Author's response to reviews

Title: Genetic risk factors for intestinal metaplasia in a high risk Singapore-Chinese population: a cohort study

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Author's response to reviews: see over
Monday, 17 August 2009

Dear Mr. Aulakh,

We thank you and the reviewers for the comments on our manuscript “Genetic factors associated with intestinal metaplasia in a high risk Singapore-Chinese population: a cohort study” (MS: 1770811709284861). Our point-by-point response to the reviewers’ comments is given in the following pages. Relevant changes (denoted by underlining) have been made in the attached manuscript.

Please do not hesitate to contact me if there is anything further to address.

Yours sincerely,

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Dr Hamajima

1. The additional genotype frequencies have been added to Table 3.

2. The reviewer is correct to point out that HWE analysis is not relevant for HP subgroups. Reference to this has been deleted from the Results and the P value shown now clearly refers to the overall group.

3. Although there is a high probably that IM+ subjects had HP infection at some stage, this cannot be confirmed. As such, we prefer not to group IM+ subjects with HP-, and rather report the groups as noted in clinical records. The quotation “However, its association with increased risk of IM in HP negative individuals suggests it may play a role independently of this factor” is based on pure observation of results and their inferences. From the data in this study, it is difficult to ascertain if IM develops without HP infection in Singapore Chinese.

4. Additional age groups are now shown in Table 2 (>50-59, 60-69, ≥70 years)

5. This nomenclature has now been changed in the Results, second paragraph.

6. The reviewer is in fact referring to reference 32 on their previous work with PTPN11. There were insufficient AA genotype individuals in the present study (n=6) to allow separate evaluation of this group.
Dr Zambon – Major

1. Additional patient information concerning eligibility, age, family history, drinking and smoking has been added to the Methods and Results.

2. Histology provides the current status of HP infection, whereas serological data indicates current or past status. Hence, these two methods are not comparable. Additional information is now included in the Methods, p5, to clarify the evaluation of HP status using serology and histology.

3. The serum PGA/PGC ratio was not known and therefore could not be used.

4. Haplotype analysis has since been performed for IL10 and STCH (as indicated in Methods) and no significant association was found (as stated in Results).

5. The very recent paper by Hishida et al is now cited (ref 45) in the final paragraph of the Discussion.

Dr Zambon - Minor

1. This was a mistake on our part and has been corrected throughout the text.

2. We agree with this suggestion and have altered the nomenclature throughout the text to refer to the relevant allele.

3. This allele appears to be absent from the Chinese population.

4. The relevant references linking the candidate polymorphisms with risk of gastric cancer have now been cited in the last sentence of the Introduction.
Dr Rabkin - Major

1. This is a discretionary revision. While we agree with the reviewer that a summary of the SNPs shown to be risk factors for gastric cancer may be interesting, we believe it is beyond the scope of the current study that deals with IM.

2. The second paragraph of the genotyping section in the Methods gives the success rate for genotyping.

3. Allele frequencies for the NQO1, IL-10 -819 and PTPN11 polymorphisms in the present study (T=15%, C =30%, G=80%, respectively) were comparable to other Asian studies.

Dr Rabkin - Minor

1. We have altered the text where appropriate by replacing “risk” with “association”. Additional information on this study cohort has been added to the Methods.

2. Additional information on the Helicoblot assay has been added to the Methods.

3. The statistical significance for the interaction is given in the Results (final sentence) and the test used is described in the Methods (Woolf test).

4. A reference for the Sydney system of classification of gastric lesions is given in the Methods.

5. Information on chronic gastritis and atrophic gastritis is now shown in Table 2. Only one case showed dysplasia.

6. A dominant genetic model was used. This is now stated in the Methods section.

7. These variables are described in the Results.

8. Genotyping failure rates are now given in the Methods and varied from 1-15% depending on the polymorphism. Failure is usually due to poor DNA quality.

9. The title of Table 3 has been changed to reflect the fact that distribution of genotypes is shown. rs numbers for each polymorphism are now included, where appropriate.

10. The issue of multiple testing has been dealt with in the statistical section of the Methods (p7).

11. Reference 3 has been corrected.