Reviewer's report

Title: SDHA Loss of Function Mutations in a Subset of Young Adult Wild-type Gastrointestinal Stromal Tumors

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Reviewer: Anthony Gill

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Major Issues

1. In the first paragraph of the introduction the authors state "Loss of SDHB expression was first identified in GIST occurring in the context of CSS with germline mutations of SDHB or SDHC" and quote the article by Janeway et al from 2011. This statement is incorrect. Loss of SDHB expression in GIST was first reported by our group (Gill et al in 2010) who reported loss of SDHB expression in the GISTs of the Carney Triad and the subset of pediatric and adult GISTs which they resemble clinically and morphologically and proposed that negative staining for SDHB identifies a new and unique type of GIST now called the SDH deficient GIST.

2. First paragraph on the methods - the authors started with 17 WT GISTs - were these selected to be SDH deficient GISTs? Our experience is that about 90 to 95% of pediatric WT GISTs are SDH deficient, but only about one quarter of adult WT GISTs are SDH deficient. The authors should explicitly state whether these GISTs were selected to be SDH deficient for inclusion in the study as I really would be surprised a consecutive series of 17 WT GISTs were all SDH deficient (unless perhaps they were all pediatric). If there was a selection bias towards pediatric GISTs this should be stated.

3. In the third and fourth paragraphs of the discussion the authors seem suggest for GIST that SDHA mutation can be germline or somatic. This is very weak evidence for this assertion given that they have only sequenced three exons. As the authors would know for SDHA,SDHB,SDHC and SDHD mutated paraganglioma virtually all mutations are germline with a second somatic 'double hit' rather than being due to two somatic events and they simply do not have enough data to comment on whether or not this may be the same in GISTs.

4. In the final paragraph the authors recommend screening for SDHA mutation in SDH deficient GISTs. At face value this seems very logical conclusion. However it is not straightforward. We do not know if patients with SDHA-deficient GIST are at increased risk for the other tumors associated with SDHx germline mutations. We do know that patients with SDHA germline mutations with more than one tumor type have not yet been reported and that although the germline nature of such mutations are now well documented, the risk to mutation carriers is also unknown. Put simply there is insufficient data to know the clinical significance of
an SDHA germline mutation. We think the penetrance is low but don’t know. What do we do with an individual or kindred with SDHA mutation? Is there sufficient evidence to offer the same screening we offer individuals with SDHB mutation? These are very challenging issues and should in some way be acknowledged.

Figure 4f - as discussed in my last review, the SDHB staining in figure 4f looks like it has not worked as there is no internal positive control (and the tumour does not demonstrate the typical morphology of an SDH deficient GIST). The authors need to review the IHC from the GIST to confirm it was genuine negative staining with a positive internal control and replace this photograph. Is this really the same GIST in panel 4E as 4F. Also the caption for this figure does not clearly indicate what IHC is used in each panel

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

'I declare that I have no competing interests'