Reviewer's report

Title: Variable expression of cerebral cavernous malformations in carriers of a premature termination codon in exon 17 of the Krit1 gene.

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Reviewer: Douglas Marchuk

Level of interest: A paper whose findings are important to those with closely related research interests

Advice on publication: Accept after discretionary revisions

This is a relatively straightforward paper describing the clinical findings in a family with hereditary cerebral cavernous malformations, including molecular analysis of the family. The family was shown to carry a KRIT1 mutation. The proband was obviously affected, and other family members were shown to be affected, some to a lesser extent. The most important finding is that an 18 year old carrier of the mutation shows no clinical findings.

Complusory Revisions. I believe the authors should discuss the issue of penetrance more thoroughly in the text. What have other studies found with regard to penetrance of KRIT1 mutations? At what age is penetrance thought to be complete in CCM1 families? Is their finding of the absence of clinical signs of affected status in the 18 year old an unusual, or a predictable finding? I believe that this is indeed not that unusual. A discussion of these issues in light of their own findings would add value to this paper.

Table 1 can be improved by includind additional clinical information including a description of any neurological symptoms for each individual, and importantly, the age (even if only approximate) at which symptoms first appeared. Alternatively, another table can be used to present this information.

There are also some changes that are required in grammar and word choice. An editorial assistant can help identify these. They are quite obvious, such as the word "de" for the, and the use of the word "deserved" to describe the identification of lesions by MRI.

Discretionary Revisions. I would improve figure 3 by including an arrow shoing the proband, as well as another symbol to indicate the individual who showed no evidence of clinical findings, despite being a mutation carrier.

Competing interests:
None declared.