The field of stroke genetics continues to make substantive advances. Large-scale partnerships have led to meta-analyses in ischemic and hemorrhagic stroke, which are yielding reproducible genetic risk factors. Most ischemic stroke risk factors seem to be specific to type, for example, large-vessel stroke. Progress is being made in understanding the pathophysiology of single-gene stroke syndromes. Genetics is also being used to potentially advance pharmacotherapeutics.

In the genome-wide association study (GWAS) era, several themes are emerging. First, heritability seems to vary by ischemic stroke subtype. Using complex trait analysis on a GWAS data set of >3000 individuals, Bevan et al found a 37.9% heritability for ischemic stroke overall, but the heritability varied widely by subtype from a high of 40.3% for large-vessel stroke to a low of 16.1% for small-vessel stroke. Second, genetic risk factors seem to be subtype-selective. Third, GWAS have yielded more reliable discoveries than candidate gene studies uninforming by GWAS. In the previously cited study by Bevan, no candidate gene previously reported as associated with ischemic stroke could be replicated using GWAS data, but 3 loci from related cardiovascular GWAS were significant even after rigorous correction for multiple comparisons.

In the area of ischemic stroke genetics, a partnership between the International Stroke Genetics Consortium and the Wellcome Trust Case Control Consortium 2, which included GWAS data from 5859 cases and 6281 controls, replicated associations of PITX2 and ZFHX3 with cardioembolic stroke and of a locus 9p21 with large-vessel stroke. The partnership also led to the discovery of an association between large-vessel stroke and histone deacetylase 9 (HDAC9). The subsequent METASTROKE collaboration, which performed a meta-analysis of data from 12389 ischemic stroke cases and 62004 controls of European descent, confirmed genome-wide significant associations of PITX2 and ZFHX3 with cardioembolic stroke and HDAC9 with large-vessel ischemic stroke. The associations remained significant when the meta-analysis was repeated, excluding populations that contributed to the original discoveries. In addition, single-nucleotide polymorphisms (SNPs) in an intergenic region of the 6p21.1 locus were found to be associated with large artery atherosclerotic stroke. There are now several loci associated with large-vessel stroke discovered by GWAS (Table).

Using a 2-SNP risk score, investigators found an association between the apolipoprotein A (LPA) gene and large-vessel ischemic stroke; however, no such association was found for small-vessel stroke or venous thromboembolism, suggesting that LPA variation and the consequent rise in blood lipoprotein A levels act through an atherosclerotic rather than a thrombotic mechanism. Testing loci from related cardiovascular phenotypes, investigators found an association of PHACTR1 with large-vessel stroke.

None of the studies identifying risk factors for large-vessel ischemic stroke included a control group of subjects with known asymptomatic carotid stenosis. From a clinical perspective, it would be interesting to know whether a genetic risk score could be created to stage risk of future ischemic stroke in patients with asymptomatic stenosis. Such a score, either in isolation or, more likely, in combination with clinical and radiographic variables could be used to select the most appropriate patients for revascularization.

Genetics has provided additional supporting evidence for sustained elevation in arterial blood pressure causing deep intracerebral hemorrhage (ICH). In 2011, the burden of risk alleles for elevated blood pressure had been shown to associate with stroke, among other cardiovascular outcomes. However, this study did not specifically assess the phenotypes of lobar and deep ICH. This year, a meta-analysis reported that blood pressure–based unweighted genetic risk score was associated with risk of deep, but not lobar, ICH. The genetic risk score involved 38 SNPs that were not in high linkage disequilibrium. Interestingly, the association with deep ICH was predominantly observed in patients not diagnosed with hypertension before stroke, suggesting misclassification.

Skeptics of genetics often question the value to public health of finding weak associations between gene variants and disease. A balanced assessment would suggest that the therapeutic gains have thus far been modest. However, genetics can be leveraged to guide drug development. A recent example that is relevant to stroke prevention is a Mendelian randomization study of the interleukin (IL)-6 receptor gene. In this study, investigators were able to demonstrate that a surrogate SNP in high linkage disequilibrium with a nonsynonymous SNP in the IL6R gene was associated with increased circulating IL-6. They also
showed that the same SNP was associated with reduced risk of coronary artery disease events. Because circulating IL-6 rises with pharmacological blockade of the IL-6 receptor with the rheumatoid arthritis drug tocilizumab, the study suggests that the drug might reduce coronary artery disease events. Clearly, this theory would need to be tested with properly controlled randomized. Had IL6R SNP associated with rising circulating IL-6 been associated with increased coronary artery disease events, enthusiasm to test the drug for a new antiatherosclerosis indication would have been dampened.

Mutations in the type 4 collagen A1 gene (COL4A1) can cause a small-vessel disease of the brain, which manifests with porencephaly, ICH, nephropathy, aneurysms, cramps, and diffuse white matter disease. In some of these patients, white matter hypersignal can be minimal and sometimes undetectable. Most mutations reported to date have been missense mutations in a conserved triple helix domain of the protein, thought to cause disease through a dominant-negative mechanism. However, 2 families with mutations leading to premature termination of message provide evidence that haploinsufficiency can cause disease. A case-control sequencing study of patients with sporadic ICH found rare nonsynonymous mutations in 2 of 96 patients. This suggests that the protein and its variation have broad importance to the pathophysiology of ICH. Mutations of the COL4A2 have now been reported to cause not only familial porencephaly but also small-vessel disease and hemorrhagic stroke in human patients. Novel molecular genetics tools also recently led to the identification of several genes involved in other stroke conditions, such as moyamoya disease, and monogenic moyamoya syndromes, opening avenues to understanding the mysteries of their pathophysiology.

Finally, it is helpful to inform patients that conventional modifiable risk factors remain relevant, despite an unfavorable genetic background. The prospective, community-based Japan Collaborative Cohort Study, which involved >110 000 individuals, suggested that a parental history of stroke imparted a population-attributable fraction of risk of stroke death of 5.4% in men and 4.3% in women. Although significant, these numbers pale in comparison with the population-attributable fraction for stroke mortality of 45.0% in men and 43.4% in women for unhealthy lifestyle behaviors. Most importantly, the inverse relationship between healthy lifestyle behaviors and stroke mortality was the same, regardless of parental history of stroke. So, extinguish that cigarette, get off of the couch, and exercise; there is no sense in blaming your parents.

### Table. Genes and Loci Associated With Large-vessel Ischemic Stroke

<table>
<thead>
<tr>
<th>Gene or Locus</th>
<th>SNP</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>9p21.3</td>
<td>rs2383207</td>
<td>1.17</td>
</tr>
<tr>
<td>HDAC9</td>
<td>rs11884041</td>
<td>1.42</td>
</tr>
<tr>
<td>6p21.1</td>
<td>rs556621</td>
<td>1.21</td>
</tr>
<tr>
<td>LPA</td>
<td>rs10455872 and rs3796220, combined in a risk score</td>
<td>1.27</td>
</tr>
<tr>
<td>PHACTR1</td>
<td>rs12526453</td>
<td>0.94*</td>
</tr>
</tbody>
</table>

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**Disclosures**

None.

**References**

ゲノムワイド関連研究（GWAS）時代になり、いくつかの新しいテーマが浮かび上がっている。第一に、遺伝性は虚血性脳卒中の病型により異なるというところである。Bevanら1によれば、虚血性脳卒中全体の37.9%に遺伝性がみられたが、大血管性脳卒中では40.3%と高かったのに対して小血管性脳卒中では16.1%と低かったという。第二に、遺伝的危険因子には病型選択性があるということである。第三に、GWASは候補遺伝子研究よりも信頼度の高い発見ができるということである。

虚血性脳卒中の遺伝学の分野では、International Stroke Genetics ConsortiumとWellcome Trust Case Control Consortium 2の共同研究により、5,859症例と6,281対照からGWASデータが収集され、PITX2およびZFHX3と心原性脳卒中との関連、およびlocus 9p21と大血管性脳卒中との関連が明らかにされた。また、この共同研究により、大血管性脳卒中とhistone deacetylase 9（HDAC9）との関連も発見された。これらの関連は、METASTROKE共同研究が12,389例の虚血性脳卒中患者と62,004例の欧州人種の対照から得られたデータのメタ解析により確認された2。

アポリポ蛋白A（LPA）遺伝子と大血管性脳卒中の関連が発見されたが、そのような関連は小血管性脳卒中や原発性血栓症ではないことが示唆される3。4型コラーゲンA1遺伝子（COL4A1）は脳小血管病の原因となり、脳卒中、脳出血、脳腫瘍、動脈瘤、小血管性脳卒中、出血性脳卒中で高頻度に発症することが報告された4。

新しい分子遺伝学の手法は、もやもや病や単一遺伝子病の症候群のような他の脳卒中病態も対象とするようになり、これらの病態生理の謎を理解する道を開くとしている。

異なった遺伝的背景があるにもかかわらず是正する一般的な危険因子を患者に知らせることが有用である。110,000人以上を対象とした前向きな地域ベースの日本共同コホート研究により、脳卒中の家族歴は男性の5.4%と女性の4.3%の脳卒中死亡予防が判明した5。しかしながら、これらの有意な数値は、不健康な生活習慣が男性の43.5%と女性の43.4%で脳卒中死亡の原因になっているという比率に比べると印象が薄くなってしまい。最も重要なことは、脳卒中の家族歴が無くても、健康な生活習慣と脳卒中死亡率は同様に逆相関することである。だから、たばこの止め、車から降り、運動すべきである。親を非難するのは意味がない。

（文責：内山真一郎）

代表的な引用文献