Abstract 033

INTERPRETATION OF GENETIC TESTING IN CHRONIC MYELOPROLIFERATIVE NEOPLASMS

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Chronic myeloproliferative neoplasms (MPNs) represent a group of clonal hematopoietic stem cell disorders characterized by uncontrolled proliferation of one or more myeloid lineages. The discovery of recurrent driver mutations has transformed the diagnostic, prognostic, and therapeutic landscape of these disorders. This article reviews the clinical relevance of genetic testing in MPNs, with a focus on driver and additional mutations, and their implications for patient management. **Introduction:** Chronic myeloproliferative neoplasms, including polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF), are defined by clonal proliferation of hematopoietic progenitors. The molecular era has revealed the critical role of somatic mutations in their pathogenesis. Genetic testing has now become integral to diagnosis, risk stratification, and therapeutic decision-making. Driver Mutations JAK2 - JAK2 V617F mutation is present in approximately 95% of PV cases and 50–60% of ET and PMF cases. - It leads to constitutive activation of the JAK-STAT signaling pathway, driving cytokine-independent proliferation. - Allele burden correlates with clinical phenotype and thrombotic risk. CALR - Detected in 20–30% of ET and PMF patients who are JAK2-negative. - Mutations, mostly frameshift in exon 9, generate novel C-terminal peptides. - CALR-mutated ET patients often present at a younger age, with higher platelet counts and relatively favorable prognosis. MPL - Mutations in the thrombopoietin receptor gene, most commonly W515L/K, occur in 3–5% of ET and PMF cases. - They lead to constitutive activation of thrombopoietin signaling and megakaryocyte proliferation. Additional Mutations - Genes such as ASXL1, EZH2, SRSF2, IDH1/2, and TP53 are frequently mutated, particularly in PMF. - These mutations are not disease-defining but provide prognostic information. - ASXL1 mutation, for instance, is associated with adverse prognosis and impacts decisions regarding allogeneic stem cell transplantation. Clinical Applications Diagnosis - The WHO (2022) and ICC (2022) classifications incorporate genetic testing into diagnostic criteria. - Identification of JAK2, CALR, or MPL mutations confirms clonality and assists in differentiating MPNs from reactive conditions. - Triple-negative patients (negative for JAK2, CALR, MPL) often exhibit more aggressive clinical behavior. Prognosis - Prognostic scoring systems such as MIPSS70, GIPSS, and DIPSS-plus include molecular findings. - The presence of high-risk mutations predicts increased risk of progression to acute leukemia and reduced overall survival. Therapeutic Implications - JAK2 allele burden informs thrombotic risk stratification and the need for cytoreductive therapy. - The detection of adverse mutations influences consideration for hematopoietic stem cell transplantation. - Targeted therapies, such as JAK inhibitors, have been developed based on the molecular pathogenesis of MPNs. Future Perspectives The integration of next-generation sequencing (NGS) panels into clinical practice allows for comprehensive molecular profiling. This facilitates the development of personalized treatment strategies, including targeted therapies beyond JAK inhibition. Ongoing clinical trials are exploring agents directed against epigenetic regulators and splicing factors. **Conclusion:** Genetic testing has revolutionized the approach to chronic myeloproliferative neoplasms. Driver mutations (JAK2, CALR, MPL) remain essential for diagnosis, while additional mutations provide prognostic and therapeutic guidance. The expanding role of molecular testing paves the way toward precision medicine in MPNs.

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Abstract 034

ATYPICAL HEMOLYTIC UREMIC SYNDROME: FROM PATHOPHYSIOLOGY TO THERAPEUTIC ADVANCES

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Introduction and Pathophysiology: Atypical hemolytic uremic syndrome (aHUS) is a rare, life-threatening thrombotic microangiopathy (TMA) distinct from Shiga toxin-producing Escherichia coli (STEC)-related HUS. It is primarily driven by genetic or acquired dysregulation of the complement system, with pathogenic variants in complement factor H (CFH), factor I (CFI), membrane cofactor protein (MCP/CD46), factor B (CFB), and C3 identified in nearly 60% of patients. The resulting uncontrolled activation of the alternative complement pathway leads to endothelial damage, platelet activation, and microvascular thrombosis, most prominently affecting renal function. Clinically, aHUS is characterized by the triad of microangiopathic hemolytic anemia, thrombocytopenia, and organ injury, most commonly renal but often involving extrarenal systems such as cardiovascular, neurological, dermatological, and gastrointestinal organs. Diagnosis is challenging, requiring exclusion of other TMAs such as thrombotic thrombocytopenic purpura (TTP) and typical HUS. Early and accurate identification is essential to prevent irreversible organ damage. **Advances in Diagnosis and Treatment:** Diagnostic workup integrates clinical, laboratory, and genetic testing. ADAMTS13 activity measurement is critical to exclude TTP, while Shiga toxin assays help differentiate typical HUS. Complement biomarkers, including soluble C5b-9 and factor Ba, are under investigation for their diagnostic and prognostic utility. Genetic testing, employing next-generation sequencing and MLPA, provides prognostic insights and guides therapy, though penetrance remains incomplete and environmental triggers (infections, pregnancy, transplantation) play a pivotal role. Therapeutically, plasma exchange was historically the first-line option, but outcomes were poor with high rates of end-stage renal disease (ESRD). The advent of complement inhibitors has revolutionized management. Eculizumab, a monoclonal antibody targeting C5, effectively halts terminal complement activation, resulting in rapid