

# JAK-2 Is a Heavy Burden to Bear in MPD

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In the past year, advances regarding pathogenesis of myeloproliferative syndromes have changed the landscape of the hematology practice. The discovery of the JAK2 kinase was pivotal to this process. JAK2 was named after Janus, the ancient gatekeeper worshipped by the Romans. This “god of two faces” inspired the name of janus kinase, a tyrosine kinase with two phosphate-transferring domains. JAK2 is active in the JAK-STAT pathway, a signalling cascade that helps determine the fate of cells.

Nearly all patients with polycythemia vera (PV) carry a mutation in the JAK2 gene, which constitutively activates the janus tyrosine kinase. Mutant JAK2 (coded by the JAK2 V617F allele) kicks JAK-STAT signaling into high gear. This finding has led to intensive interest into JAK2 as a pathogenetic contributor, a diagnostic test, and a possible therapeutic target in PV.

Abstract #5, presented at yesterday’s Plenary Session by Dr. Alessandro Vannucchi from the University of Florence, suggests that JAK2 may also play a key role in prognostication. Dr. Vannucchi’s group started their study with the knowledge that while mutant JAK2 encourages erythroid cells to grow out of control, wild-type JAK2 attempts to rein them in. Their hypothesis was that the war between mutant and wild-type JAK2 depended on copy numbers.

Peripheral blood granulocytes were collected from 116 PV patients, and the ratio of mutated to wild-type JAK2 RNA was calculated. As they had predicted, the majority of PV patients had detectable mutant JAK2 RNA. The ratio of mutant to wild-type JAK2 was variable between patients. However, Vannucchi’s group found a highly significant relationship between the burden of mutant JAK2 and several clinically relevant variables. Patients who carried a heavy burden of JAK2 also had a higher hematocrit, white count, and LDH. They also tended to have more troubling symptoms, such as splenomegaly, pruritus, and major thrombosis. These patients were more likely to require chemotherapy to control their disease than their counterparts with relatively little JAK2.

The dramatic findings of Dr. Vannucchi’s plenary abstract suggest a new and exciting role for JAK2 in the story of polycythemia vera — that of a powerful risk stratifier.