Author's response to reviews

Title: The novel p.Cys65Tyr mutation in NR5A1 gene in three 46,XY siblings with normal testosterone levels and their mother with primary ovarian insufficiency

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To
BMC Medical Genetics

Dear Sirs,

This is to submit the revised version of manuscript now entitled “The novel p.Cys65Tyr mutation in NR5A1 gene in three 46,XY siblings with normal testosterone levels and their mother with primary ovarian insufficiency” to be considered for publication in BMC Medical Genetics as a Case Report.

We have addressed all comments and criticisms received from referee to whom we present our appreciation. Details are presented below. We have done also all the corrections highlighted by the editor.

We thank you for your attention.

Yours sincerely,

Maricilda Palandi de Mello, Ph.D.

Answers to Reviewer's report

Reviewer: John Achermann

Minor issues not for publication.
The written language is much, much better
There are several minor typos I noticed:

1) background paragraph 3 - I think there is an extra "have" in the line "with infertility have [15-19]"
   We have corrected that.

2) try to use "reported" instead of "referred"
   We did that on page 6 in the phrase: “She also reported irregular menses and hot flushes, suggesting primary ovarian insufficiency”.

3) discussion - first paragraph "presented with"; fourth paragraph "Taken together" not "taking together"
   We have corrected that.

EDITOR’S COMMENTS:

1. In the background section of the abstract, an ?s? should be deleted from the word ?evidences? to read ?evidence? in the following sentence: ?Their mother, who is also heterozygous for the mutation, presents evidences of primary ovarian insufficiency?.
   We have corrected that.

2. In the background section, the sentence ?It is encoded by NR5A1 gene, which is an autosomal gene mapped to 30 kb within 9q33?, the article ?the? should be added prior to the gene symbol NR5A1.
   We have corrected that.

3. In the background section, please add word ?the? before word ?gene? in the following sentence ?Genes such as: CYPs,HSD3B2, StAR, SOX9, NR0B1, and others are among gene targets subject to SF1 transcriptional regulation.
   We have corrected that.

4. This sentence in the background section needs to be edited ?After those, over 50 mutations have been reported mainly in 46,XY DSD individuals with apparently normal adrenal function, but they were also found in 46,XX individuals with primary ovarian insufficiency and normal female phenotype and male individuals with infertility have?. Would suggest deleting: ?After those? and start the sentence with ?Over 50 mutations?? and deleting the last word ?have?.
   We have corrected that.

5. The term genital ambiguity that the authors use throughout the text should be changed to ambiguous genitalia.
   We have corrected that.

6. In the Case Presentation section, the authors made another mistake since there is a sentence that states: ?Currently, he is at Tanner stage G4P5 without hormone replacement therapy??. This makes no sense as they are confusing a stage of sexual maturity with biological parity: how many times a woman has
been pregnant and delivered a baby. This needs to be corrected and the authors have to state whether he currently is in Tanner stage 4 or 5.
We replaced that phrase by: “Currently, he is at Tanner stage 4 without hormone replacement therapy. His height is near the target.”

7. The following sentence in the Results section is not written in an appropriate way: ?Residue 65 in the NR5A1 protein corresponds to a highly conserved cysteine in mammal corresponding proteins? should be changed to ?The cysteine residue in position 65 in the NR5A1 protein is highly conserved across mammalian species?.
We have corrected that.

8. The following sentence in the Results section also needs to be corrected: ?Structural analyses demonstrated that C65 in the native protein, besides binding directly to zinc atom, it makes a hydrogen bond with R69 and hydrophobic interaction with C68 (Fig. 2D).? to ?Structural analyses demonstrated that C65 in the native protein makes a hydrogen bond with R69 and has a hydrophobic interaction with C68 (Fig. 2D).
We have corrected that.

9. On page 7, please use change word Ångstrons to Ångstroms.
We have corrected that.

10. Discussion: in the following sentence: ?Tyrosine can also be involved in phosphorylation within intracellular protein?, the plural ?proteins? should be used instead of ?protein?.
We have corrected that.