

## The Phenotype of JAK2 Exon 12-Mutated Myeloproliferative Neoplasms

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### ABSTRACT

While the majority of patients with polycythemia vera (PV) have an acquired *JAK2* V617F mutation, a minority (< 5%) harbor alternative *JAK2* mutations in exon 12 also predominantly associated with an erythroid phenotype. However, recent reports of *JAK2* exon 12 mutations in patients with other myeloproliferative neoplasms suggest that this may not be the case. These findings have potential implications for molecular diagnostic algorithms.

**Key words:** Polycythemia vera; *JAK2* exon 12 mutations; Myeloproliferative neoplasms; Molecular diagnostics

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### LETTER TO THE EDITOR

Polycythemia vera (PV) is a myeloproliferative neoplasm (MPN) characterized by clonal erythrocytosis with other features including leucocytosis, thrombocytosis, splenomegaly, thrombosis, bleeding, pruritus and a risk of myelofibrotic or leukemic transformation<sup>[1]</sup>. At the molecular level, more than 95% of PV patients harbour the *JAK2* V617F mutation with less than 5% of patients having evidence of *JAK2* exon 12 mutations. *JAK2* exon 12 mutations occur within residues 536-547 adjacent to the pseudo-kinase domain-encoding region and comprise of non-synonymous substitutions, deletion/insertions and duplications<sup>[2]</sup>. Compared to their *JAK2* V617F counterparts, PV patients with *JAK2* exon 12 mutations tend to be younger, nearly always have a lower serum erythropoietin level, and have a more pronounced bone marrow erythroid hyperplasia. Despite these trends, up to one third of patients present with a thrombocytosis<sup>[3-6]</sup>.

Two recent studies have reported the presence of *JAK2* exon 12 mutations in MPN patients with other phenotypes. Firstly, a p.H538\_K539delinsL *JAK2* exon 12 mutation was reported in a patient with myelodysplastic/myeloproliferative neoplasm with ringed sideroblasts and thrombocytosis in addition to *SF3B1* and *TET2* mutations. Sequence analysis of burst-forming units-erythroid colonies implies the acquisition of the dominant *SF3B1* mutation prior to the *JAK2* exon 12 mutation<sup>[7]</sup>. Secondly, p.H538\_K539delinsL *JAK2* exon 12 mutations were reported in two cases of myelofibrosis. The short clinical histories of both patients argue in favor of a diagnosis of primary myelofibrosis as opposed to post-PV myelofibrosis<sup>[8]</sup>.

Similar to the *JAK2* V617F that can occur in several MPN phenotypes, it is apparent that *JAK2* exon 12 mutations can occur, albeit very rarely, in types of MPN other than PV. Order of mutation acquisition is known to influence the MPN phenotype though other factors such as the burden of the driver mutation, additional mutations, germline predisposition, the bone marrow microenvironment, cell of origin, and the presence of clonal

hematopoiesis are all likely to contribute to the clinical phenotype<sup>[9]</sup>.

The impact the above findings will have on the molecular diagnostic algorithm for MPN remains to be realised as screening for *JAK2* exon 12 mutations reflexively follows that of the *JAK2* V617F in patients with a persistent erythrocytosis. However, the increasing adoption of next-generation sequencing myeloid gene panels for MPN diagnosis and prognosis may negate this requirement.

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