Controversial Molecular Classification of Human Cerebrovascular Malformations

To the Editor:

The identification of underlying causal genes in familial forms of cerebrovascular malformations allows the dissection of an increasing number of these disorders at the molecular level. In recent years, mutations in CCM1/KRIT1, CCM2/MGC4607, and CCM3/PDCD10 have been found to cause autosomal dominantly inherited cerebral cavernous malformations (CCM1, CCM2, and CCM3). Clinical penetrance appears to differ between the 3 CCM subtypes, but larger clinical studies are required to confirm this observation. A subset of patients with cerebral arteriovenous malformations also shows cutaneous capillary malformations attributable to mutations in the RASA1 gene or is affected by hereditary hemorrhagic telangiectasias (HHT) resulting from mutations in the endoglin gene (ENG, HHT1), the activin receptor-like kinase1 gene (ACVR1, HHT2), and an as yet unidentified gene (HHT3). Disease severity seems to be milder in HHT2 when compared with HHT1, but the clinical course of individual cases remains unpredictable for CCMs and HHTs requiring the investigation of additional genetic and environmental factors that may contribute to the manifestation of these disease entities.1–4

Guclu et al5 recently reported an interesting family in which the index case and her father were affected by CCMs, and the index case’s sister had a cerebral venous malformation (CVM). The different vascular phenotypes within this single family were attributed to different genotypes. The sequence data shown demonstrated a stretch of 4 Ts at nucleotide positions 2055 to 2058 of the CCM1 coding sequence in the index case and the father, but a stretch of only 3 Ts in the sister. The authors concluded that the 2 family members affected with CCM carry an insertion of a thymine (c.2058delT) causing a genuine frameshift mutation. However, at least in mice, homozygous inactivation of the CCM1 gene is embryonically lethal.6

We disagree with this interpretation of the sequence data. According to GenBank accession numbers U90268, AF296765, and AF388384, the CCM1 sequences reported by Guclu et al5 for the 2 individuals with CCM are in complete agreement with the wild-type sequence. Rather, the person affected with CVM carries a deletion of a thymine (c.2058delT) causing a genuine CCM1 frameshift mutation (p.F686fsX706). In addition, the sequences shown were likely not derived from direct sequencing as described in the methods section and the figure legend. If these were direct sequences, the authors would have discovered the very first homozygous uniparental CCM1 mutation. However, at least in mice, homozygous inactivation of the CCM1 gene is embryonically lethal.6

The authors have sequenced all 3 known CCM genes in their patients. Nevertheless, a negative result obtained by sequencing does not exclude the existence of CCM mutations. Given a mutation detection rate of currently only about 70%, affected individuals might still harbor a large CCM1, CCM2 or CCM3 deletion or insertion, a mutation in regulatory sequences of the CCM genes or a mutation in a fourth as yet unknown CCM gene. We conclude that the sequence data shown in the report by Guclu et al5 do not support the existence of 2 distinct molecular entities. Under the assumption that the patients’ samples had not been confounded, the data in the figure suggest that, like cavernous angiomas, CVMs might also in part be attributable to mutations in CCM1. Further genetic analyses of CVM patients will have to clarify whether CCM and CVM are molecularly distinct or whether both result from mutations in CCM genes.

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