Author’s response to reviews

Title: Associations of GC and NADSYN1 polymorphisms with vitamin D and metabolic profile in Non-diabetic adults

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Version: 2 Date: 21 August 2013

Author’s response to reviews: see over
August, 20, 2013

BMC Endocrine Disorders.

Editorial office

Dear editor

Please find the attached file corresponding to the revised version of the article titled: "Associations of GC and NADSYN1 polymorphisms with vitamin D and metabolic profile in Non-diabetic adults".

We would like to thank you very much for the attention given to our manuscript (Ref.: MS: 1696899073101174). We have taken into consideration the useful comments of the reviewers related to the first version.

The manuscript is 3417 words long, and included 38 references, 5 tables and 1 figure. The abstract is 249 words long.

The manuscript has not been published previously, has not been submitted for publication elsewhere.

The authors declare no conflict of interest

Please find at the bottom of this cover letter and the responses to questions from reviewers.

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Thank you for consideration.

Lydia Foucan, MD PHD

Responses to the reviewer comments.

Version: 1 Date: 12 July 2013

Title: Associations of GC and NADSYN1 polymorphisms with vitamin D and metabolic profile in healthy adults

Editorial request:
Please update your ethics statement to include the name of the ethics committee that approved your study.
R- The name of the ethics committee that approved your study is included in the revised version of the manuscript. It is “the inter-regional ethic committee (Sud-Ouest et Outre-Mer III, France)”.

Reviewer's report 1:
Reviewer: Rachel Desailloud
Reviewer's report:

Minor Essential Revisions

I. these results are interesting but question the additive or synergistic role of genes. Statistics could be completed to look at this point.

R-To answer questions from reviewers 1 and 2 we did further analysis, in conjunction with the genotypic score for each SNP as well as the combination of the score for two SNPs that were significantly associated with 25(OH)D levels. Linear regressions gave the effects of scores in different situations.

Reviewer's report 2:
Reviewer: Tamuno Alfred
Discretionary Revisions

1 -Consider constructing a VitD-raising (of insufficiency risk) allelic score based on counts of the number of vitD-raising alleles each individual has and performing additional analysis.

R-We constructed the genotype scores for the three SNPs
The genotype score was the sum of the risk allele for each SNP. Additional analyses were performed including linear regressions between the genotype scores across the SNPs and serum 25(OH)D levels.

2 -Is it appropriate to refer to these participants as 'healthy' given the high proportions of hypertension, dyslipidemia, etc?
R-In the revised version “healthy adults” is replaced by “non-diabetic adults”

3 -In the Results section reference has been made to sex differences, and this data can easily be included in Table 1 by presenting additional columns for males and females. Consider presenting other analyses stratified by sex as supplementary tables.
R-In table 1, additional columns are presented for males and females with the p-values for comparisons between groups.
The values are given for 25(OH)D levels
In table 4 (a new table) we present the frequencies of overweight according to rs2298849 T>C genotypes in men and women.

4 -In Table 1, present, numbers as well as percentages
For categorical variables, the results are now presented as numbers (percentages).

**Minor Essential Revisions**

5 -State the age range of participants and location of health centre in the abstract.
**R**-Mean age was 46.4 (range 18 - 86) years
The location of the Health Centre is now stated (Guadeloupe, France).

6-Phrases such as 'had overweight' do not read well. Replace with 'had an overweight status' or 'were overweight'. Consider having the paper read by a native English speaker.
**R**-'had overweight' was replaced by “were overweight”.
The revised version was read by a native English speaker.

7-In abstract, references such as 'TG genotype' do not make the associations clear. Please clarify by referring to the specific alleles, (e.g. the T allele was associated with increased risk) or referring to the specific genotypic comparison (e.g. TT vs GG).
**R**-For rs2282679 no patient had the GG genotype.
The sentence in the revised version is «Risks of vitD deficiency and of vitD insufficiency were increased for rs2282679 G allele carriers (OR = 3.53, P = 0.008 and OR = 2.34, P =0.02 respectively).»

8-It would be clearer for the reader if for all SNPs the alleles were coded for the analysis in the same direction in terms of effect on VitD, i.e. use appropriate reference alleles that leads to all vitD ORs being >1 (or all <1).
**R**-In the revised version, for all SNPs the alleles are coded for the analysis (logistic regression) in the same direction in terms of effect on VitD (with OR >1).

9-Authors should provide analysis to show whether the genotypes have an impact on dyslipidemia and an overweight status independent of vitD or whether the effects are only through their effects of vitD, or at least state their belief.

**R**-The logistic regression of dyslipidemia for each SNP was performed with adjustment for age, sex, BMI, 25(OH)D levels. The logistic regression of overweight for each SNP: was performed with adjustment for age, sex, 25(OH)D levels, dyslipidemia.
We noted in the abstract and in the discussion that the genotypes have an impact on dyslipidemia and an overweight status independently of vitD levels.


**R**-We thank the reviewer for these papers that are particularly important and allowed us to complete the analysis and the discussion in particular for the relationship between the genotype score and serum 25(OH)D levels and for the associations between BMI and SNPs in the vitamin D pathway.

10-Please state the linkage disequilibrium of the two GC SNPs in your study or from published data from a similar population
Study on GC SNPs in individuals of African ancestry are scarce and we can not state the linkage disequilibrium of rs2282679 T>G and rs2298849 T>C in GC gene from published data. In the revised we specified that the genotype distributions in our population the two GC SNPs were close to those observed in another study conducted among African Americans individuals. The genotype distributions were given for the two populations.

11-First sentence of the Statistical analyses section should be removed and instead an appropriate replacement should go into table footnotes.
R-The first sentence was removed and table footnotes are provided.

12-The second sentence of the Statistical analyses section seems to refer to the analysis in Table 2, but these results appear to be unadjusted and do not come from a multivariable regression model, therefore reference to adjustment should be removed. Make reference to the genotypes.
R-The reference to adjustment was removed.

13-why has 25 (OH)D been excluded from Table 1?
R-In the revised version, the values of 25 (OH)D are now given in table 1.

14-What is the heading for the first P column of Table 2? Additive?
R-The first P column corresponds to the P-values for the comparisons between the three groups (genotypes). This information was added in the table footnotes.

15-Only one comparison can be done for the analysis of rs2282679 in Table 2, Therefore, the p-values should not be repeated.
R-In the revised version, the p-values are not repeated.

16-Reference to the low sample size is limited. Include references to power calculations and the possibility of this leading to false positives.
R-In the “Limitations of the study”, a sentence related to the low power of small samples was added.