Author's response to reviews

Title: A case of Aromatase deficiency due to a novel CYP19A1 mutation

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Author's response to reviews: see over
Dear Editor

RE: Manuscript

MS: 6421902699705485
A case of Aromatase deficiency due to a novel CYP19A1 mutation

Please find to follow our responses to the comments made by the referees.

Referees 1 and 2 were satisfied with our responses and did not request any further amendments.

We thank Referee 3 for the comments. We have revised the manuscript in accordance with the instructions given by this reviewer. We trust that this revision will now be suitable for publication.

Please find to follow our response to each concern raised by Referee 3.

The manuscript has become very lengthy and does not provide a smooth precise reading. The aromatase deficiency phenotype has been described many times in the paper which may be avoided. The results of the ARKO mice will only be supportive and no direct correlation can be made with the humans. The presence of streak ovaries in the patient should not be over-emphasized based on the fact that the initial diagnosis and related investigations could be erroneous.

The length of the manuscript has been reduced substantially – the discussion section has been reduced by approximately 50% and this has been achieved by removing much of the repetition. We believe that the manuscript now reads well and continues to encompass all the salient points requiring discussion, but does so now in a much more succinct manner.

We agree that the results of the ArKO mice are only supportive and that no direct correlation may be made with humans. We have modified the statements in the manuscript as follows:

Page 7, Lines 200 and 201
The phenotype of the CYP19A1 knockout (ArKO) mouse suggests an association between aromatase deficiency and metabolic perturbations [40, 41].

Page 8, Line 231
Alternatively, extrapolating from observations in the ArKO mouse, we speculate that the streak ovaries may be an inherent manifestation of CYP19A1 deficiency [40, 41].

We have de-emphasised the presence of streak ovaries in this patient. We have removed reference to the streak ovaries in the title. We do not believe that we have overemphasised the presence of streak ovaries in this patient. We do believe it is necessary to discuss this phenotype in the paper however particularly since there is no consistent phenotype reported in the literature and the streak ovaries in our patient may simply be a reflection of the previous oestrogen treatment (see discussion page 8, lines 223-229).

Major compulsory revisions
Background:

Lines 93-99 may be deleted
We have deleted these lines as requested.

101-104 not necessary here
We have deleted these lines as requested.

111-117 variation in the phenotype............. This description has been repeated many times in the manuscript
We have removed this as alluded to by the reviewer.

118 ‘as already discussed….. later in life” may be deleted
We have deleted these lines as requested.

122-135 may be placed under discussion
We have moved these sentences to the discussion as requested. They can now be found on page 6, lines 167-177.

137 the sentence may be modified to “here we report for the first time a female patient diagnosed with aromatase deficiency during adulthood”.
We have modified this sentence as requested (now page 4, line 114).

138-143 not required
We have removed these lines as requested.

148 the sentence may be modified to ‘she was born to consanguineous parents and had reportedly abnormal genitalia at birth’ the remaining lines 149-152 may be deleted.
We have modified the statement as requested (page 4, lines 119-120) and have deleted the remaining lines as requested.

162-163 when there are no records why mention the karyotype and presence of Y chromosome?
We have removed reference to the karyotype and presence of Y chromosome as alluded to by the reviewer.

160-162 the sentence may be modified to ‘bilateral streak ovaries which were excised. Histological examination of the streak ovaries revealed……..’.
We have modified this statement as requested (page 5, lines 127-128).

180 a reference may be given here. The sentence is unclear… ‘in metaphase’
We do not see a need for a reference as karyotyping is a standard available clinical test. We have removed the phrase “in metaphase”. The karyotype was examined with cells in metaphase, but since this is a universal protocol the phrase “in metaphase” is superfluous and therefore it has now been omitted, particularly as it has caused confusion.

189 mention the SNPs detected giving the reference numbers
We have mentioned the rs ID for both SNPs (rs1057870 and rs2228104) as requested (page 6, lines 153 and 154).

203-325 may be presented in a crisp and concise manner without such lengthy sentences and descriptions. Most of the matter discussed has been repeated many times in the manuscript. There is lot of repetition in the manuscript.
We have revised this section and have done our best to present it in a crisp and concise manner as requested by this reviewer, whilst continuing to respect the comments of the
other reviewers. We have removed repetition in the manuscript. Overall, we have reduced
the amount of content in this section by almost 50% (from 122 lines to 66 lines) and this was
achieved by making the sentences and descriptions more concise and removing the
repetition in this section. We trust that this will be to the satisfaction of this reviewer.

258-260 the sentence …’it is unknown….may be deleted.
We have deleted this sentence as requested.

Kind regards
Yours sincerely

Dr Lucia Gagliardi
MBBS, FRACP, PhD

on behalf of the authors