Cognitive impairment attributable to cerebrovascular disease is a rapidly escalating public health problem. For example, up to one third of all stroke survivors exhibit dementia within 3 months after their stroke. In addition, postmortem pathological studies indicate that 15% to 34% of dementia cases (of which there are currently >4 million in the United States) show significant vascular pathology, either alone or in combination with Alzheimer disease (AD) pathology. However, dementia represents only a portion of the burden of cognitive dysfunction associated with cerebrovascular disease. In addition to patients who develop dementia, there are those who develop cognitive impairment that does not fulfill traditional criteria for dementia but that nonetheless has a significant impact on quality of life and ability to carry out activities of daily living. As a result, the older term “vascular dementia” is being replaced with a new one: “vascular cognitive impairment” (VCI), in which frank dementia may or may not be a feature. Recent studies indicate that the prevalence of VCI without dementia is equal to that of VCI with dementia, suggesting that the total prevalence of VCI (with or without dementia) could be as high as 3 million cases in the United States.

The Opportunity: Genetics of VCI So Far Unexplored

Although the prevalence of VCI approaches that of AD, research on VCI has lagged considerably behind that on AD, particularly with regard to pathogenic mechanisms. Our understanding of the pathobiology of AD vaulted forward with the discovery of genes that produce monogenic forms of the illness or contribute to polygenic forms. Similarly, the identification of genes contributing to VCI would no doubt provide insight into the cellular and molecular basis of VCI.

The genes underlying VCI must be of 2 nonmutually exclusive classes: (1) genes that predispose individuals to cerebrovascular disease, and (2) genes that determine tissue responses to cerebrovascular disease (eg, genes conveying ischemic tolerance or susceptibility, or the ability to recover from ischemic insult). With regard to the first class of genes, some progress has been made in the past few years in identifying genes that confer susceptibility to hypertension and stroke. In addition, several monogenic forms of cerebrovascular disease have been identified. The 2 best studied of these are cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) and hereditary cerebral hemorrhage with amyloidosis-Dutch type (HCHWA-D). CADASIL is a syndrome of subcortical small vessel disease accompanied by lacunar strokes, migraine, and dementia.

The disease results from mutations in the Notch 3 gene, which is normally expressed in vascular smooth muscle cells and pericytes (including those of the cerebral vasculature). The gene appears to be involved in directing smooth muscle
cell proliferation and differentiation.20–24 HCHWA-D is a syndrome of primarily hemorrhagic strokes and dementia.25,26 It is caused by a mutation in the gene for amyloid precursor protein (APP) that causes abnormal deposition of amyloid in the walls of leptomeningeal arteries and cortical arterioles (a pathological condition known as cerebral amyloid angiopathy [CAA]).27,28 Mouse models have been developed for CADA-SIL29,30 and HCHWA-D28–30 and have contributed critical insights into the cell biology of the pathogenic processes underlying them.

In contrast, little attention has been paid to the second class of genes: those that render the brain more or less susceptible to injury in response to cerebrovascular disease. Evidence for the existence of such response genes is that patients with apparently similar loads of vascular pathology (with regard to lesion type, number, and location) may range from no cognitive impairment to severely cognitively impaired.31–35 Such differences could be attributable to either genetic or environmental factors. Direct evidence for a role of genetic factors comes from studies of the heritability of white matter hyperintensities (WMH). Studies in older male twins,36 in a family-based sample of middle-aged and older men and women (the Framingham Study cohort),37,38 and in hypertensive sibs38–40 have shown that WMH volume is a highly heritable trait, indicating a large genetic contribution to development of this condition. Does the heritability of WMH volume simply reflect the heritability of underlying cerebrovascular disease? Two lines of evidence suggest not. First, in the Framingham study group, high heritability of WMH volume was seen even in younger patients in whom the prevalence of cerebrovascular injury was relatively low. Second, in the study of hypertensive sibs, levels of hypertension were controlled for. Thus, these studies suggest that there are genetic factors affecting cellular responses to cerebrovascular pathology that are different from those that cause cerebrovascular pathology itself.

One class of genes that must influence tissue responses to cerebrovascular disease are the AD genes. As was first shown in the Nun Study,39 there is an additive or synergistic interaction between AD and cerebrovascular pathologies, such that individuals with both of these pathologies show greater cognitive impairment than those exhibiting either pathology alone. This finding has been replicated.40,41 In addition, at least 3 sets of genes in the AD pathway, the presenilins, APP, and apolipoprotein E (apoE), are known to interact with the VCI disease pathway. The presenilins, mutations of which cause AD, have been shown to interact directly with Notch proteins, including Notch 3 (mutations of which cause CADA-SIL).42 Mutations in the APP gene can lead either to AD or to hemorrhagic stroke and dementia (as in HCHWA-D) depending on the site of the mutation and the subsequent cellular site of amyloid accumulation.43,44 Variants of the apoE gene appear to affect not only susceptibility to cerebrovascular disease but also recuperative responses to it (see below). Thus, there appear to be links in the biochemical pathways underlying VCI and AD pathologies, which could be responsible for the observed interactive effects of these pathologies on cognitive function.

Genes that influence brain responses to cerebrovascular disease do not appear to be limited to those within AD pathway. First, it has been shown that VCI can occur in the complete absence of AD pathology in sporadic VCI and in hereditary forms.44–46 In addition, the cognitive sequelae of pathogenic processes associated with VCI are different from those seen in “pure” AD, in that executive function appears more strongly affected in VCI than is memory.5,47–51 Consistent with these observations, different brain regions seem differentially affected in VCI and AD, with prefrontal circuits being more affected in VCI and the hippocampus in AD.52–56 There is direct evidence from both human and animal studies for specific non-AD genes that play a role in tissue responses in ischemia. First, studies in humans suggest that variants in the genes for platelet glycoprotein and α-fibrinogen affect poststroke outcomes without affecting stroke risk per se.57–61 Furthermore, studies in animal models have demonstrated that a number of proteins outside the AD pathway contribute to (or protect against) tissue injury after ischemia. These include glutamate and γ-aminobutyric acid receptors, acid-sensing ion channels, proteases, growth factors, and their receptors, and transcription factors.62–64

Genes that affect an individual’s premorbid level of cognitive ability also seem likely to affect performance in the wake of cerebrovascular disease. For example, several studies have shown now that subjects who in their youth perform better on measures of linguistic or mental ability are less likely to develop cognitive impairment or dementia later in life.65–67 Baseline cognitive function in “healthy” individuals at all ages clearly has a strong genetic component.68–70 Indeed, the heritability of certain cognitive measures (including measures of executive function) actually increases with increasing age, raising the possibility that genetic influences become even more important in later life.71

With respect to specific genes that may influence cognitive function, candidate gene studies have indicated strong associations between measures of prefrontal function and polymorphisms in the catechol-o-methyl transferase gene.70 Genetic studies of attention deficit hyperactivity disorder suggest statistically significant associations of this disorder with genes in the dopaminergic and serotonergic neurotransmitter systems;72 it remains to be determined to what extent these findings are applicable to prefrontal function in aging “normal” individuals. Studies in genetically engineered animal models have also identified specific genes that may be involved in human cognition, although much of the focus in those studies has been on hippocampal memory formation; executive function has been far less studied.

Finally, some of the genes underlying VCI are likely to affect both susceptibility to cerebrovascular disease and the response of the brain to ischemic or hemorrhagic injury. ApoE appears to be an example of gene that affects disease incidence and disease responses. On the disease incidence side, apoE genotype influences risk of intracerebral hemorrhage. In the Greater Cincinnati/Northern Kentucky population, about one third of all cases of lobar intracerebral hemorrhage are attributable to the possession of the e2 or e4 allele.73 E4 allele carriers also have a nearly 4-fold higher risk of lobar warfarin-related intracerebral hemorrhage.74 On the
injury response side, the presence of the e4 allele has been associated with reduced survival in intracerebral hemorrhage. Conversely, an increasing dose of the e4 allele has been associated with improved survival in patients after ischemic stroke, even after adjusting for baseline severity of neurological impairment.

Although a useful conceptual model, differentiating incidence from injury-response genes may be difficult experimentally. This is especially true for genes encoding for or affecting the expression of vascular growth factors such as ephrins, which have overlapping effects with neural growth factors. Because there are gene products that can have vasculotropic and neurotropic effects, human studies should encompass not only information on the presence or absence of stroke (whether symptomatic or not) but also on markers of neural injury or response to injury (such as measures of neurological deficit or cognition).

Challenge 1: Choice of Subject Population and Study Design

Acute Large Vessel Infarct

The cerebrovascular pathologies that cause VCI are heterogeneous. Hence, there are several different patient populations that could be used for genetic studies. The first of these is patients with acute ischemic stroke enrolled at the time of admission to hospital. Because only a subpopulation of these patients will develop a clinically diagnosable cognitive impairment subsequent to their stroke, one could compare the genotypes of patients with different cognitive outcomes. Use of this patient population would have distinct practical advantages: patient collection would be straightforward and would generate a cohort enriched with individuals destined for cognitive decline.

There are several obvious confounders that would have to be addressed with this patient population. Symptomatic cerebral infarction is heterogeneous with regard to lesion volume, location, and laterality. Hence, the degree of cognitive impairment seen may reflect these factors as well as the genetic factors that render neural tissue more or less resilient to injury. However, these factors could be controlled for with a sufficiently large sample size of patients with large vessel strokes in similar brain regions. A second confounding issue is that the cognitive status of the patients before stroke would depend on what phase of the poststroke tissue injury response one wished to analyze and what classes of genes one thereby hoped to target. After a discrete ischemic event, there is an acute phase of tissue injury, and it is typically during this phase that the individual presents at the hospital with clinical symptoms. Over the first 6 to 12 months after infarct, a large proportion (up to 50%) of patients with early presentation of cognitive impairment exhibit significant recovery. However, over the subsequent months and years, progressive deterioration is seen in the overall population of stroke patients. This long-term cognitive deterioration may reflect additional ischemic events (which may or may not be attended by acute symptoms), the interaction of the acquired cognitive impairment with normal aging changes, progressive nonvascular dementias such as AD, or some combination.

The likely occurrence of nonvascular cognitive impairment in a subset of individuals complicates the analysis of long-term cognitive outcomes considerably. There are neuropsychometric tools that could potentially help identify patients with significant AD; these are discussed in a later section of this article. Insights could also be gained through serial MRI, amyloid imaging, or testing for AD-related genes. However, such long-term studies ideally would be performed over a period of at least several years and would carry considerable per-patient costs. An alternative solution would be to target the initial phase of poststroke recovery. It is possible that the degree of short-term recovery would be less influenced by concomitant AD pathology than would long-term outcome. This approach might also uncover genes that promote tissue repair as well as ones that render it susceptible to damage. Such a study could be hospital based and loss to follow-up would be minimal.

Subcortical Small Vessel Disease

It has been suggested that subcortical small vessel disease produces a more homogeneous set of cognitive deficits than do large vessel infarcts, although the deficits may be milder and slower in onset. In this regard, subcortical small vessel disease could be particularly well suited to genetic studies. The major challenge with this population would be subject recruitment. Large-scale imaging studies have shown that most subcortical small vessel disease does not produce acute symptoms but rather an insidious decline in neurological function or no symptoms at all. In theory, one could screen a large number of “normal” subjects for MRI signs of small vessel disease and then compare the genotypes of subjects who do and do not subsequently develop cognitive impairment. However, only about 15% to 25% of elderly subjects show MRI signs of small vessel disease and only a subpopulation of these then go on to develop cognitive impairment. Because it has been estimated that about a thousand cases and a thousand controls would be needed for a case/control study design (John Hardy and Don Bowden, personal communications, 2004), this kind of longitudinal study design would be extremely costly.

CADASIL and CAA

CADASIL patients are another intriguing population for studying the genetics of VCI. There are 2 potential advantages in using this population. First, the population is relatively homogeneous with respect to underlying vascular disease (small artery angiopathy causing degeneration of the smooth muscle cell layer) and type of infarct (primarily subcortical lacunar). Second, despite this homogeneity in the
nature of the vascular disease, there is a high degree of variability in penetrance and age of onset of stroke and cognitive deficits.\textsuperscript{90–92} Age of first transient ischemic attack or stroke ranges from 20 to 70 years. Although almost all patients eventually develop infarcts, only $\approx 75\%$ become demented, and the degree of cognitive impairment is highly variable.\textsuperscript{93} This variable penetrance cannot be accounted for simply by variability in the severity of underlying vascular disease; as is the case for the general population, many CADASIL patients with significant white matter lesions show no measurable cognitive deficits.\textsuperscript{94} This finding suggests (as was argued for sporadic cerebrovascular disease) that the cognitive impairment seen in CADASIL is regulated in part by individual variations in susceptibility of tissue to damage, which, in turn, may be partly genetic. However, a distinct advantage of CADASIL compared with sporadic stroke or small vessel disease is the homogeneous pathogenesis of vascular disease in the former, which would greatly simplify analysis of genes regulating tissue responses to vascular disease.

CAA is not a monogenic disease like CADASIL: several familial forms have been identified, but the sporadic form is by far the most common.\textsuperscript{43,44} Nonetheless, CAA offers certain advantages for studying the genetic basis of VCI. First, it is quite common, affecting $\approx 35\%$ of the population $> 85$ years of age.\textsuperscript{95} Second, it is reasonably homogeneous with regard to lesion location; lesions are generally restricted to the cerebral cortex, leptomeninges, and cerebellum.\textsuperscript{95–97} Third, it can be diagnosed with a high degree of reliability using imaging criteria.\textsuperscript{98} Finally, as is the case for CADASIL and sporadic subcortical small vessel disease, CAA patients bearing similar lesion loads can vary widely in the degree to which they are cognitively impaired.\textsuperscript{98}

**Challenge 2: Clinical Phenotyping**

Genetic studies of VCI will require a clearly defined and easily measurable set of clinical phenotypes by which to classify subjects. Several sets of diagnostic criteria have been proposed for vascular dementia, but all have serious limitations.\textsuperscript{99–104} These include variable degrees of sensitivity and specificity and relatively high levels of inter-rater variability. In addition, these criteria produce nonconcordant results when applied to individual patient populations. For example, the percentage of cases diagnosed with vascular dementia can range from 6\% to 26\% in a single population depending on the diagnostic criteria used.

However, the overriding problem with previous diagnostic criteria for vascular dementia lies in the concept of “dementia” itself. Only about half the population of individuals with VCI exhibit dementia,\textsuperscript{78} and those who do not would be better suited to genetic studies because they are likely at earlier stages of illness. Thus, their clinical picture is less likely to be complicated by other pathologies such as AD or frontotemporal dementia. These less severely affected subjects also may be the most responsive to treatment and prevention, a major goal of genetic studies in the first place.

Given the considerations above, it is clear that criteria for cognitive impairment attributable to cerebrovascular disease must be developed to more accurately reflect the clinical picture of these patients. These criteria should follow the model of most previous criteria for vascular dementia in that they would ideally include a combination of imaging and neuropsychological criteria.

**Imaging Criteria**

Imaging is critical for 2 purposes: (1) defining the nature and extent of vascular lesions, and (2) identifying the presence of nonvascular pathology, such as the reduced hippocampal volume seen in AD. MRI is obviously superior to computed tomography (CT) for visualizing pathological features associated with VCI, especially white matter lesions and lacunes.\textsuperscript{105–107} However, MRI is expensive and not as widely available in the clinical setting relative to CT. Therefore, major issues for the future will be to assess the extent to which CT can substitute for MRI and to develop validated scoring schemes applicable to MRI and CT.

Functional brain imaging that assesses cerebral blood flow and metabolism may yield insights into VCI that cannot be obtained by purely structural imaging. This may be particularly true for small vessel disease, in which the relationship between cognition and lesion burden appears to be complex. For example, a prospective study of patients with microangiopathy diagnosed by the presence of diffuse white matter signal changes or lacunar infarction showed a correlation between cognitive impairment and cerebral blood flow assessed by single-photon emission CT and with glucose metabolism assessed by positron emission tomography.\textsuperscript{108} Another study found that subcortical infarcts produce a global reduction in the cerebral metabolic rate of glucose (CMRglu) and that CMRglu has a modest correlation with cognitive function.\textsuperscript{109} A prospective cohort study of 26 patients with radiologically diagnosed lacunes found that bilateral and right hemispheric dorsolateral frontal hypometabolism predicted cognitive decline.\textsuperscript{110} Although lesion function correlative data are essential to understand the pathophysiology of VCI, they may not be essential to discover genetic risk factors for VCI.

**Neuropsychological Criteria**

At present, there is no generally accepted test battery for identifying or classifying patients with VCI. However, there are some basic principles that can be followed in developing such a battery. One of these is that large vessel cortical strokes and subcortical small vessel disease tend to produce different kinds of deficits. The former typically present with region-specific syndromes such as aphasia, apraxia, and amnesia. The latter present with more subtle and temporally progressive deficits, often described as “executive” in nature.\textsuperscript{5,47,49–51,54} These include deficits in speed and so-called “strategic” processing (i.e., attention, planning, and monitoring) in tasks such as memory tasks. Patients may perform normally on simple tasks but reveal deficits as tasks increase in complexity. It appears that the majority of VCI patients fall into the class with subcortical small vessel disease.\textsuperscript{34,89} Thus, it seems reasonable that neuropsychological testing for VCI would include tasks testing executive function. In addition, such tests may help to differentiate patients in which either vascular or AD pathologies predominate.
With regard to specific tests, the mini mental state examination (MMSE) has been used widely in studies of cognitive impairment, including VCI. However, the MMSE is often insensitive to the effects of subcortical small vessel disease, particularly in the earlier stages. This is because the MMSE is to a great deal dependent on overlearned abilities, which are relatively spared in VCI. Tests that would be most sensitive to VCI are those that require strategic processing. These would include verbal learning tests, particularly ones that include recall as well as recognition measures. Recognition involves primarily encoding (which appears to be more spared in VCI than in AD), whereas recall involves retrieval as well (which is more related to the strategies one uses). Nevertheless, VCI patients generally perform better overall on tests of verbal recall than do AD patients, so that these tests cannot be considered selective for VCI.

Tests that might potentially discriminate VCI and AD include verbal fluency tests, which also are considered measures of strategic processing. In several studies, VCI patients performed less well on these tests than did AD patients. Verbal learning and verbal fluency tests have multiple equivalent forms and are thus repeatable with minimal practice effects.

Other desirable characteristics of a neuropsychological test battery for VCI would include the use of controls, particularly concurrently enrolled controls, to ensure that other states in the test subjects and across-site variability in test administration and interpretation are not affecting performance. Simple measures of depression, arousal, and motivation would help eliminate potential confounds.

Challenge 3: Phenotyping Large Samples

It is now well recognized that large sample sizes are important in genetic association studies of complex traits generally and stroke specifically. In 2002, there were >600 positive associations between common gene variants and disease. Often, the reported associations are not robust and consistent replication is exceptional. There are many potential reasons for inconsistent replication, including ethnic admixture resulting in population stratification, type I error attributable to insufficient statistical power, and population-specific gene–gene and gene–environment interactions. A properly designed association study of VCI would need to be sufficiently large to reliably detect small effects, control for ethnic admixture, and control for gene–environment interactions, which, in this context, might include factors such as level of education. It is estimated that several hundred individuals need to be studied to reliably detect a gene that doubles the risk of stroke. It is likely that similar numbers would be needed in the study of VCI.

To study large samples requires efficient and cost-effective phenotyping. It would therefore be useful to clarify what limited data set regarding cognitive impairment is necessary and sufficient to detect the presence of VCI and measure its severity. For practical reasons, it would be useful to have a test battery that could be administered by telephone and by relatively nonexpert personnel. Telephonic assessments of cognition have the advantage over face-to-face assessments in that they can easily be administered centrally in a multicenter clinical investigation, thereby reducing measurement variances. Telephonic assessments like the telephone interview for cognitive status might be well suited for longitudinal studies and may minimize loss to follow-up.

Conclusions

We currently have little understanding of the genetic factors that predispose individuals to cognitive impairment in response to cerebrovascular disease. There are a number of different clinical populations and study designs that seem potentially fruitful for studying this problem. Currently, the major challenge to such studies is the lack of standardized clinical criteria for diagnosing and subgrouping patients with VCI. Hence, further progress in this field is critically dependent on the development of such criteria, particularly for neuropsychological features. The development of such criteria would provide a common language by which data from different studies could be more intelligently and quantitatively compared. Importantly for genetic studies, such criteria would also enable the pooling of genetic and phenotypic data from multiple sources and hence greatly enhance the power of these studies. Thus, it will be key to identify phenotypes that can be measured relatively easily in large populations.

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Co-Chairs: Gabrielle G. Leblanc, PhD, and Vladimir Hachinski, MD.
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