Reviewer’s report

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

Version: 2 Date: 17 June 2014

Reviewer: Barry Wolf

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Borsatto and colleagues describe the biochemical and molecular characterization of 38 individuals from Brazil who had low serum biotinidase activities. The authors correlated the genotypes with the biochemical phenotypes.

The premise for their paper has been previously addressed in their Reference 12. The authors do not have to make the purpose of their work the clarifying low biotinidase activities, it is better to just report their findings and add them to what has already been reported in Reference 12. This in mind, the Introduction can be greatly shortened and concluded with their last sentence, which is what they are reporting.

The work performed in this paper is straight-forward and appropriate. However, the authors apparently did not sequence Exon 1 or any intronic regions of BTD in those individuals who had low enzymatic activity, but the genotype failed to explain the biochemical phenotype, or in those who have novel mutations.

The overriding issue I had with the paper is in the order of the patients in Table 1. As it stands, the patients seem to be presented in the order that the authors accumulated samples or some other similar reason. However, 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! They can start with the three individuals with profound biotinidase deficiency, then those with partial deficiency, then those shown to be only heterozygotes for profound deficiency, and then finally those found to be normal with no mutations found. Then the Discussion can readily include paragraphs about the novel mutations, the reasons for false positives, types of mutations, their variant frequency data, etc.

Table 2 is completely unnecessary and should be omitted. It is sufficient to say that five individuals had reduced activity and were symptomatic and they likely didn’t have biotinidase deficiency as the cause for their problems, especially when the authors are not sure if the individuals improved with biotin therapy.

Table 3 is unnecessary and should be omitted. The authors again can just relate that there was discordance between biochemical phenotype and genotype. Most of these data are in Table 1! The authors did not necessarily repeat the biotinidase activity to determine if the patients’ activities had simply not yet reaching adult levels or that the samples had lost activity for various reasons.
Table 4 is unnecessary and should be omitted. The data in Table 4 is best discussed when appropriate in the text of the Results/Discussion. For example, the three novel variants were not found in the 200 alleles screened. The D444H mutation frequency can be discussed and commented on in the text when the authors discuss partial deficiency, and the polymorphism or benign variant frequency can simply be discussed as a group in the text.

Table 5 is unnecessary and should be omitted. The in silico predictions can be discussed when one addresses the novel mutations in the text, partial deficiency and the benign variant.

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.).

In summary, this report compliments those of Reference 12 and warrants publication. The results add three novel mutations to the growing list of deleterious mutations.