Reviewer’s report

Title: Comprehensive chromosomal aberrations in a case of a patient with TCF3-HLF-positive BCP-ALL

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Reviewer: James Blackburn

Reviewer's report:

Within the manuscript "Comprehensive chromosomal aberrations in a case of a patient with TCF3-HLF-positive BCP-ALL", the authors describe a single clinical case of translocation t(17;19)(q22;p13), using FISH probing and microarray analysis. They postulate that identification of additional genomic aberrations beyond the gene fusion event may inform on the clinical course of the disease.

Whilst the study presents an interesting medical case, there are several gaps in the study approach that require addressing to support the conclusions. There are also several key issues relating to the manuscript that also require elaboration or amendment.

As a general comment, could I suggest that the authors seek manuscript editing help from someone with full professional proficiency in English? At times, the manuscript was difficult to follow, and I think improving the written communication would assist with conveying the study effectively.

For ease of reading, I've broken the manuscript comments into each relevant section, and included line numbers where appropriate.

Abstract: The abstract does not clearly state why this case is novel or why it should be reported. The authors note that the TCF3-HLF fusion has already previously been reported in the literature, albeit in a small number of cases. Though aberrations in RB1, PAX5 and NOTCH1 are further diagnosed in the study patient, the cumulative effects or implications (diagnostic or prognostic) are not stated.

Background: (Lines 55 and 56) Examples of chromosomal rearrangements, SNVs and Indels resulting in ALL should be listed and referenced here. Otherwise, these are generic empty statements.

Case Presentation: (Line 71) Abbreviations such as FISH should appear in the parentheses, with the full definition preceding this. (Lines 73 and 74) If the patient karyotype was determined by GTG band staining, the authors should show this as a figure to confirm normality. If the statement of a normal karyotype is solely based on the observed FISH results, this would only be suggestive of a lack of disruption at these select loci, and not overall patient normalcy. (Lines 84 and 85) The authors should provide definitions for HIA block and HIB block. (Lines 88 to 98) Out of all the retrospective tests that could be applied, why specifically was TCF3-HLF FISH
performed? If it was part of a battery of FISH tests, what other assessments were attempted? (Lines 91 to 96) Whilst the microarray was applied to samples at diagnosis and at relapse, TCF3-HLF FISH (and GTG band staining) only seems to have been applied at diagnosis. Why is this? Further, it would also be more comprehensive for the authors to show the effects of genomic disruption of RB1, PAX5, CDKN2A, CDKN2B and NOTCH1 through either qRT-PCR methods or IHC. I.e. show an effect on each respective gene at either the transcriptional or translational level. qRT-PCR would also provide good confirmation of the TCF3-HLF FISH result, both at diagnosis and at relapse.

Discussion and Conclusions: (Lines 108 to 110) A reference is needed for TCF3. (Lines 108 to 111) What elements of each gene are incorporated into the new fusion gene, and what are the implications of such a composition? (Lines 112 to 113) A reference is needed for the well-established deletions of PAX5, VPREB1 and BTG1. (Line 116) "Demonstrated" is a little strong here. Mouse models don't always faithfully recapitulate human disease. "Implied", or similar, may be a better substitute.

Figures: (1A) There is no description of the figure labelling or figure colours in the legend. (1B) Some of the details of this figure legend would be better served in the main body of the text. The figure itself is of very poor quality, is not well annotated and is barely legible. (2A+B) The legends for both figures lack any descriptive detail. The figures also appear to be low-quality screen snapshots, with poor labelling and unclear annotation.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

No

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Unable to assess

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

No

**Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?**
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

Not relevant to this manuscript

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