

Minireview

Germline and somatic *JAK2* mutations and susceptibility to chronic myeloproliferative neoplasms

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Abstract

Myeloproliferative neoplasms (MPNs) are a group of closely related stem-cell-derived clonal proliferative diseases. Most cases are sporadic but first-degree relatives of MPN patients have a five- to seven-fold increased risk for developing an MPN. The tumors of most patients carry a mutation in the *Janus kinase 2* gene (*JAK2*^{V617F}). Recently, three groups have described a strong association of *JAK2* germline polymorphisms with MPN in patients positive for *JAK2*^{V617F}. The somatic mutation occurs primarily on one particular germline *JAK2* haplotype, which may account for as much as 50% of the risk to first-degree relatives. This finding provides new directions for unraveling the pathogenesis of MPN.

Cancer gene identification

Although many cancers show familial clustering, identification of the predisposing germline genes is challenging. Mutations in genes such as *p53*, *BRCA1*, *CDKN2* and *HNPCC* causing high risk of tumors (often at an early age) were discovered from studies of rare families with striking tumor clusters [1]. However, these mutations explain only a small fraction of cancer susceptibility in the general population. More common cancers among older individuals also show familial aggregation and are probably the result of a combination of germline genes and environmental or other factors. The attempt to identify common susceptibility genes with smaller effects has been facilitated by the ability to conduct large-scale genome-wide association studies in cases and controls.

Somatic changes found in tumors may also be a result of germline susceptibility genes in the same region. Three

recent articles in *Nature Genetics* [2-4] successfully demonstrate the potential of this approach by identifying a gene involved in susceptibility to developing chronic myeloproliferative neoplasms (MPNs) that is likely to have both germline and somatic effects. It is useful to review the recent history around this discovery and determine the lessons learned that could be applied to other cancers.

Genetics of myeloproliferative neoplasms

On the basis of the current World Health Organization criteria, MPNs include polycythemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis (MF) [5]. They are all stem-cell-derived clonal proliferative diseases whose shared and diverse phenotypic characteristics can be attributed to dysregulated signal transduction because of acquired somatic mutations [6]. They are uncommon tumors with yearly incident rates of 2.3 in 100,000 in the

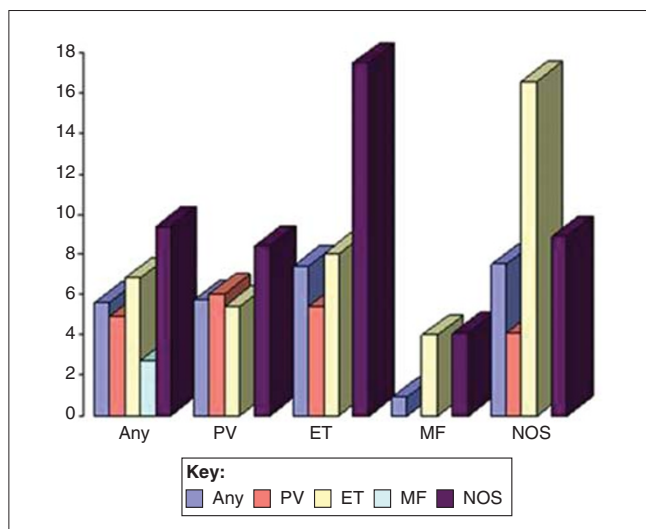


Figure 1

Risk for specific MPNs among first-degree relatives of MPN patients. The bars show relative risk estimates for specific MPNs (given on the x-axis) among first-degree relatives of patients affected with specific MPNs (see key) compared with first-degree relatives of controls.

United States [7] and primarily affect older adults, with a variable clinical presentation. For example, approximately half of all MPN patients are reported to be asymptomatic at diagnosis [5,8]. Among PV and ET patients, the major symptoms are associated with hypertension or vascular abnormalities, including an increased risk for thromboembolism and hemorrhage [9,10]. Also, patients with PV and ET have an excess risk of developing MF, or transformation to myelodysplastic syndrome or leukemia [9,10]. Although available information is limited, life expectancy of patients with ET has been reported to be similar to that of the general population; however, for PV patients, life expectancy has been observed to be reduced compared with the general population [11]. In contrast, primary MF patients have an average survival of less than 5 years [12]. Currently, the underlying causes of MPNs are mostly unknown.

A mutation in the gene for *Janus kinase 2* ($JAK2^{V617F}$) is present in erythropoietin-independent erythroid colonies in PV and gives a proliferative advantage in these cells. The mutation is present in 95% of PV patients and in approximately 50% of ET and MF patients [6]. However, given that case studies have shown that only a minority of granulocytes affected by a chromosome 20q deletion also harbored $JAK2^{V617F}$, other primary pathogenetic factors have been suggested. It has also been demonstrated that rare somatic events, such as a chromosome 20q deletion or loss of heterozygosity on 9p, have occurred more than once in subclones from the same patients, suggesting that the myeloproliferative disorder clone carries a predisposition to acquiring such genetic alteration [13]. A role for genetic factors in the etiology of MPNs has also been suggested from

case reports and smaller case series showing evidence of familial clustering of PV, ET, MF and chronic myeloid leukemia (CML) [14,15]. One study of patients from 72 families with different MPNs found no evidence for the $JAK2^{V617F}$ mutation in the germline of patients who carried the mutation in their tumor cells, and the authors concluded that the $JAK2$ gene was a later 'hit' in these families [16].

We recently published a study [17] using Swedish Registry data, showing that the risk of MPN in nearly 25,000 first-degree relatives of 11,000 cases was significantly higher (five- to seven-fold elevated) than in first-degree relatives of control individuals. The results are illustrated in Figure 1. We also found an approximately two-fold relative risk (borderline significant) for CML in relatives of MPN patients. In fact, a series of case reports has described co-existence of the $JAK2$ mutation and the $BCR-ABL$ translocation, a chromosomal abnormality associated with CML [18]. This suggests that there is a strong important hereditary component to MPN above and beyond the rare 'heavily loaded' families. We found elevated risks for PV, ET and MF among relatives of MPN patients, suggesting that there is common genetic susceptibility among the subtypes. We emphasized in that article [17] that the high recurrence risks in relatives made the search for germline risk genes compelling.

We did not have to wait long for the identification of a germline susceptibility gene. The results from the three recent studies all converge on the conclusion that the $JAK2$ gene is a susceptibility gene for MPNs both in the germline and somatically [2-4]. These studies demonstrated that the malignant clone containing the $JAK2$ mutation was strongly associated with a particular haplotype defined by nearby single nucleotide polymorphisms (SNPs) in patients that were $JAK2^{V617F}$ -positive. The study by Jones *et al.* [2] demonstrated that a single haplotype was present in clones that were homozygous for $JAK2^{V617F}$. The association was also found in a larger population of patients. Interestingly, in one family with a grandparent and grandchild both with PV, only one of the cases had the at-risk haplotype. One of the associated SNPs was also shown to be in *cis* with the $JAK2^{V617F}$ allele in the study by Olcaydu *et al.* [4]. Another nearby SNP was almost always found in *cis* with $JAK2^{V617F}$ in the study by Kilpivaara *et al.* [3]. In all three studies, these SNPs showed high relative risks when $JAK2^{V617F}$ -positive patients were compared with controls. Kilpivaara *et al.* [3] also presented association of genome-wide markers in cases and controls and showed that the $JAK2$ SNP was highly significant even in the context of a genome-wide search. The article by Jones *et al.* [2] showed weak evidence that the risk haplotype was also associated with $JAK2^{V617F}$ -negative patients.

Future directions

The evidence is now in favor of the $JAK2$ locus being an important germline and somatic hit in the pathology of

MPNs. The authors of the three studies [2-4] have speculated possible mechanisms. One possibility is that the associated SNPs are in linkage disequilibrium with an unidentified functional variant. Other possibilities are that the associated haplotype causes the *JAK2* gene to be more susceptible to mutation or allows increased survival of *JAK2*^{V617F} alleles.

But what about the high-risk families that have been described? As mentioned above, Bellanné-Chantelot *et al.* [16] did not find the *JAK2*^{V617F} mutation in the germline in MPN families and also did not see evidence for linkage to the *JAK2* region of chromosome 9. It is possible that the *JAK2* region has a role in some families but that other rare loci also exist. It is also likely that there are other common genes that contribute to risk in the population. Jones *et al.* [2] estimate that the *JAK2*-associated haplotype accounts for 50% of the risk in first-degree relatives on the basis of our relative risk estimate of 5.7 in first-degree relatives of PV patients [17]. Thus, there are likely to be additional common and rare susceptibility genes. Nevertheless, these new findings are a large step in the progress towards understanding the pathogenesis of MPN.

Abbreviations

CML, chronic myeloid leukemia; ET, essential thrombocythemia; MF, myelofibrosis; MPN, myeloproliferative neoplasm; PV, polycythemia vera; SNP, single nucleotide polymorphism.

Competing interests

The authors declare that they have no competing interests.

Author contributions

LRG and OL wrote the report. All authors read, gave comments and approved the final version of the manuscript.

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