Reviewer's report

Title: Combined mutations of asxl1, cbl, flt3, idh1, idh2, jak2, kras, npm1, nras, runx1, tet2 and wt1 genes in myelodysplastic syndromes and acute myeloid leukemias

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Reviewer: Philip Beer

Reviewer's report:

In this report, Rocquain and colleagues have looked for mutations in a number of leukaemia-associated genes by direct sequencing in 64 patients with acute myeloid leukaemia (AML) and 65 patients with myelodysplasia (MDS). The methods used and the data presented in this paper are scientifically sound and of interest to the field. The main problem lies in the conclusions drawn in the discussion section, and major revision of this section is advised prior to publication.

Major Compulsory Revisions

1) Discussion section. Although the discussion section of an article may be used as an opportunity to hypothesise and speculate, the conclusions drawn in this article are too far-fetched for publication, and contain inconsistencies with current understanding of AML biology. The division of mutations into four classes, apparently based on the cohort screened in this paper, is not justified, nor is the conclusion that there are likely to be 8 other class 1 genes yet to be discovered. RUNX1 is not generally considered as a tumour suppressor, as implied in page 12 para 2. TET2 cannot be considered as an initiator given that clonal studies have shown that TET2 mutations may be acquired as second events. The notion of ‘selector’ mutations has no support from biological studies. The grouping of IDH1/2 and WT1 is also without biological basis. Essentially the entire discussion section from ‘A repertoire of mutations’ needs to be rewritten to focus more on the data presented.

2) The above not withstanding, the distribution of mutations in this well-characterised cohort is interesting. I suggest the authors remove figure 2 and devise a new figure that illustrates which mutations coexist in individual patients. The grouping together of mutations in CBL, FLT3, JAK2 and RAS is quite reasonable in this context.

Minor Essential Revisions

1) The second sentence of the abstract ‘Background’ section does not make grammatical sense and needs rewording.

2) The authors should define complex karyotype (page 4 para 3).

3) I would suggest moving the precise details of the PCR reaction to
supplementary information and including details of which exons of each gene were sequenced in the main text.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests