Reviewer’s report

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

Version: 0  Date: 28 Nov 2016

Reviewer: Manop Pithuppakorn

Reviewer's report:

Thank you for the opportunity to review your manuscript. This is a case report about an identification of renal cancer in parent of fumaric aciduria patient.

It has been accepted that genetic mutations in one particular gene could arise with two distinct clinical phenotypes, sometimes with different pattern of inheritance. FH is one of those genes. It has been previously reported that parents of fumaric aciduria children have cutaneous leiomyomas but there is no previously reported renal cancer in those obligate carriers. There is a possibility that certain mutations in FH could be associated with HLRCC but not in autosomal recessive fumaric aciduria, or it could be that previously reported cases of fumaric aciduria had paid attention only on immediate clinical presentation of developmental delay and dysmorphology but not long term renal cancer risk in parents, thus creating 'information gap' in disease spectrum.

The clinical phenotype of the parents of this reported child is interesting. Though, sporadic tubulocystic renal cancer could arguably be presented without family history of fumaric aciduria, HLRCC or germeline FH mutations, identification of this cancer in FH heterozygote makes the strong case of its relationship with FH mutations. 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).

For minor correction, page 6, line 134. I believe the word 'oncometabolite' would be more appropriate since fumarate is a sugar, not protein.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Unable to assess
Are the conclusions drawn adequately supported by the data shown?
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Yes

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If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

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Quality of written English
Please indicate the quality of language in the manuscript:

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