Reviewer's report

Title: A comprehensive evaluation of the role of genetic variation in follicular lymphoma survival

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Reviewer: Federico Canzian

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The present manuscript reports on a genome-wide association study on survival of follicular lymphoma patients. The study is based on two series of patients of relatively small scale for a total of 586 patients. Genotyping was performed also in a relatively small scale (about 300000 SNPs in each sample set).

The study question is relevant both from the biological and the clinical point of view. The study is done with sound methodology both in terms of lab work and data analysis.

Although no variant formally reached a genome-wide level of significance, the reported association with SNPs on 17q24 are quite close, and the genes in the immediate vicinity are interesting candidates from the biological point of view.

Major Compulsory Revisions

1. My main criticism is that only the top 1000 SNPs from the SCALE study are used for replication in the UCSF study. Since both series of patients have been genotyped with arrays suitable for GWAS analysis, why not doing a full-scale genome-wide meta-analysis? This would not rehire a huge amount of additional work, and might yield additional interesting hits. The two series of patients have not been genotyped with the same array, but through imputation it is perfectly feasible to merge the datasets. If the authors choose not to do this work, I would like to see at least a compelling explanation for their reasons.

2. A point connected to the previous, is that through imputation the authors can somehow compensate the rather small scale of the arrays used for genotyping, which are not anymore state-of-the-art. This could lead to a better coverage of the genome.

Minor Essential Revisions

3. Why sex was not used as adjustment variable in the GWAS analysis?

4. It is not clear why adjustment with FLIPI 5 categories or first-line rituximab has been performed only for the analyses of validation of previous candidate SNPs and not also for the main GWAS analysis. Given the possible role of the ABC transporters where the top hit is located, it is important to check whether the observed association is independent of treatment. Although table 2 shows that FLIPI is available only for SCALE cases and rituximab only for the Swedish ones, these adjustments should be down at least for the analysis of the top hits.
5. The authors argue that progression-free survival and lymphoma-specific survival are superior to overall survival (OS). On the other hand, they acknowledge that lymphoma-specific survival may miss deaths due in part to progression. In addition, given how complex is often death certification, it is entirely possible that some deaths were attributed to other causes, but lymphoma was at least an underlying cause of death. Thus, I think there would be value in exploring also OS as an end-point.

6. Since the top SNPs are located inside a gene which is also a good candidate from the biological point of view, it would be interesting to use bioinformatics tools (e.g. RegulomeDB, eQTL analysis) to check if these SNPs (or other SNPs in high LD) have a possible function.

7. In table 3 and supplementary table 1, commas should be replaced by points.

Discretionary Revisions
8. The authors mention that power of their study to validate associations previously reported in the literature may be limited. In this respect it may be useful to add to the discussion a statement about statistical power to replicate them, taking into account the frequency of the SNPs and the HRs observed in the previous studies.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare that I have no competing interests