**Author’s response to reviews**

**Title:** Associations among IGF-1, IGF2, IGF-1R, IGF-2R, IGFBP-3, Insulin genetic polymorphisms and central precocious puberty in girls

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**Author’s response to reviews:**

March 30, 2018

Georgios Boutzios, Ph.D  
BMC Endocrine Disorders

Re: Resubmission of manuscript entitled “Associations among IGF-1, IGF2, IGF-1R, IGF-2R, IGFBP-3, Insulin genetic polymorphisms and central precocious puberty in girls”

Dear Dr. Boutzios,

We would like to thank the reviewers for their careful and thoughtful critique of our manuscript. Please find attached our revised manuscript along with a point-by-point response to the reviewers’ comments. We have addressed all the concerns raised by the reviewers. We have reorganized the Figures and Tables to improve the presentation of our data. We have included an analysis showing the correlation between IGF-1 levels and the demographic and pathological features after adjustment for bone age. Since our data showed a significant correlation between IGF-1 levels (ng/ml) and weight (z-score transformed), we used the combination of three SNPs for power calculations, as suggested by the reviewer. We have also expanded our Discussion section and added a number of references of studies describing the association between IGF polymorphisms and different demographic features. We have clarified that we found no significant association between the SNPs evaluated and z-scores of height, weight, or BMI in either the EP or CPP groups. However, our data showed that the bone ages of subjects in the IGF-IR +1013 (AG) and IGF-2 +3580 (AG + AA) groups were more advanced in the EP group. This could possibly be because although the girls did not appear to have entered puberty, their bone age had already acquired the characteristics of puberty. Although our data did not directly prove that IGF-IR and IGF-2 + 3580 polymorphisms were related to precocious puberty in girls, our results
showed that the IGF-IR G variant and the IGF-2 + 3580 A variant were associated with CPP.
We are confident that our results, describing associations between various SNPs in the IGF family and central precocious puberty in girls, are interesting and novel. We believe that our revised manuscript will be of interest to the readers of BMC Endocrine Disorders.

We thank you for your time and consideration, and look forward to a favorable response from you at your earliest.

Sincerely yours,

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Point-by-point response to reviewers’ comments:

Editor Comments:
BMC Endocrine Disorders operates a policy of open peer review, which means that you will be able to see the names of the reviewers who provided the reports via the online peer review system. We encourage you to also view the reports there, via the action links on the left-hand side of the page, to see the names of the reviewers.

Reviewer reports:
Aldo Ferreira-Hermosillo, MD, MSc (Reviewer 1):
Major concerns
1) In the Abstract section, the methods couldn't contain part of the results. The authors should place the last part of that paragraph in the Results section.
Response: The last sentence of the Methods section has now been moved to the Results section.

2) In the method section, the authors affirm that the study is a "case-control study". However according to table 2 all demographic and biochemical characteristics were different among groups. Authors must explain why they considered this as a "case-control study" instead of a two-cohort study.
Response: We agree with the reviewer, and have now replaced the term “case-control study” with “two-cohort study”.

3) Results section. Considering that bone age was statistically different among groups. Does evaluated correlations between IGF-1 and the demographic and pathological features were assessed after adjustment for BA?
Response: We have now included an analysis showing the correlation between IGF-1 levels and the demographic and pathological features after adjustment for bone age. These data are presented in Table 3-1-1, as well as in the Results section.
In the discussion section, authors should explain why associations were found between age, body mass index and weight with the SNP studied, but not with the z-score.

Response: We have expanded our Discussion section and added a number of references of studies describing the association between IGF polymorphisms and different demographic features. We have clarified that we found no significant association between the SNPs evaluated and z-scores of height, weight, or BMI in either the EP or CPP groups. However, our data showed that the bone ages of subjects in the IGF-IR + 1013 (AG) and IGF-2 + 3580 (AG + AA) groups were more advanced in the EP group. This could possibly be because although the girls did not appear to have entered puberty, their bone age had already acquired the characteristics of puberty. Although our data did not directly prove that IGF-IR and IGF-2 + 3580 were related to precocious puberty in girls, our results showed that the IGF-IR G variant and the IGF-2 + 3580 A variant were associated with CPP. In addition, we also believe that the interaction between IGF-I and IGF-2 polymorphisms could play an important role, and warrants further investigation.

Minor concerns

1) Throughout the text the authors write "gonadothropin", this must be changed to "gonadotropin".
   Response: This correction has been made.

2) In the section Background. The meaning of the abbreviations must be placed since the first time they are mentioned in the text.
   Response: All abbreviations have been expanded at their first use.

3) In the methods section, page 10, line 9. It said that testosterone test was performed to male population. This must be removed from text.
   Response: This sentence has been revised.

4) In Table 2, due to authors are adding p-value into the table, its unnecessary to repeat that those results had a p <0.05
   Response: This revision has been made, as suggested.

5) Table 4-1 and 4-2 refers to comparison of demographic and pathological features with SNP of different genes. Strictly it not contains a correlation index.
   Response: We have now revised the Tables to improve the presentation of our data. Data in the original Tables 4-1 and 4-2 are now presented in Supplementary Tables 3-1 and 3-2. These data describe the association of demographic and pathological features with SNP genotypes in the control and CPP groups.

Nihan Erginel Ünaltuna (Reviewer 2):
The manuscript is well written, but there are a few things to consider to be able to understand the main conclusions.

1) Methods section does not state the number of the patients and the controls.
   Response: We have now included this information in the Methods section.

2) The "combination of genes" is not a regular term to omit the description in the methods. Only when one looks at the table, one can deduce what the authors mean by this.
   Response: We have now clarified in the Methods as well as in the Results section that the CPP and control groups were compared to evaluate the association between demographic and pathological
features with SNP genotypes, or a combination of two or three SNP genotypes.

3) There are a lot of long tables, that can be made shorter, and clearer statements in the results can be associated with the tables.
Response: The manuscript has been revised to improve the readability. The data in the original Tables 4, 5, and 6 are now presented in Supplemental Tables S3, S4 and S5. Additionally, the Figures have been reorganized as follows: Figures 1-1 and 1-2 present the association between demographic and pathological features and SNP genotypes in the control and CPP groups, respectively. Figures 2-1 and 2-2 present the association between demographic and pathological features and a combination of two SNP genotypes in the control and CPP group, respectively. Figures 3-1 and 3-2 present the association between demographic and pathological features and a combination of three SNP genotypes in the control and CPP groups, respectively. The Results section has been revised accordingly.

Kanthi Mathi Sekar, Ph.D (Reviewer 3): Minor comments:
1. Some of the comparison (eg. Table 4-6) results can be interpreted by a better graphical representation.
Response: The Tables and Figures have been revised and reorganized to improve the presentation. The Results section has been revised accordingly.

2. Authors can provide the power calculation for the study, to support their findings.
Response: Our data showed a significant correlation between IGF-1 levels (ng/ml) and weight (z-score transformed). We therefore used the combination of three SNPs for power calculations, and the results are presented in Supplementary Table 6.