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/RFT1, 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 in the report by Guclu et al5 do not support a mutation in a fourth as yet unknown CCM gene. We conclude 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.

Sources of Funding

U.F. received an Emmy Noether grant from the Deutsche Forschungsgemeinschaft (Fe 432/6-4) and S.S. a stipend from the Graduiertenkolleg 1048.

Disclosures

None.

Sonja Stahl
Ute Felbor, MD
Department of Human Genetics
University of Würzburg
Würzburg, Germany
