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Title: JAK2 V617F MUTATION BURDEN DETECTION AND RELATIONSHIP WITH LABORATORY CHARACTERISTICS IN MYELOPROLIFERATIVE NEOPLASMS

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Background:

Myeloproliferative neoplasms (MPNs) are a group of abnormal clone proliferation diseases characterized by the aberrant increase of mature blood cells with various genetic mutations. World Health Organization (WHO) classifies MPN into chronic myelocytic leukemia (CML, BCR/ABL positive) and Ph$^-$MPN (BCR/ABL negative), including essential thrombocythemia (ET), polycythemia vera (PV), and primary myelofibrosis (PMF). JAK2 V617F, one of the most predominant driver mutations, presents in approximately 60-95% of Ph$^-$MPN patients, and was associated with disease progression, the immunophenotype, and the clinical outcome of MPN patients. In the latest WHO guidelines, JAK2 V617F mutation was determined as the main diagnostic criterion of Ph$^-$MPN. Digital PCR is a gold standard method with high sensitivity and accuracy for mutation quantification in laboratory detection.

Aims:

The purpose of our study was to compare the diagnostic applications of digital PCR with next-generation sequencing (NGS) and real-time PCR (qPCR) for JAK2 V617F mutation quantification detection. We also aim to investigate the relationship of JAK2 V617F mutation burden with various laboratory characteristics, especially with cytokines, and to highlight their clinical utility for diagnosis and treatment monitoring for MPNs.

Methods:

We retrieved and evaluated 284 MPN patients with JAK2 V617F mutation determined by digital PCR. Spearman coefficients and Bland-Altman analysis were used to access the conformance of digital PCR and NGS or qPCR methods for JAK2 V617F mutation frequency in peripheral blood cells or bone marrow samples from MPN patients. The correlation of multiple laboratory characteristics with JAK2 mutation burden was analyzed using Pearson or Spearman coefficients. The difference of 12 cytokines in plasma between MPN patients with healthy donors used Student *t*-test or Mann-Whitney test.

Results:

Our study found high conformance of digital PCR with qPCR (Spearman $r > 0.9$, $P < 0.0001$) in detecting JAK2 V617F mutation frequency and more than 95% of measured differences present within the limit of agreement. Comparing digital PCR to NGS, we also observed a strong correlation between the two methods (Spearman $r > 0.8$, $P < 0.0001$). However, the means of mutation frequency detected by qPCR and NGS (1500X depth) were lower than that by digital PCR ($P < 0.05$). We further uncovered the relationship of JAK2 V617F mutation burden with laboratory characteristics. JAK2 mutation burden was positively correlated with white blood cells, LDH and β2-MG levels in Ph$^-$MPN. High mutation burden associated with elevated hemoglobin level in PV and increased platelets in ET. Furthermore, we found that the levels of 10 types of cytokines encompassing IL1β, IL2, IL4, IL6, IL8, IL10, IL12P70, IL17, IFN-α, and TNF-α were significantly higher in Ph$^-$MPN than in healthy donors ($P < 0.05$). IL5 level was positively correlated with JAK2 mutation burden in ET. Finally, we found a CML case concurrent BCR/ABL and JAK2 subclone. The mutation frequency of JAK2 detected by digital PCR was elevated from 0.27% in primary CML to 5.85% in CML complete recovery stage. These suggested that regularly monitoring the mutation frequency of JAK2 and BCR/ABL was beneficial to clinic accessing whether the patient developed from CML to PV or PMF.

Summary/Conclusion:

In this study, we demonstrated the advantage of digital PCR in monitoring JAK2 mutation frequency in MPN and highlighted the relationship of JAK2 mutation burden with laboratory characteristics, especially with cytokines. Our study emphasized the significance of monitoring JAK2 mutation by digital PCR for clinical diagnosis, treatment, disease relapse and transformation.

Keywords: Cytokine, Diagnosis, Myeloproliferative disorder