Author’s response to reviews

Title: Cascade Fumarate Hydratase mutation screening allows early detection of kidney tumour: a case report.

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Author’s response to reviews:

Many thanks for your constructive comments on our manuscript. Please find our responses below:

1. Major weakness of this manuscript is a very poor pathology description, which (likely) stems from the fact that no pathologist specialist in GU pathology was involved as a co-author. The topic of FH deficient - renal cell carcinoma (RCC) has undergone a major rethinking lately. Some of these data is quite novel and unsurprisingly the authors may not be aware of it. FH deficient RCC is NOT a papillary type 2 cancer (a concept which is challenged currently) - but it is a different type of extremely aggressive cancer (see Am J Surg Pathol 2016 Jul;40(7):865-75 and N Engl J Med. 2016;374:135-145). FH deficient RCC is also not restricted only to patients with frank HLRCC Sy. Also 'tubulocystic pattern' is frequently seen in FH-deficient RCC (Am J Surg Pathol. 2016 Nov;40(11):1457-1472). For screening purposes - IHC for FH and 2SC may be helpful. These and few other recent publications may be of interest and for inclusion in the revised discussion (for e.g. Am J Surg Pathol. 2014;38:627-637 and Am J Surg Pathol 2016;40(5):599-6070).
Dr Alan Bates, Consultant Histopathologist with a specialist interest in renal cell carcinoma, and the reporting histopathologist in this particular case, has provided input on the histopathology part of the manuscript and has been added as a co-author. The papers mentioned above have been included in the revised discussion (lines 111-123, references 11, 13-16).

2. The diagnosis of the renal lesion in the father as 'multilocular tubulocystic carcinoma' is questionable. Was this neoplasm tested for FH and 2SC by IHC? The lesion is not well illustrated at higher magnification and it may represent a 'cystic nephroma' - an incidental benign renal neoplasm. 'Tubulocustic pattern' is frequently seen in FH-deficient RCC (Am J Surg Pathol. 2016 Nov;40(11):1457-1472), but these are aggressive neoplasms. Provide additional IHC evidence for the diagnosis (or expert review) and provide better illustrations (higher mag. details and include prominent nucleoli in the neoplasm, if seen). This would be the key to make this case report credible! Also the quality of the photos is not good (the background should be white - not yellow!).

- The neoplasm was not tested for FH and 2SC as these are not routinely carried out in clinical practice in our hospital. Please find new images attached for Figure 2 showing the multicystic tumour with cysts lined by hobnailed cells with a low mitotic index and prominent nucleoli.

3. Papillary type 2 cancer is NOT what was thought to be associated with HLRCC and many experts now believe that papillary type 2 consists of multiple tumor types, recognized during the last decade. Therefore, provide a statement that "type 2 papillary RCC" may not constitute a single entity, but may represents a pattern that may be seen in a variety of neoplasms, including, for example, Xp11 translocation RCC and collecting duct carcinoma, as acknowledged in the 2016 WHO Renal Tumor. Classification. This needs to be included in the discussion (replace sentences pertaining to Type 2 papillary RCC...lines 108-109, 114-115).

- This has been corrected in the revised discussion (lines 113, 117-120).

4. In my opinion, it would be very compelling if the second allele loss (second hit) in resected cancer could be identified, either by tumor sequencing, LOH study, immunostaining of FH protein or FH enzyme assay from the fresh tissue (if available).

- These are all excellent suggestions but unfortunately have not been done.
5. For minor correction, page 6, line 134. I believe the word 'oncometabolite' would be more appropriate since fumarate is a sugar, not protein.

- Corrected to oncometabolite (line 152)

6. If possible electropherograms or equivalent diagram from the mutation screen should be shown.

- Unfortunately this is not available.

7. Typographical and terminological mistakes at Line 139, "… hypothesised that fumarate may act as an 'oncoprotein' in FH-deficient kidney cancer." Should be hypothesized that fumarate may act as an oncometabolite in FH-deficient kidney cancer.

- Corrected to oncometabolite (line 152), as above.