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STUDY OF CYP11B2 (1799998) GENE POLYMORPHISM IN PATIENTS WITH CHRONIC HEART FAILURE

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ABSTRACT

Background: The aim of this study was to study the polymorphism of the aldosterone synthase gene CYP11B2 (1799998) in CHF patients. **Methods:** To conduct a genetic study, 152 patients with CHF aged 35-60 years of Uzbek nationality were examined, the average age of which was 53.9 ± 7.4 years. The control group consisted of 102 healthy people of Uzbek nationality. **Results:** Analysis of the results on the study of the characteristics of the allelic polymorphism of the CYP11B2 gene (rs1799998) aldosterone synthase among CHF patients revealed a trend towards an increase in the number of T / T homozygotes of the rs1799998 locus of the CYP11B2 gene in the group of CHF patients with high odds ratios, indicating an increased risk of developing CHF. **Conclusion:** The mutant T / T genotype of the CYP11B2 gene polymorphism (rs1799998) can be considered as an independent genetic marker associated with severe renal dysfunction accompanied by a significant decrease in GFR in CHF patients.

KEY WORDS: chronic heart failure, gene polymorphism, kidney dysfunction.

INTRODUCTION

Chronic heart failure (CHF) is not only a medical, but also a social problem due to its significant prevalence, high mortality, and high treatment costs. The mortality of patients with heart failure depends on the functional class (FC) and is about 20% per year, and 4-5-year survival is 25-50%. [1,2] According to the Framingham study, one of the main reasons for the development of CHF is ischemic heart disease (IHD), which accounts for more than 60% in the structure of CHF development.[3] Recent multicenter randomized trials have shown that neurohumoral systems are activated in the early stages of LV dysfunction. An increase in the activity of the sympathetic-adrenal system (SAS) promotes the activation of the renin-angiotensin-aldosterone system (RAAS) and other neurohormones and mediators, including cytokines, endothelin, aldosterone, natriuretic peptide system (NUP).[4,5] In recent years, medical genetics has been actively developing, the main task of which is to study the prevalence of polymorphism of genes that contribute to the pathogenesis, development and progression of CHF. The prognosis of the disease, as well as the possibility of individual selection of therapy for each specific patient, depends on gene polymorphism.[6] Moreover, this promising approach is associated with the possible stratification of genetic risk, determination of management tactics and prognosis for the development of complications in patients even before the development of clinical manifestations. According to studies showing that the activity of the polymorphism of the aldosterone synthase gene CYP11B2 (rs1799998) is important in the pathogenesis of CHF and is associated with a 4-fold increase in aldosterone production, the increased level of which directly correlates with unfavorable clinical outcomes among patients with heart failure.[7,8]

The aim of this study was to study the features of the polymorphism of the aldosterone synthase gene CYP11B2 (1799998) in patients with CHF.

MATERIALS AND METHODS

To conduct a genetic study, 152 patients with CHF aged 35-60 years of Uzbek nationality were examined, the average age of which was 53.9 ± 7.4 years. The patients were divided into groups according to the six-minute walk test (TSH) according to the classification of the New York Heart Association. 31 patients were with FC I, 62 - FC II and 59 patients - FC III CHF. The control group consisted of 102 healthy people of Uzbek nationality. Genetic studies were carried out by PCR at the Republican Specialized Scientific and Practical Center for Hematology. Glomerular filtration rate (GFR) was assessed by CKD – EPI.

RESULTS

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 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 unfavorable heterozygous (C / T) and mutant (T / T) genotypes of CYP11B2 gene polymorphism (rs1799998) in the development of CHF (table 1).

To identify the features of the distribution of allele frequencies and genotypes of CYP11B2 gene polymorphism (rs1799998) depending on the severity of CHF, we analyzed the results separately in groups of CHF patients with different functional classes (FC). Thus, among CHF patients with FC I (n = 46), the frequency of the C allele was determined in 47.8% (n = 44), and the T allele in 52.2% (n = 48) cases. Genotypes C / C, C / T, and T / T were detected in 26.1% (n = 12), 43.5% (n = 20), and 30.4% (n = 14) cases,

Table 1: Differences in the frequency of allelic and genotypic variants of the rs 1799998 polymorphism of the CYP11B2 gene in the main group of patients with CHF and the control sample.

Alleles and genotypes	Number of examined alleles and genotypes				χ^2	P	OR	95% CI
	CHF		Control					
	n	%	n	%				
C	125	46.6	105	51.5	1.1	0.3	1.2	0.84-1.74
T	143	53.4	99	48.5				
C/C	34	25.4	26	25.5	0.04	0.1	1.0	0.55-1.8
C/T	57	42.5	53	52.0	2.1	0.1	0.7	0.41-1.15
T/T	43	32.1	23	22.5	2.6	0.1	1.6	0.90-2.93

Respectively. In the group of CHF patients with FC II (n = 62), the C and T alleles were detected in 48.4% (n = 60) and 51.6% (n = 64) cases, and the C / C, C / T and T / T genotypes were found in 27.4 % (n = 17), 41.9% (n = 26) and 30.6% (n = 19) cases, respectively. And, finally, in the group of CHF patients with FC III (n = 26), the proportions of the frequencies of the C and T alleles were 40.4% (n = 21) and 59.6% (n = 31), and the C / C, C / T and T genotypes / T - 19.2% (n = 5), 42.3% (n = 11) and 38.5% (n = 10) cases, respectively. To clarify the role of the studied alleles and genotypes of the CYP11B2 gene polymorphism (rs1799998) in the development of CHF, the next stage was to conduct a comparative analysis of the differences in their distribution between the main (CHF, n = 134) and control (n = 102) groups, as well as between CHF groups in depending on the FC. 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%; $\chi2 = 1.1$; 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%; $\chi2 < 3.85$; p> 0.05; OR = 1.0; 95% CI: 0.55-1.8) and C / T (42.5% versus 52.0%; $\chi2 = 2.1$; 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%; $\chi2 = 2.6$; p = 0.1; OR = 1.6; 95% CI: 0.90-2.93).

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.

In order to study the peculiarities of the distribution of genotypes of the rs1799998 polymorphism of the CYP11B2 gene of CHF depending on the state of the glomerular filtration rate (GFR), the patients were divided into 2 groups: group 1 patients (n = 88) with a GFR level in the range of 60-90 ml / min / m^2 and group 2 (n = 46) with GFR below 60 ml / min / m^2. In the 2nd group of patients (n = 46), the C / C genotype was recorded very rarely both, in comparison with the control and the main group, and, in relation to the same in the 1st group of patients, accounting for 15.2% (n = 7) cases ... At the same time, the proportion of carriage of the C / T genotype (41.3%; n = 19) almost corresponded to that in the main group and in group 1 of patients, but at the same time it was recorded very rarely in comparison with the frequency in the control group (52.0%; n = 53). With regard to the proportion of carriage of the T / T genotype, its highest frequency was recorded (43.5%; n = 20) in comparison with the control, the group of CHF patients and 1 group of patients. We carried out a comparative analysis of the differences in the distribution of the frequencies of the genotypes of the CYP11B2 gene polymorphism (rs1799998) among all the studied groups. comparative analysis of differences in the frequency of genotypic variants of CYP11B2 gene polymorphism (rs1799998) between the control group and the group of patients with GFR <60 ml / min / m^2. Namely, it was statistically established that there is a tendency towards a decrease in the protective effect of the homozygous C / C genotype in relation to the formation of renal disorders, which was expressed by its

highest frequency in group 2 (15.2% versus 25.5%; $\chi 2$ = 1.9; p = 0.1; OR = 0.5; 95 % CI: 0.21-1.32). Along with this, a very high statistically significant difference was found in the distribution of the mutant genotype T / T, the frequency of which among patients was 2.6 times higher (43.5% versus 22.5%; $\chi 2$ = 6.7; p = 0.01; OR = 2.6; 95% CI: 1.25-5.6) in the absence of significant differences in the frequency of distribution of the heterozygous C / T genotype (41.3% versus 52.0%; $\chi 2$ = 1.4; p = 0.2; OR = 0.6; 95% CI: 0.32-1.31). The revealed, at the same time, statistically significant high difference in the frequency of distribution of the unfavorable homozygous genotype T / T among CHF patients with GFR <60 ml / min / m^2 compared to the control group ($\chi 2$ = 6.7; P = 0.01) allows us to highlight that the genotypic the variant of the T / T locus rs1799998 of the CYP11B2 gene plays an important role in the formation of a high risk of developing severe CHF with GFR <60 ml / min / m^2 as an independent genetic marker. According to the odds ratio, the risk of developing CHF with GFR <60 ml / min / m^2 with the carriage of this genotypic variant can increase 2.6 times. Comparative analysis of differences in the frequency of variants of genotypes of polymorphism of the CYP11B2 (rs1799998) gene between groups 1 and 2, revealed significant differences in the distribution of the wild C / C genotype, the frequency of which was higher in group 1 of patients (30.7% versus 15.2%; $\chi 2$ = 3.8; p = 0.05; OR = 0.4; 95% CI: 0.16-1.02) compared to its frequency in group 2. The established fact can be explained by the possible protective role of this genotype in relation to renal disorders and a decrease in GFR in patients with CHF in group 1 (table2).

Table 2: Differences in the frequency of genotypic variants of rs1799998 polymorphism of the CYP11B2 gene in groups 1 and 2 of CHF patients.

Genotypes	The number of genotypes examined				χ^2	P	OR	95% CI
	1group		2 group					
	n	%	n	%				
C/C	27	30.7	7	15.2	3.8	0.05	0.4	0.16- 1.02
C/T	38	43.2	19	41.3	0.04	0.8	0.9	0.44- 1.90
T/T	23	26.1	20	43.5	4.2	0.04	2.2	1.03- 4.61

The frequency of the mutant T / T genotype was 2.2 times statistically significantly higher among patients of group 2 with GFR <60 ml / min / m^2 (26.1% versus 43.5%; $\chi 2$ = 4.2; p = 0.04; OR = 2.2; 95% CI: 1.03 - 4.61). This significant difference in the distribution of the T / T genotype proves its role in the formation of renal disorders, leading to a decrease in GFR <60 ml / min / m^2.

DISCUSSION

The prognosis of patients with CHF remains extremely unfavorable: the risk of death in them is four times higher than in persons without CHF.[9,10] Therefore, CHF is one of the main problems in modern cardiology and has a global socio - economic nature. Hyperactivation of the SAS contributes to further hypertrophy and remodeling of the myocardium, the development of LV systolic and diastolic dysfunction, and the progression of CHF. Deterioration of the blood supply to organs and tissues, in particular to the kidneys, leads to the activation of the RAAS through the stimulation of renin synthesis. However, the hyperactivation of the SAS, which continues for a long time, begins to have a negative effect, due to excessive constriction of veins and arterioles, leads to an increase in pre- and afterload and a decrease in tissue perfusion. The results of epidemiological and population studies indicate that even the earliest subclinical kidney dysfunction (KD) is an independent and risk factor for CVC and death, as well as recurrent complications in patients with cardiovascular diseases.[11,12] Assessment of the functional state of the kidneys is important for the choice of preventive and therapeutic measures. Currently, the mutual negative influence of dysfunction of the heart and kidneys has been proven, expressed in the progression of KD with an increase in CHF.[13] DP is widespread among CHF patients - 45–63.6% and is an independent negative prognostic factor for the development of LV systolic and diastolic dysfunction, cardiovascular death, worsening of clinical outcomes, therefore, the assessment of the functional state of the kidneys is important for the treatment and prevention of KD in patients CHF.[14,15] As a result of our study, early predictors of the development of CHF and KD were developed, a program for predicting the course of the disease, which will help prevent the progression of both CHF and KD, and the development of new approaches to the treatment of CHF with KD, taking into account the polymorphism of the RAAS genes, helps to improve the course of the disease, increase the effectiveness of pharmacotherapy, mortality, improving the quality of life and prognosis of CHF patients with KD.[16,17]

CONCLUSION

Analysis of the results on the study of the characteristics of the allelic polymorphism of the CYP11B2 gene (rs1799998) among CHF patients revealed a tendency to an increase in the number of T / T homozygotes of the rs1799998 locus of the CYP11B2 gene in the general group of CHF patients with high odds ratios, indicating an increased risk of CHF. The revealed statistically highly significant differences in the incidence of the unfavorable T / T genotype of this gene polymorphism among CHF patients, depending on the level of GFR, prove its important role as an independent genetic

marker in increasing the risk of severe CHF with GFR <60 ml / min / m^2.

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