Author’s response to reviews

Title: De novo truncating variant in WHSC1 gene leading to mild Wolf-Hirschhorn syndrome phenotype: a case report

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- The official name for this gene, approved by HGNC, is NSD2. Please mention this and change the name in the text.

Response: We have changed the description of the gene to NSD2 in the whole manuscript, including those symbols in table and figure.

- Strictly talking, NSD2 has not been officially associated to any developmental disorder (DD) in either OMIM or DDG2P, and as reviewer 2 also stated. Thus, you should give evidence on why monoallelic, loss-of-function variants in NSD2 may cause a developmental disorder that explain part of the manifestations of WHS, such as function of the encoded protein, pLI score, expression levels seen in the GTEx Project, animal experimental data if available, interaction with DD-associated proteins, predictions given by other research groups (see https://wwwfbm.unil.ch/domino/), etc.

Response: We have revised the first paragraph in the discussion part to emphasize that: The histone modification functioning protein encoded by NSD2 is important in brain development.
NSD2 gene is intolerant of loss-of-function variants as pLi score is 1.00. Function of NSD2 encoded protein and possible interaction with other disease related proteins are rarely reported, but it is supposed that histone substrate specificity of NSD2 encoded protein may explain differences in clinical phenotypes.

- In line with last comment, reference 11 scarcely talks about relevance of histone modifications in DD. For that purpose, you should cite PMID: 29276005.

Response: We have changed the reference you suggest which is more proper here in the context.

- Please take into account carefully all reviewers comments as they addressed other relevant things.

Response: We have revised according to comments from reviewers in the previous version. We are sorry that we missed your comments which helped us to improve the manuscript in a great extent and we have revised accordingly.

- The cartoon with the protein structure and variants in NSD2 are too small and the meaning for the abbreviations of the different domains are not given. Please modify the figure and the legend accordingly.

Response: We have re-edited the figure to make these variants clear and readable and added the meaning for the abbreviations of the different domains in the legend.