Reviewer’s report

Title: New PCNT Candidate Missense Variant in a Patient with Oral and Maxillofacial Osteodysplasia: A Case Report

Version: 0 Date: 21 Jan 2019

Reviewer: Sini Skarp

Reviewer's report:

Authors describe one patient with oral and maxillofacial osteodysplasia. They have performed candidate gene analysis using next generation sequencing and identified a single variant in the PCNT gene.

Major comments:

1) Why do the authors consider this to be a genetic disorder as the patient is the only member of the family to be affected? Perhaps a short description of genetic background of osteodysplasias could clarify this.

2) Why only the mother was used as control and not both of the parents? Information that the mother was used as control should be included in the methods section.

3) The used methodology is unclearly described in the article:

First, it is unclear if whole exome sequencing (WES) or whole-genome sequencing (WGS) was used in the study. In the Abstract it is stated that "Here, we performed whole-genome sequencing (WGS)" and the use of WGS is again mentioned in the Background section (page 4). However, in the Discussion pages 8 and page 10 WES is stated as the used method and "whole exome sequencing" is also mentioned as a keyword. Please clarify the NGS method used.

Second, the study seems to use candidate gene approach together with next generation sequencing instead of utilizing the whole data and hypothesis-free NGS analysis. This could be more clearly explained in the article including the abstract and discussion. In the methods section it should be stated how many candidate genes were included in the analysis and if the reported variant in PCNT was the only variant identified in these candidate genes or were variants filtered based on something such as frequency, pathogenicity estimations or quality. The list of studied candidate genes could be added as supplemental data.

Third, the tissue where DNA was obtained and the method used in DNA extraction should be mentioned in the methods section.
4) Only Polyphen-2 was used in predicting the variant pathogenicity. Why is this? Using multiple tools, such as SIFT, Mutation taster and CADD etc. would be more convincing. I suggest that you acquire a broader in silico support for your variant.

5) The authors refer to the identified variant as "mutation". However, the preferred term would be "variant". Please see, "HGVS Recommendations for the Description of Sequence Variants: 2016 Update, Den Dunnen et al. 2016 Hum.Mut.37:564-569". The term "variant" is more neutral and the term "mutation" is often considered to be disease-causing. In this case, the variant is observed in a single patient and the term mutation can be misleading as there is no in vitro evidence or replication in other patients to support the role of this variant as the cause of disease. Please use the term "variant" instead of "mutation".

6) It would be more clear to report variants using the HGVS standard nomenclature format. Please check the HGVS guidelines (http://varnomen.hgvs.org/) for variant naming.

7) The authors conclude in abstract that "this is a new form of osteolysis related to this PCNT mutation" and in the discussion that "The WES results suggest that the osteolysis in this patient is a new disease that is related to the presence of a mutation in PCNT."

I consider these statements to be too strong and should be modified. In this study variant in the PCNT gene was observed in one patient, but I feel that considerable amount of further evidence (such as in vitro studies or replication in other patients) is needed before it can be stated that this variant is causal and leads to a new disease.

Minor comments:

1) In the abstract the heading "conclusions" appears twice, please check.

2) Chromosomal position (chr:pos) of the variant should be included in the results section.

3) GnomAD is larger database compared to for example 1000Genomes or ExAC, why was it not used?

4) Please include in the Methods section information of the genome build (eg. hg19 or hg38) used in the NGS analysis.

5) Is the reference 6 in candidate gene chapter, on page 6 correct one? Should it cite the "Nosology and Classification of Genetic Skeletal Disorders 2015 Revision AJMG 2015". This reference is mentioned in the text but missing from the reference list.

6) The Table 1 is only a list of related diseases and as such does not add much information. Including a short description of the disorders, would be beneficial.
7) Figure 5 legend: Check the naming of the variant, there seems to be misspelling

8) In page 9 the meaning of the sentence: "Although the two isoforms showed similar mobilities in mice, the mobilities were not clarified in humans", is unclear. Please, clarify this.

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

No

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

No

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

No

**Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?**
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

Not relevant to this manuscript

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