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MOLECULAR AND GENETIC BASIS OF DIAGNOSTICS OF ESSENTIAL THROMBOCYTHEMIA

Musashaykhova Shakhnoza Mamirbekovna
Assistant of the Department of preparation of GP No. 1 ASMI c. Andijan, Uzbekistan

ABSTRACT
The criteria for the chance of detecting ET based on the carrier of the polymorphic marker JAK2V617F and W515L MPL were studied by comparison with patients with PMF and IP. In the group of ET patients and in the comparison groups in patients with PMF and PV, the actual distribution of genotypes of these polymorphisms did not deviate from the expected ones, at the Hardy-Weinberg equilibrium ($\chi 2=3.84$; $p<0.05$).
KEY WORDS: *polymorphism, ET, W515LMPL, gene, CMD, JAK2V617F, genotype.*

1. INTRODUCTION

Essential thrombocytemia (ET) is a chronic tumor myeloproliferative disease of clonal nature characterized by proliferation of megakaryocytes and persistent thrombocytosis [1, p. 125; 4, p. 369]. There are no population epidemiological data on morbidity and prevalence in Uzbekistan. The incidence, according to foreign registers, is approximately 1.5-2.53:100,000 population [6, p. 162; 3, p. 683]. The classical concepts of ET as a disease mainly of elderly people with a maximum incidence of 50-60 years are currently being revised. The discovery of the involvement of molecular genetic breakdowns in the pathogenesis of the disease (mutations in the genes JAK2, MPL, etc.) and the introduction into clinical practice of methods for their determination made it possible to identify a significant proportion of young patients. The ratio of women and men is approximately equal. However, there are slightly more women than men among young patients [5, p. 2403].

The etiology of the disease has not yet been established. The leading hypothesis is the polyetiological nature of the occurrence of the disease, where the predisposition to the disease is realized under the influence of external factors that damage the genome of a normal cell and lead to its malignant transformation. Hereditary predisposition to the disease may be due to the carrier 46/1 haplotype of the JAK2 gene [2, p. 1472]. Thus, the study of CMP should be continued in order to identify and describe new specific molecular genetic markers of clonality, which may contribute to a deeper understanding of the nature of this malignant myeloproliferative disease.

2. PURPOSE OF THE STUDY

To increase the effectiveness of ET diagnosis by evaluating the genetic markers W515L MPL and JAK2 V617F.

3. MATERIAL AND METHODS OF RESEARCH

DNA samples of 162 patients with CMD (ET, PMF and PV) were used as the material for carrying out a molecular genetic study for the JAK2V617F and W515L MPL carriers. Molecular genetic studies were carried out in the Department of Molecular Medicine and Cellular Technologies of the RSSPMC of Hematology of the Republic of Uzbekistan.

The frequency distribution of alleles and genotypes in the studied genes was checked for compliance with the Hardy-Weinberg equilibrium.

4. THE RESULTS OBTAINED AND THEIR DISCUSSION

In patients with ET, despite insignificant differences, a decrease in the proportion of carrying the JAK2+ positive genotype (35.2%) was found compared with patients with PMF (35.7%) and an increase in the frequency of distribution of the JAK2-negative genotype of the JAK2V617F gene (64.8%) compared with the group of patients with PMF (62.5%) (Tab. 1).

The results of the analyses show that the presence of these genotypes of the JAK2V617F gene does not increase the chance of detecting ET compared to patients with PMF ($\chi 2=0.1$; OR=0.9; 95%CI:0.4-2.03; p=0.9 and $\chi 2=0.1$; OR=1.1; 95%CI:0.49-2.48; p=0.9) (Table 1).

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Table 1. Differences in the frequency of factor JAK2V617F in the groups of patients with ET and PMF.

Factor	Number of people examined				χ2	p	OR	95%CI
	ET		PMF					
	n	%	n	%				
Yes (JAK2+)	19	35.2	18	37.5	0.1	p = 0.9	0.9	0.4 - 2.03
No (JAK2 -)	35	64.8	30	62.5	0.1	p = 0.9	1.1	0.49 - 2.48

The data of analyses of molecular genetic studies of the JAK2V617F gene showed that the frequency of detection of the JAK2 positive genotype of the JAK2V617F gene in patients with ET was significantly lower and the proportion of occurrence of the JAK2 negative genotype was significantly higher compared to patients with IP (35.2% vs. 83.3% at χ2=27.6; OR=0.1; 95%CI:0.05-0.25; p=0.01 and 64.8% vs. 16.7% at χ2=27.6; OR=9.2; 95%CI:4.02-21.1; p=0.01, respectively) (Table 2).

Table 2. Differences in the frequency of factor JAK2V617F in the groups of patients with ET and PV.

Factor	Number of people surveyed				χ2	p	OR	95%CI
	ET		PV					
	n	%	n	%				
Yes (JAK2+)	19	35.2	50	83.3	27.6	p = 0.01	0.1	0.05 - 0.25
No (JAK2 -)	35	64.8	10	16.7	27.6	p = 0.01	9.2	4.02 - 21.1

This indicates that there is no contribution of the JAK2 positive genotype to the chance of detecting AT in comparison with patients with IP. The data obtained for the detection of driver-somatic mutations of the polymorphism of the W515L MPL gene were as follows:

The frequency of determining the MPL positive genotype of the W515L MPL gene in patients with ET was slightly lower than in patients with PMF (5.6% vs. 16.7%, respectively), and the proportion of carrying the MPL negative genotype of the W515L MPL gene was marginally higher than in patients with PMF (94.4% vs. 83.3%, respectively, at22=3.3; OR=3.4; 95%CI:0.9-12.83; p=0.01) (Table 3).

This indicates that there is no contribution of this genotype to the chance of detection of ET compared to patients with PMF.

Table 3.Differences in the frequency of factor W515LMPL in groups of ET patients and PMF.

Factor	Number of people examined				χ2	p	OR	95%CI
	ET		PMF					
	n	%	n	%				
Yes (MPL+)	3	5.6	8	16.7	3.3	p = 0.1	0.3	0.08 - 1.11
No (MPL-)	51	94.4	40	83.3	3.3	p = 0.1	3.4	0.9 - 12.83

As can be seen from Table 4, in the subgroup of patients with ET, the incidence of thrombotic complications in JAK2 positive patients is significantly higher compared to CALR1+ and TN patients (26.3%). And in the group of patients with ET out of 12 CALR1+ patients, hemorrhagic complications were detected in 2 (16.7%), which is significantly higher compared to carriers of the JAK2+ mutation and TN (Table 4).

In both cases, complications such as thrombosis were not registered in the JAK2+ and MPL+ mutations in patients with ET and hemorrhages.

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Table 4. Molecular and genetic characteristics of patients (ET) with complications.

The studied indicator, the average value (95% CI)	ET n=13/54				
	***JAK2*+** n=5/19	***CALR1*+** n=1/12	***CALR2*+** n=0/7	***MPL*+** n=0/3	**TH** n=3/13
Thrombosis + 9/13	26.3%	8.3%	--	-	23.1%
Hemorrhages+ 4/13	**JAK2+ n=1/19**	**CALR1+ n=2/12**	**CALR2+ n=0/7**	**MPL+ n=0/3**	**TH n=1/13**
	5.3%	16.7%	--	-	7.7%

5. CONCLUSION

It follows from this that the presence of the JAK2 positive genotype of the JAK2 V617F gene and the MPL positive genotype of the W515L MPL gene does not increase the chance of detecting ET compared to patients with PMF and PV.

Based on the results of this study, the JAK2 polymorphism of the positive genotype of the JAK2V617F gene and the MPL positive genotype of the W515L MPL gene are not independent markers for the detection of ET by comparison with patients with PMF and PV.

Thus, the carriage of the JAK2 positive mutation of the JAK2 V617F gene is a factor that increases the risk of thrombotic complications in ET. And in the presence of the CALR1+ genotype of the CALR gene (insTTGTC), hemorrhagic complications were more often recorded in these patients.

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