Exploiting Common Genetic Variation to Make Anticoagulation Safer

The Genes for Cerebral Hemorrhage on Anticoagulation (GOCHA) Collaborative Group*

Within the past 2 years, genomewide association studies have identified nearly 200 new chromosomal regions at which variation in DNA sequence influences risk of common human diseases as well as traits such as height and eye color. The success of the genomewide association study method, particularly given the limited success of previous approaches to find these “culprit” loci, has heightened optimism for the development of so-called personalized medicine. Perhaps more than any area, the field of anticoagulation and making it safer has raised hopes for using genetic information to improve individual patient outcomes.

Discoveries, before the genomewide association study era, that common DNA sequence variants in CYP2C9 and VKORC1 play a substantial role in determining an individual’s warfarin dose requirement, led to an update of the US Food and Drug Administration label for Coumadin/warfarin suggesting that clinicians consider genetic testing before initiating warfarin.1 Although these discoveries represent a crucial first step toward the application of genetic information to make anticoagulation safer, it is clear that identifying an individual patient’s risk for hemorrhage on anticoagulation or thromboembolism in atrial fibrillation (and other diseases) will require many more genetic discoveries.

What Causes Hemorrhage in Patients Receiving Anticoagulation?

Broadly speaking, the risk of bleeding on anticoagulation can be broken down into 2 general mechanisms: those related to the effects of anticoagulation itself on coagulation factors and clot formation and those related to specific conditions that increase risk of bleeding regardless of whether anticoagulation is present. Warfarin metabolism and sensitivity genes such as CYP2C9 and VKORC1 are likely to increase bleeding through the former mechanism. Randomized clinical trials in patients with deep vein thrombosis, artificial heart valves, ischemic stroke, atrial fibrillation, or antiphospholipid antibody syndrome with previous thromboembolism have consistently demonstrated an increased risk of bleeding among patients in whom the target intensity of anticoagulation is higher.2 Thus, individuals with genetic variants that result in heightened sensitivity to low doses of warfarin, and are therefore presumably at greater risk for supratherapeutic anticoagulation, are likely to be at increased risk of bleeding on warfarin. Indeed, variants in these 2 genes appear to influence risk of bleeding during the initiation phase of warfarin, when risk of “overshoot” is highest.3–8 Although the increased risk of bleeding attributable to VKORC1 appears to be limited to the initiation phase of anticoagulant therapy, CYP2C9 sequence variants may be associated with a continued risk of hemorrhage during the maintenance phase of anticoagulant therapy.5,9–11 Clinical trials are currently being organized to determine whether testing for polymorphisms in CYP2C9 and VKORC1 followed by genotype-guided warfarin dose selection will result in fewer warfarin-related hemorrhages and improved patient outcomes.

Although identifying those individuals at increased risk for all types of warfarin-related hemorrhage is clearly important, the health effects of these hemorrhages can vary enormously depending on the site and organ system involved. Minor hemorrhages often result in little more than a brief temporary cessation of anticoagulation. Major hemorrhages, on the other hand, are life-threatening and can lead to death or lasting disability. Among major hemorrhages, intracranial hemorrhages are the only bleeding complications that regularly produce deficits that exceed those produced by the ischemic strokes anticoagulant therapy is designed to prevent.12,13 Furthermore, the overwhelming majority of fatal or disabling hemorrhagic events on anticoagulation are due to nontraumatic intracranial hemorrhage with few, if any, persisting deficits arising from major extracranial bleeding.14 Clearly, if genetic information could be harnessed to prevent intracranial hemorrhages, a substantial alteration in the risk–benefit balance of anticoagulation could be achieved.

Warfarin Sensitivity Genes and Risk of Intracranial Hemorrhage

Several observations suggest that screening for warfarin metabolism and sensitivity genes such as CYP2C9 and...
VKORC1 is unlikely to identify those individuals at high risk for warfarin-related intracranial hemorrhage. Such hemorrhages (approximately one third are subdural in location, two thirds intracerebral), although generally rare in the setting of clinical trials, appear to increase markedly in frequency with advancing age. Among 13,559 patients with nonvalvular atrial fibrillation followed in the Kaiser Permanente Health System, risk of intracranial hemorrhage, both related and unrelated to anticoagulation, doubled among those ≥80 years of age (Figure). Furthermore, fully two thirds of these hemorrhages occur when the intensity of anticoagulation is in the therapeutic, not supratherapeutic, range. Finally, data from the Genes for Cerebral Hemorrhage on Anticoagulation (GOCHA) Collaborative (Table), in which consecutive subjects with intracerebral hemorrhage are enrolled through emergency departments at participating centers, demonstrates that >70% of these warfarin-related hemorrhages occur in patients who have been taking warfarin 1 year or longer, and >90% occur after 3 months of therapy, suggesting that any intervention to adjust initial warfarin dose based on genetic information is unlikely to prevent the vast majority of intracerebral hemorrhages.

### Genes for Age-Related Brain Conditions and Risk for Warfarin-Related Intracerebral Hemorrhage

Taken together, these data suggest that risk of warfarin-related intracranial hemorrhage is strongly related to age-associated factors, particular those involved in brain aging. Established links among severity of leukoaraiosis, cerebral amyloid angiopathy, and risk for warfarin-related intracerebral hemorrhage (ICH) highlight 2 conditions for which genetic discoveries could indeed yield novel testing approaches to stratify patients for risk of ICH on warfarin. Although testing for APOE e2 or e4, polymorphisms known to influence risk of cerebral amyloid angiopathy do not appear to have a role in screening patients before initiating anticoagulation, it is clear that there are additional genetic risk factors for cerebral amyloid angiopathy yet to be discovered.

There is, as of yet, no established panel of genetic variants that can aid in making the decision whether to offer anticoagulation to patients with, for example, atrial fibrillation. Nonetheless, clinicians can expect to hear of novel discoveries that could change this situation. The GOCHA collaborative, working within the loosely defined International Stroke Genetics Consortium (www.strokegenetics.org), has initiated the largest genomewide association study for intracerebral hemorrhage ever undertaken. Having learned the lessons of successful genomewide association studies in multiple common diseases, GOCHA investigators are assembling the thousands of cases necessary to perform a well-powered search for those common genetic variants that alter risk of ICH and warfarin-related ICH and could someday be combined with CYP2C9, VKORC1, and APOE to build an individualized screen for patients about to start anticoagulation.

### Appendix

#### The Genes for Cerebral Hemorrhage on Anticoagulation (GOCHA) Collaborative Group

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**Table. Warfarin-Related Intracerebral Hemorrhage**

<table>
<thead>
<tr>
<th>ICH</th>
<th>Control Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>237</td>
</tr>
<tr>
<td></td>
<td>234</td>
</tr>
<tr>
<td>Age, mean±SD</td>
<td>75±10</td>
</tr>
<tr>
<td>Female, %</td>
<td>47</td>
</tr>
<tr>
<td>Hypertension</td>
<td>82</td>
</tr>
<tr>
<td>ICH location, %</td>
<td>44</td>
</tr>
<tr>
<td>Lobar</td>
<td>40</td>
</tr>
<tr>
<td>Deep</td>
<td>16</td>
</tr>
<tr>
<td>Infra-tentorial</td>
<td>16</td>
</tr>
</tbody>
</table>

Duration of warfarin therapy at time of ICH, %

<table>
<thead>
<tr>
<th></th>
<th>ICH</th>
<th>Control Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤3 months</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>3 months to 1 year</td>
<td>21</td>
<td>42</td>
</tr>
<tr>
<td>≥1 year</td>
<td>71</td>
<td>55</td>
</tr>
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</table>

International normalized ratio at time of ICH, median (range)

<table>
<thead>
<tr>
<th></th>
<th>ICH</th>
<th>Control Subjects</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>2.8 (1.4–20)</td>
<td>2.3 (1.3–10)</td>
</tr>
</tbody>
</table>

*Patients assembled thus far by the GOCHA Collaborative (see Appendix for participating investigators).*

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Disclosures

None.

References


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