Author’s response to reviews

Title: PHENOTYPIC AND GENOTYPIC ASPECTS OF TOWNES-BROCK SYNDROME: CASE REPORT OF PATIENT IN SOUTHERN BRAZIL WITH A NEW SALL1 HOTSPOT REGION NONSENSE MUTATION

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Author’s response to reviews:

February 3, 2017
Dr Matteo Pasini
Editor BMC Medical Genetics
Dear Editor:

We hereby resubmit our manuscript MGTC-D-16-00040 entitled: “PHENOTYPIC AND GENOTYPIC ASPECTS OF TOWNES-BROCK SYNDROME: CASE REPORT OF PATIENT IN SOUTHERN BRAZIL WITH A NEW SALL1 HOTSPOT REGION NONSENSE MUTATION”

In accordance with your advice in your email on January 5th, 2017, we addressed the reviewers’ comments and concerns, and now are resubmitting the manuscript for your reconsideration for
publication in BMC Medical Genetics. We appreciate the reviewers’ positive and constructive comments greatly.

Specifically, we added detailed information regarding the molecular genetics, which we agree makes the article more interesting, and modified the title. Unfortunately, because we did not perform any additional genetic testing on the family, we cannot present a complete segregation study for the family. This type of testing is not customary in Brazil and genetic testing here remains cost prohibitive. We did, however, go to great lengths to determine the case etiology and provide than information in the article. The main objective of the article is to present a novel mutation that is unusual in that it is a NONSENSE mutation rather than a missense mutation. Furthermore, this case is the first case of Townes-Brock syndrome to be reported in Brazil.

We hope sincerely that you will proceed with reconsidering our article for publication in BMC Medical Genetics. After awaited patiently one year to receive feedback, we are optimistic that we will not be disappointed.

We look forward to your reply.

Sincerely,
Mara L. Cordeiro, Ph.D.
Corresponding Author

Below is an itemized response to the reviewers:

ANSWER TO Reviewer reports:

Reviewer #1: The manuscript describes a novel case of TBS and identifies a mutation in the SALL1 gene, known to be causative in cases of this syndrome. The manuscript is clearly written and the case clearly fits the clinical presentation and molecular biology of TBS.

One area that could be made clearer is how the mutation identified in this case compares to those seen in other TBS patients. In general the mutations associated with TBS are nonsense mutations in the 5' region of the gene found between the glutamine rich region and the first set of paired zinc fingers. These seem to escape NMD and act as dominant negatives, probably by sequestering full length proteins in the cytoplasm. Other mutations in SALL1 are normally associated with less severe malformations. However this case seems to involve a missense
mutation but still has a severe range of abnormalities. If the authors described in more detail how this mutation is likely to affect the protein and how this relates to other SALL1 mutations in TBS it would provide additional valuable detail to help put this case into context.

Minor point - reference 25 is from Am J Med Genet, not Am J Hum Genet. Ok, we fixed!

WE FIXED THAT AND INDEED THIS WAS A NONSENSE MUTATION.

Reviewer 2: Dear authors,

I think the manuscript is well written and I know it's difficult to get case reports published nowadays, even though they are important to enhance recognition of entities and to draw attention to some specific or uncommon feature. However, TBS has been described quite extensively before and I didn't read anything new. Maybe it's difficult to get access to all of the papers, in which case you might find another (Brazilian) journal for publication, or maybe you could try to contact other centers such as the genetic departments of e.g. the USP (SP), or the hospital for craniofacial anomalies in Bauru (SP), to try and collect a larger sample.

YES IT IS VERY DIFFICULTY TO COLLECT LARGER SAMPLE OF TBS, HOWEVER THE UNIQUE ASPECT OF OUR REPORT IS THAT IT IS REGARDING NEW SALL1 HOTSPOT REGION NONSENSE MUTATION AND IT IS NOVEL NEVER DESCRIBED BEFORE.