Letters to the Editor

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Restriction Fragment Length Polymorphism of the Apoprotein A-I–C-III Gene Cluster in Control and Stroke-Prone White and Black Subjects: Racial Differences

We wish to compliment Kasturi et al. on their recent report that applied molecular genetic techniques to the study of cerebrovascular disease. However, there were several methodological and conceptual aspects of the study that deserve comment.

When studying genetic diseases, it is vital to clearly define and accurately diagnose the phenotype of interest. In this study, the apparent phenotype was carotid stenosis, which presumably represents atherosclerosis. It is well known that the absence of carotid atherosclerosis does not exclude the presence of such lesions elsewhere in the body (i.e., coronary and femoral arteries). While these lesions may be more difficult to document than carotid stenosis, they still represent a very large part of the atherosclerotic phenotype and deserve inclusion in genetic studies. In addition, the definition of <30% stenosis as a control group is somewhat arbitrary. Although patients with such lesions may have a reduced risk of stroke, there is no evidence to support the concept that an atherosclerotic lesion producing 20% stenosis is genetically different from a 40% lesion, since many such lesions increase in severity over time.

Atherosclerosis is likely to be a complex trait, meaning that it is produced by interactions among multiple genes and environmental factors. Attempting to study such a trait based primarily on polymorphisms at one gene locus could produce inaccurate results because several important epidemiological risk factors for atherosclerosis were not analyzed. Age, gender, smoking status, hypertension, diabetes, and the concurrent presence of coronary artery disease have all been established as significant risk factors for the development of atherosclerosis. In the report by Kasturi et al., there were no data presented regarding the distribution of these risk factors between the two study groups. It is possible that the observed differences in the severity of carotid stenosis between the two groups were due to an unequal distribution of risk factors.

Future studies of the molecular genetics of atherosclerosis using specific candidate genes may be very fruitful. However, such studies should control for the many risk factors of atherosclerosis or use other advanced genetic linkage techniques such as the affected pedigree member method and sib-pair analysis.

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References


Response

Atherosclerosis is, of course, a diffuse process, and the selection of carotid disease alone in our studies is not intended to imply that strokes due to atherosclerosis possess a different pathogenetic mechanism from those originating elsewhere. However, because of the view that reduced high density lipoprotein (HDL) may play a pathogenetic role in atherothrombotic brain infarction (ABI), we designed our study to investigate restriction fragment length polymorphism (RFLP) of HDL’s major apoproteins, which include A-I and C-III, with the view that polymorphism may provide a genetic marker for accelerated ABI.

The designation of carotid lesions <30% for control subjects was arbitrary but is a level frequently difficult to separate incisively from clearcut pathology. Clearly, longitudinal studies on the ultimate extent of stenosis and progression, as we previously reported, are crucial. Nonetheless, because this option is impractical, the power of randomization for age- and sex-matched controls and stenotic subjects was expected to segregate and distribute whatever gene changes might exist.

Atherosclerosis is clearly multifactorial, and the analysis of the tandemly linked genes for A-I–C-III–A-IV was not intended to reduce this complexity to one gene locus. However, in selecting our study population, we sought subjects evaluated in our noninvasive laboratory who were nonhypertensive, nondiabetic, and nonsmoking; we were quickly confronted by the impracticality of these criteria since precious few patients fit this category. Despite this dilemma presented by the reality of the human condition, we were able to exclude all diabetic subjects. In black subjects who demonstrated significant RFLP to A-I–C-III, the occurrence of hypertension and smoking were similar although not equal. As we defined them, risk factors were as follows in black control subjects and stroke subjects, respectively: for hypertension, 83% and 68%; for smoking, 42% and 43%; and for obesity, 50% and 18%. Those with none of the customary risk factors numbered none in the control and one in the stroke group. These percentages are not dissimilar and, in fact, favor the stroke group with reduced risk factors. However, in the white subjects, the risk factor percentages were not as comparable and may indicate the diverse nature of that population, always a concern in studies without a homogenous racial group. Our results in white subjects, at variance with other published studies, may be attributable to the possibly inhomogeneous (both racially and by risk factors) population.

Finally, recognition of the multifactorial nature of atherosclerosis has led us to pursue additional gene studies of factors affecting the
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