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The authors:

Solovyova Yulia Alekseevna, postgraduate student of "Normal and Pathological Physiology" department, Federal State Autonomous Educational Institution of Higher Education "M. K. Ammosov North-Eastern Federal University". Address: 27 Oyunskogo Street Yakutsk, 677000. Office number: +7 (914) 276-71-20. E-mail: md.pop@mail.ru;

Borisova Natalya Vladimirovna, Doctor of Medical Sciences, Professor of "Normal and Pathological Physiology" department, Medical Institute, Federal State Autonomous Educational Institution of Higher Education "M. K. Ammosov North-Eastern Federal University". Address: 27 Oyunskogo Street Yakutsk, 677000. Office number: +7 (4112) 36-30-46. E-mail: borinat@yandex.ru;

Sleptsova Snezhana Spiridonovna, Doctor of Medical Sciences, Professor of "Infectious diseases, phthisiology and dermatovenereology" department, Medical Institute, Federal State Autonomous Educational Institution of Higher Education "M. K. Ammosov North-Eastern Federal University". Address: 27 Oyunskogo Street Yakutsk, 677000. Office number: +7 (4112) 43-22-25. E-mail: sssleptsova@yandex.ru;

Kurtanov Khariton Alekseyevich, Candidate of Medical Sciences, Chief researcher, Head of Department of Molecular Genetics, Yakut Science Centre of complex medical problems. Address: 4 Sergelyakhskoye shosse Yakutsk, 677000. Office number: (4112) 32-19-81. E-mail: hariton_kurtanov@mail.ru;

Pavlova Nadezhda Ivanovna, Candidate of Biological Sciences, leading researcher, Head of Hereditary Pathology laboratory, Yakut Science Centre of complex medical problems. Address: 4 Sergelyakhskoye shosse Yakutsk, 677000. Office number: (4112) 32-19-81. E-mail: solnishko_84@inbox.ru;

Solovyova Natalya Alekseevna, Candidate of Medical Sciences, leading researcher of Yakut Science Centre of complex medical problems. Address: 4 Sergelyakhskoye shosse Yakutsk, 677000. Office number: (4112) 32-19-81. E-mail: sonata608@yandex.ru.

T.N. Aleksandrova, N.I. Pavlova, Kh.A. Kurtanov, I.I. Mulina, V.N. Yadrikhinskaya

GENETIC HETEROGENEITY OF PH-NEGATIVE CHRONIC MYELOPROLIFERATIVE DISEASES

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ABSTRACT

Chronic myeloproliferative diseases are clonal diseases of the hematopoietic system, characterized by uncontrolled proliferation of myeloid line cells. Classic Ph-negative chronic myeloproliferative diseases include polycythemia vera, essential thrombocythemia and primary myelofibrosis. Main complications that occur in patients with chronic MPD include thrombosis and transformation to secondary acute myeloid leukemia. A key factor of pathogenesis of this group of diseases is presented by activation of the JAK-STAT signaling pathway due to *JAK2* and *MPL* gene mutations, as well as mutation of *CALR* gene. These mutations play an important role in diagnosis and defining of disease prognosis and scoring possible complications. *JAK2*V617F mutation was demonstrated to be the most important risk factor for thrombosis, but did not have any affect in overall survival. *CALR*-positive patients with essential thrombocythemia and primary myelofibrosis have better prognosis than those with *JAK2* mutation. The worst prognosis has «triple-negative» patients with primary myelofibrosis.

Keywords: chronic myeloproliferative diseases, *JAK2, MPL, CALR.*

Introduction. Chronic myeloproliferative diseases (chronic MPD) include clonal diseases which originate from multipotent hematopoietic stem cell. Diseases pathogenesis is caused by excessive proliferation of one or more myeloid lineages (erythroid, megakaryocytic, granulocytic), differentiating into mature forms. Classical Ph-negative MPDs include polycythemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis (PMF).

PV is characterized by clonal stem cell proliferation of the erythroid, granulocytic, megakaryocytic lines, and splenomegaly [4]. In ET prominent proliferation of megakaryocytic line occurs [1]. Patients with PV and ET are usually asymptomatic over several years. Most commonly diseases manifest with symptoms of microcirculation disorders after a long period of latent increase in blood cells counts. Primary myelofibrosis (PMF) is characterized by bone marrow replacement with fibrous tissue, leading to development of cytopenia and extramedullary hematopoiesis, primarily in the spleen. Patients with PMF have the poorest prognosis among the patients with Ph-negative MPD. The average life expectancy of these patients is 5-7 years [3]. Patients with chronic MPD have a high risk of thrombohemorrhagic complications and disease progression with transformation to secondary acute myeloid leukemia (AML) [2].

Modern ideas about the pathogenesis of chronic MPD

Discovery of *JAK2* gene mutation in 2005 significantly improved understanding of Classical Ph-negative MPD pathogenesis. It was demonstrated that 1849 G/T point mutation in exon 14 of *JAK2* gene, leading to the substitution of valine for phenylalanine at position 617 of the nucleotide chain leads to an activation of the JAK2 tyrosine kinase gene product and uncontrolled proliferation of myeloid germ cells [10]. JAK2 is a non-receptor tyrosine kinase, which plays a key role in signal transduction from cytokines to receptors via the JAK-STAT signaling pathway. Seven homologous regions of the enzyme (JH) include domains - JH1, JH2, SH2 (JH3 and JH4) and FERM (JH6 and JH7) (Fig.). The JH1 domain, an active kinase domain, located at the C-terminus (carboxyl) of protein, while the JH2 (pseudokinase) domain is considered to be catalytically inactive region. Pseudokinase domain inhibits the JH1 domain causes inhibition of JAK2 activity. The FERM and SH2 domains provide for the binding of JAK kinase and transmembrane cytokine receptors and regulate the kinase activity of the enzyme. When tyrosine kinase is affected by cytokine ligands (erythropoietin, thrombopoietin, interleukins), tyrosine is phosphorylated at the end of the JH1 domain, which causes signal transmission through the STAT5 proteins, STAT3, PAS-MARK and PI3K-AKT. The V617F mutation, located on the JH2 regulatory domain, results in the loss of autoinhibitory properties of JAK2 tyrosine kinase, its hyperactivation and cytokine-independent differentiation of myeloid cells [5, 6, 14]. In most cases, among patients with PV and PMF *JAK2*V617F, the mutation occurs in homozygous state with an allele burden of more than 50%. In these patients, as a result of mitotic recombination of chromosome 9p and duplication of mutant allele, the heterozygous mutation *JAK2*V617F transforms to the homozygous form. Among patients with ET heterozygous form of mutation with an allelic load of less than 50% is commonly observed [17].

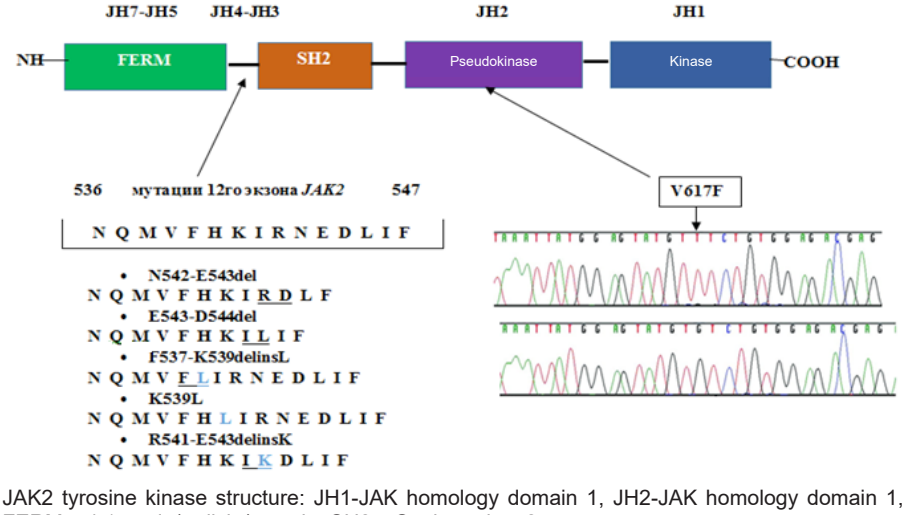
The second clinically significant mutation of *JAK2* gene is 12 exon mutation, which includes more than 40 different mutations located between the pseudokinase and SH2 domains (Fig.). The most common of these include mutations N542-E543del (23%), E543-D544del (11%), F537-K539delinsL and K539L (10%), and R541-E543delinsK (8%) [12, 24]. By changing the structure of the JH2 domain, they lead to a modification of the response to growth factor [2].

In the pathogenesis of megakaryocyte line proliferation, mutations in the *MPL* and *CALR* genes play a leading role. The *MPL* gene (myeloproliferative leukaemia virus) is located on chromosome 1p34, encodes a thrombopoietin receptor and is a key factor in the proliferation and differentiation of megakaryocytes. Clinical importance have mutations in 515 position of the *MPL*: W515L mutation (replacement of tryptophan with leucine at position 515) and W515K (replacement of tryptophan with lysine) [20]. Tryptophan at position 515 (W515) is a part of transmembrane domain, normally support the thromboprotein receptor in an inactive state, inhibiting its dimerization [29] .W515L/K mutations lead to spontaneous activation of the MPL receptor, increasing its sensitivity to thrombopoietin and cytokine-independent proliferation of hematopoietic cells.

The *CALR* gene (calreticulin) is located on the short arm of chromosome 19 (19p13.2). Calreticulin is a multifunctional protein expressed in the endoplasmic reticulum, cytoplasm, cell surface, extracellular matrix. Its main role is to keep calcium homeostasis, and also participates in the processes of proliferation, apoptosis, phagocytosis and the immune response [28]. To date, two mutations of exon 9 of *CALR* have been described, which plays an important role in the development of chronic MPD — a type 1 mutation (p.L367fs*46), representing a 52 b.p. deletion and mutation type 2 (p.K385fs*47) is an insertion of TTGTC. *CALR* mutations lead to a shift in the reading frame, the formation of a new C-terminal protein sequence and the loss of the KDEL signal sequence [3].

The prevalence of *JAK2*V617F mutation among patients with PV is more than 95%, and mutation of exon 12 – 4%. Among patients with ET and PMF, *JAK2*V617F mutation is detected in 60% of cases. Among patients with ET and PMF, *CALR* mutations are detected in 20-25% of cases, MPL is detected in 5%, and no mutations are detected in 5-10% [26].

Mutations of the *JAK2*, *MPL* and *CALR* genes are drivers that activate the JAK2 signaling pathway. In addition to the main driver mutations, a number of somatic mutations (in genes *TET2, ASXL1, DNMT3A, CBL, LNK, IDH1*



JAK2 tyrosine kinase structure: JH1-JAK homology domain 1, JH2-JAK homology domain 1, FERM – 4.1, ezrin/radixin/moesin, SH2 – Src homology2

/ 2, IKF1, EZH2, TP53, SRSF2) are described, encoding transcriptional and epigenetic factors. The role of these mutations, according to some authors, is to modulate the activity of the disease [26].

Hereditary predisposition to the development of chronic MPDs

Despite the fact that chronic MPDs are triggered by somatic mutations, family cases of this group of diseases are described [11]. The search of correlations between driver somatic mutations and different single nucleotide polymorphisms (SNPs) in the four candidate genes (EPOR, MPL, GCSFR and JAK2) by different groups of scientists led to the discovery of a link between the presence of specific SNPs *JAK2* gene and the development of chronic MPDs [17]. As a result of the conducted research, it was proved that hereditary predisposition to chronic MPDs is caused by carrying the haplotype 46/1 of *JAK2* gene. It is represented by 4 main SNPs (rs3780367, rs10974944, rs12343867 and rs1159782), which lead to the replacement of three thymidine residues (T) and one cytosine (C) with two guanosine (G) and two cytosine (C), forming a combination of “GGCC” [28].

The prevalence of *JAK2* 46/1 haplotype in a healthy population is about 24%, compared to 40–80% and 64% in *JAK2*V617F and 12 exon mutated patients with chronic MPDs. The potential link between the GGCC_46/1 haplotype and the somatic *JAK2* mutations is explained by the hypothesis of “hypermutability”, according to which the haplotype can somehow stimulate the mutation frequency in the *JAK2* gene [28].

Mutational status and disease phenotype

The determination of allele burden of the *JAK2*V617F mutation has a great importance in predicting the development of complications and outcomes of chronic MPD. Many studies have shown that the higher the allele burden cause more aggressive source of disease with high blood counts, massive splenomegaly and high risk of thrombotic complications [2].

The level of allele burden *JAK2*V617F is higher in patients with PV, compared with patients with ET and PMF [13]. *JAK2*V617F-positive patients with PV are more often characterized by three-lineage proliferation, when patients with 12 exon mutation of *JAK2* demonstrate a high level of hemoglobin, relatively low levels of platelets and leukocytes. In general, isolated erythrocytosis in PV, especially in young people, is a characteristic for *JAK2* exon 12 mutation [2].

In ET, *JAK2*V617F-positivity is characterized by clinics similar to PMF — a high level of hemoglobin, a relatively mild thrombocytosis [29], and a high rate of progression to PV [16]. Mutation of the *CALR* gene in patients with ET is associated with hyperthrombocytosis (> $1000*10^9$), but the risk of thrombotic complications is lower than in patients with the mutation *JAK2*V617F [7]. When comparing groups of patients with PV and ET and *JAK2*V617F mutation, the frequency of thrombosis did not differ, which suggests that the V617F mutation of the *JAK2* gene is the main marker of thrombogenic risk [28]. The high prevalence of thrombosis among JAK2-positive patients with ET is associated with hyperviscosity syndrome due to increased hematocrit and leukocytosis. The role of *MPL* mutation in patients with ET is not fully understood. According to some authors, the presence of *MPL* gene mutation is associated with a high frequency of transformation to secondary myelofibrosis and low survival rates [21, 22].

Patients with PMF with the *JAK2*V617F mutation have massive splenomegaly, high leukocytosis, thrombocytosis, low hemoglobin levels, which are unfavorable factors for the development of blast crisis and low overall survival rates [2]. *CALR*-positive patients with PMF usually have young age, low leukocyte count, and high thrombocytosis. During long-term follow-up of patients with *CALR* mutation, it was demonstrated that, compared with other mutational groups, they have a lower cumulative risk of developing anemia, thrombocytopenia, leukocytosis more than $25x10^9$/l and a longer interval of development of massive splenomegaly. The risk of thrombosis and blast transformation is also lower in patients with *CALR* mutation [11].

Mutational status and prognosis of the disease

ET and PV are diseases with a relatively benign course (average survival is 19,8 and 13,5 years, respectively), when PMF is characterized by low average survival rates (5,9 years), high risk of blast transformation and associated mortality [18].

The mutational status of *JAK2* does not affect the disease outcome. Clinical studies have demonstrated that the incidence of thrombotic complications, the development of secondary myelofibrosis, acute leukemia and death does not differ between patients with *JAK2*V617F and exon 12 mutations [19]. However, patients with a high allele burden are more likely to have thrombosis and transformation to myelofibrosis [25]. Allele burden did not demonstrate any affect to patients survival [15].

Among patients with ET, patients with *CALR* mutation have a more favorable prognosis compared with patients with *JAK2* mutation [1]. For *CALR*-positive patients, the best response to interferon therapy was demonstrated, and for *MPL*-positive patients, according to some authors, there is a high incidence of transformation to postthrombocythemic fibrosis [18] and low overall survival rates [22].

In case of PMF, the presence of a *CALR* mutation is also associated with a favorable prognosis of the disease with late development of anemia, leukocytosis, massive splenomegaly and low incidence of thrombosis (average overall survival of 17,7 years, cumulative 10-year risk of blast transformation 9,4%). *JAK2*-positive patients with PMF more frequently develop thrombotic complications, as in the case of PV and ET. The worst prognosis have patients with “triple negativity”, for whom the risk of blast transformation is 34%, and the average overall survival is 3.2 years [25].

Conclusion. The discovery of mutations in *JAK2*, *MPL* and *CALR* genes radically changed the understanding of the pathogenesis of Ph-negative chronic MPD. The introduction into clinical practice of various methods of molecular genetic research has improved the diagnosis of diseases, contributed to the development of prognostic scales and a personalized approach to therapy. Because of diversity of chronic MPDs phenotypes, due to genetic heterogeneity, practicians need molecular genetic tests to identify driver mutations and determine the prognosis, the risk of complications and the choice of patient management approach. However, more research is needed to clarify the role of other molecular events in the pathogenesis and formation of the phenotype of diseases.

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The authors:

Aleksandrova Tuiara Nikonovna – junior researcher of the laboratory of heritable pathology alexandrova_tuyara@mail.ru

Pavlova Nadezhda Ivanovna – PhD, temporary acting chief scientifc offcer - head of the laboratory of heritable pathology E-mail: solnishko_84@ inbox.ru;

Kurtanov Khariton Alekseevich – PhD, Chief Scientifc Offcer - Head of the Department of Molecular Genetics. Tel.: +7 (914) 106 00 30. E-mail: hariton_kurtanov@mail.ru.

Mulina Inna Ivanovna – Head of the Department of hematology National centre of Medicine

Yadrikhinskaya Vera Nikolaevna – candidate of medical sciences, associate professor of department «Hospital therapy, professional diseases, clinical pharmacology» Medical Institute of North-Eastern Federal University