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# Significance of Polymorphism G1691A of the FV Gene to the Risk of the Occurrence of Thrombophilic Conditions in Chronic Myeloproliferative Diseases

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**Abstract** The aim of the study was to study the role of the FV gene mutation (G1691A) in the risk of developing thrombophilic conditions in chronic myeloproliferative diseases. The results indicate differences in the frequency of occurrence of the unfavorable allele A and the heterozygous genotype G/A of the FV gene polymorphism (G1691A) between the studied groups of patients and controls. In particular, the G/A genotype carriage was registered only in the group of patients with chronic myeloproliferative diseases (CMP) with the highest frequency among patients with thrombosis ($\chi 2$ = 1.7; P = 0.2; OR = 4.4; 95% CI 0.391 -48.6). In turn, these facts confirm the low diagnostic significance of the studied genetic marker in the development of thrombosis in chronic myeloid leukemia (CML) and polycythemia vera (PV), which emphasizes the need to study several genetic markers that predispose to thrombosis.

**Keywords** Chronic myeloproliferative diseases (CMP), Chronic myeloid leukemia (CML), Polycythemia vera (PV), Carriage, Gene, Allele, Genotype

## 1. Introduction

Currently, one of the urgent and important problems of modern hematology are vascular thrombosis [2,3]. The high probability and difficulty of treating thromboembolic complications in hematological diseases necessitate the timely diagnosis of factors or early prediction of the risk of developing thrombophilic complications in patients with hemoblastosis, in particular in chronic myeloproliferative diseases (CMP) [4-6].

Recent studies have shown that important potential genetic risk factors for thrombosis are mutation of the FV gene (G1691A) [1,8]. Numerous studies on the role of the FV gene (G1691A) in susceptibility to the development of thrombosis have revealed the presence of this mutation in all populations of Europe and Asia, which predominate among people of European descent (5-10% vs. 2-3%) [7,9].

In this regard, we conducted a study of the frequency of occurrence of the FV gene (G1691A) among patients with CMP and conditionally healthy individuals.

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## 2. Main Body

### 2.1. The Purpose of Our Research

Study of the role of the FV gene mutation (G1691A) in the risk of developing thrombophilic conditions in chronic myeloproliferative diseases.

### 2.2. Material and Methods of Study

The work was performed on DNA samples isolated from the peripheral blood of patients with the most common CMP — chronic myeloid leukemia (CML, n = 32) and polycythemia vera (PV, n = 79), as well as the control group (n = 114). The collection of material for the study was carried out on the basis of the SRI H&BT MH RUz clinic among people of Uzbek nationality. All patients included in the study according to nosology were divided into 2 groups: Group 1 - persons with CML, Group 2 - with PV, each group being divided into two subgroups A - with thrombosis and B - without thrombosis.

Genotyping of the samples and detection of the FV gene mutation (G1691A) was performed by PCR on an Applied Biosystems 2720 device (USA) using the reagents of Scientific Production Association (SPA) Litech (Moscow, Russia), according to the manufacturer's instructions. Statistical analysis of the results was carried out using the

statistical software package "OpenEpi 2009".

### 2.3. Results of the Study

The frequency of alleles of the polymorphism of the FV gene (G1691A) was characterized by the fact that in the main group of patients the proportion of allele G and A was 99.1% and 0.9%, respectively, in the control group their values were slightly different and amounted to 99, 6% and 0.4%, respectively. Analysis of the distribution of genotypes G / G and G/A in the main (98.2% and 1.8%) and control groups (99.1% and 0.9%) shows that the proportion of heterozygous genotype among patients is 2 times higher than in the control group (table. 1).

An increase in the frequency of G/A genotype detection in the main group was observed due to patients with thrombosis, among whom this indicator was 3.8%, which was more than 4 times higher than its frequency in the control group ($\chi 2 = 1.7$; P = 0.2 ; OR = 4.4; 95% CI (0.391-48.6). Among patients with CMP without thrombosis, the carriage of this genotype was not detected, which proves the role of the G/A genotype of the FV gene polymorphism (G1691A) in the development of thrombosis in CMP (Table 2).

In the group of patients with CML, the proportion of alleles G and A was 98.4% and 1.6%, and the genotypes G / G and G/A - 96.9% and 3.1%. The increase in the frequency of detection of the allele A and the genotype G/A in the main group, with respect to the control, was noted due to the subgroup “A”, that is, among patients with thrombosis (10.0% and 9.1%, respectively), whereas in the “B” subgroup of patients without thrombosis their carrier state was not observed.

In the group of patients with true polycythemia, there was also a slight increase in the frequency of detection of the allele A (0.6% versus 0.4) and the G/A genotype (1.3% versus 0.9%) in comparison with the indicators in the control group. In subgroup “A” of patients with thrombosis, the detection rate of this allele and genotype was 1.2% and 2.4%, while in subgroup “B” they were not detected.

From the above values, it can be seen that the frequency of the adverse minor A allele and the heterozygous genotype G/A in the group of CML patients, in relation to patients with PV (1.6% versus 0.6% and 3.1% versus 1.3%), and also in comparison with the frequency of their detection in the control group (1.6% versus 0.4% and 3.1% versus 0.9%).

**Table 1.** Frequency of distribution of alleles and genotypes of the FV gene polymorphism (G1691A) in groups of patients with CMP and control

| Groups | | | Frequency distribution | | | | |
|---|---|---|---|---|---|---|---|
| | | | *Alleles* | | *Genotupes* | | |
| | | | G | A | G/G | A/G | A/A |
| Name | | *n* | % | | | | |
| CMP | | 111 | 99.1 | 0.9 | 98.2 | 1.8 | 0.0 |
| “A”, with | thrombosis | 53 | 98.1 | 1.9 | 96.2 | 3.8 | 0.0 |
| “B”, without | thrombosis | 58 | 100.0 | 0.0 | 100.0 | 0.0 | 0.0 |
| CML | | 32 | 98.4 | 1.6 | 96.9 | 3.1 | 0.0 |
| “A”, with | thrombosis | 11 | 95.4 | 4.5 | *90.9* | *9.1* | 0.0 |
| “B”, without | thrombosis | 21 | 100.0 | 0.0 | *100.0* | *0.0* | 0.0 |
| PV | | 79 | 99.4 | 0.6 | 98.7 | 1.3 | 0.0 |
| “A”, with | thrombosis | 42 | 98.8 | 1.2 | *97.6* | *2.4* | 0.0 |
| “B”, without | thrombosis | 37 | 100.0 | 0.0 | *100.0* | *0.0* | 0.0 |
| Control | | 114 | 100.0 | 0.0 | 100.0 | 0.0 | 0.0 |

**Table 2.** The difference in the frequency distribution of alleles and genotypes of the FV gene polymorphism (G1691A) in groups of patients with CMP with thrombosis and control

| Frequency distribution | | Groups | | Statistical significance | | | | |
|---|---|---|---|---|---|---|---|---|
| | | CMP with thrombosis | Control | | | | | |
| *n:* | | *73* | *75* | | | | | |
| *Alleles* | | | | $\chi^2$ | P | RR | OR | 95% CI: |
| G | abs | 104 | 227 | 1.7 | 0.2 | 4.3 | 4.4 | 0.391 - 48.6 |
| A | abs | 2 | 1 | | | | | |
| *Genotypes* | | | | | | | | |
| G/G | abs | 51 | 113 | 1.7 | 0.2 | 0.9 | 0.2 | 0.020-2.54 |
| G/A | abs | 2 | 1 | 1.7 | 0.2 | 4.3 | 4.3 | 0.3929-49.98 |
| A/A | abs | 0 | 0 | - | - | - | - | - |

Along with this, the observed and expected frequency distribution of the genotypes of the FV gene polymorphism (G1691A) in the main group of patients with CPMP and the control group corresponded to the theoretically expected one if the Hardy-Weinberg balance corresponded ($p > 0.05$).

In the main group of patients with CMP (0.98 and 0.95) and in the control group (0.99 and 0.99), the expected frequency of G / G genotype detection corresponded to the observed frequency, which indicates their Hardy-Weinberg balance ($p > 0.05$).

Thrombophilic conditions, in particular in chronic myeloproliferative disorders that lead to thrombotic complications, which often cause the death of patients, are an important medical and social problem [2,6].

In recent years, ideas about the molecular mechanisms of the formation of thrombophilic states have been significantly expanded [4]. Of particular interest is the study of polymorphisms of genes of congenital thrombophilia, namely the polymorphism of the FV gene (G1691A) [9].

## 3. Conclusions

Considering that we studied the role of the FV gene polymorphism (G1691A) in the development of thrombophilic conditions in patients with CMP, the results indicate differences in the incidence of the unfavorable allele A and the heterozygous genotype G/A of the FV gene polymorphism (G1691A) between the studied groups of patients and control. In particular, the carriage of the genotype G/A was recorded only in the group of patients with CPS with the highest frequency among patients with thrombosis ($\chi 2 = 1.7$; $P = 0.2$; $OR = 4.4$; 95% CI 0.391-48.6). In turn, these facts confirm the low diagnostic significance of the studied genetic marker in the development of thrombosis in CML and PV, which underlines the need to study several genetic markers that predispose to thrombosis.

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