Author’s response to reviews

Title: Insulin gene polymorphisms in type 1 diabetes, Addison’s disease and the polyglandular autoimmune syndrome type II

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**Insulin gene polymorphisms in type 1 diabetes, Addison’s disease and the autoimmune polyglandular syndrome type II**

We thank you for reviewing our manuscript and for providing us with the opportunity to submit a revised version. All comments and questions have been addressed as follows:

**Reviewer 2**

1. In order to clarify and give a supported hypothesis, we reformulated our research question (Introduction, page 3 and 4, last and 1st paragraph, respectively):

   T1D and Addison’s disease (AD) may occur in the same patient to form a polyglandular syndrome type II (APS-II) [12]. Although the precise function of the VNTR is uncertain, it is conceivable that through its potential effect on the thymic expression level of insulin, the VNTR could affect the development of immune self tolerance not only to antigenic peptides derived from insulin but also to other endocrine targets: this could occur through local insulin signalling by affecting other genes’ expression levels thereby leading to differences in thymic expression levels of thyroid or other endocrine antigens. Therefore the VNTR region could confer susceptibility not only to T1D but also to other autoimmune endocrine disease such as Addison’s disease (AD), Hashimoto’s thyroiditis (HT) or Graves’ disease (GD) by causing an abnormal thymic tolerance [13].

2. The description of the methods’ section was meticulously rechecked in order to be sure that all necessary information was addressed. Concerning the points a and b:
   a. Although the information on page 5 (4th and 5th paragraph) give a complete information about age and sex of patients and controls, we added the following lines (page 5, 2nd paragraph):
Age- and sex-matched HC were volunteer blood-donors from the Red Cross Blood Transfusion Centre in Frankfurt am Main (Germany), staff personal or medical students from the University Hospital Frankfurt am Main (Germany) without family history of T1D, HT, GD or AD.

b. Usually a power calculation has to be performed before a study is started. Nevertheless we performed a power calculation in retrospect and added the following sentence (page 7, 2nd paragraph):

3. In order to detect a statistical difference (p<0.05) at an OR 1.8 (as seen for T1D) we calculated for the -2221Msp(C/T) SNP that 276 chromosomes (138 patients vs. 138 HC) and for -23HphI(A/T) 224 chromosomes (112 patients vs. 112 HC) are necessary to reach a power of 80% using the software version 2.1.30 (www.mc.vanderbilt.edu/prevmed/ps/index.htm).

4. As mentioned by the reviewer the manuscript is now better adhering to the relevant standards for reporting and data deposition.

5. The discussion and conclusions were adequately supported by the data (as mentioned by the reviewer) so that references and the data published by others have been discussed clearly. Also, what references contribute how to the study hypothesis or the discussion were addressed as follow (page 8, 1st paragraph, 2nd sentence):

Therefore our data are in line with previous reports, which found that the -2221 MspI SNP and the -23HphI SNP are associated with T1D, where the -2221 MspI SNP was only part of a susceptibility insulin gene haplotype and the -23HphI SNP was found with the strongest association to T1D [4,9].

Instead
The -2221 MspI SNP is only part of a susceptibility insulin gene haplotype where the -23HphI SNP has been found with the strongest association to T1D [4, 9].

9. The manuscript has been rechecked meticulously for writing still. Thus the manuscript was improved for errors as the use of type 1 diabetes instead T1D.

As mentioned by the Senior Assistant Editor a meta-analysis is not appropriate for a manuscript presenting original research. Therefore as suggested we performed a power calculation (see point 2b).

Additional change:
Reference 13, 14 and 15 were removed

Finally, we hope to have addressed all comments and questions to the reviewer’s and your satisfaction. We are convinced -as mentioned by the reviewer- that the data are of relevance for the BMC Medical Genetics community and look forward to the final decision at your earliest convenience.

Yours sincerely

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