Reviewers report

Title: Gaucher disease: Single gene molecular characterization of one-hundred Indian patients reveals novel variants and the most prevalent mutation.

Version: 0 Date: 17 Dec 2018

Reviewer: Irene Paradisi

Reviewer's report:

Comments on the manuscript MGTC-D-18-00440: "Gaucher disease: Single gene molecular characterization of one-hundred Indian patients reveals novel variants and founder mutation"- General comments: The manuscript is well written, and all the important details that were suggested to the authors for their previous publication were taken into account. The text is easy to read and understand. There are some minor and major comments:

Abstract:- Using the word "variant" to denote pathogenic mutations is not recommended. "Variants" can be used in both normal and abnormal DNA changes; the herein reported changes are clearly damaging.

Background section: Page 6, line 123: the cytogenetic location of the gene according to OMIM; NCBI Gene ID: 2629, GeneCards, etc. is 1q22

Methods section- Page 7, line 155; page 15, line 357: correct 4-methylumbeliferryl by 4-methylumbeliferyl

Results section:- Page 9: What is the average inbreeding coefficient in the biological related families? Or, what is the most frequent consanguineous relationship? First degree relatives?

In the Abstract, line 75, patients are described as "unrelated". But 26% of them are indeed related. A more specific description of this issue should be included. - Page 9-10, lines 218-220: Since India is a very large country, I would suggest to give more specific data (in a summarized way) about the geographic origin of the patients (perhaps mentioning the States, plus the Regional Area: West, North, etc.)-

Page 10, line 236: "prevalence in 62% patients affected with GD"... this prevalence figure corresponds to the identified mutations in the patients sample i.e. 93 patients. It might be better described as... its frequency was 62% of the mutations detected..." or something like this.- Page 10, lines 241-242: mutations included in the complex alleles should be mentioned in the text, in addition to the Table 2 legend.- Page 11, line 247: the sentence "Each mutation was present in two patients" is confusing, since there would be five mutations in four chromosomes (two patients)?

Discussion section:- Page 13, line 296, please correct the mutation nomenclature.- Page 13, line 306: "it is justifiable to consider p.Leu483Pro as the founder mutation in the Indian population" To propose that there is a founder effect in the population, it is necessary to study markers / haplotypes that inform on the common genetic origin (IBD= identical by descent) of the mutation in the country, or if it is an Identical by state (IBS) mutation in India. There are several examples in which the same mutation has different genetic origins in a population (see for example: J Genet. 2017, 96(4):583-589; Eur J Med Genet. 2015; 58(2):59-65).

Page 13, line 314, please include the current nomenclature for the mutation 84GG- Page 14, line 335-336: "Long term follows up of our patients with type 1 GD will help to understand the heterogenic effect of the said genotype on the phenotype".... There is no description along the text whether the
patients are receiving enzyme replacement therapy. If so, it is difficult to establish a genotype-phenotype correlation and/or a long term evolution of phenotypic manifestations, since enzyme activity is being provided to the patients; this should be mentioned.- Table 2, page 24: check minor corrections highlighted in yellow.

Major comments:
The research provides useful and valuable data on the epidemiological genetics of Gaucher disease in that country. It is a quite complete manuscript, in which the pathogenic effects of the new variants were evaluated. Nevertheless, some aspects regarding population genetics should be included in the discussion:

1 - The high frequency of the pan-ethnic mutation L444P (p.L483P) is an interesting finding, which however could be discussed a little more. Its frequencies vary between geographical regions in the country? Is it more frequent in the 26% of consanguineous families?

2 - As mentioned, proposing p.L483P as a founder mutation in India must be based in genetic evidence (haplotypes) and/or historical records documenting the classical genetic forces that contributes to a founder effect (isolation, bottleneck, genetic drift, gene frequency). This discussion is lacking in the text. Moreover, using "founder mutation" in the article title can suggest that this phenomenon was indeed demonstrated. Perhaps "founder" can be replaced by "prevalent".

**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?**
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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