Author’s response to reviews

Title: The p.Phe174Ser mutation is associated with mild forms of Smith Lemli Opitz Syndrome

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Milan, December 4th 2015
Dear Editor,

Thank you for accepting for potential publication in the BMC Medical Genetics journal our article: “The p.Phe174Ser mutation is associated with mild forms of Smith Lemli Opitz Syndrome”, provided that we carry out some essential revisions suggested by the reviewers. Please find our comments to the reviews below.

Reviewer #1: Major changes:

1. With hindsight the clinical case satisfies at large a diagnosis of SLOS and it is unclear why biochemical screening for elevated 7-dehydrocholesterol and 8-dehydrocholesterol was not considered as a low-priced, first-tier diagnostic testing. This is also considering a recent work (Anal Bioanal Chem 2015; 407:5227-5233) offering rapid and cheap LC-MS/MS-based quantification of cholesterol and related metabolites in DBS from patients.

   Thank you for revising our article. One diagnostic test for SLOS is indeed an elevation of serum concentration of 7-DHC, but unfortunately it is unavailable in our hospital as a routine test.

2. The authors discuss their findings properly but refer to literature too much updated. Please refer to more recent works on SLOS and DHCR7. I have noticed that a special issue on SLOS can be found in the supplements of the American Journal of Medical Genetics Part C (Seminars in Medical Genetics). Even more recent work on SLOS can be cited properly. The authors might consider "rejuvenating" the bibliography of this manuscript.
Thank you for suggesting the more recent articles found in the supplements of the American Journal of Medical Genetics Part. We have revised the bibliography as follows:


Minor changes:

1. Please, cite the present age of this boy (page 8, ln 1).

   We have added the patient’s current age.

2. Please, indicate the genotype of the patient’ sib.

   Unfortunately the patient's sibling was unavailable for testing.

3. Please, mitigate your conclusion. Page 11, ln 23 say: "This study offers further clinical significance to the p.Phe174Ser variant …" and not "This study confirms the pathogenicity of the p.Phe174Ser variant …" since no functional studies to address directly the pathogenetic consequences of the gene change were adopted.

   We have changed the sentence as suggested.
Reviewer #2: Thank you for asking me to review this case report.

This is a well-written case report of a child with Smith-Lemli-Optitz syndrome (SLOS) with a previously reported mutation c.521T>C, p.Phe174Ser submitted for publication to illustrate the pathogenicity of this mutation. The report is a bit repetitive and could use tightening (e.g., the fact that there are over 140 mutation in DHCR7 is stated three times). I suggest shortening by at least 20%.

Thank you for revising our article. We have shortened the article from 2100 words to 1780, and removed all the repetitive sentences.

It is indeed sad that a patient with such a typical facial appearance and the typical 2-3 toe syndactyly as this patient demonstrates was not diagnosed until age four years and that testing for Noonan syndrome, which this patient does not resemble at all, was performed first.

It can be hard indeed to diagnose SLOS patients. Our patient presents with facial dysmorphisms that are typical for SLOS and yet non-specific for this syndrome. Ptosis, epicanthal folds, hypertelorism and posteriorly rotated ears along with growth failure are also present in Noonan syndrome, which is significantly more common than SLOS (1:1000-2500 live births versus 1:10000-60000). With this report however, we stress out the importance of recognizing 2,3 toes syndactyly associated with microcephaly as a major diagnostic handles for SLOS.

There are two second degree relative with "mild intellectual disability" reported in the Case Presentation. Were they tested for SLOS? It is not uncommon to have secondary cases because of the relative high carrier rate in the general population.

Thank you for this observation. Unfortunately the relatives affected by mild intellectual disability were unavailable for testing.

For references I suggest replacing the dated Kelley and Hennekam 2000 paper with the GeneReview review from 2013 http://www.ncbi.nlm.nih.gov/books/NBK1143/. I also

Thank you for suggesting newer papers. We have indeed replaced some of the bibliography as mentioned above.

I hope that you will find the revised version of the paper suitable for publication and look forward to hear from you in due course.

Yours faithfully,

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