Reviewer’s report

Title: Premature ovarian insufficiency as a variable feature of blepharophimosis, ptosis, and epicanthus inversus syndrome associated with p.Leu75Phe FOXL2 mutation: a case report.

Version: 1 Date: 23 Feb 2019

Reviewer: Petra Liskova

Reviewer's report:

General comments

The paper has been improved during the revision process however there are still many issues that need to addressed.

Abstract should indicate whether the mutation is novel. The mutation in the abstract should be also described at DNA level not only at the protein level.

The authors claim that "The following case study is the first report of endocrine impairments typical for menopausal transition in young female with FOXL 2 gene mutation previously associated with BPES type 2.

However published literature indicates that some mutations have been described in association with both phenotypes, please see for example De Baere, et al., Am. J. Hum. Genet. 72:478-487, 2003. Please reword.

The introduction of the paper is too narrative. The case report should more focused not a review. I would suggest to reword (mainly delete) especially the historical background.

Minor comments

1. Line 35, Abstract

Ovarian insufficiency (POI). Two types of BPES were described in the literature. BPES type 2 is a simple association of inherited developmental defects of the eyelid area, while in type 1 female patients additionally suffer from premature ovarian insufficiency.

POI abbreviation has been introduced previously and should be used
2. Line 39 impairments typical for menopausal transition in young female with FOXL2 gene mutation

FOXL2 - Typing error

3. Line 49-50 The presenting patient remains in a constant observation.

This sentence does not add any value to the manuscript, please delete.

4. Line 51 The authors found mutations in the p.(Leu75Phe) FOXL2 gene in young women with hormonal disorders suggesting menopausal transition

Why plural, i.e. disorders?

5. Line 55 blephariphimosis,

Typing error correct is blepharophimosis

6. Line 57 blepharimosis

Typing erro

7. Line 59 The prevalence in general population is unknown but is estimated as 1 per 50000 people.

Please change for 50,000.

8. Line 66 All the BPES cases described in the literature are caused of inherited or de-novo mutations of the FOXL2 gene (chr. 3q23) or its regulatory regions.

Please add appropriate references

9. Line 69 The structure of FOXL2 contains two domains: the DNA binding forkhead domain (FHD)
There is no need to introduce the abbreviation as it is not used further in the manuscript.

10. Line 70 Previously, several types of rearrangements in 3q23 region affecting the FOXL2 gene were described. It has been suggested that FOXL2 mutations leading to truncation of the protein before polyalanine tract are associated with POI, while those causing polyalanine expansion tend to cause BPES type 2 (5, 6). However, in case of other described mutations (missense mutations or microdeletions), the genotype-phenotype correlation was not apparent.

   This information would be more appropriate into discussion, however to keep the paper focused the best would be to delete it and only add that reliable genotype-phenotype correlations can be made.

11. Line 121 AMH abbreviation should be introduced in the text when first used, i.e. not in line 208 Anti-Müllerian hormone (AMH).

12. Line 170 Family study using amplicon deep sequencing (ADS) confirmed

   Why italics font?

13. Line 186 The present study is the first literature report of blepharimosis, ptosis, and epicanthus inversus syndrome in Polish population

   BPES abbreviation has been introduced previously and should be used, in addition there is a typing error 'blepharimosis'

14. Line 188 Although our proband had typical ophthalmologic symptoms

   Ophthalmic, please correct

15. Line 191 The p.(Leu75Phe) mutation in the FOXL2 gene was previously found by Xue et al. in three women of two Chinese families. (14).

   Typing error/ please remove a dot.
16. Line 227 Worth underline is that it is the first in literature description of mutations BPES type 1 with association of hormonal disorders.

As already mentioned in the General comments it is a known fact that some mutations can be associated with both BPES types.

17. Line 230 We found mutations in the p.(Leu75Phe) FOXL2 gene in young women with hormonal disturbances.

Incorrect, please reword.

18. There is no need to have Figure 1 and Figure 2/ please join them together

19. Line 324 Figure 1. Ophthalmological phenotype of presented patient.

Please add of 'the' presented patient

20. Line 327 B) NGS results of variant p.(Leu75Phe) in FOXL2 gene in proband using Integrative Genomic Viewer (IGV). C) Amplicon deep sequencing (ADS) results in FOXL2 gene in studied family (IGV view).

Abbreviation NGS has not been introduced in the text.

**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.

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

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Please indicate the quality of language in the manuscript:

Needs some language corrections before being published

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