Reviewer’s report

Title: The haplotype of UBE2L3 gene is associated with Hashimoto's thyroiditis in a Chinese Han population

Version: 0 Date: 29 Nov 2015

Reviewer: Jochen Schneider

Reviewer’s report:

Summary

The ubiquitin-proteasome system (UPS) is a key player in maintaining cellular homeostasis by protein ubiquitination, a multi step enzymatic process regulating stability, function and localization of modified proteins. This system is highly regulated by post-translational modification and covalent binding.

Little information so far is available regarding the transcriptional regulation of the genes involved in the process. Ube213 is an E2 ubiquitin-conjugating enzyme, that participates in ubiquitination of substrates leading to the degradation of target molecules.

Genetic variants in Ube213 have been reported in various inflammatory diseases such as rheumatoid arthritis, SLE and Crohn’s gastroenteropathy. The authors investigated several SNPs in Ube213 in a cohort of 1028 patients with autoimmune thyreopathies such as graves and Hashimoto thyreopathy as well as healthy controls including subphenotypes. The present study reports an association between one Ube213 haplotype and Hashimoto thyreopathy (HT) in the Chinese population. The haplotype TCGGC was increased in frequency in subjects with HT (OR 1.44, P=0.031)

The authors conclude that the Ube3L2 is likely a susceptibility locus for HT.

Major comments:

The study is interesting. The authors implicate an important cellular protein degradation and metabolic pathway with autoimmune endocrine thyroid diseases.

However, the manuscript is lengthy and appears blown up given the degree of novelty added to the existing body of literature.

1. The selection of SNPs is somehow conceivable, but is at least arbitrarily enough that correction for multiple testing must be performed. This exercise is especially difficult when the variations are in close proximity to each other as shown by the haplotype block. This reviewer has severe doubts that the significant increased frequency of the TCGGC haplotype stays significant when corrected for multiple testing. A condervative procedure for that would be dividing the original p value by the 4 existing haplotypes to obtain the corrected p value: 0.05/4= 0.0125.
2. The methods section could be shortened by 1/3

3. The results section should be shortened by 1/3

4. The discussion is lengthy and it very speculative. The authors cannot make any assumption as to what the mechanism of this finding might be, it is even unclear whether it holds when tested in other cohorts, thus the conclusion drawn by the authors is not supported by the data shown.

5. The manuscript is, when proofread by an English language speaker, and revised (see above) potentially well suited for a short report.

6. Table 1 may be in supplement (nice to show primer sequences and protocols)

7. Table 3-5 can be omitted and summarized in the text by 1-2 sentences.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

No

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I recommend additional statistical review

Quality of written English
Please indicate the quality of language in the manuscript:

Not suitable for publication unless extensively edited

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