Dr. Qingyi Wei

Editor in Chief, Cancer Medicine

December 15, 2013

Dear Dr. Wei:

Thank you for your letter of November 29, 2013 regarding our manuscript entitled “"Significant SNPs have limited prediction ability for thyroid cancer”. Our appreciation also goes to the reviewers for their helpful comments. We have revised the manuscript following the reviewer’s comments and your instructions.

Enclosed please find the revised version of the manuscript along with a point by point description of our responses to the reviewer’s comments. We hope that the manuscript is now acceptable for publication in Cancer Medicine. Thank you again for your letter and for your editorial assistance.

Sincerely yours,

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**Responses to Reviewer 1’s comments**

We first thank the reviewer for the helpful comments. In the revised manuscript, we have incorporated the reviewer’s comments.

1. **Comments**: “Table 2 should also report the significance of the variants in addition to the effect sizes”

**Response**: In the revised manuscript, we have added the P-values of the variants in Table 2.

**2.** **Comments**: “It is not clear how the genotyping was performed for case and control cohorts. Was it performed separately? If so, what measures have the authors taken to confirm that there is no batch effect (such as using a known null variant as negative control)?”

**Response**: The genotyping was simultaneously performed in both cases and control cohorts which had been descripted clearly in our previous report.

**3. Comments:** “There are a couple formatting errors, such as spaces are omitted in many places, such as "therelative" and "heterozygotesrelative". I'd recommend a thorough proof reading.”

**Response:** In the revised manuscript, we have corrected all these misprints.

**Responses to Reviewer 2’s comments**

We first thank the reviewer for the helpful comments. In the revised manuscript, we have incorporated the reviewer’s comments.

**1. Comments: “**The authors claimed that five SNPs (rs965513, rs944289, rs116909374, rs966423 and rs2439302) were associated with thyroid cancer in Han Chinese. However, the association results were not showed in this paper.”

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**Response:** These association results were showed in Table 1, which is included both odds ratio and P-value. We have been reported this in our previous article (Journal of medical genetics 50 (10), 689-695). So we didn’t repeat reported these result in present paper. In this manuscript, we are focusing on familial relative risk and prediction ability based on these SNPs.

**2. Comments:** “In factor, only four SNPs, instead of five SNPs were associated with thyroid cancer, since rs116909374 was not polymorphic in in Han Chinese.”

**Response:** Yes, only four SNPs were used in the prediction analysis. However, in our manuscript we take these five SNPs as a panel, since they are significant in other populations. We have state this situation in the manuscript.

**3. Comments:** “The authors stated that “Most common diseases are caused by multiple genetic rather than few loci”. In fact, GWAS addressing common variants have comes to its limit and missing heritability for most complex disorders is very high. Only less than 5-10% heritability was found based on CDCVmodel”.

**Response:** This is a good point. In our discussion, we have added these comments in the revised manuscript.

**4. Comments:** “The authors demonstrated that “Intuitively, the variants with highly significant associations will make large contributions to disease risk prediction”. In fact, this is not the case, since the effect size of most individual common variants is small.”

**Response:** We agree with the reviewer’s comments. In the revised manuscript, we have removed this sentence.

**5. Comments:** “ Why the authors did not add traditional risk factors, i.e., iodine intake, family history, to their prediction model. The heritability and the risk of family history of thyroid cancer are so high that only putting four SNPs with modest effect size into the prediction model is far from enough.”

**Response:** Yes, we should add these important risk factors in the prediction model. Unfortunately, these traditional risk factors in controls are not available. Our major point in this manuscript is that using a few significantly associated SNPs is not sufficient to predict risk of thyroid cancer.

**6. Comments:** “The prediction power in Han Chinese is far less than that in the original OSU cohort and the Polish cohort. The differences should be discussed.”

**Response:** Difference for prediction power comes from two reasons. First, this is due to heterogeneity of thyroid cancer. The genetic structure of thyroid cancer in Chinese population may be different from that on Caucasian population. Second, in the original OSU cohort and the Polish cohort studies, they did not use cross validation to calculate prediction precisions.