The Stroke Genetics Network
Living Up to Its Potential

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Unraveling the genetics of a heterogeneous condition such as stroke is challenging. Even the recognized subtypes of ischemic stroke have multiple underlying causes (the subtypes have subtypes). For example, cardioembolic stroke can be caused by atrial fibrillation, cardiomyopathies, congestive heart failure, and endocarditis (to name just a few entities). Should investigators focus on the genetic underpinnings of cardioembolic stroke as a single entity or focus more narrowly on each particular underlying cause? In comparison with other clinical phenotypes such as coronary artery disease, for which dozens of novel loci have been discovered, genome-wide association studies on stroke have been relatively uninformative, at least, in part, because of small sample sizes (only a few thousand genotyped cases) and because of the heterogeneity of causes for subtypes of ischemic stroke that have been bundled together as a single entity.

With the recognition of the need to consider stroke subtypes, progress has been made in more recent genome-wide association studies. Investigators from Iceland found that variants on chromosome 4q25, previously associated with atrial fibrillation, were also associated with cardioembolic stroke. Several loci have been found to be associated with large-vessel ischemic stroke, including the locus on chromosome 9p21.

In this issue of *Stroke*, Meschia et al describe plans for expansion of the US National Institute of Neurological Disorders and Stroke–funded Stroke Genetics Network and enhanced TransAtlantic collaboration with European centers. The Network will now comprise 24 research centers in the United States and Europe altogether. The Network plans to genotype an additional 10,296 carefully adjudicated stroke cases, raising the number of genotyped stroke patients to 14,549. All cases will be genotyped on the same array platform. Publicly available cohorts will provide the control population. Along with the increase in the power of genetic studies afforded by the increased sample size, a priority is to rigorously assign ischemic stroke cases to subtypes whose definitions are standardized across the Network. The Network is also assembling all available brain MR images into a central platform to facilitate future studies of imaging phenotypes.

What are the greatest opportunities for this expanded Network? The Network will be well positioned to perform the next wave of genome-wide association studies on ischemic stroke and its subtypes, as well as clinical and imaging phenotypes that may emerge as being of high interest to stroke researchers. The Network also provides a kernel to nucleate even larger consortia that will undoubtedly be needed to scale up stroke genetics studies to the level already reached with other clinical phenotypes for which more than a hundred thousand individuals have been studied. With an eye toward the future, the Network is poised to take advantage of next-generation sequencing technologies—exome sequencing and eventually whole-genome sequencing—as they become cheaper and practical to apply to thousands of individuals. Finally, and perhaps most importantly, the Network is committed to making its data available to the scientific community via database of Genotypes and Phenotypes, which will ensure that stroke genetics research will live up to its fullest potential.

Disclosures
Dr Chaturvedi is a consultant to Abbott Vascular, WL Gore, Boehringer-Ingelheim, and the BMS/Pfizer partnership. The other author reports no conflicts.

References

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