Author's response to reviews

Title: Biotinidase deficiency: clinical and genetic studies of 38 Brazilian patients

Authors:

Taciane Borsatto (taciborsatto@hotmail.com)
Fernanda Sperb-Ludwig (fesperb@ig.com.br)
Louise LC Pinto (lapagesselou@gmail.com)
Gisele R De Luca (giselegenetica@gmail.com)
Francisca L Carvalho (fligliacarvalho@hotmail.com)
Carolina FM De Souza (cfsouza@hcpa.ufrgs.br)
Paula FV De Medeiros (paulafvmedeiros@gmail.com)
Charles M Lourenço (charlesgenetica@gmail.com)
Reinaldo LO Filho (reinaldo.luna@gmail.com)
Eurico C Neto (eneto.voy@terra.com.br)
Pricila Bernardi (pricila.bernardi@gmail.com)
Sandra Leistner-Segal (sandralsegal@gmail.com)
Ida VD Schwartz (idadschwartz@gmail.com)

Version: 3
Date: 16 July 2014

Author's response to reviews: see over
Dear Mr. Sands,

We are enclosing the second version of the manuscript “Biotinidase deficiency: clinical and genetic studies of 38 Brazilian patients” which was reformulated on the basis of reviewers’ comments. We appreciate the reviewers’ comments and made some changes in the manuscript with the intention of making it clearer and less repetitive. The following is a point-by-point response to the concerns and/or description of the changes made.

Please, feel free to contact us if you wish any additional change to improve the understanding of the reader. We look forward to hearing from you in a near future.

Sincerely yours,

Taciane Borsatto (corresponding author)
BRAIN Laboratory, Center for Experimental Research (CPE)
Hospital de Clinicas de Porto Alegre
Rua Ramiro Barcelos 2350
90035-903 – Porto Alegre – RS - Brazil
Email: taciborsatto@hotmail.com
Phone + 55 51 33598309
Fax + 55 51 33598010

Editorial requirements:
“Please include the email address of all authors in the title page.”
Answer: Done.

“Please update your ethics statement to include the names of the ethics committees that approved your study.”
Answer: Done.

Referee 1:
“Laboratories B, C, D have identical reference ranges for biotinidase activities? Are these reference ranges adjusted for age?”
Answer: Yes, laboratories B, C and D have identical reference ranges for biotinidase activity. The normal reference range is 5.0–10 nmol/min/mL. There aren’t ranges adjusted for age.
“What is the basis for the reference ranges for profound biotinidase deficiency (BTD) versus partial BTD versus heterozygosity?”
Answer: According to the literature, individuals with profound and partial biotinidase deficiency (BD) have respectively less than 10% and within 10-30% of average normal activity in serum, and heterozygotes individuals have intermediate activity between that of partial BD and normal individuals. Since laboratories’ normal reference range is 5.0–10 nmol/min/mL, we considered the value of 7.5 nmol/min/mL as average normal activity in serum to calculate the ranges for profound BD (<0.75 nmol/min/mL), partial BD (0.75–2.25 nmol/min/mL) and heterozygosity (2.26–4.9 nmol/min/mL).

“What is the frequency of the novel variants in the various databases (e.g. dSNP and others)?”
Answer: The variants called “novel variants” were so named because they are not described in none of the researched databases. This information is included in the text.

“How many centers were contacted? What was the response rate?”
Answer: Medical geneticists from all over Brazil were contacted through the mailing list of the Brazilian Society of Medical Genetics (at least 10 times during two years). This information was included in the text. It includes about 200 medical geneticists, but we do not have the information about how many of them work on neonatal screening or metabolic disorders field. So, we cannot calculate the response rate.

“The number of tables can be reduced. For example tables 4 and 5 can be condensed into a single table.”
Answer: The number of tables was reduced. The information of the tables which were removed was placed in text form.

Referee 2:
“…This in mind, the Introduction can be greatly shortened and concluded with their last sentence, which is what they are reporting.”
Answer: The Introduction was shortened.

“The overriding issue I had with the paper is in the order of the patients in Table 1. (…) the current order only makes the paper more confusing to follow. The authors can easily correct this by simply regrouping the patients into their ultimate genotypes!”
Answer: We reorganized the order of the patients in Table 1 in accordance with their genotypes.

“Then the Discussion can readily include paragraphs about the novel mutations, the reasons for false positives, types of mutations, their variant frequency data, etc.
Answer: All these points are addressed in the discussion, even so we tried to shorten it.

“Table 2 is completely unnecessary and should be omitted.”
Answer: We agreed with the suggestion and omitted the table 2, since there is enough information about it in the text.
“Table 3 is unnecessary and should be omitted.”
Answer: We agreed with the suggestion and omitted the table 3, since there is enough information about it in the text.

“Table 4 is unnecessary and should be omitted.”
Answer: We agreed with the suggestion and omitted the table 4. Its information was placed in text form in “3.2 Genetic assessment”.

“Table 5 is unnecessary and should be omitted.”
Answer: We agreed with the suggestion and omitted the table 5. Its information was placed in text form in “3.2 Genetic assessment”.

“Reorganization of the entire paper would make the paper’s flow so much clearer. As is, it jumps around too much. Reorganization would allow the reader to understand and follow the results and discussion in appropriate locations in the paper (profound deficiency, partial deficiency, novel mutations, variants, discordance, etc.).
Answer: We tried to make the paper clearer, although we did not fully agree with the reviewer regarding the necessity of a “big” reorganization.

Referee 3:
“As a discretionary recommendation I would suggest to add a table reviewing what is known from the literature about the correlations between the biochemical phenotype (profound, partial, heterozygous deficiency) and the molecular basis (various possible combinations of alleles, either mutant or normal, including cis/trans status). This table might help the reader who is not specialist in the field of biotinidase deficiency.”
Answer: We consider this suggestion very important and added an explanatory box in the Introduction (Figure 1). So, in “2.4 Genotype-phenotype correlation” we replaced the text that explained how we established the expected biochemical phenotype by a reference to Figure 1.