Reviewer's report

Title: Whole-exome sequencing of a rare case of familial childhood acute lymphoblastic leukemia reveals putative predisposing mutations in Fanconi anemia genes.

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Reviewer: Maria Castella

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The authors seek to characterize inherited genetic variation that drives childhood ALL. They perform exome sequencing in a family with 2 affected siblings and their parents that were previously found to carry rare mutations in PRDM9 gene. They describe a set of other mutations found, under a recessive disease model, and discuss the potential contribution of rare variants in Fanconi anemia genes in driving the leukemic process in this family. Identifying genetic variants that contribute to disease progression in ALL patients is of major significance in the field as it can translate into a better assessment of potential risk and disease prognosis, as well as provide bases for more efficient and personalized therapies for patients with ALL. However, the contribution of the variants found in the Fanconi anemia genes (FANCA and FANCP/SLX4) in the leukemogenic process is highly speculative.

Major compulsory revisions

1. Although several genes are shown to carry potentially deleterious variants that segregate with the disease, only FANCA and FANCP/SLX4, together with PRDM9, are considered to have the potential to drive ALL in this family. It is unclear why the authors choose to focus only in the Fanconi anemia proteins and disregard the others. For example, variants found in GEN1 (a Holliday junction resolvase) or CEP55 and PDE4DIP (centrosomal proteins) could also contribute to this process and should be discussed in the paper.

2. Supplementary table S1 contains key data and should be part of the main text.

3. The paper revolves around the variants found in FANCA and FANCP/SLX4. However, whether these variants have a deleterious effect is unknown. Although the authors claim that the variants are predicted to have a deleterious effect by in silico analyses, other reports have stated the opposite (Bakker et al. 2012 and Litim et al. 2012). Several algorithms or a more conclusive assessment of variant pathogenicity (such as functional assays) should be used.

4. The siblings are reported to have a non-syndromic form of ALL. However, they are carriers of potentially deleterious variants in both alleles of FANCP/SLX4 which is consistent with Fanconi anemia diagnostic. ALL is rare in Fanconi anemia patients, but not unheard of and the lack of other symptomatology does not rule out the diagnostic. Therefore, the possibility that the siblings are Fanconi
anemia patients exits and should be addressed.

5. The authors state that heterozygous carriers of mutations in FA genes can present malformations (line 193), although no bibliography is cited. This sentence should be revised, FA mutation carriers are not known to have any symptomatology.

Minor Essential Revisions
7. Line 180 and 181: Letter “w” is used in the equation and “q” in the explanation.
8. Line 187: “To date, 15 FA genes...”. There are 17 FA genes described.
9. Line 194: Include references instead of “(ref).”
10. Supplementary table S1: It is unclear why there are 4 different entries for the gene DNAH2 with different combinations of 2 SNPs.

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

Quality of written English: Acceptable

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