**Reviewer’s report**

**Title:** Novel Loss-of-Function Variants of TRAPPC2 Manifesting X-linked Spondyloepiphyseal Dysplasia Tarda: Report of Two Cases

**Version:** 0  **Date:** 27 Feb 2019

**Reviewer:** Esra Dikoglu

**Reviewer's report:**

This manuscript represents two patients with X-Linked Spondyloepiphyseal Dysplasia Tarda (SEDT-XL). Both patients had disproportionately short stature with a relatively short trunk and barrel-shaped chest that were diagnostic for SEDT-XL.

The methodology of the study consists of characterization of the disease radiologically and clinically, molecular confirmation of the disease and molecular consequences of two novel variants in TRAPPC2 that were found in these patients.

Both mutations were found by Sanger sequencing of TRAPPC2 gene. Then in order to explore the effect of the mutations on the protein, an in vitro experimental system was set up: expression studies and reverse transcription polymerase chain reaction (RT-PCR) were performed. They found that both mutations (one was causing loss of the start codon and the other was early termination) result in lack of TRAPPC2 protein and showed that these mutations were causative of SEDT-XL.

It is good to see such a detailed explanation of radiographic and phenotypic findings of SEDT-XL and a molecular study to show the effect of these de novo changes in the causative gene. It shows the importance of performing molecular confirmation of SEDT-XL, and understanding the underlying mechanism of such a rare disease is a great contribution to the literature. This article expands the spectrum of TRAPPC2 mutations and is helpful for the diagnosis of this rare disease.

There are some weaknesses of the manuscript and it would be nice if authors would consider including minor details mentioned below into the manuscript for the completeness of the case report:

1. The prevalence of SEDT-XL is estimated to be 1 in 150,000 to 200,000 people worldwide (1). Since it is a very rare disease, it would be great if authors can add more background and clinical details for these two cases such as ethnicity, prenatal, postnatal history, if patients had any dysmorphic pattern, details regarding parent's heights, any other affecteds in these
two families, what kind of treatments were provided for their pain etc. on page 4, in the Case Presentation section.

2. By keeping in mind that with older patients, it always has the limitations to access earlier imaging studies, I believe it would be great if authors could include X-Rays from individuals' earlier ages to show disease progression since SED-XL is a puberty onset disease (2,3).

3. Overall, discussion part goes very well even though it only mentions expression study of the mutations and the effect of the mutations on protein level. Authors may wish to discuss about clinical and radiological diagnosis of SEDT-XL, differential diagnosis and management of the disease here.

4. The sentence in "Discussion and Conclusions" section in the last paragraph; "Our data that absence of proteins could still produce relatively healthy individuals suggest that there is an alternate pathway that bypasses TRAPPC2." requires a little bit more explanation. Whole paragraph might need to be re-written, I am missing details about how authors concluded that absence of proteins can produce healthy individuals and which pathways are the major ones are interacting with TRAPPC2 protein etc. (4)

5. Please include Reference sequence ID/NM number from Ensembl (http://useast.ensembl.org/index.html) (NM_001011658) in Figure 2A.

Specific questions:

1. Is there any specific population at increased risk for SEDT-XL?

2. Was there any abnormal X-Ray finding on 15-year-old individual's mother whom found to be carrier of c.40delG mutation even though she was stated asymptomatic in the manuscript? If yes, it would be great to declare these in the manuscript. Please also define if 49-year-old patient's mother was checked for the mutation and if there was any abnormality on radiograms or abnormal clinical findings such as arthralgias.

Corrections:

1. On Page 3, 4th line in "Background" section, there is a typo error. Please correct "liked" to "linked" ("SEDT-XL has been liked with mutations in transport protein particle complex subunit 2 (TRAPPC2).")
2. HGMD Professional 2018.4 database (5) (checked on 02/18/2019) lists 57 mutations (32 insertion or deletion, 10 splicing, 9 nonsense, and 6 missense mutations) whereas it is written "31 insertion or deletion, 9 splicing, 9 nonsense, and 6 missense mutations of TRAPPC2 gene", total 55 mutations in the manuscript. It would be great if the author can update the numbers.

References:


5. HGMD Professional 2018.4 database (http://www.hgmd.cf.ac.uk/ac/index.php)

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
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Yes
Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
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