Author’s response to reviews

Title: Case Report: A synonymous VHL mutation (c.414A→G, p.Pro138Pro) causes pathogenic familial hemangioblastoma through dysregulated splicing

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Version: 1 Date: 26 Jan 2020

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MGTC-D-19-00311

Case Report: A synonymous VHL mutation (c.414A→G, p.Pro138Pro) causes pathogenic familial hemangioblastoma through dysregulated splicing Fang Liu, PhD; Barbara Calhoun; Md Suhail Alam, PhD; Miaomiao Sun; Xuechun Wang; Chao Zhang, PhD; Kasturi Haldar, PhD; Xin Lu, PhD BMC Medical Genetics

Editor Comments:

The manuscript has been reviewed by two people and their comments are included here. Essentially, this study has a potentially interesting observation regarding splice alterations from a synonymous change in VHL. The manuscript may be considered for publication after incorporating the (minor) revisions suggested by the reviewers.

Au: We really appreciate the comments and suggestions from the editor Dr. Chitra Kannabiran and the two reviewers Dr. Neha Varshney and Dr. Zhengmao Hu. We have followed the suggestions and revised our manuscript, which we believe has improved the report significantly.
Reviewer reports:

Neha Varshney, M.D (Reviewer 1): - I would like to see pathology pics and some description.

Au: We contacted the patient family and requested pathology reports for the proband. However, the hospital where he was treated (Neurologic & Orthopedic Hospital of Chicago) closed shortly after his surgery. All of the medical records in his possession (and transferred to us) are results of genetic testing and MRI, which we submitted in the original manuscript. Currently there is no readily available source to retrieve any pathology records for the proband.

With respect to the twin daughters, we also only have the medical records for genetic testing and MRI. Based on our inquiry so far, it will be a lengthy process (months) with significant barriers to obtain additional medical records. Therefore, we apologize that it is unfortunately impossible to retrieve and include pathology pictures and descriptions of the hemangioblastoma and pheochromocytoma of the patients within the time window given to return the revised manuscript.

However we think that this does not detract from the main significance and implications of the study, because the MRI results and the first report on molecular analyses of the fibroblasts included in the manuscript provide definitive clinical and genetic evidence for VHL disease.

- Add more references especially newer ones from last two years. There are only 13, must be around 25.

Au: We have added 12 more references in appropriate places throughout the manuscript with most of them published since 2017.


- Discussion is very weak. Needs additional information about what is already known in the article.

Au: We have expanded the Discussion. We have taken the reviewer’s advice to start the discussion with what is known, followed by discussion of molecular analyses using fibroblasts and the need to include splicing-altering synonymous mutations into the screening for VHL disease.

If it is felt that additional discussion is needed, we will be glad to provide that but would appreciate guidance from the Editor on specific points of omission that need to be addressed.

Zhengmao Hu (Reviewer 2):

The comments to authors:
1. In page 6 "Review of the family history identified that the proband’s father, paternal grandmother and paternal great grandfather all had clinical history of PHEO". In fig1A, I can’t find the proband’s paternal great grandfather, but I find that the proband’s father, paternal grandmother, maternal great grandfather and maternal great grandmother had clinical history of PHEO. Where the VHL variation c.414A\text{\textgt}G come from?

Au: We apologize for the confusing representation of the pedigree tree in the original Figure 1A. We have verified the pedigree and provided the correct Figure 1A in the revised manuscript.

2. In page 7 "The proband has three children: a son and younger twin daughters". Are the twins monozygotic or heterozygotic? It should be indicated in fig1A.

Au: We appreciate the reviewer’s question and have modified the lines to indicate that the twin daughters are heterozygotic (i.e. fraternal) in Figure 1A.