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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Level of interest: A paper of limited interest

Advice on publication: Unable to decide on acceptance or rejection until the authors have responded to the compulsory revisions

Lucas et al

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

The authors present a rigorously detailed account of a family with cerebral cavernous malformations correlating clinical symptoms with the presence of a point mutation in the Krit1 gene. This is the first example of a research study designed to correlate the phenotype with the genotype in a family with this disease. The authors point out that after analyzing each family member clinically, through medical histories and MRI investigations, there is a clear inheritance pattern, confirmed through SSCP and RFLP illustrating a point mutation in exon 17 of the Krit1 gene. Indeed, finding mutations in Krit1 in a family with CCM is not a new phenomenon, and the authors cite this accordingly. The authors find, in effect, that the genotype and the phenotype do not correlate adequately or in any definable pattern as the severity of the disease doesn't correspond with the patients' age. Also of note is the absence of disease in a patient harboring the mutant allele. These two facts are the limits of their quantitative analysis.

It is important to note that the authors contribute very little to the current understanding of this disease. It is already known that this disease has variable penetrance and the phenotype has been difficult to 'nail down'. As they point out, the proband is a 4 year old who presented with hemorrhage. All of the other symptomatic patients were not known to be affected and were only determined to be so by MRI and anecdotal clinical vignettes of seizure and apoplexy. Those of us who routinely treat this disease understand the difficulty in counseling families with Krit1 mutations as to what they should expect their lives to be like, especially children harboring mutated alleles. If the authors were presenting a novel phenotype, or a penetrance pattern differing from that reported by previous studies (see Craig et al 1998, Gunel et al 1996 and Gunel et al 1995, none of which were cited by the authors), this manuscript would add to the current understanding of the disease. Furthermore, some of the typographical errors and grammatical structures of sentences are awkward only making the understanding of the paper more difficult.
We feel that this paper, though detailed and adequately researched, provides little new information to clinicians and basic scientists alike, who try to understand the pathogenesis of this disease. The notion that there exists variable penetrance with Krit1 mutations, and those affected often have multiple cavernous malformations is not new information. There exists a need for a phenotype-genotype correlative study, but this paper does not provide that information.

**Competing interests:**

None declared.