Reviewer’s report

Title: GERMLINE c.1A>C HETEROZYGOUS PATHOGENIC VARIANT IN SDHA REPORTED FOR THE FIRST TIME IN A YOUNG ADULT WITH A GASTRIC GASTROINTESTINAL Stromal TumoR (GIST): A CASE REPORT

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Reviewer: Thomas v. O. Hansen

Reviewer's report:

In the paper by Carrera et al., the authors identify a heterozygote germline SDHA c.1A>C, p.(Met1?) variant in a young adult with a GIST negative for c-KIT or PDGFRα mutations. Family history revealed that the paternal grandfather died as a consequence of a pituitary adenoma. Genetic analysis moreover revealed that the patient's brother did not have the variant, while the patient's father and paternal uncle both had the variant. According to the authors this is the first description of a GIST tumor in a SDHA c.1A>C carrier. Carrera et al., conclude that all patients with GIST without c-KIT or PDGFRA mutations should be referred to genetic counselling regardless of the age at presentation or the absence of a family history.

Major points

1) The authors should include the methodology used for mutational analysis of c-KIT and PDGFRα genes. Which exons are examined?

2) The authors state that the sequencing data is processed taking into account the SDHA and SDHC pseudogenes. How is that done?

3) c.1A>C should not be described as a missense variant (it's a start codon variant). At the protein level it should be described as p.(Met1?). This should be changed throughout the manuscript, including the discussion.

4) I would suggest that the authors clearly indicate in Fig. 1 individuals that are carriers and non-carriers (brother) using +/- . Moreover, remove the color in the father and uncle. Finally, include a more comprehensive figure legend (e.g. explain squares and circles, carriers etc.).

5) In the results section (line 46-47) the authors state that "a new upstream state codon, resulting in an mRNA transcript that will be different from the original". This is only correct if the variant affects splicing and should therefore be rewritten.
6) What does the authors mean by "true" in the sentence "a true negative/positive result" (results section, line 48-51).

7) The authors state in the result section (line 51-54), that "these results confirmed that the parental grandfather … was obligate carrier. I do not agree in this and would not use the term obligate carrier. In line with this, currently I do not agree that the variant co-segregates with the disease (mentioned in the discussion and conclusion section). It is true that the grandfather has a phenotype, but you cannot rule out that the variant was inherited from the grandmother. I would suggest that you test the grandmother - and if possible tissue from the grandfather.

8) Have the hepatic metastases been examined for c-KIT and PDGFRA variants?

9) The pathogenic classification in ClinVar by OMIM is based on data from ref 29. Therefore, the paragraph in the discussion and conclusion section should be rewritten. Moreover, the authors do not need to describe the variant once more but focus on the putative consequence and the functional data.

10) The manuscript should be read thoroughly by an English-speaking person.

Minor points

11) Please use italics when genes are described.

12) Please include information regarding the frequency of the c.1A>C variant in the general population (e.g. gnomAD).

13) If space allows I would suggest that the authors include a figure with an electropherogram showing the SDHA c.1A>C variant.

Level of interest

Please indicate how interesting you found the manuscript:

An article whose findings are important to those with closely related research interests

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