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LETTER TO EDITOR

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# THE *JAK2* V617F MUTATION IN LUNG CANCER: *CAVEAT EMPTOR*

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As acquisition of the *JAK2* V617F is considered to be restricted to myeloid malignancies, the recurrent identification of this mutation in non-small cell lung cancer (NSCLC) merits discussion, particularly in the light of accumulating evidence which suggests that the *JAK2* V617F may not be a true driver mutation of NSCLC. Targeted exon sequencing (TES) of solid tumors by a variety of next-generation sequencing approaches has become incorporated into routine laboratory practice with the ability to identify clinically actionable targets with increasing precision and sensitivity. Previous TES studies of NSCLC specimens have repeatedly identified the *JAK2* V617F and proposed that lung tumors harboring this mutation would be amenable to therapy with JAK inhibitors [1, 2]. While the percentage of samples appears small, these findings are not trivial when considering the global incidence of NSCLC.

The *JAK2* V617F mutation is the most common, somatic driver mutation in the Philadelphia chromosome-negative myeloproliferative neoplasms (MPN), present in nearly all polycythemia vera (PV) patients and in more than half of patients with essential thrombocythemia and primary myelofibrosis. Acquisition of this mutation results in constitutive activation of the JAK-STAT pathway, critical for hematopoietic growth factor signalling, and a consequent expansion of mature myeloid cell types. Present in three distinct diseases, supplementary genetic, epigenetic and host factors are all likely to interact and play a role in determining the phenotype. The discovery of the *JAK2* V617F mutation in 2005 has led to the breakthrough of a plethora of JAK1/2 inhibitors for MPN patients currently in routine use, in clinical trials, or in drug development pipelines [3]. While found predominantly in MPN, the *JAK2* V617F is also present at lower frequencies in other myeloid malignancies such as myelodysplastic/myeloproliferative syndromes and acute myeloid leukemia. Intriguingly, founder clones driven by the *JAK2* V617F and mutations in other myeloid malignancy-associated, epigenetic modifier genes such as *DNMT3A* and *TET2* have been detected in the blood of hematologically normal individuals with this clonal hematopoiesis of indeterminate potential (CHIP) cumulatively accruing with advancing age [4].

Evidence for the casual nature of the *JAK2* V617F in NSCLC has come from several sources. Firstly, after the first description of the *JAK2* V617F in MPN patients, analysis of solid tumor cell lines, cultured free from hematopoietic cells, did not reveal presence of this mutation [5]. Secondly, misattribution of a *JAK2* V617F mutation to a solid cancer (duodenal) was provided in an informative case of known PV in which TES of tumor and constitutional DNA highlighted this nuance [6]. Furthermore, the variant allele frequency of NSCLC driver mutations is high: in contrast, the variant allele frequency of *JAK2* V617F mutations reported in NSCLC is almost invariably less than 10% [1, 2] reflecting the presence of a low number of cells with this mutation. Lastly, recently published studies have shed some light on the magnitude of CHIP contamination in TES analysis: comparison of tumor and paired peripheral blood samples revealed CHIP mutations erroneously ascribed to the tumor in a significant number of cases [7–9]. This phenomenon has also been observed in TES studies of cell free DNA where nearly all *JAK2* mutations detected were derived from CHIP [10]. Therefore, with clinical exclusion of a co-existing MPN, the *JAK2* V617F more than likely represents hematopoietic-derived CHIP in tumor samples advocating caution in assigning clinical relevance to these mutations.

By classical definition, tumor cells have a growth advantage over their neighbours and in order for this growth to be perpetuated, a blood supply is required. Therefore, all tumor specimens must be considered to possess at least some degree of hematopoietic cell infiltration in which either somatic or CHIP-associated mutations are more likely to be identified by the enhanced sensitivity of TES technologies and bioinformatics. It would appear that simultaneous TES analysis of patient tumor and matched peripheral blood is now necessary (especially in elderly patients) to exclude the presence of a *JAK2* V617F-positive MPN, other co-existing hematopoietic malignancies or CHIP, prompting review of both sample acquisition procedures and economic impact. In both lung and other solid tumors, abnormalities of the JAK-STAT signalling pathway are well documented; however, recent evidence suggests a limited role, if any, of the MPN-associated *JAK2* V617F in these diseases.

## CONFLICTS OF INTEREST

The author declares no competing financial interests.

## REFERENCES

**1. Lipson D, Capelletti M, Yelensky R, *et al*.** Identification of new ALK and RET gene fusions from colorectal and lung cancer biopsies. Nat Med 2012; **18**: 382–4.

**2. Li SD, Ma M, Li H, *et al*.** Cancer gene profiling in non-small cell lung cancers reveals activating mutations in JAK2 and JAK3 with therapeutic implications. Genome Med 2017; **9**: 89.

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*Abbreviations used*: CHIP – clonal hematopoiesis of indeterminate potential; MPN – myeloproliferative neoplasm; NSCLC – non-small cell lung cancer; PV – polycythemia vera; TES – targeted exon sequencing.

**3. Griesshammer M, Sadjadian P.** The BCR-ABL1-negative myeloproliferative neoplasms: a review of JAK inhibitors in the therapeutic armamentarium. Expert Opin Pharmacother 2017; **18**: 1929–38.

**4. Gibson CJ, Steensma DP.** New insights from studies of clonal hematopoiesis. Clin Cancer Res 2018; **24**: 4633–42.

**5. Scott LM, Campbell PJ, Baxter EJ, *et al*.** The V617F JAK2 mutation is uncommon in cancers and in myeloid malignancies other than the classic myeloproliferative disorders. Blood 2005; **106**: 2920–1.

**6. Lee J, Axilbund J, Dalton WB, *et al*.** A polycythemia vera JAK2 mutation masquerading as a duodenal cancer mutation. J Natl Compr Canc Netw 2016; **14**: 1495–8.

**7. Severson EA, Riedlinger GM, Connelly CF, *et al*.** Detection of clonal hematopoiesis of indeterminate potential in clinical sequencing of solid tumor specimens. Blood 2018; **131**: 2501–5.

**8. Coombs CC, Gillis NK, Tan X, *et al*.** Identification of clonal hematopoiesis mutations in solid tumor patients undergoing unpaired next-generation sequencing assays. Clin Cancer Res. doi: 10.1158/1078-0432.CCR-18-1201.

**9. Ptashkin RN, Mandelker DL, Coombs CC, *et al*.** Prevalence of clonal hematopoietic mutations in tumor-only clinical genomic profiling of solid tumors. JAMA Oncol. doi: 10.1001/jamaoncol.2018.2297.

**10. Hu Y, Ulrich B, Supplee J, *et al*.** False positive plasma genotyping due to clonal hematopoiesis. Clin Cancer Res 2018; **24**: 4437–43.

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