Reviewer’s report

Title: A Novel Germline ARMC5 Mutation in a Patient with Bilateral Macronodular Adrenal Hyperplasia: a case report

Version: 1 Date: 18 Feb 2018

Reviewer: Amrik Sahota

Reviewer's report:
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This case report describes the identification by whole exome sequencing (WES) of an inactivating germline mutation (c. 517C>T, p. Arg173*) in one allele of armadillo repeat containing 5 (ARMC5), a putative tumor suppressor gene, in a 51-year-old female with bilateral macronodular adrenal hyperplasia (BMAH), which is a rare cause of Cushing syndrome (CS). Subsequent WES of the excised tumor tissue identified a wide range of variants, including single nucleotide polymorphisms, indels, and loss of function mutations, but none of them were related to CS. Thus, the authors state that the germline mutation alone was sufficient to induce BMAH in this patient.

The inability to detect a somatic mutation in tumor tissue may be due to limitations of WES rather than to the absence of the mutation per se. Structural alterations that cannot be detected by WES include inversions and copy number changes.

What the author describe, but do not call it by name, is haploinsufficiency, a well-known mechanism of disease causation. Thus, BMAH in this patient may be due to haploinsufficiency rather than to inactivation of ARMC5 through a two-hit mechanism. While the two-hit model explains many cases of the inactivation of tumor suppressor genes, there are reports of
alternative mechanisms of tumor initiation. These include haploinsufficiency and epigenetic changes (for review, see Paige AJ (2003). Cel Molec Life Sci 60: 2147-2163).

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

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