The Genetic Architecture of Intracerebral Hemorrhage

Natalia S. Rost, MD; Steven M. Greenberg, MD, PhD; Jonathan Rosand, MD, MSc

Background and Purpose—Intracerebral hemorrhage (ICH), the acute manifestation of a common progressive cerebrovascular disease of the elderly, is the most fatal and least treatable form of stroke. There is a desperate need for ICH-specific therapeutics and effective primary prevention strategies, a need that is certain to grow with the aging of the population. Data point to a sizable genetic component to ICH susceptibility. Identification of ICH-related genes therefore holds promise for identifying novel biological targets for ICH prevention. This review focuses on evidence for a genetic contribution to ICH, delineates approaches to genetic studies of ICH, and explores foundations for their future applications.

Summary of Review—ICH occurs both sporadically and as part of familial syndromes. Monogenic disorders associated with ICH or microscopic bleeding, such as hereditary cerebral amyloid angiopathy, CADASIL, and collagen type IV A1–associated vasculopathy, demonstrate the potent effect of rare mutations. Dissecting the more complex genetics of sporadic ICH, however, will likely require defining multiple common DNA variants with weaker effects. Advances in high-throughput genotyping technology, computational and analytic methodologies, and large-scale collaborative efforts have already led to the identification of new genetic risk factors for dozens of common diseases. Such whole-genome association studies are being undertaken in sporadic ICH.

Conclusions—Investigations of genetic risk factors for sporadic ICH have thus far been limited to candidate gene polymorphisms. Genome-wide association studies currently hold the greatest hope for robust discovery of ICH genes, which can generate novel insights into ICH biology and strategies for prevention. (Stroke. 2008;39:2166-2173.)

Key Words: genetics ■ association ■ intracerebral hemorrhage ■ stroke prevention ■ review
vessel disease. Easily identified as a focus of hyperattenuation on cranial CT scans, ICH is routinely classified according to the region of the brain in which it occurs—the thalamus, basal ganglia, brain stem, and cerebellum (“nonlobar”), or at the junction of the cortical gray matter and subcortical white matter (“lobar”). Lobar ICH accounts for 25% to 35% of ICH depending on the population studied. Pathological studies demonstrate that the location of ICH in the elderly frequently signals different underlying small vessel diseases. For example, whereas chronic hypertension has long been recognized as a leading cause of ICH, the majority of ICH in lobar brain regions may be unrelated to hypertensive vasculopathy, arising instead from cerebral amyloid angiopathy (CAA; Table 1). The Greater Cincinnati/Northern Kentucky population-based case-control study, for example, demonstrated that hypertension, although a potent independent risk for development of nonlobar ICH, had little if any apparent role in susceptibility to lobar ICH. This finding is consistent with the absence of an effect of hypertension on risk of recurrent lobar ICH in a cohort of lobar ICH survivors. Control of hypertension nonetheless remains a prudent approach after all type of ICH and the mainstay of both primary and secondary prevention for this disorder.

Whereas lobar ICH in the elderly appears to have unique biological features, other risk factors are shared by both lobar and nonlobar ICH. For example, alcohol exposure appears to predispose to both lobar and nonlobar ICH as does leukoaraiosis, discussed below. Furthermore, susceptibility to both lobar and nonlobar ICH appears to have a substantial genetic component. Familial aggregation, the increased risk of disease among family members compared to the general population, can be attributable to both shared environmental and genetic exposures. Although no studies of ICH heritability (the proportion of disease risk attributable to genetic factors) have been performed, data on familial aggregation point to a strong familial contribution to ICH, both lobar and nonlobar, a requisite characteristic for any genetic disease. This is in contrast to data on familial aggregation of ischemic stroke subtypes, which do not support such familiality. In addition, this familial aggregation is not explained by the effect of any identified candidate gene such as APOE or other identified risk factors such as hypertension. These data suggest that there are undiscovered genes that contribute to lobar and nonlobar ICH. Whether they will be the same for both subtypes, however, remains to be seen.

Leukoaraiosis: A Potential Shortcut to Finding Genes for ICH

The small vessel pathologies responsible for ICH can also cause other forms of brain injury. Most notable among these are microbleeds, visible as dot-like susceptibility artifact on MRI, and leukoaraiosis, the white matter rarefaction sensitively detected by CT or MRI (Figure 1). These observations raise the question of whether microbleeds or leukoaraiosis might serve as useful phenotypes for genetic studies of ICH-related small vessel disease. Leukoaraiosis is particularly attractive in this context because it is extremely common in the aging population, readily quantifiable, and strongly heritable.

Leukoaraiosis occurs in virtually all monogenic and sporadic forms of ICH attributable to small vessel disease. Consistent with a shared pathophysiology, leukoaraiosis predicts symptomatic ICH in both lobar and nonlobar locations. Furthermore, control of hypertension both slows progression of leukoaraiosis and reduces risk of ICH. These data suggest that ICH may occur as the culmination of severe or longstanding small vessel disease or from the interaction of other biological processes (eg, alterations in hemostatic pathways) with small vessel disease.

Leukoaraiosis is endemic in the elderly population. In population-based MRI surveys of the elderly, well over 2/3 of individuals are affected. A community-based study in Austria found that 70% of individuals (ages 50 to 75) had some degree of white matter hyperintensity (WMH), whereas the figure for hypertensive siblings in the USA (mean age 65) was 73%. In the Rotterdam scan study, only 5% of 1075 individuals aged 60 to 90 lacked any subcortical or periventricular white matter lesions. In all of these populations the volume of these WMH increased markedly with advancing age. ICH, in contrast, is a relatively rare event. Indeed, even if the prevalence of ICH and asymptomatic microbleeds are combined, such a measurement is unlikely to exceed a small proportion of the elderly population. Leukoaraiosis is thus potentially both a more prevalent and more quantitative measure of the small vessel pathologies that underlie ICH.

### Table 1. Boston Criteria for Diagnosis of CAA-Related Hemorrhage#

1. **Definite CAA**
   - Full postmortem examination demonstrating:
     a. Lobar, cortical, or corticosubcortical hemorrhage
     b. Severe CAA with vasculopathy
     c. Absence of other diagnostic lesion

2. **Probable CAA with Supporting Pathology**
   - Clinical data and pathologic tissue (evacuated hematoma or cortical biopsy) demonstrating:
     a. Lobar, cortical, or corticosubcortical hemorrhage
     b. Some degree of CAA in specimen
     c. Absence of other diagnostic lesion

3. **Probable CAA**
   - Clinical data and magnetic resonance imaging or computerized tomography demonstrating:
     a. Multiple hemorrhages restricted to the lobar, cortical, corticosubcortical or cerebellar region
     b. Age ≥55
     c. Absence of other cause of ICH*

4. **Possible CAA**
   - Clinical data and magnetic resonance imaging or computerized tomography demonstrating:
     a. Single lobar, cortical, or corticosubcortical hemorrhage
     b. Age ≥55
     c. Absence of other cause of ICH*

*Modified from reference 13.

*Potential causes of ICH: excessive anticoagulation (INR >3.0); antecedent head trauma or ischemic stroke; CNS tumor, vascular malformation, or vasculitis; blood dyscrasia.
The epidemiological and presumed biological links between leukoaraiosis and ICH suggest that when the genetic determinants of leukoaraiosis are discovered, they will be excellent candidates for testing in ICH. Studies of leukoaraiosis demonstrate substantial heritability across multiple populations. Among 74 monozygotic and 71 dizygotic male American male twin pairs age 68 to 79 at time of MRI, heritability of WMH volume was 0.71 (95% CI 0.66 to 0.76), adjusted for age and head size.26 This figure is roughly equivalent to the heritability estimate of 0.67 (adjusted for sex, age, systolic blood pressure, and brain volume) obtained from an analysis of 210 hypertensive non-Hispanic white Americans from the GENOA-Rochester study,23 as well as to the estimate of 0.55 (adjusted for age, sex, and brain volume) in 1330 stroke-free and dementia-free individuals from the Framingham Heart Study.27 These data point to the relatively large contribution of inherited genetic variation to leukoaraiosis volume, a particularly remarkable finding given not only how common leukoaraiosis is among the elderly, but also its large list of associated risk factors, including hypertension, atherosclerosis, homocysteine, and smoking.28

**Identified Single-Gene Disorders**

Rare mutations in several genes are sufficient to cause ICH. For example, mutations in KRIT1 and malcavernin, the proteins encoded by the genes at the CCM1 and CCM2 loci, respectively, are responsible for the majority of familial cerebral cavernous malformations. Unlike these disorders, in which macroscopic vascular malformations develop, familial disorders of the cerebral small vessels such as cerebral amyloid angiopathy, CADASIL, and COL4A1-related cerebrovascular disease share many manifestations with the sporadic small vessel diseases that cause ICH.

**Familial Cerebral Amyloid Angiopathy**

CAA (Figure 1) occurs both as spontaneous ICH (Table 1) in the elderly and as a rare familial syndrome manifesting earlier in life. Although a few kindreds have been described with mutations in other genes (cystatin C, BRI, transthyretin) and accumulation of proteins other than β-amyloid peptide (Aβ) within vessels, most familial forms of CAA involve mutations within the gene for the β-amyloid precursor protein (APP). At histopathologic analysis of autopsy or biopsy tissue, CAA is identified by deposition in and destruction of the vessel walls of capillaries, arterioles and small- and medium-sized arteries of the cerebral cortex, leptomeninges, and cerebellum. The regional specificity of sporadic and APP-related CAA is such that vessels in other regions, including the deep hemispheric structures (eg, thalamus and basal ganglia) and brain stem, are generally spared. Vascular amyloid, like the amyloid plaques in Alzheimer disease (AD), is composed chiefly of Aβ, a 39- to 43-amino acid proteolytic fragment of APP. Involvement ranges from mild, where amyloid accumulates at the border of the media and adventitia of the vessel, to severe, in which there is total replacement of the smooth muscle media with amyloid accompanied by vasculopathic changes that can include microaneurysm formation, concentric splitting of the vessel wall, chronic inflammatory infiltrates, and fibrinoid necrosis.29

All APP mutations associated with CAA cluster within the Aβ-coding region of the gene (exons 16 and 17).30 In addition to point mutation within APP, duplication of the APP locus on chromosome 21 has also been identified in families with familial early-onset AD and CAA.31 A striking observation is that different kindreds with the same mutation may have dramatically different clinical presentations. For example, one kindred with the “Iowa” substitution of asparagine for aspartate at position 23 of Aβ, had recurrent ICH, while in another, individuals have dementia and leukoaraiosis, but no ICH, suggesting there are additional genetic factors that modify the strong effect of this mutation.32

**CADASIL**

Microbleeds, but not ICH, commonly occur in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), a monogenic disorder caused by mutations in Notch3. The cell-surface receptor encoded by Notch3 is expressed on the surface of vascular smooth-muscle cells, and appears to have a role in blood vessel development. Most of the CADASIL-associated mu-
tations alter the number of cysteine residues within the extracellular domain of the protein. Possession of a culprit mutation causes a familial syndrome of recurrent strokes, progressive cognitive impairment, psychiatric disturbances, migraines with aura, and occasionally ICH. The hallmark on neuroimaging is diffuse leukoaraiosis on MRI with particular involvement of bilateral anterior temporal lobes and external capsule, as well as presence of microbleeds.33

Although the degree to which the leukoaraiosis of CADASIL shares biological features with the much more common sporadic leukoaraiosis of the elderly remains to be determined, certain features of both phenomena highlight important opportunities for gene discovery. Susceptibility to both Notch3-related WMH and sporadic WMH appears to be under strong genetic influence. In families with CADASIL, there is a strong modifying influence of genetic factors distinct from the causative Notch3 mutation on leukoaraiosis volume.34 Because genetic factors appear to play a large role in interindividual variability in sporadic leukoaraiosis of the elderly, it is possible that both CADASIL and sporadic leukoaraiosis may have overlapping genetic architecture and hence overlapping biology. The discovery of these novel genes could therefore yield further insight into ICH biology.

COL4A1-Related Cerebrovascular Disease

The recent discovery that rare mutations in COL4A1 cause autosomal dominant syndromes including ICH has added another gene to the list of those with a confirmed role in vessel rupture and ICH. Type IV collagens (COL4A1 and COL4A2 are the most abundant) are basement membrane proteins expressed in all tissues, including the vasculature. When imaged with electron microscopy, basement membranes of mice harboring COL4A1 mutations are uneven, with inconsistent density and focal disruptions.35 Although pathological changes in the basement membrane occur in other tissues, the major site of hemorrhage is the brain. Consistent with its fundamental role in the strength of basement membranes, mutations in COL4A1 have been linked to a spectrum of cerebrovascular disease in humans, including perinatal ICH with consequent porencephaly, adult-onset ICH, microbleeds, lacunar strokes, and leukoaraiosis.35-37

Like APP in CAA and Notch3 in CADASIL, multiple rare mutations have been identified in COL4A1-related cerebrovascular disease. The majority of the COL4A1 protein forms a triple helical domain, consisting of Gly-X-Y residue repeats, which is essential for its association with other proteins in the formation of extracellular basement membranes. All but one of the mutations thus far identified in humans are missense mutations involving Gly residues, whereas the remaining mutation results in deletion of an exon within the triple helical domain.

The apparent role of COL4A1 in the cerebral vessels’ tolerance of minor head trauma is particularly distinctive, as surgical delivery of mouse pups bearing a mutated COL4A1 allele can prevent severe perinatal cerebral hemorrhage.35 In humans, impaired responses to even mild trauma may range from subclinical microbleeds tosubarachnoid hemorrhage or devastating ICH. Thus, recognition of COL4A1 familial syndromes may offer immediate benefit to affected individuals.

Sporadic ICH

Sporadic CAA

Reliably diagnosed noninvasively with imaging and clinical information alone (Table 1), sporadic CAA accounts for an estimated 2/3 of lobar ICH in the elderly. Multiple independent studies demonstrating a relationship between APOE ε2 and ε4 and risk of lobar ICH, recurrent lobar ICH, ICH related to CAA, and warfarin-related ICH in the lobar brain regions support a biological link between common variation in APOE and susceptibility to sporadic CAA in the elderly.14,30,38 In contrast to APP mutations, which have such a potent biological effect that their presence inevitably results in disease, possession of APOE ε2 or ε4 does not inevitably lead to CAA. In fact, approximately half of individuals with sporadic CAA lack either of these culprit alleles. Sporadic CAA also differs phenotypically from the familial forms described above in that it occurs at an older age and does not affect family members in an autosomal dominant pattern. Other clinical features, such as microbleeds, leukoaraiosis, cognitive decline, and of course, ICH, occur in both familial and spontaneous CAA.

Although at autopsy CAA is often found in association with AD, the clinical manifestations of CAA appear largely distinct from those of AD. The majority of patients with CAA-related ICH do not have preexisting symptoms of AD, whereas CAA-related ICH appears to occur in only a fraction of individuals with AD. These two conditions, in which Aβ is deposited in vessels to cause CAA, or the parenchyma to cause AD, share an established genetic risk factor in APOE. Possession of APOE ε4 predisposes both to AD and to CAA-related ICH. Paradoxically, APOE ε2, which increases risk for CAA-related ICH, is protective in AD. In CAA, ε4 is associated with increased amounts of vascular Aβ, similar to its association with increased plaque amyloid in AD, whereas ε2 is associated with pathological signs of increased vessel damage due to Aβ deposition, such as concentric vessel splitting and fibrinoid necrosis.

“Hypertensive” ICH

The results of the population-based Cincinnati/Northern Kentucky study point to a large role for genetic variation in the epidemiology of spontaneous ICH, both nonlobar as well as lobar. In analyses of population attributable risk (PAR), the risk factor accounting for the largest proportion of cases was hypertension (PAR 0.34 [95%CI 0.22 to 0.44]), followed by previous ischemic stroke, possession of APOE ε2 or ε4, frequent alcohol use, and the presence of a first-degree relative with ICH.12 Overall, 32% of the attributable risk remained unexplained by any detected risk factor, which, when combined with the 5% PAR estimate for possessing a family history of ICH in a first-degree relative and the 10% PAR for APOE, yields a rough estimate of 47% of ICH risk attributable to nonmodifiable risk factors.12 Even when nonlobar ICH was analyzed separately, hypertension accounted for only 54% of cases, and at least 34% of PAR was undefined or attributable to family history. Although the
The possibility exists that undiscovered genetic determinants of hypertension may indirectly affect risk of ICH, it is clear that even among patients with “hypertensive” ICH, there are likely to be DNA sequence variants unrelated to blood pressure that affect ICH risk.

### Candidate Gene Studies of Sporadic ICH

Candidate gene association studies test the hypothesis that common genetic variants (that is, polymorphisms in which the minor allele frequency exceeds $\approx 5\%$ in the population) are associated with the disease of interest. In contrast with the

<table>
<thead>
<tr>
<th>Gene</th>
<th>Variant</th>
<th>RR/OR (95% CI)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>APOE</td>
<td>$\epsilon2$</td>
<td>1.32 (1.01 to 1.74)*</td>
<td>Stroke. 2006;37:364–70.</td>
</tr>
<tr>
<td></td>
<td>$\epsilon4$</td>
<td>1.16 (0.93 to 1.44)*</td>
<td></td>
</tr>
<tr>
<td>$\beta$-1-tubulin (TUBB1)</td>
<td>Q43P</td>
<td>2.78 (1.16 to 6.63)</td>
<td>Haematologica. 2007;92:513–8.</td>
</tr>
<tr>
<td>CD-14</td>
<td>C/T</td>
<td>1.62 (1.17 to 2.29)</td>
<td>Circ. J. 2006;70:1240–8.</td>
</tr>
<tr>
<td>ESR1</td>
<td>(c.454–397) T/T</td>
<td>2.31 (1.16 to 4.60)</td>
<td>Cerbrovasc Dis. 2007;24:500–8.</td>
</tr>
<tr>
<td>Factor VII</td>
<td>(323) 10-bp In/Del</td>
<td>1.54 (1.03 to 2.72)</td>
<td>Blood. 2001;97:2979–82.</td>
</tr>
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<td>FBN1</td>
<td>T/C</td>
<td>1.47 (1.09 to 1.99)</td>
<td>Circ. J. 2006;70:1240–8.</td>
</tr>
<tr>
<td>LPC</td>
<td>G/A</td>
<td>1.43 (1.04 to 2.01)</td>
<td>Circ. J. 2006;70:1240–8.</td>
</tr>
<tr>
<td>PECAM1</td>
<td>C/G</td>
<td>1.49 (1.08 to 2.09)</td>
<td>Circ. J. 2006;70:1240–8.</td>
</tr>
<tr>
<td>VKORC1</td>
<td>(+2255) T/C</td>
<td>1.68 (1.29 to 2.20)</td>
<td>Circulation. 2006;113:1615–21.</td>
</tr>
<tr>
<td>Lobar ICH</td>
<td>APOE $\epsilon2$</td>
<td>1.8 (0.8 to 3.7)</td>
<td>Stroke. 2002;33:1190–6.</td>
</tr>
<tr>
<td></td>
<td>$\epsilon4$</td>
<td>1.7 (0.9 to 3.2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$\epsilon4$</td>
<td>3.7 (1.1 to 11.7)</td>
<td></td>
</tr>
<tr>
<td>Warfarin-related ICH</td>
<td>APOE $\epsilon2$</td>
<td>3.8 (1.0 to 14.6)</td>
<td>Neurology. 2000;55:947–51.</td>
</tr>
<tr>
<td>Sporadic CAA</td>
<td>APOE $\epsilon2$</td>
<td>(P=0.003)**</td>
<td>Ann Neurol. 1997;41(6):716–721.</td>
</tr>
<tr>
<td></td>
<td>$\epsilon4$</td>
<td>2.9 (1.1 to 7.4)</td>
<td>Ann Neurol. 1995;38(2):254–9.</td>
</tr>
<tr>
<td>NEP</td>
<td>GT repeat</td>
<td>(P=0.005)**</td>
<td>J Neurol. Neurosurg Psychiatry. 2003;74:749–51.</td>
</tr>
<tr>
<td>PS-1</td>
<td>1/2 polymorphism (intron 8)</td>
<td>(P=0.013)**</td>
<td>Stroke. 1997;28:2219–21.</td>
</tr>
<tr>
<td></td>
<td>APO (a)</td>
<td>TTTTA repeat (PNTR)</td>
<td>1.24 (0.91 to 1.68)</td>
</tr>
</tbody>
</table>

Candidate genes were selected from comprehensive review of the recent literature (PubMed, 1996–2007) of at least one study reporting positive and significant association with ICH. In cases of multiple positive reports concerning an identical polymorphism, only the initial positive study is cited. RR - relative risk, OR - odds ratio, CI - confidence interval (95%) *meta-analysis **no CI available for reference ***no estimates of RR/OR available for reference.
rare mutations in APP, Notch3 or COL4A1, these variants (APOE ε2 and ε4, for example,) presumably have a much smaller effect on disease susceptibility and are found in both affected and unaffected individuals. As in many other complex diseases, there have been numerous publications in which the frequencies of candidate gene polymorphisms have been compared between cases of ICH and unaffected controls. Predictably, investigators have focused on potential “weak links” suspected to precede, incite, or propagate development of ICH, such as genes implicated in vascular wall integrity, endothelial function, vessel wall reactivity, or coagulation (Table 2). With the exception of APOE and its role in CAA-related ICH, the results of such candidate gene studies have not been robustly replicated, presumably because the studies were too small to exclude a false-negative result or the probability value thresholds too generous to exclude a false-positive result.

An additional limitation to the candidate gene approach has been the small number of polymorphisms included in any given study. Thus, while recent evidence shows that there are many common genetic variants that do contribute to risk of common diseases, the validated disease-associated variants have often been outside of genes previously identified as “candidates,” and even outside of coding regions. Experience from successful genetic studies thus far demonstrates that the current state of scientific understanding of the relationship between genome sequence variation and disease biology may be too limited to allow accurate prediction of the genes or genetic regions likely to be involved with disease.

Whole Genome Association
Unbiased assessments of the contribution of genetic variation to disease susceptibility can generally take the form of linkage analysis, in which inheritance patterns of chromosomal segments are compared to inheritance patterns of disease, or association, in which the frequencies of alleles are compared between cases and controls. While family-based linkage analysis remains practical for genome-wide searches of disease variants, its greatest yield has been in rare, monogenic, or oligogenic diseases. However, even in the presence of substantial heritability, the success of linkage studies in complex diseases has been limited. This is likely because of the fact that many alleles contributing to risk of complex diseases have modest effect sizes (ie, relative risk <1.5), a situation where association designs have substantially increased power compared to linkage designs. Conversely, alleles that are common can have a substantial population effect without giving a strong linkage signal.

Comprehensive unbiased searches for common genetic variants that influence susceptibility to ICH are now feasible, made possible by extensive knowledge of common single nucleotide polymorphisms (SNPs) and haplotypes across the human genome, technologies for genome-wide genotyping, and development of the required population genetic and statistical analyses (Figure 2). Current technology allows the assessment of nearly all the 10 million common SNPs that exist within the human genome. Genome-wide association studies are therefore both hypothesis-driven (common SNPs contribute to disease) and hypothesis-generating (any findings that emerge must be confirmed in independent samples). Investigators using this approach make no assumptions about causality or location of the potentially disease-associated markers; thus, an unbiased and comprehensive study of genetic association can be completed.

Fundamental to the success of recent whole genome association studies has been the assembly of large numbers of
well-characterized patients by collaborating groups of investigators. The need for large sample sizes is explicitly illustrated by recent discoveries in diabetes, in which 4 novel gene variants were discovered in a combined sample of more than 32,000 individuals. The estimated odds ratios of the associated novel variants ranged from 1.12 to 1.20. The implications of these effect sizes are striking. For a case-control association study to detect these variants with 80% power, at a nominal probability value threshold of 0.05, it would require between 3,400 and 4,800 combined cases and controls. The required sample size would be substantially larger for genome-wide association studies in which probability value thresholds are set at between $10^{-6}$ and $10^{-8}$.

From Genetic Variation to ICH Prevention

Although development of novel biologically-based preventative therapies is a crucial long-term goal, the identification of genetic risk factors for ICH has the potential to provide immediate clinical impact by improving risk assessment. An important opportunity for application of such genetic screening is decision-making for chronic anticoagulation. Use of warfarin increases both the frequency and the severity of ICH. Thus, even at the annual rate of 0.2% to 0.6% observed in randomized trials of conventional-intensity anticoagulation, warfarin-related ICH exerts a major effect on clinical decision-making. Risk of ICH plays a similarly important role in other clinical situations where the risks and benefits of anticoagulation may be closely balanced, such as in dilated cardiomyopathy or after total hip replacement. It is therefore plausible that even relatively weak risk factors for ICH on warfarin might sway the balance in favor or against treatment. Improved prediction of an individual’s risk for ICH would allow the subgroup of patients at highest risk to be spared antithrombotic therapy for all but the most compelling indications. It might also offer an opportunity to identify patients at particularly low risk for ICH, who could be safely treated even when the expected benefit is modest. Thus, the discovery of genetic variants that alter individual response to anticoagulation may provide immediate practical benefits to clinicians advising patients on the decision to start anticoagulation.

Major progress has been achieved in identifying common genetic variants governing warfarin metabolism and thereby determining an individual’s dose requirement for this agent. Common variants in VKORC1 (Figure 2) and CYP2C9 contribute to approximately 50% of inherited interindividual differences in warfarin maintenance dose. Clinical trials are underway to determine whether screening for these variants at the time of warfarin initiation reduces the risk of supratherapeutic anticoagulation and hemorrhagic complications. It is important to note, however, that fully 67% of warfarin-related ICH occur in the setting of a nonsupratherapeutic international normalized ratio. Optimizing dose is therefore unlikely to eliminate the risk of warfarin-related ICH, which is expected to arise from the same underlying vascular pathologies responsible for nonwarfarin ICH.

Conclusion

The devastating injury caused by ICH highlights the pressing need for effective strategies for prevention. Limited understanding of ICH pathogenesis remains a formidable barrier to developing these strategies. The recent success of whole genome association methods in identifying novel genetic risk factors for common diseases highlights the opportunity of applying this technique in ICH, for which a substantial proportion of risk may be genetic. Large-scale multi-center collaborative efforts led by groups such as the International Stroke Genetics Consortium (www.strokegenetics.org) are already assembling the requisite large sample sizes for whole genome ICH studies. If lessons from other diseases apply to ICH, the results of these studies are likely to redefine our understanding of the role of genetic variation in ICH and identify novel lines of research that will benefit generations to come.

Sources of Funding

This work was supported by the National Stroke Association, National Institutes of Neurological Disorders and Stroke (K23 NS42695, R01 NS04217), and the Deane Institute for Integrative Study of Atrial Fibrillation and Stroke.

Disclosures

None.

References

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Stroke. 2008;39:2166-2173; originally published online May 8, 2008;
doi: 10.1161/STROKEAHA.107.501650
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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