American Journal of Medicine and Medical Sciences 2021, 11(8): 598-601
DOI: 10.5923/j.ajmms.20211108.11

Association of the Polymorphism rs1799998 CYP11B2 Gene with Left Ventricular Diastolic Function in Patients with Chronic Heart Failure

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Abstract The aim of our study was to evaluate the role of polymorphism rs1799998 CYP11B2 gene in patients with chronic heart failure (CHF). In patients with CHF 152 Uzbeks have been studied the alleles and genotypes rs1799998 CYP11B2 gene. A relationship has been established between the carriage of the homozygous T / T genotype of the rs1799998 polymorphism of the CYP11B2 gene with an almost twofold increase in the risk of the formation of a restrictive form of CHF, which allows us to make an assumption, regarding this genotypic variant, about its prognostic role in increasing the risk of developing this form of CHF.

Keywords Chronic heart failure, rs1799998 CYP11B2, Gene

1. Introduction

Chronic heart failure (CHF) is not only a medical, but also a social problem due to the significant prevalence, high mortality rate and high costs of treating patients with CHF. It is expected that in the next 20-30 years the prevalence of CHF will increase by 40-60% [1]. An increase in the activity of the sympathetic-adrenal system (SAS) and the renin-angiotensin-aldosterone system (RAAS) and other neurohormones, mediators, including cytokines, endothelin, natriuretic peptide system plays a leading role in the pathogenesis of CHF [2]. There are circulating and tissue RAAS in the body. The circulating RAAS (10-15%) as a "quick" response system provides a short-term influence and control over the cardiovascular system (CVS), and the tissue RAAS is a system of long-term regulation. Adaptive-compensatory reactions at the initial stage of CHF development are provided mainly by the circulating RAAS. With prolonged activation in CHF, tissue RAAS is also significantly activated, including myocardial and renal [3]. If the main link of the RAAS is angiotensin II (AT II), then aldosterone is an equally important link and its adverse effects, in many respects similar to the effects of AT II. The secretion of aldosterone is influenced by AT II, sodium and potassium levels, ACTH, vasopressin, natriuretic peptide and endothelin. Aldosterone is synthesized not only in the adrenal cortex, but also in the myocardium and in the vascular endothelium. Aldosterone promotes tissue fibrosis through several mechanisms: induction of inflammation and fibrinoid necrosis of small arteries and arterioles; effects on the corresponding receptors localized in the cytosol of vascular fibroblasts; stimulation of apoptosis of cardiomyocytes [4,5]. Aldosterone synthetase is a human enzyme encoded by the CYP11B2 gene (cytochrome P450, family 11, subfamily B, polypeptide 2) on chromosome 8. Aldosterone synthase belongs to the cytochrome P450 superfamily and provides the synthesis of the hormone aldosterone. The gene for aldosterone synthetase is mapped to chromosome 8 at q24.3. It is located next to the 11beta-hydroxylase gene (CYP11B1). The CYP11B2 gene is highly homologous to the CYP11B1 gene encoding 11-beta-hydroxylase. Despite significant research efforts, it is still unclear how the C-344T polymorphism affects steroid biosynthesis at the molecular level. On chromosome 8q24, the genes encoding the aldosterone synthase CYP11B2 and 11B-hydroxylase CYP11B1 are located in close proximity [6].

The most fully investigated polymorphism of the aldosterone synthase gene, which manifests itself in the substitution of cytosine for thymine at the 344th position of the nucleotide sequence, in the regulatory region of the gene. This site is the binding site for the steroidogenic transcription factor SF-1, which regulates the expression of the aldosterone synthase gene. According to recent studies, the T allele leads to an increase in aldosterone production, which in turn is associated with hypertension, as well as with fibrosis and myocardial hypertrophy and with the risk of hypertensive complications of pregnancy. A relationship was found between the aldosterone synthetase gene

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Received: Aug. 15, 2021; Accepted: Aug. 26, 2021; Published: Aug. 30, 2021
Published online at http://journal.sapub.org/ajmms

polymorphism and the size, weight, and diastolic function of the LV in young people. The aldosterone synthase gene has been assigned to candidate genes in the development of cardiovascular remodeling [7,8].

The aim of our study was to association of the polymorphism rs1799998 CYP11B2 gene with left ventricular diastolic function in patients with chronic heart failure (CHF).

2. Materials And Methods

In patients with CHF 134 of Uzbek nationality have been studied the genetic determinants of alleles and genotypes rs1799998 CYP11B2 gene. The control group consisted of 102 healthy individuals— men of Uzbek nationality. The study was performed according to the standards of Good Clinical Practice (Good Clinical Practice) and the Declaration of Helsinki. The study protocol was approved by the ethics committees of all participating clinical centers. Before inclusion in the study all participants provided written informed consent. All patients were divided into three groups of functional class (FC) of CHF according to the New York Heart Classification (NYHA) according to the test of 6-minute walk: the first group consisted of 31 patients with CHF FC I, the second group 62 patients with FC II and 3 group — 59 patients with FC III classification NYHA. Study polymorphism rs198389 NPPB gene was conducted using polymerase chain reaction on programmable thermocycler CG-1–96 «Corbett Research» (Australia) and 2720 «Applied Biosystems» (USA), using kits LLC "Medlab" (St. Petersburg), according to the manufacturer's instructions. In our work allele polymorphism G/T894 revealed after digestion of the amplified fragment of 206 bp containing the polymorphic site. Evaluation of deviation of the distribution of genotypes of studied polymorphisms of DNA from the canonical distribution of Hardy-Weinberg equilibrium was performed using the computer program for the analysis of genetic data "GenePop" ("Genetics of Population"). To calculate the "odds ratio" (OR — odds ratio) with 95% confidence intervals (CI— confidenceinterval), $\chi 2$ and pvalues used statistical package statistical software package «OpenEpi 2009, Version 2.3».

3. Results

Analysis of the frequency distribution of the genotypes of the rs 1799998 polymorphism of the CYP11B2 gene in the group of CHF patients showed a congruence for RHV. In particular, the frequencies of the C and T alleles were 0.47 and 0.53, while the observed frequencies of the C / C, C / T and T / T genotypes corresponded to 0.25; 0.42 and 0.33, and their expected frequencies were 0.22; 0.5 and 0.28 with a statistically insignificant difference ($\chi 2 = 2.8$; $p = 0.1$) and a heterozygosity index (D) equal to -0.16 (Table 1).

Table 1. Expected and observed frequencies of distribution of alleles and genotypes of the CYP11B2 gene polymorphism (rs 1799998) in the group of patients with CHF

Alleles	Allele frequency				
T	0.47				
C	0.53				
Genotype	Genotype frequency				
	Observed Ho	Expected He	$\chi 2$	p	df
T/T	0.25	0.22	0,8	0.1	1
T/C	0.42	0.5	1.4		
C/C	0.33	0.28	0.6		
Total	1.0	1.0	2.8		

In the control group, allelic frequencies (T and C) corresponded to 0.51 and 0.49, while the observed frequencies of the C / C, C / T, and T / T genotypes were 0.25; 0.52 and 0.23, and the expected ones are 0.26; 0.5 and 0.24, also with a statistically insignificant difference ($\chi 2 = 0.16$; $p = 0.7$). At the same time, the difference between the expected and observed frequencies of heterozygosity (D) corresponded to +0.04.

In the control group (n = 102), the proportion of carriage of the frequencies of the C and T alleles was 51.5% (n = 105) and 48.5% (n = 99). At the same time, carriage of C / C and C / T genotypes was detected in 25.5% (n = 26) and 52.0% (n = 53) cases. At the same time, it is important to point out that in this group, cases of carriage of a functionally unfavorable genotype T / T were also recorded, which amounted to 22.5% (n = 23).

At the same time, the frequencies of the C and T alleles in the main group of patients with CHF (n = 134) had slightly different values, namely, they were registered in 46.6% (n = 125) and 53.4% (n = 143) cases. In addition, with respect to the frequency of the C / C genotype, almost the same proportion was established, corresponding to 25.4% (n = 34). However, a slightly larger proportion compared to the control was recorded among carriers of the C / T (42.5%, n = 57) and T / T (32.1%, n = 43) genotypes, which indicates a possible role of functionally heterozygous (C / T) and mutant (T / T) genotypes of CYP11B2 gene polymorphism (rs1799998) in the development of CHF.

Thus, in the main group of CHF patients, compared with the control group, the T allele was 1.2 times more frequent (53.4% versus 48.5%; $\chi 2 = 1.1$; $p = 0.3$; OR = 1.2; 95% CI: 0.84-1.74). At the same time, in relation to the frequencies of the C / C genotypes (25.4% versus 25.5%; $\chi 2 < 3.85$; $p > 0.05$; OR = 1.0; 95% CI: 0.55-1.8) and C / T (42.5% versus 52.0%; $\chi 2 = 2.1$; $p = 0.1$; OR = 0.7; 95% CI: 0.41-1.15) significant differences were not found. Whereas in relation to the T / T genotype among patients with CHF, there was a pronounced tendency to an increase in its frequency by 1.6 times (32.1% versus 22.5%; $\chi 2 = 2.6$; $p = 0.1$; OR = 1.6; 95% CI: 0.90-2.93).

The study of the distribution of the genotypes of the rs1799998 polymorphism of the CYP11B2 gene in various

types of left ventricular diastolic dysfunction (LVDD) in patients with CHF (with impaired relaxation, pseudonormal and restrictive) made it possible to identify their frequencies in CHF with impaired relaxation (n = 52) recorded in 32.7% (n = 17) for the C / C genotype, in 40.4% (n = 21) for the C / T genotype, and in 26.9% (n = 14) cases for the T / T genotype. The proportion of carriage of these genotypes in pseudonormal LVDD CHF (n = 45) was 24.4% (n = 11), 44.4% (n = 20) and 31.1% (n = 14) of the cases, respectively, and in the restrictive type of LVDD CHF (n = 37) - 16.2% (n = 6), 43.2% (n = 16) and 40.5% (n = 15) cases, respectively.

In accordance with these data, there is a decrease in the frequency of the C / C genotype and, on the contrary, an increase in the frequency of the T / T genotype in the following pattern: CHF with impaired relaxation> CHF pseudonormal> CHF restrictive and CHF with impaired relaxation <CHF pseudonormal <CHF restrictive. Consequently, the lowest frequency of the C / C genotype and the maximum frequency of the T / T genotype were recorded among patients with the restrictive type of LVDV.

A comparative analysis of the distribution of the genotype frequencies of the rs1799998 polymorphism of the CYP11B2 gene between the subgroups of patients with CHF with impaired relaxation and pseudonormal types of LVDV did not reveal the presence of statistically significant differences in relation to all three genotypes: for the C / C genotype (32.7% versus 24.4%; $\chi2 = 0.8$; p = 0.4; RR = 1.1; 95% CI: 0.7-2.54; OR = 1.5; 95% CI: 0.61-3.7); for the C / T genotype (40.4% versus 44.4%; $\chi2 = 0.2$; p = 0.7; RR = 0.9; 95% CI: 0.57-1.45; OR = 0.8; 95% CI: 0.38-1.9) and for the T / T genotype (26.9% versus 31.1%; $\chi2 = 0.2$; p = 0.6; RR = 0.9; 95% CI: 0.46-1.6; OR = 0.8; 95% CI: 0.33-1.96).

The results of the analysis carried out between the subgroups of CHF patients with relaxation impairment and restrictive type differed in features expressed in the presence of significant differences in relation to the frequencies of the C / C and T / T genotypes. Thus, the frequency of the C / C genotype in the subgroup of patients with the restrictive type of LVDV decreased markedly compared with patients with CHF with relaxation impairment (16.2% versus 32.7%; $\chi2 = 3.1$; p = 0.08; RR = 0.5; 95% CI: 0.22-1.13 ; OR = 0.4; 95% CI: 0.14-1.13), and the frequency of the T / T genotype almost doubled (40.5% versus 26.9%; $\chi2 = 1.8$; p = 0.2; RR = 1.5; 95% CI: 0.83- 2.7; OR = 1.8; 95% CI: 0.75-4.5) in the absence of significant differences in the frequency distribution of the C / T genotype (43.2% versus 40.4%; $\chi2 = 0.07$; p = 0.8; RR = 1.1; 95% CI: 0.65- 1.76; OR = 1.1; 95% CI: 0.48-2.6). The results of the analysis prove the protective effect of the favorable C / C genotype in relation to the development of a restrictive form of CHF with an increased risk of its development in carriers of the unfavorable T / T genotype of the rs1799998 polymorphism of the CYP11B2 gene.

The absence of significant differences for the genotypic frequencies of the rs1799998 polymorphism of the CYP11B2 gene was found between the subgroups of patients with restrictive and pseudonormal CHF: for the C / C genotype (16.2% versus 24.4%; $\chi2 = 0.8$; p = 0.4; RR = 0.7; 95% CI: 0.27- 1.6; OR = 0.6; 95% CI: 0.19-1.81); for the C / T genotype (43.2% versus 44.4%; $\chi2 = 0.01$; p = 0.9; RR = 1.0; 95% CI: 0.6-1.6; OR = 0.9; 95% CI: 0.39-2.3) and for the T / T genotype (40.5% versus 31.1%; $\chi2 = 0.8$; p = 0.4; RR = 1.3; 95% CI: 0.73-2.3; OR = 1.5; 95% CI: 0.61-3.75). A weak relationship was found between the carriage of the homozygous T / T genotype of the rs1799998 polymorphism of the CYP11B2 gene with an almost twofold increase in the risk of the formation of a restrictive form of CHF ($\chi2 = 1.8$; P = 0.2; OR = 1.8; 95% CI: 0.75- 4.54), which allows us to make the assumption, in relation to this genotypic variant, about its prognostic role in increasing the risk of developing this form of CHF.

4. Discussion

Aldosterone - a mineralocorticoid, which is mainly synthesized by the glomerular zone of the adrenal cortex from deoxycocorticosterone by the mitochondrial cytochrome p450 enzyme aldosterone synthetase increases the number of ATII type 1 receptors in the cardiovascular disease and potentiates the effects of RAAS. Aldosterone synthesized by the adrenal cortex mainly affects receptors located in the region of the distal renal tubules, the collecting ducts of the nephrons. By binding to intracellular mineralocorticoid receptors (type 1 corticoid receptors), aldosterone interacts with hormone-sensitive DNA elements and modulates the transcription of specific proteins [9]. At the same time, in recent years, the idea has been formed that aldosterone is synthesized not only in the adrenal cortex, but also in the myocardium, vascular endothelium, brain tissue and exerts its effect directly at the site of synthesis. It has been shown that aldosterone receptors are expressed on cardiomyocytes, endothelial cells, and human heart fibroblasts. Through activation of these receptors and possibly other, so far hypothetical, mechanisms, aldosterone increases collagen synthesis and induces fibroblast proliferation [10].

Studies have shown that the activity of the RAAS is to a certain extent controlled at the genetic level and the functional significance of the RAAS in the processes of changing the geometry of the heart from the standpoint of molecular genetics is probably due to the level of AT II production, which in turn partially depends on the expression of the renin, angiotensinogen and ACE genes. aldosterone, as well as the density and functional activity of receptors present in the myocardium and blood vessels, because [11].

5. Conclusions

Thus, the data obtained show a high frequency of occurrence of the T allele and the T / T genotype in the main group of patients compared to the control group by 1.2 and 1.6 times, which proves the presence of a tendency on their part to increase the risk of the formation of disorders leading

to the development of CHF. A relationship has been established between the carriage of the homozygous T / T genotype of the rs1799998 polymorphism of the CYP11B2 gene with an almost twofold increase in the risk of the formation of a restrictive form of CHF, which allows us to make an assumption, regarding this genotypic variant, about its prognostic role in increasing the risk of developing this form of CHF.

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