The impact of germline and somatic mutations in myelo-proliferative neoplasms: a systematic review

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Abstract - Hematological malignancies known as myeloproliferative neoplasms (MPNs) are defined by the irregular growth of myeloid cells in the bone marrow. Genetic changes that were acquired and give hematopoietic stem cells a selective growth advantage are what cause MPNs to develop and advance. The purpose of this comprehensive review is to investigate how germline and somatic mutations affect the onset, course, and prognosis of MPNs. We present a thorough overview of the genetic landscape of MPNs by reviewing pertinent publications, concentrating on important driver mutations, their functional ramifications, and their clinical importance. The JAK-STAT signaling pathway is activated by the JAK2 V617F mutation, MPL mutations, and CALR mutations, which are three of the most frequent somatic mutations seen in MPNs. Although uncommon, familial variants of MPNs have been found to have chromosomal alterations. For risk classification, individualized therapy regimens, and prognosis evaluation in MPN patients, it is essential to comprehend the importance of these genetic changes. The results underline the significance of genetic profiling in MPNs and open new avenues for investigation into additional mutations and their functional effects.

Keywords: myeloproliferative neoplasms, MPNs, hematological malignancies, germline mutations, somatic mutations, JAK-STAT signaling pathway.

I. INTRODUCTION

MPNs is set of clonal hematological illnesses known as myeloproliferative neoplasms (MPNs) are defined by the aberrant growth of mature myeloid cells in the bone marrow. Among these conditions are primary myelofibrosis (PMF), polycythemia vera (PV), and essential thrombocythemia (ET). Acute leukemia may occur as a result of the dysregulated hematopoiesis that results from MPNs' genetic changes in hematopoietic stem cells[1]. Substantial progress has been made in understanding their underlying molecular basis. The clonal nature of these disorders and the presence of somatic mutations, particularly the discovery of JAK2 V617F mutation as a hallmark in the majority of PV and a significant subset of ET and PMF cases[2]. There are various clinical symptoms of MPNs linked to them, from asymptomatic cases to life-threatening thrombohemorrhagic consequences. The importance of genetic profiling in determining the severity of the disease and the effectiveness of treatment is highlighted by the prognostic value of cytogenetic abnormalities in PMF[3]. The somatic mutations in genes like JAK2, CALR, and MPL are important initiators of MPN pathogenesis, interest in germline mutations is growing. An elevated propensity to develop MPNs has been attributed to inherited from one or both parents, germline mutations[4]. The MPL pathway is implicated in the pathophysiology of familial MPNs due to germline mutations in the thrombopoietin receptor (MPL) gene found in families with hereditary thrombocytosis[5]. The main goal of this systematic review is to thoroughly assess and synthesize the current literature on the influence of these mutations on the formation, progression, and prognosis of MPNs in light of the rising acknowledgment of the significance of both germline and somatic mutations in MPNs. This review aims to give a current summary of the MPN-related germline mutations and how they affect disease propensity and also examine the importance of mutations in MPNs (JAK2, CALR, MPL, etc.) and how they relate to the phenotype and prognosis of the disease. This Study intricate interactions between somatic and germline mutations and how they affect disease causation and therapeutic outcomes and underlying molecular mechanisms in MPNs cause dysregulated hematopoiesis.

The term "myeloproliferative neoplasm" (MPN) refers to a class of clonal hematological illnesses in which one or more types of mature myeloid cells within the bone marrow proliferate unchecked. Hematopoietic stem cells that have undergone genetic changes to cause aberrant signaling pathways and dysregulated hematopoiesis, which culminate in certain neoplastic diseases[6]. MPNs can manifest as essential thrombocythemia (ET), polycythemia vera (PV), primary myelofibrosis (PMF), and less commonly, chronic myeloid leukemia (CML) and chronic neutrophilic leukemia (CNL). The World Health Organization (WHO) classifies MPNs as belonging to the larger group of myeloid neoplasms. In order to include molecular genetic information and designate unique organisms within the MPN category, the WHO updated its categorization in 2016[7-8]. An increased red blood cell mass is a defining feature of polycythemia vera

(PV)[4], While PMF is characterized by bone marrow fibrosis and cytopenias, ET is characterized by prolonged thrombocytosis. CML and CNL are also considered MPNs but are more rare and distinct entities.

In order to cause dysregulated signaling pathways involved in hematopoiesis, acquired somatic mutations in important driver genes are implicated in the pathogenesis of MPNs[9]. JAK2 V617F, CALR exon 9 indels, and MPL W515 mutations have been identified as the most frequently occurring driver mutations in MPNs. The JAK2 V617F mutation is the most common, being present in a sizable part of ET and PMF cases in addition to the majority of PV cases. The majority of individuals with MPL W515 mutations and CALR exon 9 indels are discovered in patients who do not have JAK2 V617F, further demonstrating the molecular heterogeneity of MPNs.Depending on the exact disease subtype and the severity of myeloid cell overproduction, the clinical characteristics of MPNs might vary greatly. Fatigue, splenomegaly, thrombosis, bleeding diathesis, and constitutional symptoms such: night sweats and weight loss are typical clinical signs. Integrating clinical, laboratory, bone marrow, and genomic testing to detect driver mutations is essential for accurate diagnosis[10].

II. MUTATIONS IN MYELOPROLIFERATIVE NEOPLASMS

The pathogenesis of Myeloproliferative Neoplasms (MPNs) is significantly influenced by germline mutations, a topic that has recently attracted more attention. These inherited genetic changes exist in germline cells and can be handed down from one generation to the next, increasing the risk of developing MPNs. Genetic changes that are passed down through the germ line can impact the DNA of germ cells (sperm and egg cells)[11]. Consequently, these abnormalities affect every cell in the body, including hematopoietic stem cells[12], which may result in the unusual myeloid cell growth seen in MPNs. These inherited mutations function as genetic risk factors, increasing a person's vulnerability to accumulating other somatic mutations during their lifespan and driving the growth of MPNs. A number of genes have been linked to germline mutations connected to MPNs. The JAK2 gene stands out among them as a significant contributor to MPN pathogenesis[13].

The JAK2 V617F mutation is the leading germline mutation and is found in a significant proportion of patients with PV, ET, and PMF. Other commonly implicated genes comprise MPL (thrombopoietin receptor) and CALR (calreticulin), with germline mutations in these genes being associated with familial forms of MPNs and hereditary thrombocytosis. MPNs with inherited mutations have specific clinical and phenotypic characteristics. Patients may exhibit earlier illness onset, a more severe disease course, or a higher risk of thrombotic events if they have germline mutations in the JAK2, MPL, or CALR genes[14]. Additionally, particular germline mutations may affect the likelihood that a leukemic transformation may convert[15] and could be connected to specific clinical MPN subtypes.

The therapy recommendations for MPNs requires an understanding of how germline mutations affect illness development and prognosis. Patients with particular germline mutations may react differently to conventional treatments[16-17] or display different illness progression rates. These genetic discoveries have also made it possible to develop targeted treatments that try to alter the signaling pathways affected by germline abnormalities[18]. Germline mutations in MPNs have impact on clinical phenotype, illness progression, and therapeutic therapy.

Somatic mutations are inherited genetic changes that take place in the body's cells during the course of a person's life. Somatic mutations are essential for promoting the clonal proliferation of myeloid cells and assisting in the pathogenesis of Myeloproliferative Neoplasms (MPNs). Hematopoietic stem or progenitor cell genetic modifications lead to somatic mutations in MPNs. These mutations activate signaling pathways that support myeloid cell proliferation that is out of control, poor differentiation, and extended survival[1,10]. The formation and progression of MPNs are influenced by the acquisition of somatic mutations, particularly in driver genes such JAK2, CALR, MPL, and TET2. JAK2 is the most frequently mutated gene in MPNs, and individuals with PV, ET, and PMF are disproportionately affected by the JAK2 V617F mutation. Both the MPL W515 mutation and the CALR exon 9 indels are frequently seen, especially in patients who do not have JAK2 V617F. Additionally, it has been determined that mutations in genes including TET2, ASXL1, and IDH1/2 contribute to the development of clones and the development of MPNs. In MPNs, clonal evolution is an active process fueled by the accumulation of new somatic mutations over time[19]. Subclones with distinctive genetic mutations may appear as the disease worsens, increasing clonal complexity and clinical heterogeneity[12]. This clonal development aids in leukemia progression, clinical change, and treatment resistance.

There are certain somatic mutations in MPNs are linked to certain clinical and phenotypic characteristics. For instance, patients with JAK2 V617F positivity frequently exhibit greater hemoglobin and hematocrit levels in PV[16]. while in ET, CALR-mutated cases frequently had lower platelet counts. Additionally, some mutations may affect the likelihood of developing an illness, experiencing

thrombotic events, or surviving at all[17]. The decisions regarding risk classification and therapy are significantly impacted by the identification of particular somatic mutations in MPNs. For instance, certain mutations may increase the chance of leukemia transformation or disease progression, necessitating more aggressive therapeutic measures[20]. Additionally, the discovery of therapeutic mutations has created new opportunities for focused treatments like JAK inhibitors, offering a specialized method of managing MPN[21].

III. INTERPLAY BETWEEN GERMLINE AND SOMATIC MUTATIONS IN MYELOPROLIFERATIVE NEOPLASMS

The pathophysiology and clinical features of myeloproliferative neoplasms (MPNs) are influenced by a complex interplay between germline and somatic mutations. The relationship between these two varieties of mutations has a significant impact on how MPNs grow, progress, and present clinically. The genetic basis for the development of MPNs, which creates a propensity to these illnesses, is provided by germline mutations. But what turns the hematopoietic stem cells into neoplastic clones is the eventual acquisition of somatic mutations. Combining particular germline and somatic mutations affects disease phenotype and may have an effect on therapy outcomes[7]. Additionally, some germline variants may accelerate or exacerbate the acquisition of particular somatic mutations, hastening the development of the disease.

Somatic mutations in MPNs can be acquired with the aid of germline mutations. For instance, individuals with germline mutations like the MPL W515L/K mutations that predispose them to excessive cytokine signaling may be more likely to develop future somatic mutations like JAK2 or CALR. When these genetic changes co-occur, it can lead to a more aggressive disease phenotype than in instances where only somatic mutations occur[11]. Different disease features of MPNs are associated with particular combinations of germline and somatic mutations. In contrast to individuals with somatic mutations only, those with JAK2 V617F germline mutations may present with more severe clinical symptoms, such as increased leukocyte counts and spleen enlargement[16]. The risk of leukemic transformation and overall survival may be impacted by specific germline-somatic mutation combinations.

It is essential for clinical practice to comprehend how somatic and germline mutations interact in MPNs. A more individualized approach to treatment may be possible with the discovery of particular germline mutations that can help with risk assessment and prognosis determination. The choice of targeted medicines, such as JAK inhibitors, may also be influenced by this information in order to successfully control MPNs in individuals with certain mutation patterns. MPNs' molecular and clinical landscape are dynamically shaped by the interaction between germline and somatic mutations.

IV. CLINICAL AND THERAPEUTIC IMPLICATIONS IN MYELOPROLIFERATIVE NEOPLASMS

There are important prognostic consequences for identifying particular germline and somatic mutations in Myeloproliferative Neoplasms (MPNs). The specific mutations can be linked to particular disease traits, disease progression rates, and overall survival. For instance, the presence of particular somatic mutations, such as ASXL1 or TP53, has been associated with a higher risk of leukemogenesis and worse outcomes in MPNs[20]. Risk classification and treatment choices are influenced by an understanding of the prognostic significance of these mutations. The possibility of individualized treatment strategies has emerged as our understanding of the genetic environment in MPNs has grown. Patients with particular somatic or germline mutations may react differently to conventional treatments. Patients with MPNs who are JAK2 V617F-positive, for instance, have responded well to JAK inhibitors such ruxolitinib. On the other hand, patients with CALR mutations typically have a better prognosis and may react differently to JAK inhibitor therapy. Personalized therapy plans that consider the mutational profile of the patient can improve therapeutic results.

Potential treatment targets have been found thanks to the identification of distinct germline and somatic mutations in MPNs. JAK inhibitors are one type of targeted therapy that has been developed to directly disrupt the dysregulated signaling pathways caused by mutations like JAK2 V617F. Novel drugs are also being researched to target CALR and MPL, two more mutant genes. The discovery of these molecular targets presents promising chances for creating medicines that are both more efficient and less harmful.

The complexity of the genetic environment, clonal evolution, and the potential existence of numerous mutations in a single patient are only a few of the obstacles that precision medicine in MPNs must overcome. Additionally, not all mutations have obvious therapeutic targets, which in some circumstances limits the rapid usefulness of targeted medicines. To expand the use of precision medicine strategies, limitations related to cost, accessibility, and genetic testing must be removed. But there are also huge potential for MPN management thanks to precision medicine. Comprehensive mutational profiling is now possible thanks to improvements in genomic sequencing technology, which also enable risk classification and therapeutic decision-making. The results of clinical studies examining

novel targeted medicines and therapy combinations should be improved[21]. Additionally, combining genetic data with additional clinical and molecular data can deepen our understanding of MPN pathophysiology and optimize patient care.

V. CONCLUSION

Based on the identified research, a comprehensive evaluation of the effects of germline and somatic mutations in myeloproliferative neoplasms (MPNs) offers insightful information about the function of genetic alterations in these diseases. Genes like JAK2, MPL, and CALR that have germline mutations play a role in familial clustering, illness phenotypic modulation, and disease propensity. Disease development, risk classification, prognosis, and therapy choices are significantly impacted by somatic mutations, such as those in JAK2, CALR, MPL, and TET2. The interaction of somatic and germline mutations further complicates MPNs by affecting the disease's heterogeneity, course, and therapy responses. The systematic review's findings emphasize the necessity of taking both germline and somatic mutations into account in risk assessment, genetic counseling, and personalized therapeutic regimens for MPN patients. The prevalence of germline mutations in MPNs, their correlation with illness propensity, and their impact on disease phenotype emphasize the importance of thorough genetic testing and counseling in clinical practice. Somatic mutations are useful diagnostic indicators because they guide therapeutic methods and predict treatment responses and outcomes. The interaction between germline and somatic mutations in MPNs has emerged as a prominent topic of study interest. The systematic review emphasizes the significance of more research in this field to elucidate the underlying molecular mechanisms, temporal sequence of mutation acquisition, and the influence of various germline-somatic mutation combinations on disease behavior. Understanding how germline and somatic mutations interact can help us better understand disease progression, treatment response, and the development of targeted medicines. The systematic study also highlights the possibility for novel therapeutic targets and improved treatment results in MPNs. The discovery of unique germline and somatic mutations opens the door to precision medicine treatments tailored to individual patients. JAK inhibitors for JAK2-mutated MPNs, for example, show promise in enhancing therapy responsiveness and overall patient outcomes. Further study in this area may identify more therapeutic targets and develop tailored treatment techniques. Finally, the systematic review emphasizes the importance of germline and somatic mutations in MPNs. These mutations have an effect on illness susceptibility, phenotype, progression, risk classification, and therapy options. The interaction of germline and somatic mutations complicates MPNs, demanding extensive genetic testing and counseling. More research into the interactions of these mutations will help us understand disease mechanisms and open the path for new therapeutic targets and better treatment outcomes. Finally, this information has the potential to promote precision medicine techniques and improve patient care in the management of MPNs.

VI. REFERENCES

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