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: 0 Date: 17 Dec 2018

Reviewer: Petra Liskova

Reviewer's report:

General comments

The authors report a case with BPES type 2 carrying a known p.(Leu75Phe) mutation in FOXL2, which has been previously associated with BPES type 1. The manuscript illustrates that phenotypical predictions based solely on the genotype are uncertain as some FOXL2 mutations can be associated with both BPES type 1 and 2.

The paper needs shortening and scientific language editing. Some of the expressions and/or sentences used do not match standard way of medical English writing.

As Sanger sequencing of FOXL2 is more cost effective than WES, can the authors explain why WES was used as the primary approach?

Specific comments

1. 18 years old nulliparous woman was diagnosed of secondary amenorrhea.

42 Blood tests revealed decreased levels of AMH

Abbreviation AMH has not been introduced.

2. 103 On physical examination acne and abnormal eyelid development (ptosis, and microphthalmia) were observed.

The diagnosis of microphthalmia should be supported by axial length measurements

3. 110 patient reported similar phenotype (concerning ophthalmologic alternations, Fig. 1.) in her father (MF, Fig. 2.), sister (MS) and half-sister (MH).
131 The other three family members (MF, MS and MH)

Are these initials of the family members? If yes, remove, published data need to be anonymized as much as possible.

4. 136 Informed consent was obtained for each patient.

141 and half-sister). DNA was obtained using standard salting out method. Written informed consent was obtained prior to genetic testing from all subjects.

There is no need to repeat twice that consent was obtained.

5. 156 Bioinformatics analysis of whole exome sequencing (WES)

WES abbreviation has been introduced previously in the text.

6. allele is likely to be damaging with a CADD score of 22.2. Moreover

Please explain what CADD means.

7. Moreover, the pathogenicity estimation by Polyphen2 and Mutation Taster predicted this mutation as deleterious

More tools could be used for analysis, for example MutPred, SNP and GO.

8. Table 1 c.223C>T p.(Leu75Phe)

In the table the authors use correct p. description with brackets however in the text they don't. Please be consistent.

9. We found mutations in the p.Leu75Phe FOXL2 gene in young women with hormonal disturbances.
Gene symbols should be in italics.

**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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