Author's response to reviews

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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Letter to the reviewer, Dr. Murat Gunel

I wish to thank the comments and I hope that the amended version of the manuscript answers the points raised.

1.- Typographical and grammatical errors have been modified according to a professional English editor.

2.- In the amended version we include the reference to Craig HD, Gunel M, Cepeda O et al in Discussion: “The penetrances of clinical CCMs among apparent carriers in kindreds linked to CCM1, CCM2 and CCM3 have been estimated as 88, 100 and 63% respectively”.

3.- We have not found a different clinical, phenotype and penetrance pattern but a very variable penetrance in individuals sharing the described mutation and haplotypes within a family.

4.- We agree with Dr. Gunel that "there exists a need for a phenotype-genotype correlative study". As the reviewer comment in his report "This is the first example of a research study designed to correlate the phenotype with the genotype in a family with this disease". The main difficult is to account with a large number of patients with the same mutation. Besides we may wait the discovery of genes in CCM2 and CCM3 (see Craig et al 1998). Meta-analysis of reports "rigorously detailed account of families with CCMs correlating clinical symptoms with the presence of point mutations in the Krit1 gene" (see report of Dr Gunel) can be important to analyse genotype/phenotype relations.