (p=0.043), and in recessive model, TC + CC the frequency was higher. A difference was detected in the distribution of ADAMTS-13

Table VI. Associations of ADAMTS-13 rs3094374, rs28503257, and rs34054981 polymorphisms with clinical indexes.

Locus	Genotype	INR			BNP (pg/mL)			D-dimer (mg/L)		
		Hypertension group	AF group	*p*	Hypertension group	AF group	*p*	Hypertension group	AF group	*p*
rs3094374	TT	1.2	2.2	0.034	376	432	0.263	0.17	0.44	0.134
	TC	1.3	2.4		256	456		0.17	0.22	
	CC	1.2	3.1		321	478		0.22	0.36	
rs28503257	GG	1.1	2.1	0.372	356	421	0.047	0.16	0.41	0.033
	GA	1.3	2.4		378	501		0.17	0.35	
	AA	1.2	2.2		253	456		0.25	0.65	
rs34054981	CC	0.9	2.1	0.037	374	412	0.171	0.14	0.43	0.111
	CT	1.2	2.4		325	418		0.15	0.49	
	TT	1	2.5		266	498		0.21	0.51	

gene CAT haplotype (p=0.012) and CGT haplotype (p=0.031) between AF group and hypertension group. The linkage disequilibrium of ADAMTS-13 rs3094374 and rs28503257 was relatively high (D'=0.293). These results imply that ADAMTS-13 may affect hypertension-induced AF through influences on multiple genotypes of the same locus or multiple loci.

Furthermore, there was an association between ADAMTS-13 rs34054981 polymorphism and the expression of ADAMTS-13 gene (p<0.05), and the expression of ADAMTS-13 gene was lowered in patients with TT genotype in AF group, suggesting that the effects of ADAMTS-13 gene polymorphism on the susceptibility and progression of hypertension-induced AF may be achieved by regulating the expression of ADAMTS-13 gene. The expression patterns of ADAMTS-13 are diverse due to different ADAMTS-13 genotypes in populations, thus affecting the progression of the disease. In this study, the clinical indicators of patients were compared, and it was discovered that ADSMTS-13 rs3094374 polymorphism was correlated with INR (p=0.034), and rs28503257 polymorphism was related to the levels of BNP (p=0.047) and D-dimer (p=0.033). The above results demonstrate that ADAMTS-13 gene polymorphism may be associated with the progression of hypertension-induced AF, and the progression of the disease can be predicted by detecting ADAMTS-13 gene polymorphism, so that quick responses can be made in advance.

Conclusions

The above results demonstrate that ADAMTS-13 gene polymorphism may be associated with the progression of hypertension-induced AF, and the progression of the disease can be predicted by detecting ADAMTS-13 gene polymorphism, so that quick responses can be made in advance.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Funding Support

This work was supported by the National Natural Science Foundation of China, Youth Science Foundation Project (81500321) and Open Foundation from Beijing Key Laboratory of Hypertension Research (2017GXY-KFKT-01).

References

1) Monahan M, Jowett S, Lovibond K, Gill P, Godwin M, Greenfield S, Hanley J, Hobbs F, Martin U, Mant J, McKinstry B, Williams B, Sheppard JP, McManus RJ. Predicting out-of-office blood pressure in the clinic for the diagnosis of hypertension in primary care: an economic evaluation. Hypertension 2018; 71: 250-261.
2) Jin L, Lin X, Yang L, Fan X, Wang W, Li S, Li J, Liu X, Bao M, Cui X, Yang J, Cui Q, Geng B, Cai J. AK098656, a novel vascular smooth muscle cell-dominant long noncoding RNA, promotes hypertension. Hypertension 2018; 71: 262-272.
3) Li YH, Zhang GG, Wang N. Systematic characterization and prediction of human hypertension genes. Hypertension 2017; 69: 349-355.
4) Wang Z, Zeng C, Villar VA, Chen SY, Konkalmatt P, Wang X, Asico LD, Jones JE, Yang Y, Sanada H, Felder RA, Eisner GM, Weir MR, Armando I, Jose PA. Human GRK4gamma142V variant promotes angiotensin II Type I receptor-mediated hypertension via renal histone deacetylase Type 1 inhibition. Hypertension 2016; 67: 325-334.
5) Vidal-Petiot E, Greenlaw N, Ford I, Ferrari R, Fox KM, Tardif JC, Tendera M, Parkhomenko A, Bhatt DL, Steg PG. Relationships between components of blood pressure and cardiovascular events in patients with stable coronary artery disease and hypertension. Hypertension 2018; 71: 168-176.
6) Ishii M, Ogawa H, Unoki T, An Y, Iguchi M, Masunaga N, Esato M, Chun YH, Tsuji H, Wada H, Hasegawa K, Abe M, Akao M. Relationship of hypertension and systolic blood pressure with the risk of stroke or bleeding in patients with atrial fibrillation: the Fushimi AF registry. Am J Hypertens 2017; 30: 1073-1082.
7) Nardini L, Holm I, Pain A, Bischoff E, Gohl DM, Zongo S, Guelbeogo WM, Sagnon N, Vernick KD, Riehle MM. Influence of genetic polymorphism on transcriptional enhancer activity in the malaria vector Anopheles coluzzii. Sci Rep 2019; 9: 15275.
8) Dutta S, Mondal P, Saha NC, Moitra S, Podder S, Ghosh A, Saha GK. Role of offending out-door aero-allergen and CD14 C(-159)T polymorphism in development and severity of asthma in a Kolkata patient population. Afr Health Sci 2017; 17: 1101-1109.
9) Luo XH, Li GR, Li HY. Association of the CYP4F2 rs2108622 genetic polymorphism with hypertension: a meta-analysis. Genet Mol Res 2015; 14: 15133-15139.
10) Yang W, Wang J, Ye W, Li X. Quantitative evaluation of PPAR-gamma2 Pro12Ala polymorphism with hypertension. Herz 2018; 43: 719-727.
11) Fan Z, Wu G, Yue M, Ye J, Chen Y, Xu B, Shu Z, Zhu J, Lu N, Tan X. Hypertension and hypertensive left ventricular hypertrophy are associated with ACE2 genetic polymorphism. Life Sci 2019; 225: 39-45.
12) Ren LQ, Sun XX, Guan Y. Effects of sevoflurane or propofol combined with remifentanil anesthesia

on clinical efficacy and stress response in pregnant women with pregnancy-induced hypertension. Eur Rev Med Pharmacol Sci 2018; 22: 1825-1829.

13) Kallistratos MS, Poulimenos LE, Manolis AJ. Atrial fibrillation and arterial hypertension. Pharmacol Res 2018; 128: 322-326.

14) Dan GA, Badila E, Weiss E, Laroche C, Boriani G, Dan A, Tavazzi L, Maggioni AP, Crijns HJ, Popescu R, Blommaert D, Streb W, Lip G. Arterial hypertension in patients with atrial fibrillation in Europe: a report from the EURObservational Research Programme pilot survey on atrial fibrillation. Int J Cardiol 2018; 254: 136-141.

15) Kiuchi MG, Chen S, Hoye NA, Purerfellner H. Pulmonary vein isolation combined with spironolactone or renal sympathetic denervation in patients with chronic kidney disease, uncontrolled hypertension, paroxysmal atrial fibrillation, and a pacemaker. J Interv Card Electrophysiol 2018; 51: 51-59.

16) Barrios V, Escobar C, Prieto VL, Lobos JM, Vargas-Ortega D, Polo J, Marin MN. Blood pressure control in anticoagulated patients with hypertension and atrial fibrillation. Blood Press 2017; 26: 279-283.

17) Obermeier HL, Riedl J, Ay C, Koder S, Quehenberger P, Bartsch R, Kaider A, Zielinski CC, Pabinger I. The role of ADAMTS-13 and von Willebrand factor in cancer patients: results from the Vienna cancer and thrombosis study. Res Pract Thromb Haemost 2019; 3: 503-514.

18) Katneni UK, Ibla JC, Hunt R, Schiller T, Kimchi-Sarfaty C. von Willebrand factor/ADAMTS-13 interactions at birth: implications for thrombosis in the neonatal period. J Thromb Haemost 2019; 17: 429-440.

19) Schooling CM, Luo S, Johnson G. ADAMTS-13 activity and ischemic heart disease: a Mendelian randomization study. J Thromb Haemost 2018; 16: 2270-2275.

20) Arning A, Jeibmann A, Kohnemann S, Brokinkel B, Ewelt C, Berger K, Wellmann J, Nowak-Gottl U, Stummer W, Stoll M, Holling M. ADAMTS genes and the risk of cerebral aneurysm. J Neurosurg 2016; 125: 269-274.