Reviewer’s report

Title: WHAT TO CONSIDER WHEN PSEUDOHYPOPARATHYROIDISM IS RULED OUT: iPPSD AND DIFFERENTIAL DIAGNOSIS

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Reviewer: Giedre Grigelioniene

Reviewer's report:

Ms by Pereda, Garin and Perez de Nanclares "WHAT TO THINK ABOUT WHEN PSEUDOHYPOPARATHYROIDISM IS RULED OUT: iPPSD AND DIFFERENTIAL DIAGNOSIS".

Authors describe that 12 out of 23 patients who presented brachydactyly E (BDE) have mutations in PDE4D, PRKAR1, TRPS1 and PTHLH genes.

General comments:

1. English is deficient and needs revision.
2. What do authors mean by term "non-classical (epi) genetic alterations of GNAS"?
3. What was working hypothesis? What criteria were used for the inclusion into the study. The patient population seems to be a bit heterogenous, because individuals with TRPS1 have typical clinical, radiological presentation on skeletal survey, how could this syndrome me included into the unclassified BDE or PHP study?

Specific comments:

Abstract: what do the authors mean "reclassification". Please specify what methods did they used to reclassify the patients: Radiology? Genetics?

Background:

Line 6 what is "a constellation of sings"

Line 6 "short stature" instead of "small stature"
Line 13 "normal renal function. [1]." Should spell normal renal function [1]."

Line 31-37: please shorten and clarify the sentence. It is hard to understand what you mean by the statement in these lines.

Methods:
HDAC4 del analysis was performed using microsatellites, what is the distance between them and could small deletions be missed? Please comment on this question and explain why you did not use a method with a better resolution?
PTLH and HOXD13, why only sequencing and not del dup analysis by MLPA or targeted cCGH array?
Authors state that BDE is common in Turner syndrome (TS), it is also a feature in more common skeletal dysplasia Leri-Weill dyschondrosteosis (incidence with 1:5000). However it seems they did not evaluate their patients who were negative for the mutations in the above mentioned genes for TS or microdeletions of the pseudoautosomal region including the SHOX gene.

Results:
Page 6
24-31, three out of 4 patients with PRKAR1 mutations were already reported.
51-54, it seems that the patient with the PDE4D mutation was also previously reported.
Page 7
The same is for the TRPS1 patients (2 out of 4) were also reported.

Discussion:
P 8. Line "As is known, BDE was initially described as variable shortening of the metacarpals/metatarsals with more or less normal length of phalanges [39]." I do not agree with this interpretation. In clinical practice, an important fact to emphasize is that in BDE mostly metacarpals 3-5 are affected and also that brachydactyly (eg short fingers) may be a feature of BDE.
Line 25. What do you mean by the term "spaced eyes"? Hypertelorism? Please check terminology of human morphology so called HPO term according to http://human-phenotype-ontology.github.io/.

Lines 45-48 "In our series of patients, all the iPPSD4 patients presented PTH resistance, and also the iPPSD5 one (PHP06) initially presented it, though it could be associated with the initial vitamin D deficiency" PTH elevation in vit D deficiency should be interpreted and discussed presenting numerical values, please revise.

Line 57, p8 to line 14 p9. Radiographic features of TRPS1 syndrome are specific, and should be discussed adequately. It is difficult to understand why these patients were included in the study overall, because as authors mention, the dysmorphologic and radiographic features in the skeleton overall, provides a very specific diagnosis leading to testing for monogenic disease.

In summary I recommend a revision of the manuscript.

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.

Yes

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

Yes

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

Quality of written English
Please indicate the quality of language in the manuscript:

Not suitable for publication unless extensively edited
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