Author’s response to reviews

Title: Further evidence that mutations in INS can be a rare cause of Maturity-Onset Diabetes of the Young

Authors:

Trine W Boesgaard (tweb@steno.dk)
Stepanka Pruhova (pruhova@seznam.cz)
Ehm A Andersson (ehaa@steno.dk)
Ondrej Cinek (ondrej.cinek@lfmotol.cuni.cz)
Barbora Obermannova (obermannova@seznam.cz)
Jeannet Lauenborg (jeannet@lauenb.org)
Peter Damm (pdamm@dadlnet.dk)
Regine Bergholdt (rber@steno.dk)
Flemming Pociot (fpoc@steno.dk)
Charlotta Pisinger (chpi@glo.regionh.dk)
Fabrizio Barbetti (fabrizio.barbetti@spr-r.it)
Jan Lebl (jan.lebl@lfmotol.cuni.cz)
Oluf Pedersen (oluf@steno.dk)
Torben Hansen (toha@steno.dk)

Version: 5 Date: 17 December 2009

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

Regarding the manuscript; MS: 1784730594297591 - Further evidence that mutations in INS can be a rare cause of Maturity-Onset Diabetes of the Young

We are most grateful for your thorough review and for giving us the opportunity to re-submit our manuscript. Based upon the comments we have carefully re-edited the manuscript and made some changes and clarifications. Please, find below our specific answers and our derived actions.

We have also carried out a thorough proof-reading of the text and made a considerable number of corrections throughout the manuscript. All changes are marked in red font.

I am leaving for vacation without regular access to emails from 19th of December to 2 of January 2010. If necessary please mail both me and my colleagues on; tweb@live.dk, tweb@hagedorn.dk, toha@hagedorn.dk and ehaa@hagedorn.dk during this period – Thanks.

Sincerely yours

Trine Welløv Boesgaard, MD
Reviewer 1
Reviewer: Pal R. Njolstad

Major questions/comments
1. The authors should define their criteria for “conventional” maturity-onset diabetes of the young. These may vary among various centers.

The question is very relevant and we have included the sentences below:
Our criteria for conventional MODY in the Danish MODYX are:

Diabetes diagnosed before 25 years of age in at least one family member. No treatment with insulin and/or measurable C-peptide at least one year after diagnosis. Autosomal dominant inherited diabetes with known diabetes in at least two consecutive generations. Page 3 line 8-11.

2. The mean age of onset of diabetes for the Danish maturity-onset diabetes of the young probands was high (24 years). Could several of the probands rather have early-onset type 2 diabetes?

Eight Danish MODYX patients were diagnosed after 25 years of age. However these 8 patients all have at least one member of the family diagnosed with diabetes before 25 years of age. Thus all MODYX families included in this study fulfil criteria for MODY.

3. What is “family history of diabetes”? Only probands with a diabetic parent or child should be included since the authors were looking for monogenic diabetes.

We totally agree. At page 3 line 14 we have added the following sentence: Only probands with a diabetic parent or child were included.

Minor questions/comments
1. Exchange “A R46Q…..” with “An R46Q…..”. The same applies for R6C and L68M.

Thanks. This mistake has been corrected.

2. The last sentence of the Background is imprecise. The authors have not investigated type 2 diabetes.

Thanks for the comments. We have revised this sentence. Page 2 line 22.

3. Choose either singular or plural for the various species listed in the Results and Discussion.

We have reviewed and corrected the text.
Reviewer 2

**Reviewer:** Sergey Nejentsev

**Reviewer's report:**

**Major**

The authors found 1 heterozygous subject with R6H and 1 heterozygous subject with R46Q out of 116 MODY patients tested and none among 209 non-MODY subjects. I think it would help if additional Danish and Czech controls (e.g. 500 subjects or more) could be genotyped for the R6H and R46Q polymorphisms. If rare alleles are not found, it would strengthen the argument that both these variants are indeed MODY mutations and not just very rare neutral polymorphisms.

We agree that this is important to exclude that R6H and R46Q are not just rare neutral polymorphisms.

We believe, however, that there is clear indication that these variants are not rare neutral polymorphisms. In already published studies (Rubio 2009, Bonfanti R 2009, Edghill 2008 and Molven 2008) a total of 1560 individuals primarily of Northern European ancestry have been screened. The R46Q mutation was only identified in one Norwegian MODY family (Molven 2008). The mutation segregated with diabetes in the family indicating that it is not a rare neutral polymorphism. The R6H mutation has not been identified in the 1560 examined individuals. Furthermore, we have screened additional 74 Danish individuals (data not shown) without identifying the two mutations. We have added a section discussing whether the variants are rare polymorphisms or disease causing mutations at page 5 line 3-9.

**Minor**

**Background**

"For example was MODY initially..." should be "For example MODY was initially..."

**Thanks we have corrected the error.**

Figure 1 title. RH6 should be R6H.

**Thanks again.**