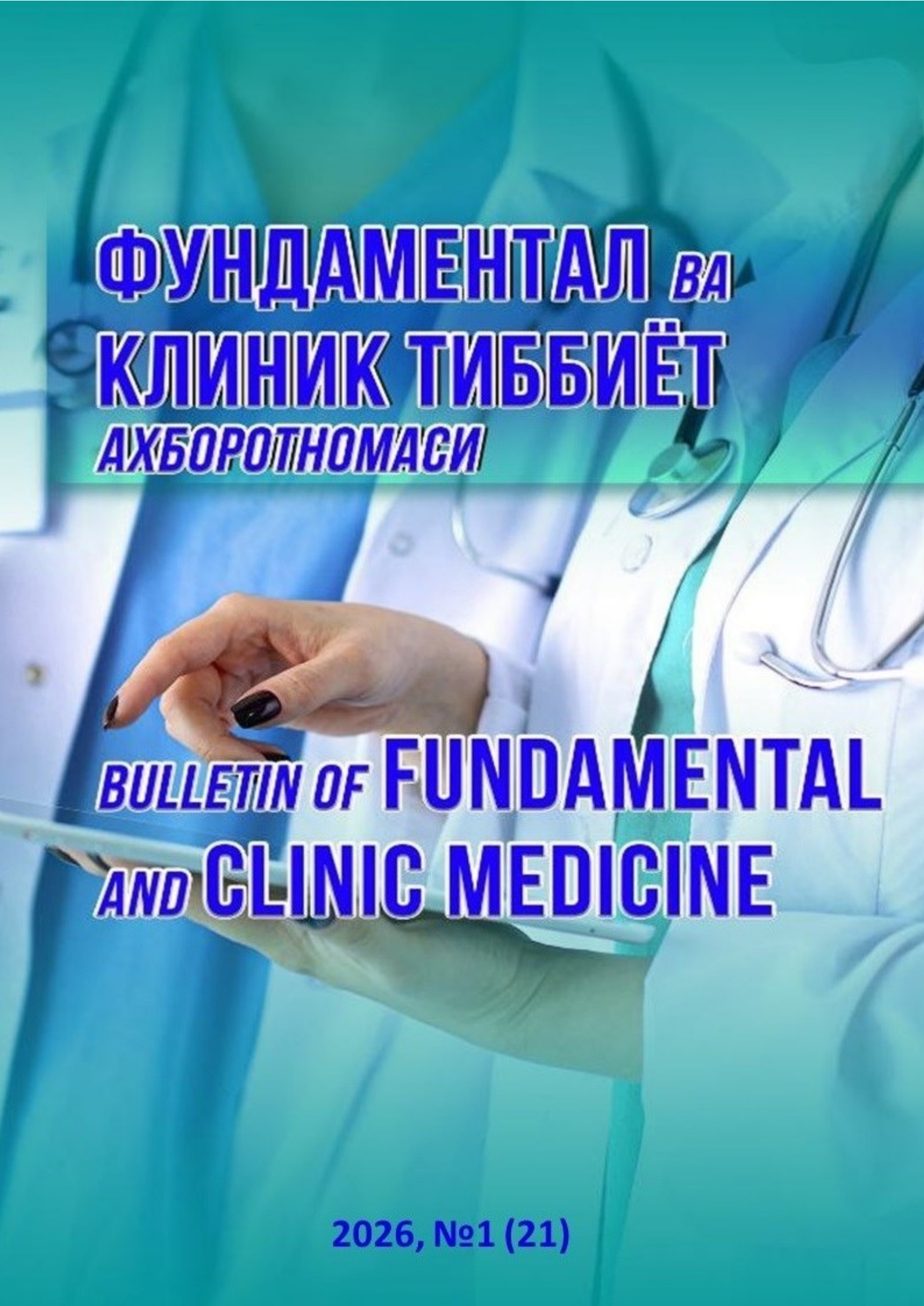

ФУНДАМЕНТАЛ ВА КЛИНИК ТИББИЁТ АХБОРОТНОМАСИ

BULLETIN OF FUNDAMENTAL AND CLINIC MEDICINE

2026, №1 (21)

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THE SIGNIFICANCE OF DRIVER GENE MUTATIONS JAK2, CALR, AND MPL IN CHRONIC MYELOPROLIFERATIVE DISEASES

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Resume. *Driver mutations in the JAK2, CALR, and MPL genes play a crucial role in the diagnosis of myeloproliferative disorders, enabling accurate identification of their type and exclusion of other diseases with similar symptoms. Purpose. To determine the role of driver gene mutations (JAK2, CALR, and MPL) in chronic myeloproliferative neoplasms (MPNs), including their significance in pathogenesis, diagnosis, and clinical management.*

Keywords: *Myeloproliferative diseases, diagnosis, driver genes: JAK2, CALR, MPL*

ЗНАЧЕНИЕ ДРАЙВЕРНЫХ МУТАЦИЙ ГЕНОВ JAK2, CALR, MPL ПРИ ХРОНИЧЕСКИХ МИЕЛОПРОЛИФЕРАТИВНЫХ ЗАБОЛЕВАНИЯХ

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Резюме. *Драйверные мутации генов JAK2, CALR и MPL играют важную роль в диагностике миелопролиферативных заболеваний, позволяя точно идентифицировать их тип и исключить другие заболевания со схожими симптомами. Цель. Определить роль мутаций драйверных генов (JAK2, CALR и MPL) в хронических миелопролиферативных новообразованиях (МПН), включая их значение в патогенезе, диагностике и клиническом ведении.*

Ключевые слова: *миелопролиферативные заболевания, диагностика, драйверные гены: JAK2, CalR, MPL.*

СУРУНКАЛИ МИЕЛОПРОЛИФЕРАТИВ КАСАЛЛИКЛАРДА JAK2, CALR ВА MPL ДРАЙВЕР ГЕН МУТАЦИЯЛАРИНИНГ АҲАМИЯТИ

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Резюме. *JAK2, CALR ва MPL генларидаги драйвер мутациялар миелопролифератив касалликларнинг диагностикасида муҳим роль ўйнайди. Улар касаллик турини аниқлаш ва ўхшаш симптомларга эга бўлган бошқа касалликларни истисно этиш имконини беради. Мақсад. Сурункали миелопролифератив неоплазмаларда (МПН) драйвер ген мутацияларининг (JAK2, CALR ва MPL) ролини, шу жумладан уларнинг патогенез, ташхис қўйиш ва клиник бошқарувдаги аҳамиятини аниқлаш.*

Калит сўзлар: *миелопролифератив касалликлар, диагностика, драйвер генлар: JAK2, CALR, MPL*

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Chronic myeloproliferative neoplasms (MPNs) represent a group of chronic malignant blood disorders characterized by the clonal proliferation of hematopoietic cells. This group includes diseases such as chronic myeloid leukemia (CML), polycythemia vera, essential thrombocythemia, and primary myelofibrosis. These diseases constitute a significant clinical challenge in modern hematology and oncology, and their importance is driven by both medical and socio-economic factors.

Chronic myeloid leukemia (CML) is a malignant myeloproliferative neoplasm characterized by the uncontrolled proliferation of granulocytic cells in the bone marrow. The key molecular feature of CML is the presence of the Philadelphia chromosome, which results from the reciprocal translocation t(9;22)(q34;q11), leading to the formation of the hybrid *BCR-ABL1* gene. The product of this gene—a tyrosine kinase with constitutive activity—triggers pathological signaling pathways responsible for uncontrolled cell growth and

survival.

Clinically, CML most commonly progresses through three phases: the chronic phase, the accelerated phase, and the blast crisis. During the chronic phase, the disease may be asymptomatic for a prolonged period or present with non-specific symptoms such as weakness, weight loss, night sweats, and splenomegaly. The diagnosis is confirmed using cytogenetic and molecular methods (PCR, FISH). Modern treatment is based on the use of tyrosine kinase inhibitors, which has significantly improved patient prognosis and life expectancy.

Polycythemia vera (PV) is a chronic myeloproliferative neoplasm characterized by a predominant increase in red cell mass, often accompanied by elevated leukocyte and platelet counts. The pathogenesis in most cases involves the JAK2 V617F mutation, or less frequently, mutations in exon 12 of the JAK2 gene, leading to constitutive activation of the JAK–STAT signaling pathway and erythropoietin-independent cell growth.

The clinical manifestations of PV include headaches, dizziness, aquagenic pruritus (itching after contact with water), erythromelalgia, and an increased risk of thrombosis. Splenomegaly is also frequently detected. Diagnosis is based on WHO criteria, incorporating clinical-laboratory parameters and molecular genetic testing. Treatment is aimed at reducing the hematocrit and preventing thrombotic complications.

Essential thrombocythemia (ET) is a myeloproliferative neoplasm whose primary hallmark is a persistent elevation in the platelet count in the peripheral blood. Mutations in the *JAK2*, *CALR*, and *MPL* genes play a key role in the pathogenesis of ET, leading to dysregulation of megakaryocytic lineage proliferation.

The clinical course of ET can be asymptomatic or be accompanied by thrombotic and hemorrhagic complications, headaches, and microcirculatory disturbances. The disease is characterized by a relatively favorable prognosis but requires long-term monitoring. The diagnosis is established by excluding other causes of thrombocytosis, assessing morphological changes in the bone marrow, and detecting characteristic driver mutations.

Primary myelofibrosis (PMF) is the most severe form of classic myeloproliferative neoplasms, characterized by progressive bone marrow fibrosis, disruption of normal hematopoiesis, and the development of extramedullary hematopoiesis. As with ET and PV, mutations in *JAK2*, *CALR*, or *MPL* are frequently identified in the pathogenesis of PMF.

The clinical presentation includes pronounced weakness, anemia, splenomegaly, weight loss, and constitutional symptoms. As the disease progresses, severe cytopenias and transformation into acute myeloid leukemia may occur. Diagnosis is based on histological examination of the bone marrow and molecular genetic analysis. The prognosis in PMF is less favorable compared to other MPNs.

In 1951, William Dameshek consolidated chronic myeloid leukemia (CML), polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF) into a single group of myeloproliferative neoplasms (MPNs). Based on characteristic morphofunctional and pathological criteria, this group was further expanded to include other malignant myeloproliferative tumors such as chronic neutrophilic leukemia, chronic eosinophilic leukemia, mastocytosis, and unclassifiable MPNs. The classic *BCR-ABL1*-negative (Ph-negative) MPNs comprise three main diseases: PV, ET, and PMF [1].

The discovery that many patients with polycythemia vera, essential thrombocythemia, and primary myelofibrosis express a mutation in the Janus kinase 2 (JAK2 V617F) gene—a kinase essential for the normal development of red blood cells, granulocytes, and platelets—provided a molecular explanation for the unregulated hematopoiesis typical of these disorders and offered a diagnostic test to distinguish them from other types of myeloproliferative disorders. This discovery also enabled the development of targeted therapy that could potentially avoid the toxicity associated with conventional chemotherapeutic agents currently used for their treatment [13,14].

The understanding of the genetic basis of myeloproliferative neoplasms began in 2005 when the JAK2 V617F mutation was identified in polycythemia vera, essential thrombocythemia, and primary myelofibrosis. Subsequently, JAK2 exon 12 and MPL exon 10 mutations were discovered in patients, and subclonal driver mutations in other genes were found to be associated with disease progression. Currently, somatic mutations in the CALR gene, encoding calreticulin, are known to be present in the majority of patients with essential thrombocythemia or primary myelofibrosis who lack JAK2 and MPL mutations. The detection of CALR mutations has increased the molecular diagnostic rate for ET and PMF to approximately 90%. It has been shown that JAK2V617F is not a unique event in disease pathogenesis [18].

The JAK-STAT pathway appears to be constitutively activated in all myeloproliferative neoplasms, regardless of the initiating driver mutation [9,10,16]. The most common mutation, JAK2 V617F, activates three major myeloid cytokine receptors (the erythropoietin receptor, the granulocyte colony-stimulating factor receptor, and MPL), whereas CALR or MPL mutants are limited to the activation of MPL. This explains why JAK2V617F is associated with polycythemia vera, essential thrombocythemia (ET), and primary myelofibrosis

(PMF), while CALR and MPL mutations are typically found in cases of thrombocythemia and myelofibrosis.

The JAK2V617F mutation is detected in nearly 95% of patients with polycythemia vera [8] and in 50–60% of patients with essential thrombocythemia or primary myelofibrosis [19]. Mutations in exon 12 of the JAK2 gene are found in approximately 4% of patients with polycythemia vera [12]. According to some researchers, the JAK2 gene harboring the V617F mutation activates V(D)J recombinase in the myeloid tumor cells of patients with chronic myeloproliferative neoplasms [2].

The positive predictive value of the JAK2 (V617F) PCR test is 95% for diagnosing PV and approximately 50% for ET and MF. The WHO-defined JAK2(V617F)-positive ET encompasses three distinct phenotypes at the clinical and bone marrow level when applying the integrated WHO and European Clinical, Molecular, and Pathological (ECMP) criteria: normocellular ET (WHO-ET), hypercellular ET due to increased erythropoiesis (prodromal PV), and hypercellular ET associated with megakaryocytic-granulocytic myeloproliferation (MGM-ET). Four major molecular subtypes of clonal MPN can be delineated: JAK2(V617F)-positive ET and PV; wild-type JAK2 ET carrying MPL(W515) mutations; CALR (calreticulin) gene mutations in wild-type JAK2/MPL ET and MF; and, in a small subset of patients, ET and MF that are wild-type for JAK2, MPL, and CALR [4].

According to some authors, the driver mutation determines the pathological features of MPNs, including lineage hyperplasia, laboratory findings, and the clinical phenotype [7,17,18]. MPNs with JAK2 mutations exhibited erythroid, granulocytic, and/or megakaryocytic hyperplasia, whereas MPNs with CALR and MPL mutations demonstrated granulocytic and/or megakaryocytic hyperplasia. The degree of lineage hyperplasia was strongly correlated with a higher mutant allele burden and the corresponding peripheral blood cytosis [7].

Diagnostic criteria for myeloproliferative neoplasms (MPNs) lacking the Philadelphia chromosome have been established by the World Health Organization, which classifies them as blood cancers. Acquired gain-of-function mutations in one of the three disease-driver genes (*JAK2*, *CALR*, and *MPL*) are causal events capable of initiating and sustaining MPNs on their own, without necessarily requiring additional cooperating mutations. Factors influencing the transition from clonal hematopoiesis to overt MPN disease include hereditary predisposition and the acquisition of additional somatic mutations.

Considering a range of other studies and publications, it can be concluded that chronic myeloproliferative neoplasms present a complex diagnostic challenge. Diseases belonging to this group often manifest with similar clinical signs, and laboratory findings commonly reveal myeloproliferation. Therefore, the clinician must accurately interpret the nature of changes in the complete blood count and discern the underlying causes of thrombocytosis, erythrocytosis, and leukocytosis.

Activation of the JAK-STAT pathway is a central element in the pathogenesis of MPNs. The **JAK2 V617F** mutation leads to constitutive kinase activation, causing the autonomous proliferation of hematopoietic cells independent of cytokine stimulation. Mutations in **CALR**, predominantly indel types (type 1 and type 2), alter the protein's structure, facilitating its pathological interaction with the MPL receptor and subsequent activation of JAK2. Mutations in **MPL** (most commonly W515L/K) similarly result in the constitutive activation of this signaling cascade.

In addition to the classic driver mutations, accompanying (co-occurring) mutations play a crucial role in the pathogenesis of MPNs, particularly in the stages of disease progression. These include alterations in genes regulating epigenetics (ASXL1, TET2, DNMT3A, EZH2), spliceosome components (SRSF2, U2AF1), and tumor suppressor genes (TP53). The accumulation of these mutations is associated with an unfavorable prognosis, an increased risk of bone marrow fibrosis, and transformation into acute myeloid leukemia. The detection of these changes via next-generation sequencing (NGS) is becoming the standard for risk stratification in patients with PMF.

In cases with ambiguous clinical and morphological presentation and negative results for *JAK2*, *CALR*, and *MPL* mutations, as well as for prognostic assessment in confirmed PMF, extended genetic testing is recommended. This may include screening for rare driver alterations in genes such as *CSF3R* and *FLT3*, as well as analysis of a panel of associated mutations (e.g., *ASXL1*, *SRSF2*, *EZH2*, among others).

Modern diagnosis and management of patients with MPNs now transcend the mere identification of the three principal driver mutations. Comprehensive genomic profiling, which includes the detection of associated mutations, not only aids in clarifying the diagnosis in complex cases but also enables the assessment of an individual risk profile, thereby paving the way for truly personalized therapy.

It is noteworthy that different driver mutations differentially influence the cellular epigenetic landscape. For instance, the *JAK2* V617F mutation has been shown to be associated with alterations in DNA methylation patterns and histone modifications, thereby promoting clonal expansion and disease progression.

The type of driver mutation holds prognostic significance. *CALR* mutations (particularly type 1) in

patients with ET and PMF are associated with a lower risk of thrombotic complications and better overall survival compared to *JAK2* V617F. The allele burden of *JAK2* V617F correlates with the severity of symptoms, the risk of bone marrow fibrosis, and transformation to acute leukemia. Patients with *MPL* mutations more frequently present with marked splenomegaly and have a higher risk of myelofibrosis progression.

The modern diagnostic algorithm for suspected Ph-negative MPNs should include:

1. Clinical and laboratory evaluation (CBC, biochemistry, abdominal ultrasound).
2. First-line molecular genetic testing: PCR for *JAK2* V617F.
3. If negative, proceed to sequencing of *JAK2* exon 12, *MPL* exon 10, and the *CALR* gene.
4. In complex cases and to detect co-occurring mutations: use of NGS panels, which is crucial for risk stratification.
5. Histological examination of the bone marrow with immunophenotyping.

The discovery of driver mutations has led to the development of targeted therapies. JAK2 inhibitors have proven effective in reducing symptoms and splenomegaly in patients with PMF, regardless of their mutation status. However, the search for selective inhibitors for patients with CALR and MPL mutations remains an important challenge. The potential of combining JAK inhibitors with other agents (e.g., peginterferon, histone deacetylase inhibitors) to overcome clonal resistance is being actively explored.

The distribution of driver mutations can vary among different populations. Studies in Uzbek patients with MPNs have also confirmed the leading role of *JAK2*, *CALR*, and *MPL* mutations; however, their precise frequency and the spectrum of rare variants require further data accumulation. Investigating ethnic characteristics is crucial for tailoring and optimizing diagnostic panels within the region.

Conclusion. Thus, driver mutations in the *JAK2*, *CALR*, and *MPL* genes represent the cornerstone for understanding the pathogenesis, diagnosis, and prognosis of chronic myeloproliferative neoplasms. Their detection enables not only precise differentiation within this disease group but also risk stratification of patients and, in many cases, guides targeted therapeutic decisions. Modern clinical practice for diagnosing MPNs is unfeasible without the application of molecular-genetic methods. Further research in genomics and the development of novel therapeutic agents will pave the way for a truly personalized management approach to these diseases, ultimately improving patient quality of life and survival outcomes.

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