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 again for your time and constructive comments on our manuscript. Please find our responses below:

Reviewer 1

1. The diagnosis of the tumor labelled "multilocular tubulocystic carcinoma" is questionable. Tubulocystic carcinoma is not "multilocular". Neither a good description of the morphology, nor an IHC profile of this tumor is provided in the text. A pathology description of the tumor in the report is non-existent and no figure legends are provided?! In the view of this reviewer the morphology does not reflect the typical morphology of either FH-deficient or HLRCC-associated RCC.

- We agree that tubulocystic carcinoma is not multilocular (this has been amended) and is not the classical morphology described in HLRCC-associated RCC. We do state in the discussion that these cancers are a histologically heterogenous group and, as there are no absolute certainties in pathological diagnoses, it is our opinion that this tumour represents a
low-grade tubulocystic carcinoma. We have inserted the full pathology description of the tumour on lines 95-100 with the associated IHC profile available. The Figure legends were provided at the end of the main body of text (lines 287-289).

2. This tumor was rather small - max 2cm; this may have been an incidental detection of a benign tumor, prompted by the surveillance. Based on the photos provided this may represent either a "cystic nephroma" or a genuine "tubulocystic carcinoma" - both indolent renal tumors - and typically NOT found in HLRCC patients.

- FH-deficient RCC have a high chance of early invasion and metastasis even when the lesion diameter is < 1cm. Therefore in a young man with a genetic predisposition to RCC, early resection of even very small suspicious lesions is recommended.

3. No FH or 2SC IHC screening of the tumor was performed (and although this was declared in the response to the reviewer - this statement is not included in the text?!).

- This has now been included on line 99-100.

4. In the absence of compelling evidence to label the described tumor "kidney cancer" related to HLRCC Sy - the statement in the conclusion that "this is the first report of identification of a parent with kidney cancer by screening performed for this indication" is incorrect and simply stretches the truth.

- We have taken on board your comments and amended the phrase 'kidney cancer' to 'kidney tumour' at various points in the manuscript.

Reviewer 3:

One minor correction. The complete name of NRF2 is "nuclear factor, erythroid 2 like 2"

- this has been amended in line 154 and in the abbreviations section.