

Analysis of the Association of the Glu429Ala Polymorphism of the MTHFR Gene in the Development of Chronic Heart Failure in Patients with Coronary Heart Disease

Musashaykhov U. Kh.¹, Makhsudov O. M.¹, Aripov O. A.², Boboyev K. T.³

¹Andijan State Medical Institute, Uzbekistan

²Center for Professional Qualification Development of Medical Workers, Uzbekistan

³Republican Specialized Scientific and Practical Medical Center of Hematology, Uzbekistan

Abstract The study evaluated the role and significance of the Glu429Ala polymorphic markers in the MTHFR gene in the development of chronic heart failure (CHF) in 103 patients with ischemic heart disease (IHD). The actual distribution of genotypes of the Glu429Ala polymorphism of the MTHFR gene in the studied groups corresponded to the expected indicators according to the Hardy-Weinberg equation (HWE) ($p < 0.05$). When studying the effect of alleles and genotypes of the Glu429Ala polymorphism of the MTHFR gene in patients with II-IV FC of CHF. It was found that carriers of the Ser allele and Pro/Ser heterozygous genotype have an increased risk of developing CHF.

Keywords Chronic heart failure, IHD, Genotypes, Glu429Ala polymorphism in the MTHFR

1. Introduction

Chronic heart failure (CHF) is a syndrome that develops as a result of impaired myocardial ability to fill and/or empty, which in turn is accompanied by inadequate perfusion of organs, systems, and tissues. This manifests in symptoms such as fatigue, weakness, shortness of breath, and, as the condition progresses, edematous syndrome. CHF, being the outcome of all cardiovascular diseases (CVD), represents one of the significant challenges in modern healthcare. According to epidemiological data, the global prevalence of CHF is 2.4%, with its frequency increasing with age (among individuals over 45 years, it reaches 2.5%), and approximately 50% of patients, despite the use of combination therapy, die within 5 years [3].

The prevalence of chronic heart failure (CHF) continues to steadily increase, as CHF represents the outcome of the so-called cardiovascular continuum and remains one of the primary challenges in clinical cardiology. Over the past decade, CHF has garnered heightened attention from cardiologists. This is attributed to five main reasons: the growing number of patients with CHF, the poor prognosis of the disease, the rising number of hospitalizations due to CHF exacerbations, the unsatisfactory quality of treatment, and the increasing costs associated with managing CHF [2].

CHF is closely linked to disturbances in myocardial metabolic

processes, intracardiac and peripheral hemodynamic changes, and structural remodeling of the heart. Clinical diagnosis, disease stages and progression, as well as survival rates, life expectancy, and the risk of developing various cardiovascular complications in patients, are increasingly regarded as the most critical criteria for assessing the significance of specific factors in CHF [1].

It is becoming clear that there is a need to search for effective methods of early diagnosis and successful treatment of cardiac decompensation. Studies in recent years have shown that 16% of patients with chronic heart failure (CHF) experience an exacerbation of decompensation within the first month after discharge from the hospital, while 37% experience it within the first three months of follow-up [4].

It is becoming clear that there is a need to search for effective methods of early diagnosis and successful treatment of cardiac decompensation. Studies in recent years have shown that 16% of patients with chronic heart failure (CHF) experience an exacerbation of decompensation within the first month after discharge from the hospital, while 37% experience it within the first three months of follow-up [5,6].

These data highlight the significant importance of studies aimed at elucidating the mechanisms of the formation and progression of chronic heart failure (CHF), contributing to the development of new approaches for timely preventive measures against cardiovascular diseases through the early and accurate diagnosis of risks associated with pathological myocardial changes. This confirms the relevance of this topic.

2. Main Body

2.1. Purpose of the Study

To study the frequency of distribution and evaluate the relationship of the Glu429Ala polymorphism in the MTHFR gene in patients with chronic heart failure.

2.2. Material and Methods of Research

For our study, 103 patients with CHF were recruited. These patients were hospitalized in the 1st therapy department of the clinic of the Andijan State Medical Institute. Clinical and laboratory examinations were performed at the Republican Specialized Scientific and Practical Hematology Center under the Ministry of Health of the Republic of Uzbekistan.

The diagnosis of CHF was made based on current clinical recommendations. For this, clinical and laboratory examinations were performed, including: anamnesis data, patient complaints and clinical examination results, 6-minute walk test, laboratory tests - biochemical blood analysis, High-tech laboratory studies: molecular genetic analysis.

Genotyping of polymorphism Glu429Ala polymorphism in the MTHFR It was carried out on the basis of the method of Tag Man probes on an amplifier Rotor-Gene Q (Quagen Germany), using the commercial test kit of Syntol LLC (Russia).

Statistical processing of the results was performed using a standard application software package OpenEpi V.9.2. Analysis of the deviation of empirical genotype frequencies from The theoretically expected Hardy-Weinberg distribution was performed using the Statistica 6.0 software package.

2.3. The Results Obtained and Their Discussion

Comparative analysis of the allele frequency distribution of the MTHFR gene Glu429Ala polymorphism in samples

from patients with CHF, FC II, and comparison groups showed that in this group of patients, the proportion of the wild-type Glu allele was 76.0%, which was insignificantly lower than in the control group, while the mutant Ala allele was detected in 24% of cases and was insignificantly higher than in the reference group. In the control group, these alleles were 77.0% and 23.0%, respectively ($\chi^2 = 0.02$; $p = 0.9$; OR = 1.0; 95% CI: 0.50–1.82 and $\chi^2 = 0.02$; $p = 0.9$; OR = 1.1; 95% CI: 0.55–2.01) (Table 1).

At the same time, in the group of patients with CHF, FC II, the frequency of occurrence of the wild-type homozygous Glu/Glu and mutant Ala/Ala genotypes was observed to be statistically insignificantly lower than in the control group, amounting to 59.0% versus 54.6% and 5.7% versus 3.0%, respectively ($\chi^2 = 0.2$; $p = 0.6$; OR = 0.6; 95% CI: 0.38–1.83 and $\chi^2 = 0.4$; $p = 0.5$; OR = 0.5; 95% CI: 0.06–4.45) (Table 1).

During the study of the significance of the heterozygous Glu/Ala genotype in the development of CHF, it was found that in the group of patients with CHF and FC II, the frequency of occurrence of this genotype was 42.4%, with an odds ratio (OR) of 1.4, but it did not significantly differ from the group of conditionally healthy individuals (35.2%) ($\chi^2 = 0.6$; $p = 0.5$; 95% CI: 0.61–3.01) (Table 1).

In the next stage of our study on the significance of the MTHFR gene Glu429Ala polymorphism in the pathogenesis of CHF development in patients with IHD, an examination was conducted on a group of 105 conditionally healthy individuals. The distribution of alleles for this polymorphism showed that the Glu wild-type allele accounted for 77.0% while the Ala unfavorable allele was observed in 23.0% of cases. In a smaller group of 37 patients diagnosed with CHF, functional class III, the allele distribution revealed that the Glu wild-type allele was found in 73.0% of cases, whereas the Ala minor allele was present in 27.0% of cases.

Table 1. Comparative analysis of the prevalence of alleles and genotypes of the MTHFR gene Glu429Ala polymorphism in samples of patients with CHF, FC II and comparison groups

| Allele/Genotype | CHF, FC- II (n=33) | Control Group (n=105) | p | OR (95% CI) |
|-----------------|--------------------|-----------------------|-----|-----------------|
| Glu | 76.0% (n=50) | 77.0% (n=161) | 0.9 | 1.0 (0.50-1.82) |
| Ala | 24.0% (n=16) | 23.0% (n=49) | 0.9 | 1.1 (0.55-2.01) |
| Glu/Glu | 54.6% (n=18) | 59.0% (n=62) | 0.6 | 0.8 (0.38-1.83) |
| Glu/Ala | 42.4% (n=14) | 35.2% (n=37) | 0.5 | 1.4 (0.61-3.01) |
| Ala/Ala | 3.0% (n=1) | 5.7% (n=6) | 0.5 | 0.5 (0.06-4.45) |

Table 2. Comparative analysis of the prevalence of alleles and genotypes of the MTHFR gene Glu429Ala polymorphism in samples of patients with CHF, FC III and comparison groups

| Alleles and genotypes | Number of tested alleles and genotypes | | | | χ^2 | p | OR | 95%CI |
|-----------------------|--|------|---------------------------|------|----------|-----|-----|-----------|
| | CHF, FCIII n=37 | | Comparison group n=105 | | | | | |
| | n | % | n | % | | | | |
| Glu | 54 | 73.0 | 161 | 77.0 | 0.4 | 0.5 | 0.8 | 0.45-1.50 |
| Ala | 20 | 27.0 | 49 | 23.0 | 0.4 | 0.5 | 1.2 | 0.67-2.23 |
| Glu/Glu | 19 | 51.4 | 62 | 59.0 | 0.7 | 0.4 | 0.7 | 0.35-1.55 |
| Glu/Ala | 16 | 43.2 | 37 | 35.2 | 0.7 | 0.4 | 1.4 | 0.65-3.01 |
| Ala/Ala | 2 | 5.4 | 6 | 5.7 | 0.005 | 0.9 | 0.9 | 0.18-4.89 |

Table 3. Alleles and genotypes of the MTHFR gene Glu429Ala polymorphism in samples of patients with CHF, FC IV and comparison groups

| Allele/Genotype | CHF, FC-IV (n=33) | Control Group (n=105) | p | OR (95% CI) |
|-----------------|-------------------|-----------------------|-----|-----------------|
| Glu | 67.0% (n=44) | 77.0% (n=161) | 0.1 | 0.6 (0.33-1.11) |
| Ala | 33.0% (n=22) | 23.0% (n=49) | 0.1 | 1.6 (0.9-3.0) |
| Glu/Glu | 45.5% (n=15) | 59.0% (n=62) | 0.2 | 0.6 (0.26-1.27) |
| Glu/Ala | 42.4% (n=14) | 35.2% (n=37) | 0.5 | 1.4 (0.61-3.01) |
| Ala/Ala | 12.1% (n=4) | 5.7% (n=6) | 0.2 | 2.3 (0.60-8.62) |

In other words, among these patients, the frequency of the Glu allele was observed to be 1.1 times lower compared to the reference group, while the frequency of the Ala allele was found to be 1.2 times higher. However, despite this, the differences in the distribution of the MTHFR gene Glu429Ala polymorphism alleles between the studied groups were not statistically significant (for the Glu allele: $\chi^2 = 0.4$; $p = 0.5$; OR = 0.8; 95% CI: 0.45–1.50; for the Ala allele: $\chi^2 = 0.4$; $p = 0.5$; OR = 1.2; 95% CI: 0.67–2.23) (Table 2).

The results obtained from studying the frequency of occurrence of the Glu/Glu, Glu/Ala, and Ala/Ala genotypes of the MTHFR gene Glu429Ala polymorphism also showed that there was no sharp difference in the group of patients with CHF and FC III compared to the control group indicators ($\chi^2 > 3.84$; $p < 0.05$).

In the group of patients with CHF and FC III, the distribution of the Glu/Glu, Glu/Ala, and Ala/Ala genotypes was 51.4%, 43.2%, and 5.4%, respectively. In the control group, the Glu/Glu genotype was detected in 59.0% of cases, the heterozygous Glu/Ala genotype in 35.2%, and the unfavorable Ala/Ala genotype in 5.7% of cases (Table 2).

In the group of patients with CHF and FC IV, the frequency of occurrence of the minor Ala allele and the mutant Ala/Ala genotype was characterized by a 1.6- and 2.3-fold increase compared to the control group (33.0% vs. 23.0%; $\chi^2 = 2.6$; $p = 0.1$; OR = 1.6; 95% CI: 0.9–3.0 and 12.1% vs. 5.7%; $\chi^2 = 1.5$; $p = 0.2$; OR = 2.3; 95% CI: 0.60–8.2). In other words, despite statistically insignificant differences, there is a tendency suggesting that in patients with CHD, the presence of the minor Ala allele and the mutant Ala/Ala genotype of the MTHFR gene Glu429Ala polymorphism is associated with an increased risk (1.6 and 2.3 times) of the onset and progression of severe CHF (FC IV) (Table 3).

In the group of patients with CHF and FC IV, a slight decrease in the proportion of the positive Glu allele and the Glu/Glu genotype was observed compared to the control group (67.0% vs. 77.0%; $\chi^2 = 2.6$; $p = 0.1$; OR = 0.6; 95% CI: 0.33–1.11 and 45.5% vs. 59.0%; $\chi^2 = 1.9$; $p = 0.2$; OR = 0.6; 95% CI: 0.26–1.27) (Table 3).

3. Conclusions

Thus, in the group of patients with CHF and FC IV, an increase in the proportion of the minor Ala allele and the

unfavorable Ala/Ala genotype was observed compared to the CHF FC II-III group and the group of conditionally healthy donors. This, in turn, indicates that in patients with CHD, the detection of the minor Ala allele and the unfavorable Ala/Ala genotype of the MTHFR gene Glu429Ala polymorphism is associated with the likelihood of CHF development and a more severe clinical course.

The results of these analyses further confirm the importance of genetic testing in developing individualized approaches for conditions associated with CHD and CHF.

Such scientific investigations contribute to a better understanding of the pathogenesis of diseases and the development of effective treatment methods.

REFERENCES

[1] Galyavich A. S., Nedogoda S. V., Arutyunov G. P., Belenkov Yu. N. On the classification of chronic heart failure. Russian Journal of Cardiology. 2023; 28(9): 5584.

[2] Pieske B, Tschöpe C, de Boer RA, et al. How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). Eur J Heart Fail. 2020; 22(3): 391-412.

[3] Tereshchenko S. N., Galyavich A. S., Uskach T. M. Chronic heart failure. Clinical guidelines 2020. Russian Journal of Cardiology. 2020; 25(11): 4083. DOI: 10.15829/1560-4071-2020-4083.

[4] Drapkina O. M., Boytsov S. A., Omelyanovsky V. V. et al. Socioeconomic damage caused by chronic heart failure in the Russian Federation. Russian Journal of Cardiology. 2021; 26(6): 4490. DOI: 10.15829/1560-4071-2021-4490.

[5] Polyakov D. S., Fomin I. V., Belenkov Yu. N., et al. Chronic heart failure in the Russian Federation: what has changed over 20 years of observation? Results of the EPOCH -CHF study. Cardiology. 2021; 61(4): 4-14.

[6] Lam CSP, Voors AA, Piotr P, et al. Time to rename the middle child of heart failure: heart failure with mildly reduced ejection fraction. Eur Heart J. 2020; 41(25): 2353-5.

[7] Irtyuga O. B., Nedogoda S. V., Sitnikova M. Yu., et al. Results of the survey of the Russian Society of Cardiology "Chronic Heart Failure. Unresolved Problems". Russian Journal of Cardiology. 2024; 29(6): 5944.