Role of Germline Genetic Factors in MPN Pathogenesis

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KEYWORDS

• Myeloproliferative neoplasms • Hereditary predisposition • Familial clustering
• *JAK2* haplotype • Germline variants • Penetrance

KEY POINTS

- Myeloproliferative neoplasms (MPNs) are mainly driven by somatically acquired point mutations and chromosomal aberrations.
- Germline factors can predispose to the development of MPN, acquisition of somatic mutations, and chromosomal aberrations, as well as modify the clinical course of the disease.
- Familial clustering of MPN in 5% to 10% of cases, increased risk of the disease in relatives of patients with MPN, and the existence of biclonal MPN provide evidence of germline MPN susceptibility.
- Hereditary thrombocytosis and erythrocytosis have similar clinical symptoms as MPN; however, these disorders show distinct features, such as polyclonal hematopoiesis, single lineage involvement, and absence of disease progression.
- Germline mutations in *JAK2*, *MPL*, and *THPO* cause hereditary thrombocytosis, whereas germline mutations in *EPOR*, oxygen-sensing pathway genes, or genes affecting oxygen affinity of hemoglobin result in hereditary erythrocytosis.
- The common *JAK2* GGCC haplotype predisposes to the development of JAK2-postive MPN.
- A nonsynonymous germline variant in the *ERCC2* (*XPD*) gene increases the risk of leukemic transformation and the development of new primary tumors in patients with MPN.
- Rare germline variants in the regions of loss of heterozygosity can have an influence on MPN pathogenesis.
- The germline mutations responsible for the familial cases of MPN have not been identified so far.

INTRODUCTION

Myeloproliferative neoplasms (MPNs) are chronic hematological malignancies of clonal origin characterized by the predominant involvement of myeloid lineages, accumulation of terminally differentiated blood cells, and the tendency to transform to

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Hematol Oncol Clin N Am 26 (2012) 1037–1051
http://dx.doi.org/10.1016/j.hoc.2012.07.005 **hemonc.theclinics.com**
0889-8588/12/$ – see front matter

secondary acute myeloid leukemia (sAML). MPNs are a heterogeneous group of disorders and include 9 disease entities according to the 2008 World Health Organization classification.[1] The classic MPN or Ph-chromosome-negative MPN include polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF). The MPN disease subtypes exhibit specific phenotypic features but share many clinical and molecular features.[2] MPNs are characterized by high numbers of differentiated cells of myeloid origin in peripheral blood, mainly red blood cells in PV or platelets in ET. Patients with PMF usually have a lower number of myeloid cells as a result of bone marrow fibrosis, and consequent extramedullary hematopoiesis often manifests with splenomegaly. PV and ET may progress into secondary myelofibrosis, which has a similar clinical presentation as PMF but a much higher rate of transformation to sAML.[3] Patients with MPN frequently have thrombotic or hemorrhagic complications; in some cases those complications are the first presentations of the disease.[2] Typically, MPNs are diseases of the elderly; the age of onset is around 50 to 60 years, although cases in younger ages are also observed, especially in the presence of familial history.[4] The life expectancy of patients with PV and ET is more than a decade. In PMF, the life expectancy is 3 to 5 years on average, whereas after the transformation to sAML, the median survival is a few months with no effective treatment available.[5] The treatment in MPN is directed toward controlling the symptoms and the progression of the disease; it proves to be enough in most cases.[6]

ROLE OF SOMATIC MUTATIONS IN MPN

Acquired genetic changes drive clonal progression in MPN, as in other cancers. Several recurrent chromosomal aberrations and point mutations have been identified in the pathogenesis of MPN, with variable frequency in PV, ET, and PMF. The most common somatic mutation in MPN is the V617F mutation in the Janus kinase 2 (*JAK2*) gene, observed in about 95% of patients with PV and 50% to 60% in ET and PMF.[7–10] The JAK2-V617F mutation is often associated with acquired uniparental disomy on the short arm of chromosome 9 (9pUPD), which makes the mutation homozygous particularly in PV and PMF.[9] Mutations in exon 12 of *JAK2* are present in 1% to 3% of PV cases.[11,12] Somatic activating mutations in the thrombopoietin receptor gene (*MPL*) are detected in 1% to 5% of the cases of PMF and ET, predominantly in a mutually exclusive manner with *JAK2* mutations.[13] Other mutations commonly found in patients with MPN are in *TET2*,[14–16] *CBL*,[17,18] *EZH2*,[19,20] and *ASXL1*,[21] with variable frequency in 3 MPN subtypes (**Fig. 1**). Another group of mutations are acquired during the disease progression and transformation to sAML, such as *TP53*,[22,23] *RUNX1*,[22,24,25] *NPM1*,[25,26] *FLT3*, *IDH1*, and *IDH2*.[27–29] Several recurrent

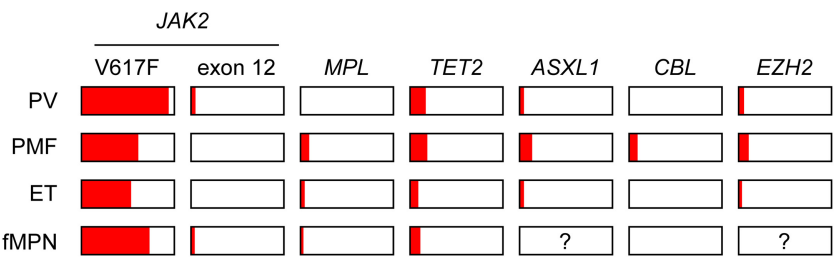

Fig. 1. The frequencies of common somatic mutations in 3 classic MPNs and in familial cases of MPN (fMPN). The red bars display the average frequency of the mutations obtained from multiple reports.