Reviewer’s report

Title: RAS mutations in early age leukaemia modulated by NQO1 rs1800566 (C609T) are associated with second-hand smoking exposures

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Reviewer: Anthony V, Moorman

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Andrade and colleagues report an epidemiological study of acute leukaemia in young children investigating the potential interaction between acquired genetic abnormalities (MLL rearrangements, RAS mutations), predisposing factors (NQ01 status) and environmental factors (e.g. smoking). The overall conclusion is that there is an association between second-hand smoking and RAS mutations and the NQ01 genotype.

Major Compulsory Revisions

1) The outcome of ALL patients <13 months has not be presented. The authors should add these data or explain why they cannot be added.

2) The frequency association between RAS mutations and NQ01 genotype should be presented. This is especially important given the data presented in Table 5 regarding the effect of smoking on the development of leukaemia in cases with NQ01 1609 CT/TT and a RAS mutation.

3) In tables 4, 5 and 6 and in the text the authors need to clarify exactly how the NQ01 genotype status has been analysed. I assume it is always CC v CT/TT. However, this is not clear.

4) The authors should show the data referred to in the following sentence: “… and no association between maternal smoking and ALL or AML was found (data not shown).”

5) In addition, the authors should show the association of smoking with MLL-r, RAS mutations and NQ01 genotype. The latter two are presented in Table 5 in combination, they should also be presented separately.

6) The final multivariate models should be presented in full.

7) I find the results perplexing. Does the variable “someone in the house ever smoked” include the mother themselves? Or is it “other” smokers. Either way I find it puzzling how these “other smokers” can be having such a large effect; given that there is no discernible effect at all for the mother herself smoking and the risk of NQ01609CT/TT and/or RAS mutated leukaemia. In fact there is almost a negative correlation. It is counterintuitive that “first” hand smoke has no effect whereas second hand smoke does. This apparent paradox needs to be acknowledged and discussed.
8) Given the above paradox, further details of the “smoking” questions in the questionnaire should be provided; along with details of exactly how the variables are constructed.

9) The conclusion states that “The present data suggest that second-hand tobacco smoking exposures are associated with increased risk of EAL with MLL-r and RASmut modulated by NQO1 rs1800566 (C609T).” However, the authors do not present smoking data with respect to MLL-r status.

Minor Essential Revisions

1) There is a typo “the?” in the second sentence of the second paragraph in the introduction.

2) In the last paragraph of the results the authors refer to the “…risk of developing leukaemia…”. This is incorrect as all the cases have leukaemia. They should rephrase emphasising that they are measuring an association between smoking and the presence of selected genetic characteristics.

Discretionary Revisions

1) Table 2, 3 and 4 should be in the supplementary information.

2) There are five major variables considered in this paper: ALL/AML, MLL-R, RAS mutation, NQ01 genotype and smoking. Hence the results are complicated and can be difficult to follow. I would suggest that the authors consider if all these variables are required. For example, do they need to separate ALL and AML in this context? The key results seem to be very similar. In addition, the division of cases by MLL status does not appear to add to the central message. The paper would be clearer if it were more focussed.

3) As FLT3 and BRAF mutations also result in deregulation of the MAPK pathway, one could argue that these cases could be combined with the RAS mutations to form a “RAS pathway mutated” group.

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

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

I declare that I have no competing interests