Lack of association between C3123A polymorphism of the angiotensin II type 2 receptor gene and hypertension in Tunisian population

Ilhem Ayadi Kabadou[1], Hayet Soualmiaa[2]*, Riadh Jemaa[1], Moncef Feki[1], Ameni Kallel[1], Omar Souheil[1], Sameh Haj Taieb[1], Haifa Sanhaji[1], Naziha Kaabachi[1]

[1]: *Research Laboratory LR99ES11, Department of Biochemistry, Hospital la Rabta, Tunis, Tunisia.*
[2] *Higher Institute of Medical Technologies of Tunis, Zouheir Essafi Street, Tunis, Tunisia*
Tunis El Manar University

I. Ayadi Kabadou, H. Soualmiaa, R. Jemaa, M. Feki, A. Kallel, O.Souheil, S. Haj Taieb, H. Sanhaji, N. Kaabachi

Absence d'association entre le polymorphisme C3123A du gène du récepteur de type 2 de l'angiotensine II et l'hypertension artérielle dans une population Tunisienne.

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RÉSUMÉ

Prérequis: L'hypertension artérielle est une maladie polygénique. Plusieurs polymorphismes du système rénine angiotensine ont été étudiés en relation avec l'hypertension.
But: Evaluer l'association du polymorphisme C3123A du récepteur de type 2 de l'angiotensine II avec l'hypertension artérielle dans un échantillon de la population Tunisienne.
Méthodes: Notre étude a comporté 403 sujets normotendus et 382 patients hypertendus. Le génotypage a été réalisé par la méthode de polymérisation en chaine suivie de digestion par l'enzyme de restriction Alu I.
Résultats: Chez les hommes hypertendus, la fréquence du génotype AA (0,50) n'était pas significativement différent de celle des normotendus (0,43) (χ^2 =1,18; p=0,16). L'odds ratio pour l'hypertension était de 0,77 (95% IC: 0,49-1,22, p=0,27). Après ajustement des facteurs indépendants, l'odds ratio était de 1,49 (95% IC: 0,84-2,63, p=0,16). Chez les femmes, nous n'avons pas obtenu de différences significatives des fréquences génotypiques entre les deux groupes (χ^2=3,16; p=0,20). Par ailleurs, l'analyse multiple de régression a montré que le génotype AA n'était pas associé avec l'hypertension (OR: 1,09, 95% IC: 0,58-2,06, p=0,77), bien qu'il existait une association significative entre l'hypertension et l'âge, l'indice de masse corporelle et la glycémie.
Conclusion: Nos résultats montrent que le polymorphisme C3123A du gène du récepteur de type 2 de l'angiotensine II n'est pas un facteur prédisposant à l'hypertension artérielle dans la population tunisienne.

Mots-clés

Hypertension, polymorphisme, récepteur de type 2 de l'angiotensine II

SUMMARY

Background: Hypertension is a polygenic disease. Various single-nucleotide gene polymorphisms of renin angiotensin system have been explored in hypertension. Angiotensin II, the major biologically active component of this system, exerts its effect via two pharmacologically distinct subtypes of angiotensin II receptors, the angiotensin II type 1 receptor and the angiotensin II type 2 receptor.
Aim: To examine whether the 3123 C/A polymorphism of angiotensin II type 2 receptor gene is involved in hypertension in a sample of Tunisian population.
Methods: A total of 403 normotensive subjects and 382 hypertensive patients were included in the study. Genotyping was performed by polymerase chain reaction followed by Alu I restriction digestion.
Results: The frequency of "A" genotype was not significantly different between the two groups in men (χ^2=1.18; p=0.16). The estimated odds prevalence for hypertension ("A" versus "C") was 0.77 (95% CI 0.49 to 1.22, p=0.27). After adjustment for confounding factors, the OR for hypertension remained no significant (OR: 1.49, 95% CI: 0.84-2.63, p=0.16). In women, genotype distributions for C3123A variant in hypertensive patients were not significantly different from normotensive subjects (χ^2=3.16; p=0.20). Multiple logistic regression analysis showed that the AA genotype was not significantly associated with hypertension (OR: 1.09, 95% CI: 0.58-2.06, p=0.77).
Conclusion: In the present study, we showed that the 3123 C/A polymorphism of AGT2R gene is not a significant factor for hypertension in a sample of Tunisian population.

Key-words

Angiotensin II type 2 receptor; gene; hypertension; polymorphism.

Hypertension (HTA) affects 20 to 30% of the population worldwide and contributes significantly to cardiovascular mortality and morbidity [1]. It is a multi factorial and polygenic disorder where several susceptible genes interact with the environmental factors and play a role in its pathogenesis [2]. The renin angiotensin system (RAS) plays an important role in blood pressure (BP) regulation. Angiotensin II (Ang II), the major biologically active component of this system mediates its effects through two major subtype receptors Ang II type 1 receptor (AGT1R) [3] and Ang II type 2 receptor (AGT2R). The AGT2R opposes many of AGT1R effects by inducing vasodilatation and natriuresis [4, 5]. The AGT2R is also involved in the inhibition of cell proliferation and apoptosis mechanism [6, 7]. In addition, the balance of these two types receptors seems to be important in the determination of vascular and cardiac remodeling [8]. The AGT2R gene is located on the X-chromosome (q22-q23). It consists of three exons interspaced by two introns [9]. Several polymorphisms have been described in human AGT2R gene. Among these, the 3123 cytosine/Adenine (3123 C/A) polymorphism located in the 3' untranslated region of exon 3 has been described in essential hypertension, myocardial infarction and hypertrophic cardiomyopathy [10-12]. This polymorphism has been poorly investigated in relation to HTA [10, 13-15]. Only one study has reported that the AGT2R 3123A allele is an important determinant of the BP response to dietary salt intake [16]. Thus, the AGT2R 3123 C/A variant gene may be an attractive candidate gene for HTA. To identify this genetic variant of AGT2R gene in Tunisian population and to determine whether the AGT2R polymorphism is associated with HTA, we undertaken this study.

In the present work, we examined the allelic and genotypic frequencies of X-linked AGT2R C3123A gene polymorphism in hypertensive patients and in normotensive subjects so as to identify their association with HTA in the Tunisian population.

PATIENTS AND METHODS

Patients

Seven hundred and eighty five unrelated individuals were included in the study. They consisted of three hundred eighty two hypertensive patients (264 women and 118 men) with a mean age of 55.1 ± 9.9 years. The control group consisted of 403 unrelated subjects (195 women and 208 men) with a mean age of 52.0 ± 13.1. The control groups were matched for age with hypertensive patients (HT). HT patients were ambulatory subjects attending the hypertension consultation of the Cardiology Department of Rabta University Hospital of Tunis. Both patients and controls belonged to the same ethnic background and all shared a common geographic origin in North Tunisia. BP was measured using a mercuric sphygmomanometer with appropriate size cuffs in conformity with the guidelines established in the VII report of the joint national committee [17]. Three consecutive BP measurements were taken and the mean of the three readings was used for analysis. Hypertensive subjects had a previous diagnosis of HTA and were being treated with antihypertensive medications, or their systolic/diastolic blood pressure (SBP/DBP) was ≥ 140/90 mmHg. All subjects had no symptoms of coronary artery disease, heart failure, stroke, or peripheral arterial disease and hepatic or renal insufficiency. Subjects using hormonal replacement therapy for women were not included. Secondary causes of HTA were ruled out after complete clinical, biochemical and radiological examinations. Controls were unrelated healthy volunteers; randomly collected among hospital staff families. Their SBP and DBP were less than 140 and 90 mmHg, respectively and they did not take antihypertensive treatment. Weight and height were measured and body mass index (BMI) was calculated as weight divided by height squared (Kg/m2). Diabetes mellitus was defined as hyperglycaemia, requiring antidiabetic drugs or fasting blood glucose over 7.0 mmol/L [18]. Dyslipidemia was classified as either fasting plasma total cholesterol (TC) ≥ 6.2 mmol/L or between 5.2 and 6.2 mmol/L, with the ratio of TC to high-density lipoprotein- cholesterol (HDL-C) being ≥ 5.0, and/or fasting plasma triglycerides (TG) ≥ 2.3 mmol/L [19]. Cigarette smoking was quantified based on daily consumption and duration of smoking. All participants resided in Tunisia and all were from North Tunisia. Approval for this study was obtained from the local research committee (Rabta Hospital Ethics Committee, Tunis) and all subjects gave informed written consent before participating in the study.

Biochemical analysis

Blood samples were obtained after an overnight fast. Plasma glucose, uric acid, creatinine concentrations, TC, TG and HDL-C were measured by standardized enzymatic methods using commercial kits (Roche Diagnostics, Mannheim. Germany) on a Hitachi 912 autoanalyzer.

DNA analysis

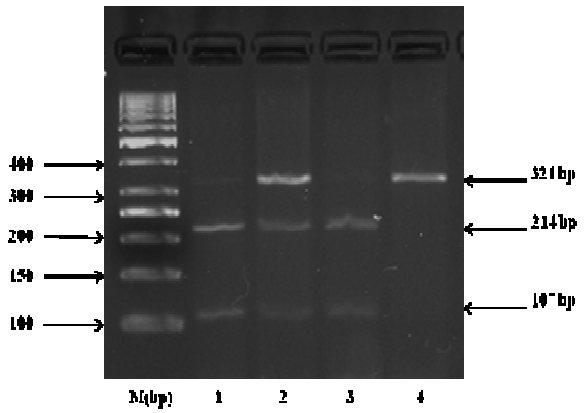
Genomic DNA was extracted from peripheral blood leukocytes using the phenol extraction method [20].

Genotype determination for AGT2R 3123 C/A polymorphism

The AGT2R 3123 C/A genotypes were determined by polymerase chain reaction (PCR) amplification of the relevant region followed by restriction with Alu I, as previously described with minor modifications [21]. Because the AGT2R gene is harboured on the X chromosome, alleles were "A" or "C" in men and AA or AC or CC in women respectively. PCR amplification of the C3123A polymorphism was performed with the following sense: 5' GGATTCAGATTTCTCTCTTGAA 3' and anti-sense primers 5' GCATAGGAGTATGATTTAATC 3'. After an initial step at 94°C for 5 min, 35 cycles of 94°C for 1 min, 54°C for 1 min and 72°C for 1 min were performed with a 50 μl reaction mixture that contained 25 pmol each primer, 200μM each dNTP, 1U Taq DNA polymerase (MBI Fermentas) and 1.5 mmol/L MgCl2. The PCR product was digested with the restriction enzyme Alu I (Fermentas), electrophoretically resolved on 3% agarose gel, and visualized under UV illumination. The undigested product (CC genotype) shows a band of 321 base pair, and the complete digestion of the PCR product (AA genotype) generates bands of

114 and 207 base pair. Heterozygous (CA genotype) displays the 3 bands mentioned above (Figure 1). Approximately 10% of the samples were quality control specimens. We selected an equal number of samples known to be of the AA genotype, the CA genotype and the CC genotype and randomly, repeatedly placed them throughout the batches to total 10% of the samples.

Figure 1 : Polymerase chain reaction genotyping of AGT2R 3123 C/A polymorphism. Electrophoresis in 3% agarose gel shows a 321 bp C-allele and a 107 bp and 214 bp A-allele. M (bp): molecular size marker (50-1000 bp). Lanes 1 and 3 are homozygous AA, lane 2 is heterozygous CA and lane 4 is homozygous CC.



Statistical Analysis

Data for continuous variables are presented as means ± standard deviation. The differences in anthropometrical and clinical characteristics between hypertensive and controls were analyzed by a student's t-test for quantitative variables and chi-square ($^{-}2$) test for categorical ones. The data of each continuous variable were examined for normality using the kolmogorov-Smirnov test. The levels of the variables between the genotype groups were compared by analysis of variance (ANOVA). Because the AGT2R gene 3123 C/A polymorphism was X chromosome-linked, we analyzed the data by sex. Genotype distributions were compared between groups by using the $^{-}2$ test. Hardy-Weinberg equilibrium was verified by comparison of the observed and expected genotype frequency using the $^{-}2$ test. The 3123 C/A polymorphism was first assessed in three genotype categories (wild-type, heterozygote, homozygote variants) and then grouped in two categories with heterozygote and homozygote variants combined because of the dominant model of inheritance observed for this polymorphism. We calculated unadjusted and multiadjusted odds ratio (OR) together with their 95% approximate confidence intervals (95% CI) as estimators of the relative risk of hypertension for the AGT2R 3123 C/A genotypes. A binary logistic regression analysis was performed for the determination of the independent predictors for hypertension. Goodness of fit of logistic models was satisfactory. Analysis of data was performed using SPSS software for windows (version 11.5). P-values less than 0.05 were considered as indicative of statistical significance.

RESULTS

Table 1 summarizes clinical profile and metabolic characteristics of all participants according to the BP phenotype. There were significant differences for the frequencies of diabetes ($p<0.001$), obesity ($p<0.001$) and dyslipidemia ($p<0.001$) between the hypertensive patients and control group. A statistically significant difference was observed between the two groups in the BMI, BP level, creatinine concentration, uric acid, fasting glucose and lipid profile ($p<0.001$), except in HDL-C.

Table 1: Demographic and clinical characteristics of the study population

Variables	Normotensive subjects (n=403)	Hypertensive patients (n=382)	p value
Age (years)	52.0 ± 13.1	55.1 ± 9.9	0.62
BMI (Kg/m2)	26.50 ± 4.09	28.35 ± 3.71	<0.001
SBP (mmHg)	118.71 ± 10.66	151.91 ± 18.76	<0.001
DBP (mmHg)	71.62 ± 6.92	87.83 ± 11.11	<0.001
Heart rate (beats/min)	78.74 ± 7.72	79.74 ± 7.53	0.68
Diabetes mellitus (%)	6.7	30.6	<0.001
Obesity (%)	22.3	36.8	<0.001
Dyslipidemia (%)	19.1	31.1	<0.001
Smoking (%)	19.6	33.6	<0.001
Fasting glucose (mmol/L)	5.44 ± 1.83	6.60 ± 3.10	<0.001
Creatinine (μmol/L)	80.44 ± 13.52	86.80 ± 34.29	0.001
Uric acid (μmol/L)	289.05 ± 83.65	315.11 ± 75.56	<0.001
TG (mmol/L)	1.44 ± 0.90	1.78 ± 1.04	<0.001
TC (mmol/L)	4.86 ± 0.96	5.33 ± 1.01	<0.001
HDL-C (mmol/L)	1.27 ± 0.33	1.29 ± 0.33	0.08

The data presented are means ± SD or % of patients
BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; TC: total cholesterol; TG: triglycerides; HDL-C: high-density lipoprotein-cholesterol

Because the AGT2R gene is located on the X chromosome, we analyzed the possible association between the 3123 C/A polymorphism and HTA in men and women separately. In men, the genotype distribution of the 3123 C/A polymorphism did not deviate significantly from Hardy–Weinberg equilibrium in hypertensive ($\chi^2 = 0.75$, $p = 0.38$) and control groups ($\chi^2 = 0.42$, $p = 0.51$). Also, in women, genotypes in both cases ($\chi^2 = 1.34$, $p = 0.51$) and controls ($\chi^2 = 1.81$, $p = 0.40$) were in Hardy-Weinberg equilibrium.Due to hemizygous genotype (XY) in males, the allelic status is equivalent with the genotypic status.

In men, the frequencies of "A" genotype in hypertensive and normotensive subjects were 50%/43.8% respectively. There were no significant differences in the 3123 C/A genotype distributions (¯2=1.18; p=0.27).

The AGT2R 3123A allele was not associated with hypertension in men (OR: 0.77, 95% CI: 0.49-1.22, p=0.27). Furthermore, multivariate logistic regression model, showed that the risk of hypertension in "A" carriers increased, although the trend was not statistically significant (OR: 1.49, 95% CI: 0.84-2.63, p=0.16) (Table 2). In women, three models of inheritance have been tested. Neither in the co-dominant, nor in the dominant and recessive models were statistically significant differences found in the distribution of genotypic frequencies between HT patients and controls (p=0.55, p=0.64 and p=0.14), respectively. HTA risk for each of these models was also estimated. Neither in the crude estimations, nor in those adjusted for age, diabetes, obesity, dyslipidemia and smoking was a higher HTA risk with variant allele found for this polymorphism (Table 2).

The clinical and metabolic characteristics according to 3123 C/A genotypes showed that there were no significant differences in BMI, SBP and DBP in hypertensive men. However, the "A" genotype carriers exhibited significantly lower TC (p=0.002) and TG (p=0.02) than homozygous C genotype carriers. Therefore, in normotensive women, there were significant differences in the SBP (p=0.02), DBP (p=0.02) and creatinine concentration (p=0.04), between the 3123 C/A genotypes. There was no notable difference between the genotype-based groups in the other metabolic parameters in both sexes.

DISCUSSION

In the present study, we have examined the association between the X-linked AGT2R 3123 C/A polymorphism and hypertension in a sample of Tunisian population because the role of this polymorphism was not explored before in our population. Our results showed a lack of association between the AGT2R 3123 C/A polymorphism and hypertensive status neither in male nor in female subjects. This suggested that this polymorphism does not play a significant role in the regulation of BP in our study. This is consistent with previous studies conducted on the 3123 C/A polymorphism which were not able

Table 2 : Genotype and allele frequencies of C3123A AGT2R polymorphism and OR (95% CI) for hypertension among men and women

Genotype and n (%)	Normotensive Subjects (n =403)	Hypertensive patients (n =382)	Unadjusted odd ratios	p	Multi-adjusted odd ratiosa	pa
Women						
Codominant						
CC	51 (26.2)	64 (24.2)	1b	0.30	1b	0.49
CA	88 (45.1)	140 (53)	0.79 [0.50-1.24]	0.55	1.21 [0.69-2.13]	0.77
AA	56 (28.7)	60 (22.7)	1.17 [0.69-1.96]		1.09 [0.58-2.06]	
Dominant						
CC	64 (24.2)	51 (26.2)	1b	0.64	1b	0.85
CA+AA	200 (75.8)	144 (73.8)	0.90 [0.59-1.38]		0.85 [0.50-1.44]	
Recessive						
AA	56 (28.7)	60 (22.7)	1b	0.14	1b	0.96
CC+CA	204 (77.3)	139 (71.3)	1.37 [0.89-2.09]		0.96 [0.57-1.59]	
Allele frequency						
C	49	51	-	0.54		
A	51	49	0.92 [0.70-1.21]			
Men						
CC	117 (56.2)	59 (50)	1b	0.27	1b	0.16
AA	91 (43.8)	59 (50)	0.77 [0.49-1.22]		1.49 [0.84-2.63]	

a : adjusted for age, obesity, diabetes, dyslipidemia and smoking
b : Reference genotype

to demonstrate a clear and direct relationship of this polymorphism with hypertension [10,13-15]. Only one study has reported an association between systolic and diastolic BP with 3123A in presence of high salt intake [16]. However, other studies observed a positive association but with others variants, the 1334 T/C and -1332 G/A (sometimes designated as 1675 G/A) polymorphisms of AGT2R and hypertension in male [22-23] and the 4599 C/A polymorphism in women [24]. This sex specific association in women may be explained by the AGT2R estrogen upregulation, and reactivity difference. Because, estrogen may up regulate AGT2R, involving reduced BP in AC and CC genotypes carriers and failed to reduce the BP in the AA genotype carriers [25-26]. On the other hand, the AGT2R gene polymorphisms were predominantly associated with certain cardiovascular phenotypes in hypertensive patients. Indeed, the 1675 G/A variant in intron 1 has been shown associated with early left ventricular structural changes in young males [27-30] and with premature coronary artery disease and left ventricular mass [31]. The role of AGT2R in HTA development and cardiovascular diseases is not fully clarified yet but a counter regulatory protective role of AGT2R is suggested to oppose the AGT1R effect [13] by inducing vasodilatation, natriuresis, and antiproliferation [32].

In addition, association studies have been reported between the AGT2R 3123 C/A gene polymorphism and cardiovascular diseases as myocardial structure and fat tissue growth [11]. Indeed, the AGT2R is involved in obesity-linked metabolic parameters. Thereby, this polymorphism might be a polymorphic marker related to BMI in women [33]. Moreover, the AGT2R genes were associated with attenuated effects on blood pressure as well as lipid profiles after weight loss. Another study has reported an association between glycemic control and A allele carriers of AGT2R gene in Japanese women [34]. As, the AGT2R 3123 C/A polymorphism is located in untranslated regions of the AGT2R gene located on X-chromosome, so the association with glycemic control parameters might be explained by linkage disequilibrium in a functional variant of the same or a different gene.

In conclusion, a lack of association was found between AGT2R 3123 C/A polymorphism and hypertension in Tunisian population. This suggests that this polymorphism does not play a significant role in the regulation of BP in our population.

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