



SDI Review Form 1.6

Journal Name:	<u>British Journal of Medicine and Medical Research</u>
Manuscript Number:	2015_BJMMR_17689
Title of the Manuscript:	Mutations and pathogenesis of myeloproliferative neoplasms: Review
Type of the Article	Review Article

General guideline for Peer Review process:

This journal's peer review policy states that **NO** manuscript should be rejected only on the basis of '**lack of Novelty**', provided the manuscript is scientifically robust and technically sound.

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PART 1: Review Comments

	Reviewer's comment	Author's comment <i>(if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)</i>
<u>Compulsory</u> REVISION comments		
<u>Minor</u> REVISION comments	This manuscript "Mutations and pathogenesis of myeloproliferative neoplasms" is a scholarly and thorough review. I have no major objections. There are a number of typos pertaining to the spelling of "erythropoietin" in the first few pages which should be checked and corrected. Line 128: Table 1 should be put as a separate table at the end of the manuscript. It is spilt on 2 pages. Further, I think it is also irrelevant in this day and age. The frequency of the JAK2 mutation depends upon the accuracy of the clinical diagnosis of PV. I think the variations as reported reflects the clinical diagnosis rather than any genetic variation. Thus this statement is misleading. This issue has also been discussed several times in the literature. There is an article by Tefferi, Silver and Verstovsek in Blood some years ago pertaining to this very point. Line 121: those patients that do not have the JAK2 mutations may have EXOn 12 mutations. This sentence should include that known fact. Line 121 – line 123 is also confusing.	-The manuscript was checked for spelling errors and corrected. -Table 1 was removed from the manuscript. Instead, a new table summarizing the impact of various mutations was added and named as table 1 at the end of the manuscript. -Line 121-123: The following sentence under the heading JAK exon 12: The low sensitivity of the methods used for genotyping, the presence of hereditary genetic diseases related to erythrocytosis, procedures such as the use of interferon that have the potential to eliminate JAK2 mutated clones may



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	Line 128: this looks like a typo: “ET and PMF patients do not carry” (Of course approximately 50% do). Line 132: I would spell out W515L and W515K since these are new abbreviations. Line 140: insert “a” after “treatment of” Line 146: this must have a reference, since the use of a bone marrow for trying to distinguish W515K is valueless clinically. Likewise, there should be a reference in line 146. This is a weak section. Line 164: insert “a” after “pathogenesis of” Line 287: please provide reference. Line 354: please provide reference Line 404: please provide reference Conclusion: The conclusion is very meaningful and I would amplify it into this detailed discussion of all the mutation, which are <u>those</u> that are clinically relevant. The author make a very good exposition regarding TET2. I would like to see this done for the other mutation in prospective.	be accounted for the aferomentioned finding. The presence of additional hereditary phenomena not yet described may as well be considered responsible for disease phenotype was deleted. Instead, the following sentence was added: Although only a minority of sporadic PV patients do not carry the JAK2V617F mutation, the proportion of familial cases of JAK2V617F-negative PV patients is definitely higher. JAK2 exon 12 mutations seem to account for the majority of mutations in PV patients negative for JAK2V617F. -Line 128: The sentence ET and PMF patients mostly do not carry JAK2V617F mutations was removed and rewritten as follows: Only approximately 50% of patients with ET and PMF carry the JAK2V617F mutation. -Line 132: W515L and W515K were spelled out as follows: 60% of MPL mutations are
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		W515L and the remaining 40% are W515K mutations, which result in the substitution of tryptophan with leucine and lysine, respectively. -Line 140: 'A' was added after 'treatment of' -Line 146: A new paragraph and a new reference were added to this section as follows: In ET, a correlation between W515L and low haemoglobin (Hgb) levels and between W515K alleles and high platelet counts were reported.³⁸ Also, bone marrow examination in W515L/K mutation-positive patients showed reduced total and erythroid bone marrow cellularity, whereas the number of megakaryocytes, megakaryocytic clusters, and small-sized megakaryocytes were all significantly increased.³⁸ These data show that MPLW515L/K mutations do not define a distinct phenotype in ET.
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		-Line 164: in the pathogenesis of myeloproliferative disease was rewritten as in the pathogenesis of myeloproliferative diseases -Line 287: A reference was added for the following sentence: In clonal analysis studies held in patients with MPNs, no certain chronological line of events were observed between acquisition of TET2 and JAK2 mutations. -Line 354: The sentence Contrary to the presence of detailed clinical studies assessing the impact of ASXL1 mutations on lifespan and response to therapy in AML and MDS, there have been few studies including limited number of patients as regards to ASXL1 in MPNs was revised as follows: A number of studies have assessed the impact of ASXL1 mutations in MPNs. Also, new references were added for the aforementioned sentence.
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		-Line 404: A reference was added for the following sentence: Boissel N.et al. reported that mutant IDH2 was a poor prognostic factor in normal karyotype AML.
<u>Optional/General</u> comments		