Author's response to reviews

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

Authors:

Fredrik Baecklund (fredrik.baecklund@ki.se)
Jia-Nee Foo (foojn@gis.a-star.edu.sg)
Paige Bracci (paige.bracci@ucsf.edu)
Hatef Darabi (hatef.darabi@ki.se)
Robert Karlsson (robert.karlsson@ki.se)
Henrik Hjalgrim (hhj@ssi.dk)
Richard Rosenquist (richard.rosenquist@igp.uu.se)
Hans-Olov Adami (hadami@hsph.harvard.edu)
Bengt Glimelius (bengt.glimelius@onkologi.uu.se)
Mads Melbye (mme@ssi.dk)
Lucia Conde (lconde@uab.edu)
Jianjun Liu (liuj3@gis.a-star.edu.sg)
Keith Humphreys (keith.humphreys@ki.se)
Christine F Skibola (cskibola@uab.edu)
Karin E Smedby (karin.ekstrom.smedby@ki.se)

Version: 3
Date: 26 August 2014

Author's response to reviews: see over
Dear Editor,

We hereby resubmit the manuscript “A comprehensive evaluation of the role of genetic variation in follicular lymphoma survival” after a second round of revision. Below please find our specific responses to the remaining issues.

Most sincerely,

Fredrik Baecklund, on the behalf of all authors

Stockholm, 25 August 2014
Reviewer: Niels Weinhold

Answers to major compulsory revision points 1, 2 and 4-10 were satisfying.

Minor Compulsory Revision

Point 3 (Was there any association of the promising candidate at 17q24 with established prognostic factors like performance status or lactate dehydrogenase levels?):
The authors should add to the discussion that the association of rs10491178 was independent of established prognostic risk factors as their aim was to explain variability in prognostic groups defined by established risk factors.

We thank the reviewer for pointing this out. We added this information to the discussion section (page 16, rows 15-17).

Major Compulsory Revision

Point 11 (…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.): This data does not provide further support of a role of variation in IL8 in FL progression. An association of this variation with progression was only shown in this study. The outcome variable in the original studies was OS. The authors may write that they found an association that has to be confirmed.

We have changed the wording in the passages mentioned (page 16, rows 7-9 and page 21, rows 15-17) in line with the suggestion of the reviewer.

Additional Major Compulsory Revision in revised text

1B: On page 17, line 8 the authors wrote that “…rs113464685…was the best candidate to explain the observed association…”. The HR for this SNP (3.10) was lower than the HR for rs10491178 (3.17). This difference might be due to uncertainties in imputation but if the imputed genotypes are 100% correct, rs10491178 is still a better candidate. A low RegulomeDB score does not mean that the functional basis of association has been found. Of note, according to ENSEMBL data rs10491178 causes a stop codon in transcript ABCA10-001.

We agree with the reviewer that rs113464685 is not necessarily “the best candidate to explain the observed association with the region”, but rather an alternative candidate to explain the functional basis of the association observed. We have...
clarified this in the discussion section (page 17, rows 7-12). We also added the information that rs10491178 may cause a stop codon according to ENSEMBL data (page 17, rows 3-5). The estimated HRs and 95% CIs for the two SNPs rs10491178 and rs113464685 were identical in the SCALE cohort (HR=3.10, 95% CI 1.98-4.89, p=1.12 x10^-6). The HR=3.17 for rs10491178 was observed in the meta-analysis of SCALE and UCSF. We did not impute the genotype or estimate the HR for rs113464685 in the UCSF data but, most likely, we would get the same results as for rs10491178, given the strong LD between the SNPs in 1000 Genomes CEU population (r^2=1.00) and SCALE (r^2=1.00).

**Additional Minor Compulsory Revision in revised text**

2B: The authors should delete “Bonferroni corrected prandom” (e.g. page 3, line 22). In case of standard GWAS the Bonferroni correction is Pvalue*1.000.000. That is why the rs10491178 association is not genome-wide significant (P=0.0524).

The Bonferroni corrected results have been deleted throughout the GWAS part of the manuscript. In the candidate gene part, we have kept the Bonferroni corrected p-values.

**Additional Discretionary Revisions in revised text**

3B: The authors may present the results of power calculations before the candidate SNP association results.

We thank the reviewer for this suggestion. We changed the presentation of results accordingly (page 14, rows 18-22).