There have been advances in understanding the molecular underpinnings of risk and response to stroke hailing from genetic research. Traditional linkage studies were limited to identifying genetic mutations, representing small fractions of human disease burden. Yet with large-scale genotyping, RNA expression studies and microRNA analyses, modern genetic research has opened the possibility of understanding the greater complexity of variation.

Saugstad writes of the nascent understanding of microRNAs in ischemic brain injury. MicroRNAs regulate messenger RNA (mRNA), the template for all proteins. mRNA levels are under complex regulation. One microRNA can target several mRNAs, and 1 mRNA can be the target of several microRNAs. A normal gene that is dysregulated may lead to diseased or increased risk, just as mutation of a gene may. Adding to the complexity of studying this system is that commercial assays vary in their output, suggesting that more work is needed to optimize and standardize the assays. Despite these complexities, studies suggest that ischemia changes the microRNA environment. Unsurprisingly, on the road to cell death, changes occur in microRNA levels. The crucial question is whether microRNA changes perpetuate or accentuate ischemic injury, or whether the changes are merely a consequence of injury without pathological role. The answer to the cause or consequence question will ultimately determine whether this line of inquiry will translate into effective treatments.

Sharp and Jickling provide an update on research examining mRNA content produced by genes. Otherwise, normal genes that are upregulated or downregulated may affect disease risk or response to injury. Unknown stroke may represent as much as 40% of ischemic stroke subtypes. Yet, by comparing unknown to known stroke subtypes, Sharp et al suggest that the gene expression profiles of unknown stroke most often seem most like that of cardioembolic stroke. Expression profiling might also help differentiate true transient ischemic attack from nonischemic events.

Genome-wide association studies have yielded at least 8 loci for intracranial aneurysms. Foroud et al performed whole-exome sequencing in a handful of highly selected multiplex families (50 individuals) with intracranial aneurysms. Exome sequencing examines all exons within the human genome and can evaluate not only the risk of a single variation but also the burden of variants within a gene. After filtering, 96 candidate genes were identified and are now being sequenced in 400 additional familial cases. Reporting of the results of this work is eagerly awaited.

Disclosures

None.

References


Keywords: ischemia  messenger RNA  microRNA
Genetics of Stroke: Impact and Limitations of Evolving Technology: Introduction
Daniel Woo and James F. Meschia

Stroke. 2013;44:S16
doi: 10.1161/STROKEAHA.112.680041
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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