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Letter to the Editor

MPL mutations are over-represented in patients with dual driver-mutated myeloproliferative neoplasms: an Irish cohort study

Dear Editor

Singular mutations in either *JAK2*, *CALR* or *MPL* genes are the most frequent drivers of the myeloproliferative neoplasms (MPN) with variants in other myeloid-associated genes contributing to disease phenotype and clinical course. MPN molecular diagnostic algorithms can be either sequential or simultaneous with each technology employed possessing its own sensitivities, specificities and clinical applicability [1]. An increasingly recognised, minor subgroup of MPN patients, particularly those with essential thrombocythemia (ET) and primary myelofibrosis (PMF), harbor two driver mutations [2]. Prior evidence suggests a second driver mutation occurs more commonly in low variant allele frequency (VAF) *JAK2* V617F-mutated MPN with the presence of two mutations affecting the phenotype such as a higher platelet count [3,4].

In order to evaluate the incidence and molecular diversity of the dual driver phenomenon in the Irish MPN population, an audit was performed on all requests received at a center for molecular diagnosis of MPN. Mutations in *JAK2* (exons 12 and 14), *CALR* (exon 9), and *MPL* (exon 10) were identified using a previously described single-molecule, molecular inversion probe-based next-generation sequencing (NGS) methodology [5,6]. From March 2023 to November 2025, 1275 consecutive, new patients were identified with either *JAK2* V617F (n = 1011; 79.3%), *JAK2* exon 12 (n = 12; 0.9%), *CALR* exon 9 (n = 168; 13.2%) or *MPL* exon 10 (n = 84; 6.6%) mutations. This cohort consisted of 665 females and 610 males with a median age of 68 years (range: 21–97 years). Of these 1275 patients, thirteen (1.0%) were identified with ET (n = 12) or PMF (n = 1) with two driver mutations. This group comprised eight females and five males with a median age at presentation of 71 years (range: 61–89 years) and a median presenting platelet count of 853 $\times$ 10^9/L (range: 562–1244 $\times$ 10^9/L) (Table 1). Of the 26 mutations in 13 patients, eleven (42.3%) were *JAK2* V617F, eleven (42.3%) were in *MPL* exon 10 and four (15.4%) were in *CALR* exon 9. Of the eleven patients with a *JAK2* V617F, seven (63.6%) had a VAF ≤5% (Table 1).

In this European cohort, 1% of MPN patients presented with dual driver mutations, similar to the recently described rate of 1.5% [7]. The association of dual driver mutations in patients with a low *JAK2* V617F VAF is also confirmed [8,9]. In agreement

Table 1 – Myeloproliferative neoplasm patients with dual driver mutations. Largest variant allele frequency (VAF) mutation first.

Case	Sex	Age (years)	MPN	Platelets (x 10^9/L)	Mutation #1	VAF (%)	Mutation #2	VAF (%)
#1	F	64	ET	615	*MPL* p.(Trp515Leu)	27.0	*JAK2* p.(Val617Phe)	2.0
#2	F	84	ET	736	*JAK2* p.(Val617Phe)	47.0	*CALR* p.(Leu367Thrfs*46)	3.9
#3	F	71	ET	1147	*CALR* p.(Lys385Asnfs*47)	3.5	*JAK2* p.(Val617Phe)	1.1
#4	F	70	ET	958	*JAK2* p.(Val617Phe)	6.1	*MPL* p.(Trp515Leu)	2.7
#5	M	67	ET	787	*CALR* p.(Leu367Thrfs*46)	30.0	*JAK2* p.(Val617Phe)	3.2
#6	F	61	ET	1113	*MPL* p.(Trp515Leu)	31.0	*JAK2* p.(Val617Phe)	1.5
#7	F	89	ET	1244	*MPL* p.(Trp515Arg)	4.4	*JAK2* p.(Val617Phe)	1.1
#8	F	85	ET	853	*MPL* p.(Trp515Arg)	9.6	*MPL* p.(Ser505Asn)	9.3
#9	F	86	ET	1100	*JAK2* p.(Val617Phe)	7.2	*MPL* p.(Ser505Asn)	5.4
#10	M	70	PMF	857	*JAK2* p.(Val617Phe)	17.0	*MPL* p.(Trp515Leu)	2.8
#11	M	69	ET	532	*MPL* p.(Trp515Leu)	16.0	*JAK2* p.(Val617Phe)	2.3
#12	M	72	ET	624	*MPL* p.(Trp515Leu)	2.5	*CALR* p.(Glu371Metfs*42)	2.3
#13	M	81	ET	795	*MPL* p.(Trp515Ala)	11.0	*JAK2* p.(Val617Phe)	3.4

with a proposal that a platelet count higher than 700 × 10^9/L acts as a general discriminator for identifying dual driver mutations [4], only three of thirteen patients presented with a lower platelet count. The relatively small size and short follow-up of this cohort preclude any clinical correlation. In MPN patients with a single driver mutation, *MPL* exon 10 mutations are present in approximately 5% and 9% of patients with ET and PMF respectively with the W515L allele being most prevalent. In contrast, *MPL* exon 10 mutations account for >40% of variants in this dual-driver population; these include the less common *MPL* S505N, W515R, and W515A mutations. This study provides confirmation of the prevalence of this molecular subtype in a national MPN cohort and demonstrates a distinct pattern of *MPL* mutations in dual driver MPN. This brief audit further underscores the molecular and clonal complexity of this subset of MPN patients.

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Ethical approval

This non-interventional, observational study was performed under routine standard of care procedures in accordance with the 1964 Helsinki declaration and its later amendments. Informed consent was obtained from participants at the referring centers.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflicts of interest

All authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Editor

Erich Vinicius De Paula

REFERENCES

1. Liu X, Krishnamurthy K, Naeem R, Yitzchak Goldstein D. A comparison of sequential polymerase chain reaction-based cascade testing vs next-generation sequencing in molecular profiling of myeloproliferative neoplasms: improving testing strategies in light of evolving molecular landscapes. Lab Med. 2025;56:511–6.
2. Wang Y, Ran F, Lin J, Zhang J, Ma D. Genetic and clinical characteristics of patients with Philadelphia-negative myeloproliferative neoplasm carrying concurrent mutations in JAK2 V617F, CALR and MPL. Technol Cancer Res Treat. 2023;22:15330338231154092.
3. Lebecque B, Croizier C, Tassin T, Louis E, Tribalat N, Bombardier W, et al. Contribution of molecular characterization to the diagnosis of MPN in patients with a low JAK2 V617F variant allele fraction in a real-world cohort. Ann Hematol. 2025;104:1587–96.
4. Mora B, Siracusa C, Rumi E, Maffioli M, Casetti IC, Barraco D, et al. Platelet count predicts driver mutations co-occurrence in low JAK2 mutated essential thrombocythemia and myelofibrosis. Leukemia. 2021;35:1490–3.
5. Eijkelenboom A, Kamping EJ, Kastner-van Raaij AW, Hendriks-Cornelissen SJ, Neveling K, Kuiper RP, et al. Reliable next-generation sequencing of formalin-fixed, paraffin-embedded tissue using single molecule tags. J Mol Diagn. 2016;18:851–63.
6. Lee-Tokar L, Kearney L, Langabeer SE. Detection of JAK2 exon 12 mutations in suspected polycythemia vera by next-generation sequencing. Clin Lab. 2022;68:244–6.
7. He R, Ollila PL, Zhang X, Yuan J, Shi M, Rangan A, et al. Prevalence of concurrent (double-positive) JAK2, CALR, or MPL mutations and corresponding clinicopathological features: analysis of 21556 Mayo Clinic NGS studies including 2651 informative cases. Am J Hematol. 2025;100:2431–5.
8. Usseglio F, Beaufils N, Calleja A, Raynaud S, Gabert J. Detection of CALR and MPL mutations in low allelic burden JAK2 V617F essential thrombocythemia. J Mol Diagn. 2017;19:92–8.
9. Mansier O, Luque Paz D, Ianotto JC, Le Bris Y, Chauveau A, Boyer F, et al. Clinical and biological characterization of MPN patients harboring two driver mutations, a French intergroup of myeloproliferative neoplasms (FIM) study. Am J Hematol. 2018;934:E84–6.

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