Reviewer’s report

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

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Reviewer: Niels Weinhold

Reviewer’s report:

Baecklund et al. have investigated the role of genetic variation in follicular lymphoma outcome. Using data from GWAS they identified a promising association at 17q24, a region which codes for ABC transporter proteins. In addition to that they validated a set of SNPs recently published and could show an effect for some of them. The data are of potential interest for the scientific and medical communities but some points have to be explained, discussed or modified, as described in the following section:

Major Compulsory Revision

Methods:

How did the authors calculate the first three principal components using Eigenstrat? Did they use the complete SNP set or a pruned one including only unlinked SNPs?

The authors adjusted the GWAS for age at diagnosis and population stratification. Analyses for candidate gene associations were additionally adjusted for sex. Why didn’t the authors adjust for sex in the GWAS although the data was available? If sex was not associated with the frequency of identified candidate SNPs they should at least mention that. What about FLIPI adjustment in GWAS?

Results:

Was there any association of the promising candidate at 17q24 with established prognostic factors like performance status or lactate dehydrogenase levels?

Was there any association between the promising candidate at 17q24 and lymphoma progression in the Swedish cohort?

Fifty-four of the SNPs were nominally significantly associated with lymphoma-specific death in the UCSF cohort... -> How many of them showed the same direction of effect in comparison to the SCALE cohort?

Results of the candidate SNP study are difficult to follow. The authors should not write that in their study the opposite allele showed the opposite effect. They should use the same order of alleles. If there were large differences between published results and their own data that should be described in the results part
and not only in discussion as this was a confirmation study, e.g. rs18001131 in MTHFR. In addition to that they should mention in the results part which sets they used for validation and for which association (death/progression). Rs2466571 in CD46 is an example for a SNP showing an effect for progression but not for lymphoma-specific death. This could be just by chance but nevertheless there might be SNPs being associated with progression/event free survival but now overall survival. If the authors want to validate published results they should use the same outcome variable as used in previous studies. In addition to that they could present data for lymphoma specific death and discuss differences or comparable results. Finally, the authors should calculate the power of their study to demonstrate a relationship between published SNPs and outcome, at the 5% threshold.

How many SNPs which were associated with FL risk were tested for an association with survival in this study, 5 (page 8) or 6 (page 13)?

Figure 1: SNPs were treated as continuous variables but in the plots only data for wildtype and variant are presented (dominant model).

Table 3: The results in this table should be reduced to the best SNP per linkage block. Complete results might be presented in supplementary tables.

Discussion:

The authors should discuss the results of the GWAS and the validation analyses in separate paragraphs. Furthermore if they think that imputation might have caused misclassification of genotypes they should check some cases using another method, e.g. sequencing, if possible.

...we found further support of a role for [...] and two SNPs in IL8 [...] in FL progression. -> In the original studies IL8 SNPs were associated with OS! The authors should not mix outcome variables.

Discretionary Revisions

In case of the confirmation study the authors could perform meta analyses with published and their own data and present the results.

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 have no competing interests.