Many attempts have been made to identify parameters with predictive value that could aid in the identification of individuals susceptible to aneurysmal rupture. The paper by Khurana, et al., in the current issue provides a significant contribution in this respect. Using a genetic approach, the authors have identified three polymorphisms in the endothelial nitric oxide synthase (eNOS) gene that independently or in combination are associated with a tendency to rupture. The data are clear and convincing. Nevertheless, although a role for eNOS has been clearly indicated in the pathogenesis of aneurysms in general (cerebral and noncerebral), caution must be exercised when interpreting the present findings. Genes that are closely linked physically on the same portion of DNA (haplotypes) tend to segregate together during cell division. Thus, a role for a second, probably unrelated gene close to eNOS cannot be excluded. Of greater significance, however, is the lack of information concerning the phenotype associated with these polymorphisms. A polymorphism is the regular and simultaneous occurrence in a given population of two or more alleles of a gene, in which the frequency of the rarer allele(s) is greater than can be explained by recurrent mutation alone (typically > 1%). Polymorphisms may involve, but are not limited to, a single nucleotide (so-called single nucleotide polymorphisms [SNPs]). Two of the polymorphisms in the present study are SNPs (T786C and G894T). The former is found in the eNOS promoter and the latter in exon 7. These polymorphisms have been associated with cerebral and coronary vasospasm and carotid and coronary atherosclerosis, respectively. The third polymorphism, 27VNTR, occurs in intron 4 and has been associated with cerebral and aortic aneurysms and occlusive coronary artery disease. Although alterations in levels of eNOS protein expression and enzyme activity have been described in association with these polymorphisms, the challenge now will be to define clearly the role of eNOS in the pathophysiology of cerebral aneurysm rupture. Who knows, maybe this will allow us to move from a predictive parameter to a therapeutic target.

RESPONSE: We thank Prof. Pepper for his thoughtful and incisive comments regarding our latest study. Although we duly acknowledge the pivotal role played by eNOS in the cardiovascular system, we agree that the precise relevance of eNOS to the pathobiology of intracranial aneurysms remains to be elucidated. We too would like to reiterate that, owing to yet undetermined genetic linkage phenomena, our findings should not necessarily imply that the eNOS gene is the one and only aneurysm gene. Rather, the primary and novel finding of our work is that the presence of two or more polymorphisms of the eNOS gene in a patient harboring an intracranial saccular aneurysm appears to correlate significantly and strongly with the rupture phenotype. Therefore, if our findings can be validated by a larger cooperative study, we believe that, regardless of the true identity of the aneurysm gene(s), the eNOS genotype of an aneurysm-harboring patient may be rapidly and cost-effectively screened and the results used as part of a more advanced algorithm to predict the risks of a cerebral aneurysm rupture. Such an algorithm would take into account factors both anatomical (such as aneurysm size, shape, and location) and genetic (for example, the eNOS genotype). Another important message of our study is that what were once regarded as sporadic (that is, nonfamilial and nonhereditary) cerebral aneurysms (accounting for up to 95% of all cerebral aneurysms) may in fact turn out to have a genetic predetermination to form and rupture. Finally, as articulated elsewhere,1 we can infer from our data that there are indeed two distinct subpopulations of intracranial aneurysms—distinguishable anatomically and genetically—one of which is more prone to rupture than the other. We eagerly await the results of other investigations in this field, including a larger, multicenter study.

**Response**

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Reference