Reviewer's report

Title: A novel MANBA mutation resulting in residual beta-mannosidase activity associated with severe leukoencephalopathy: a pseudodeficiency variant?

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Reviewer: Maria Clara Sa Miranda

Reviewer's report:

General comment: Human beta-mannosidosis is a very rare disease, so it is very important to publish all the information concerning the characterization at different levels of all patients diagnosed. In this manuscript a specific missense MANBA mutation is expressed in HEK cells and the enzymatic activity of the transfected cells is determined, showing that some residual activity is associated with that mutation, although the protein was not characterized by western blot analysis.

Based on a residual activity close to 10% of controls obtained in the expression studies and in the leukocytes, lymphocytes and plasma of the patient, the author’s raises the question if this mutation corresponds to a pseudodeficiency. However, accordingly with the literature the lysosomal enzyme pseudodeficiencies described present a higher activity 20-40%. Moreover, several causal mutations for other lysosomal diseases (ex.Gaucher and Fabry diseases) present residual activities around 10-15% of controls.

Major Compulsory Revisions:

In this manuscript the authors complete the study published in ref.22, by doing expression studies of the missense MANBA mutation reported in the referred paper.

1-In my view, it must be clearly stated in the text that the MANAB mutation has been previously identified and published. Accordingly, the title must be changed; “a novel MANBA mutation” must be removed.

2-It was interesting to characterize the mutant protein, if possible in the patient cultured skin fibroblasts, since the patient is homozygous for the mutation.

3- It is not said if the patient excreted oligosaccharides in the urine, this study and morphological studies in a skin biopsy could be relevant to the patient characterization.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a
statistician.

Declaration of competing interests:
I declare that I have no competing interests’.