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The *JAK2* 46/1 haplotype: a marker of inappropriate myelomonocytic response to cytokine stimulation, leading to increased risk of inflammation, myeloid neoplasm, and impaired defense against infection?

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The 46/1 haplotype of chromosome 9p, present in about 45% of the general population, is associated with a predisposition to mutations in the Janus Kinase 2 (*JAK2*) gene on the same allele and to chronic myeloproliferative neoplasms (MPN): polycythemia vera, essential thrombocythemia and primary myelofibrosis.[1-4] The 46/1 haplotype is also associated with a predisposition to MPN with no mutation of *JAK2*, and with MPN with mutation in *MPL*, a gene located on a different chromosome (1p).[5,6] An increased frequency of the 46/1 haplotype in patients with splanchnic vein thrombosis has also been reported but these findings remain controversial.[7,8] The 46/1 haplotype has been studied in chronic myelogenous leukemia and in chronic myelomonocytic leukemia; no significant increase in frequency was noted (Table 1). Last year Andrikovics *et al.* reported that patients with acute myeloid leukemia (AML) with the 46/1 haplotype had a higher frequency of normal karyotype (NK).[9] In the present issue of Haematologica, the same group found that the *JAK2* 46/1 haplotype is associated with an increased frequency of acute myelomonocytic leukemia and a tendency to reduced survival because of death from infection in patients with NK-AML.[10] The latter findings need confirmation by other studies, for it is of great interest to establish whether the *JAK2* 46/1 haplotype is in fact a marker of myelomonocytic dysfunction and subsequently an unfavorable risk factor in NK-AML, as Nahajevszky *et al.* suggest, and/or in other disease categories.[10] In fact, although the majority of studies have failed to detect any association of the 46/1 haplotype with hematologic and clinical parameters (Table 1), Tefferi *et al.* found that the 46/1 haplotype status influenced survival in primary myelofibrosis, and evolution toward myelofibrosis in polycythemia vera.[5] Moreover, it has been reported that the frequency of the *JAK2* 46/1 haplotype is increased in the context of severe inflammation, for instance Crohn's disease.[11,12] Altogether, the literature (reviewed in Table 1) shows that the common 46/1 haplotype is associated with predisposition to several types of disorders of variable severity: rare myeloid malignancies with or without *JAK2/MPL* mutation, including MPN and perhaps also acute myelomonocytic leukemia and NK-AML; inflamma-

tory diseases; and possibly, reduced defense against infection. The mechanisms that underlie the increased risk of acquisition of MPN and *JAK2/MPL* mutation in carriers of the 46/1 haplotype are not understood. Additionally, the mechanisms that make the V617F mutation occur preferentially in the *JAK2* gene of the 46/1 allele remain largely unknown.

A haplotype (contraction of "haploid genotype") is a set of closely linked genetic markers present on the same chromosome, which are not easily separable by recombination and thus tend to be inherited together, and can be identified by patterns of single nucleotide polymorphisms. The 46/1 haplotype, represented in Figure 1, is a 280 Kb-long region of chromosome 9p that includes three genes in their entirety: *JAK2*, *INSL6* (Insulin-like 6) and *INSL4*. Of the three genes, only *JAK2* is expressed in hematopoietic cells. The so-called "GGCC" part of the 46/1 haplotype begins in intron 10 and finishes in intron 15 of the *JAK2* gene and is characterized by four single nucleotide polymorphisms located in introns 10, 12, 14 and 15. The four single nucleotide polymorphisms are in complete linkage disequilibrium, meaning that they are always inherited together. The four single nucleotide polymorphisms replace three thymidines (T) and one cytosine (C) by two guanosines (G) and two cytosines, resulting in a G G C C pattern, hence the phrase *JAK2* "GGCC" haplotype (not to be confused with "GC-rich"). The "GGCC" part of the 46/1 haplotype is not "GC-rich" but it includes sequences frequently mutated in MPN: *JAK2* exons 14 and 12, and to a lesser degree, exons 13 and 15. A plausible explanation for the high frequency of mutations in *JAK2* exons 14 and 12 and in *MPL* exon 10 in association with MPN combines the presence of flanking DNA repeat elements (represented in Figure 1) and the fact that the three exons encode for protein domains critical for the function of the Jak2/Mpl couple. Activating mutations in these exons are likely to be detected as they confer growth advantages to the mutated clone, whereas silent mutations typically remain below the detection level of most diagnostic assays.[13] DNA repeat elements include GC- or AT-rich sequences; they can be mutation "hot spots", cause mismatching during DNA replication, or form fragile chromosomal break

Table 1. *JAK2* 46/1 allele frequencies and clinical correlations reported in the literature.

Mutation studied	Reference	Disease type (N. of patients)	Mutation frequency	46/1-allele DNA origin	Frequency	Clinical correlation
JAK2V617F	Jones *et al.* Nat Genet 2009;41(4):446-9.	V617F+ PV (n=192) V617F+ ET (n=221) V617F- ET (n=136) V617F+ PMF (n=41) IE (n=76) Unclassified MPN (n=124)	100%, 100% 0% 100% 0% 100%	PB	0.54* 0.46* 0.33 0.48* 0.27 0.56*	Less CFU-GM for 46/1 carriers
JAK2V617F	Olcaydu *et al.* Nat Genet 2009;41(4):450-4.	MPN (n=333)	63.9%	Gra	N/A	Not studied
JAK2V617F	Kilpivaara *et al.* Nat Genet 2009;41(4):455-9.	V617F+ MPN (n=245) V617F- MPN (n=74)	100% 0%	Gra	0.50* 0.34	Not studied
JAK2V617F	Colaizzo *et al.* J Thromb Haemost 2009;8(2):413-6.	SVT (n=180)	N/A	N/A	0.30	No association with biological and clinical parameters
JAK2V617F	Pardanani *et al.* Leukemia 2010;24(1):110-4.	V617F+ ET (n=118) V617F- ET (n=108)	100% 0%	BM	0.44* 0.38*	No association with biological and clinical parameters
JAK2V617F	Tefferi *et al.* Leukemia 2010; 24(1):105-9.	V617F+ PMF (n=77) V617F- PMF (n=53)	100% 0%	BM	0.50* 0.36*	Reduced survival for 46/1 non-carriers
JAK2V617F	Tefferi *et al.* Leukemia 2010; 24(7):1302-9.	PV (n=242) ET (n=412) PMF (n=277) V617F+ Post-PV MF (n=36) Post-ET MF (n=24) V617F+ Post-PV AML (n=11) Post-ET AML (n=5) Post-PMF AML (n=28)	N/A N/A N/A 100% N/A 100% 60.0% N/A	BM PB or Gra	22.7% NU* 38.1% NU 35.0% NU 2.8% NU* 29.2% NU 36.4% NU 20.0% NU 32.1% NU	Reduced survival for 46/1 non-carriers with chronic-phase or blast-phase PMF
JAK2V617F	Trifa *et al.* Ann Hematol 2010; 89(10):979-83.	V617F+ MPN (n=107) V617F- MPN (n=42)	100% 0%	PB	0.49 0.32	Not studied
JAK2V617F	Andrikovics *et al.* Leukemia 2010;24(10):1809-13.	MPN (n=312) V617F+ PV (n=153) V617F+ ET (n=78) V617F- ET (n=53) V617F+ PMF (n=20) V617F- PMF (n=8) AML with abnormal karyotype (n=188) with normal karyotype (n=129)	80.4% 100% 100% 0% 100% 0% 0% 0%	N/A	0.46* 0.48* 0.47* 0.33 0.55* 0.44 0.25 0.33	Increased risk of myelofibrosis for 46/1 HM PV patients Increased frequency of normal karyotype for AML 46/1 carriers
JAK2V617F	Guglielmelli *et al.* Leukemia 2010;24(8):1533-7.	V617F+ PMF (n133) V617F- PMF (n=69)	100% 0%	Gra	0.41* 0.33	No association with biological and clinical parameters
JAK2V617F	Hsiao *et al.* Leuk Lymphoma 2011;52(3):478-82.	V617F+ ET (n=34) V617F- ET (n=27)	100% 0%	PB	0.48* 0.24	Not studied
JAK2V617F	Kouroupi *et al.* Blood 2011; 117(21):5777-8.	V617F+ SVT (n=75) V617F- SVT (n=95)	100% 0%	PB	0.27 0.28	Not studied
JAK2V617F	Olcaydu *et al.* Haematologica 2011;96(3):367-74.	V617F+ familial MPN (n=61) V617F- familial MPN (n=27) V617F+ sporadic MPN (n=481) V617F- sporadic MPN (n=202)	100% 0% 100% 0%	Gra	0.48* 0.33 0.46* 0.31	Not studied
JAK2V617F	Rumi *et al.* Haematologica 2011;96(3):454-8.	V617F+ MPN (n=442) V617F- MPN (n=236) V617F+ LPN-MPN (n=11)	100% 0% 100%	T-cells	0.44* N/A 0.41	Increased risk of developing lymphoid, neoplasm not linked to 46/1 haplotype, for MPN patients
JAK2V617F	Smalberg *et al.* Blood 2011;117(15):3968-73.	SVT (n=199) V617F+ BCS (n=34) V617F- BCS (n=73) V617F+ SVT (n=20) V617F- SVT (n=72)	27.1% 100% 0% 100% 0%	Gra	0.32 0.44* 0.33 0.40 0.24	Increased levels of hemoglobin, hematocrit and red blood cell counts for 46/1 carriers
JAK2V617F	Villani *et al.* Leukemia Res 2011; [Epub ahead of print]	non MPN SVT (n=56) V617F+ MPN SVT (n=76) V617F- MPN SVT (n=32)	0% 100% 0%	Gra	0.24 0.51* 0.28	Not studied
JAK2V617F	Nahajevszky *et al.* Haematologica 2011; (this issue)	AML (n=176) AML with normal karyotpe (n=81)	N/A N/A	N/A N/A	0.40 46/1 carriers: 58.1%	Increased frequency of myelomonocytic AML for 46/1 carriers Reduced survival and increased risk of death by infection for 46/1 carriers

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JAK2 exon 12	Olcaydu et al. Leukemia 2009; 23(10):1924-6.	PV (n=44)	100%	N/A	46/1 carriers: 64%	Not studied
JAK2 exon 12	Jones et al. Blood 2010; 115 (22):4517-23.	MPN (n=69)	100%	PB or Gra	0.39*	No association with biological and clinical parameters
MPL exon 10		MPN (n=176)	W515L (n=110) W515K (n=58) other MPL variants (8)		N/A	
MPL exon 10	Patnaik et al. Leukemia 2010;24(4):859-60.	ET and PMF (n=22)	W515L (n=16) W515K (n=6)	BM	0.25	Not studied
	Spolverini et al. Ann Hematol 2011;90(3):365-6	CML (n=331)	N/A	N/A	0.29	Not studied
	Smith et al. Blood 2011; 116(19):3923-32.	CMML (n=16)	N/A	BM	0.28	Not studied

The mutation frequency is the percentage of patients carrying the mutation. The 46/1 allele frequency is the fraction of 46/1 alleles in total alleles of a cohort: for instance, the 46/1 allele frequency in the general population is 0.24 according to the Welcome Trust Case Control Consortium (WTCCC), meaning that 45% of individuals are 46/1 carriers. The 46/1 haplotype is associated with predisposition to several types of disorders: reduced defense against infection, inflammatory disease, and myeloid malignancy including MPN, acute myelomonocytic leukemia, and NK-AML. * Results with P value <0.05. Abbreviations: MPN: myeloproliferative neoplasm; PV: polycythemia vera; ET: essential thrombocythemia; PMF: primary myelofibrosis; IE: idiopathic erythrocytosis; AML: acute myeloid leukemia; V617F+ and V617F-: positive or negative for the JAK2V617F mutation; SVT: splanchnic vein thrombosis; post-PV MF: post-PV myelofibrosis; LPN: lymphoid neoplasm; BCS: Budd-Chiari syndrome; CML: chronic myelogenous leukemia; CMML: chronic myelomonocytic leukemia; PB: peripheral blood; Gra: granulocyte; BM: bone marrow; HM: homozygous; NU: nullizygosity; N/A: not available.
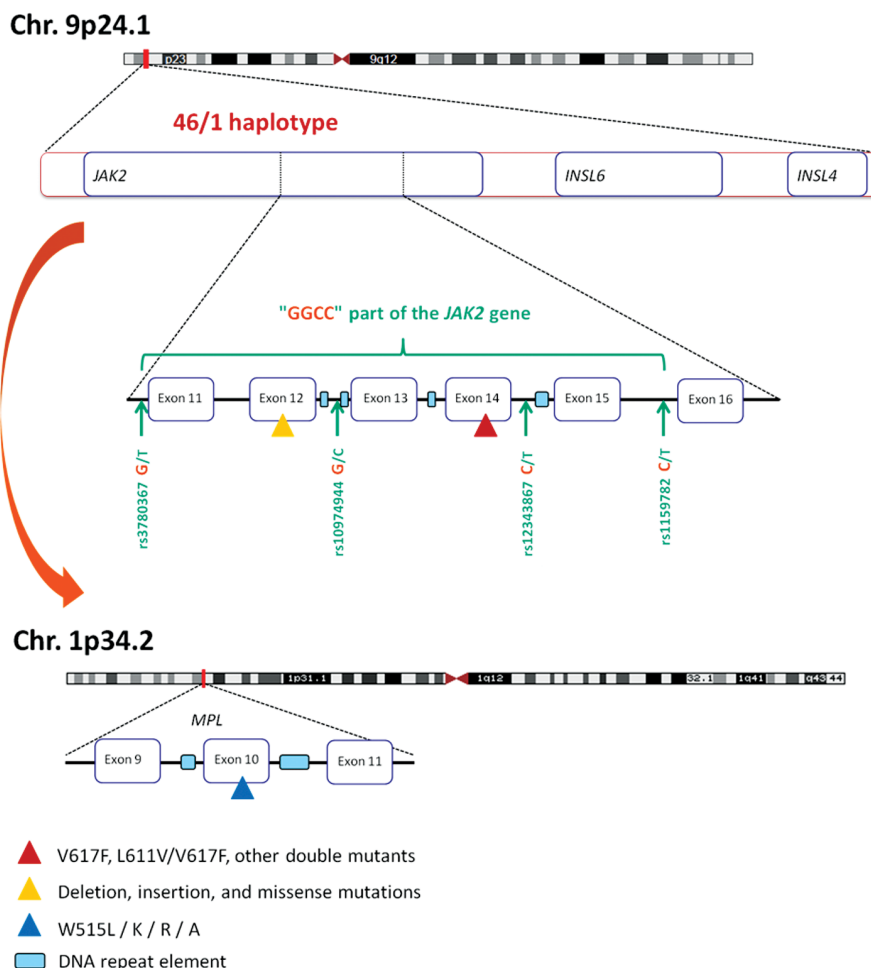

Figure 1. The 46/1 haplotype associated with a predisposition to mutation in the *JAK2* and *MPL* genes and MPN. The 46/1 haplotype is a 280 Kb-long region of chromosome 9p which includes the entire *JAK2*, *INSL6* and *INSL4* genes. Most of the *JAK2* mutations detected in MPN are localized in the "GGCC" part of the *JAK2* gene, represented in green. The "GGCC" part, which begins in intron 10 and finishes in intron 15 of the *JAK2* gene, is characterized by four single nucleotide polymorphisms: rs3780367 in intron 10, rs10974944 in intron 12, rs12343867 in intron 14, and rs1159782 in intron 15. These four single nucleotide polymorphisms are in complete linkage disequilibrium. The "GGCC" part of the 46/1 haplotype includes the most frequently mutated *JAK2* exons: exon 14 (mainly the V617F mutation, represented by a red triangle), exon 12 (mutations and deletions are represented by a yellow triangle) and to a lesser degree, exons 13 and 15. In addition, the 46/1 haplotype has been reported to be associated with a predisposition to the acquisition of mutations in exon 10 of the *MPL* gene, located on a different chromosome. *MPL* exon 10 mutations are represented by a blue triangle. DNA repeat elements (represented by light blue rectangles) can be found close to *JAK2* exons 12-15 and close to *MPL* exon 10. Such repeat sequences are known to increase the risk of DNA mutation or recombination. The presence of repeat elements being independent of the 46/1 haplotype, the mechanisms that make individuals carrying the 46/1 haplotype at higher risk of *JAK2* and *MPL* mutation and MPN are currently not understood.

points – in short, these elements increase the risk of error when DNA is copied during cell division. DNA repeat elements can also influence gene expression by altering promoter accessibility, methylation or the chromatin structure. Our preliminary unpublished observations suggest that DNA repeat intronic sequences vary depending on individuals and MPN patients and that they can be present in the *JAK2* gene independently of the 46/1 haplotype.

In fact, the *JAK2*V617F mutation and all three types of MPN occur in individuals who do not carry the 46/1 haplotype. In MPN patients who carry the 46/1 haplotype, the V617F and other *JAK2* mutations can be found located in
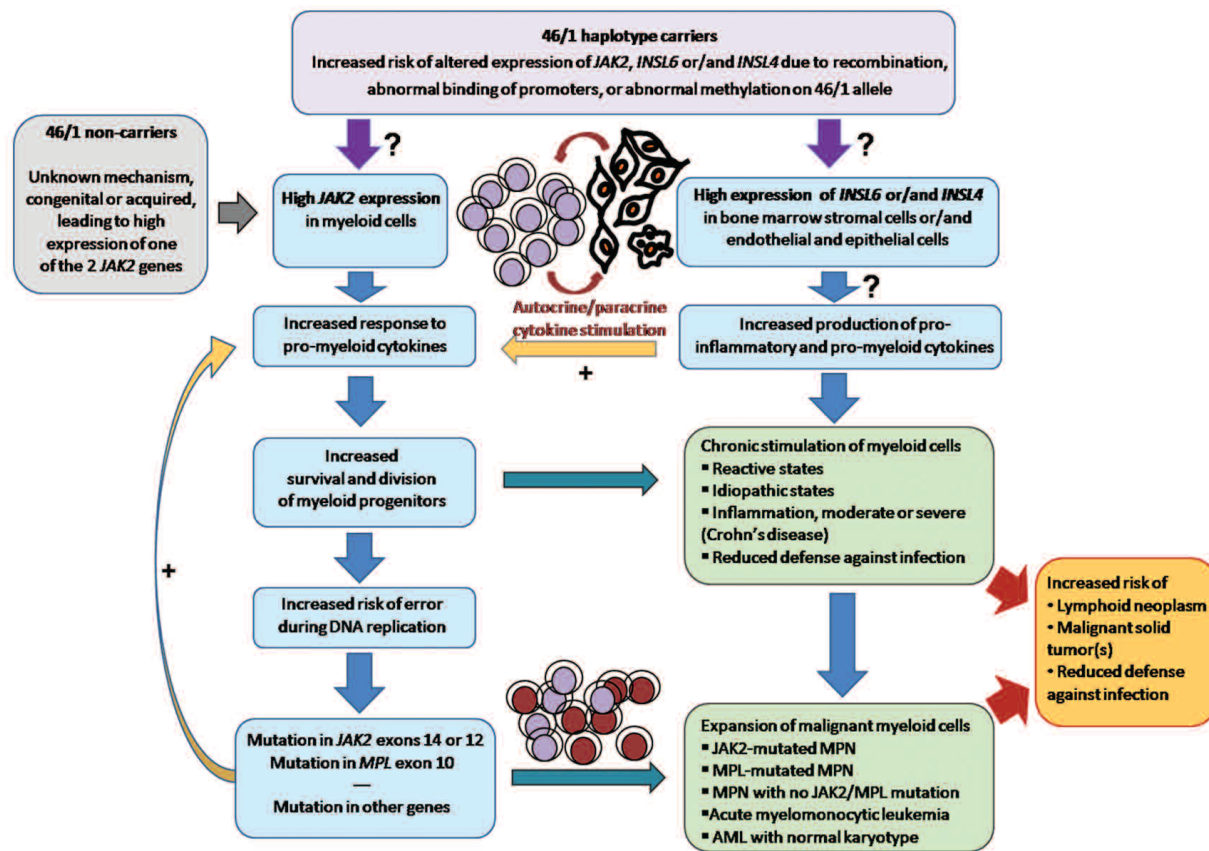
Figure 2. The *JAK2* 46/1 haplotype as a marker of inappropriate myelomonocytic response to cytokine stimulation, leading to increased risk of inflammation, myeloid neoplasm, and impaired defense against infection. One hypothesis is that the 46/1 haplotype may be linked to high expression of the *JAK2* gene and/or of other genes that constitute the haplotype: *INSL6* and *INSL4*. The 46/1 haplotype could lead to high expression of the *JAK2* gene on the recombined allele through DNA recombination, mutation, altered promoter accessibility or abnormal methylation. This hypothesis is supported by the fact that high mRNA expression of *JAK2* is frequently observed in MPN patients, and required for certain MPN phenotypes in murine models. Thanks to high Jak2 levels, affected myeloid cells would be more likely to divide in response to Jak2-activating cytokines, making genes important for myelopoiesis, such as *JAK2* and *MPL*, at greater risk of copy errors. Acquisition of mutations in *JAK2*, *MPL* or other genes would accelerate progression toward myeloid neoplasms. For patients who develop MPN, the presence of the 46/1 haplotype could influence disease evolution and survival. Carriers of the 46/1 haplotype who develop AML with normal karyotype (NK-AML) could have reduced survival due to death from infection, according to Nahajevszky *et al.* (this issue).[10] In addition, the 46/1 haplotype may facilitate expression of *INSL6* and *INSL4* in non-hematopoietic cells, for instance in bone marrow stromal cells. Possible consequences could be excessive production of cytokines with dual action, pro-myeloid and pro-inflammatory, which would further stimulate expansion of myelomonocytic cells and thus facilitate an inflammatory response and perhaps impair defense against infection. Finally, patients with MPN, AML or severe chronic inflammation have been reported to be at greater risk of lymphoid neoplasms and malignant solid tumors.

the other (TCTT) allele yet more than 80% of all V617F mutations occur on the 46/1 allele.[4,14] Accordingly, the literature shows that the proportions of patients with essential thrombocythemia and primary myelofibrosis with the 46/1 haplotype are significantly higher in *JAK2*V617F-positive cohorts than in *JAK2*V617F-negative cohorts (Table 1). Moreover, the 46/1 haplotype can be associated with alterations other than mutations in the *JAK2* gene, notably repeated recombination of *JAK2* prior to and after the V617F mutation is associated with high *JAK2* mRNA expression, as we recently described in patients with polycythemia vera.[14] Hence one hypothesis is that the 46/1 haplotype may include unidentified intronic DNA repeat sequences that somehow facilitate DNA recombination and over-expression of the *JAK2* gene located in the recombined allele. In such cases, as Jak2 transmits the proliferation signals from all the cytokines critical for myelopoiesis, the 46/1 haplotype would logically predispose carriers to chronically excessive stimulation of myelopoiesis, thereby exposing myeloid progenitors to more frequent cell division and further increased risk of error and mutation in genes more important for myelopoiesis, such as *JAK2* and *MPL* but also *TET2*, *CBL*, *LNK*, *EZH2*, *ASXL1* (list not exhaustive) (representation in Figure 2). We and others have begun to analyze *JAK2* mRNA expression in relation to the 46/1 haplotype with discordant results likely due to the small numbers of patients studied.[3,6,14,15] However, it is clear that mRNA expression of both wild-type and mutated *JAK2* is frequently higher in leukocytes of MPN patients, and that high *JAK2* expression is relevant to MPN pathogenesis since it is necessary to reproduce polycythemia vera and primary myelofibrosis phenotypes in murine models.[15,16] Further studies specifically designed to analyze the rela-

tionship of *JAK2* mRNA expression in function of the 46/1 haplotype status of MPN patients, associated with intron sequencing, will prove or disprove association of the 46/1 haplotype with high *JAK2* expression.

However, *JAK2* is only one of the three genes that constitute the 46/1 haplotype. Because they are presumably not expressed in hematopoietic cells, *INSL6* and *INSL4* have been disregarded so far. Yet *INLS6* is expressed in rat bone marrow stromal cells, and *INSL4* expression was reported as forming an autocrine loop in cancer cells.[17,18] Thus we should perhaps not exclude that the 46/1 haplotype could be associated with altered expression of *INSL6* and/or *INSL4*, for instance in bone marrow stromal cells, eventually leading to altered cytokine production. There is proof of yet unexplained *JAK2*V617F-independent cytokine over-production in MPN, by both bone marrow stromal cells and malignant hematopoietic progenitors.[19,20] The cytokines that were found to be over-produced were all linked to inflammation as well as capable of stimulating myelopoiesis, an unsurprising finding since evidence of inflammation in MPN is abundant.[21] Future studies investigating the possible expression and consequences of *INSL6* and *INLS4* expression in cell types relevant to myelopoiesis and their relationship to the 46/1 status of patients should bring new and important insights into the pathogenesis of myeloid neoplasms as well as of inflammatory diseases.

Finally, the model according to which the 46/1 haplotype could predispose carriers to increased myelomonocytic response to cytokine stimulation is consistent with the well established fact in MPN that the burden of *JAK2*V617F alleles (typically 46/1 alleles) correlates better with leukocyte cell counts than with hematocrit or platelet counts.[15] A chronic tendency to myelomonocytic expansion would be consistent with increased risks of more severe inflammatory response compared to the risk in 46/1 non-carriers. It would also constitute fertile ground for the acquisition of mutations in genes critical for myelomonocytic expansion and differentiation, eventually leading to malignant transformation toward MPN or AML. It is to be hoped that new genome wide association technologies that investigate both exonic and intronic sequences will provide a detailed analysis of the consequences of the 46/1 haplotype in terms of expression of the *JAK2*, *INSL6* and *INSL4* genes and will allow progress in understanding the complex mechanisms that underlie the association of the 46/1 haplotype with predisposition to myeloid neoplasms and inflammation.

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