Reviewer's report

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

Authors:

Mr Miguel Lucas (lucas@us.es)
Alzenira F Costa (alzenira@yahoo.com)
Jose M Garcia-Moreno (sinue@arrakis.es)
Francisca Solano (paquisol@hotmail.com)
Miguel A Gamero (magam@supernet.es)
Guillermo Izquierdo (ayuso@arrakis.es)

Version: 7 Date: 11 Jun 2003

Reviewer: Murat Gunel

Level of interest: A paper of limited interest

Advice on publication: Reject

We have read the author's revised manuscript and comments in response to our initial review. We still agree that the authors present a thoroughly detailed account of a family with cerebral cavernous malformations - correlating clinical symptoms with the presence of a point mutation in the KRIT1 gene. However, as we stated in the original review, this manuscript provides little new information to us, as clinicians, who try to understand the pathogenesis of this disease. The authors comment that their main difficulty is in finding large families or many patients with the same mutation. This assertion, though intended to imply one sentiment, is precisely the fault of this report. They only show one family with CCM and a single mutation in KRIT1. No clinical or pathological correlation between genotype and phenotype can be made (illustrating the variability of clinical sequelae or otherwise) based solely on a single family. Indeed, there does exist a large population of individuals known to have the same mutation, namely Hispanic-Americans of Mexican ancestry. Simply stating that a meta-analysis of reports such as this one (i.e. more are on the way?) will suffice to satisfy our concerns of the scientific merit of this manuscript is not adequate and does not resolve our criticism. We know this disease has variable penetrance. This has already been published. We also know that as is seen with any genetic disease, the severity of the phenotype can vary as there may be meta-genetic phenomena at play (environmental cues). Additionally, CCM1 is thought to be caused by KRIT1 mutations through a 'two-hit' theory which would indicate that variability of phenotype among any non-sense or frameshift mutations is unlikely in the absence of said environmental or polygenetic influences. Again, we question whether or not this report merits publication in BMC Neurology.

Competing interests:

I also work on the molecular genetics and biology of cavernomas