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A major challenge in genetic association studies is the choice of appropriate candidate genes based on plausible biologically driven hypotheses. The current study by Voetsch and coworkers1 in this issue of Stroke illustrates how the integration of traditional epidemiological approaches, such as case-control studies, and experimental data from the laboratory can be used to assess the role of genetic factors in disease causation. Plasma glutathione peroxidase (GPx-3) is a selenocysteine-containing protein with antioxidant and antithrombotic properties. A familial deficiency in GPx-3 activity has been reported in children with idiopathic stroke, suggesting that polymorphisms in the plasma GPx-3 promoter gene may modify stroke risk.

The authors previously identified a novel, functional transcription start site in the GPx-3 gene with a promoter regulated by hypoxia2, prompting further analyses of this candidate gene. In the present study, the authors postulate that by influencing GPx-3 transcription and plasma GPx-3 enzyme levels, distinct variants in the GPx-3 gene may be influencing the pathogenesis of nonatherogenic stroke.

To test the hypothesis that GPx-3 promoter polymorphisms contribute to nonatherosclerotic stroke risk in children and young adults, the effect of GPx-3 polymorphisms on stroke risk was comprehensively assessed in 2 independent study populations. In the initial cohort, comprised of 123 young adult stroke patients and 123 healthy control subjects matched by age, gender and ethnicity, the frequencies of adult stroke patients and 123 healthy control subjects matched populations. In the initial cohort, comprised of 123 young adult stroke patients and 123 healthy control subjects matched by age, gender and ethnicity, the frequencies of adult stroke patients and 123 healthy control subjects matched populations. In the initial cohort, comprised of 123 young adult stroke patients and 123 healthy control subjects matched by age, gender and ethnicity, the frequencies of adult stroke patients and 123 healthy control subjects matched populations. In the initial cohort, comprised of 123 young adult stroke patients and 123 healthy control subjects matched by age, gender and ethnicity, the frequencies of adult stroke patients and 123 healthy control subjects matched populations.

Identical results: an increased prevalence of the H2 haplotype in affected children (13.4%) compared with unaffected controls (7.9%), with an OR of 2.13.

Recognizing that the identification of the H2 risk haplotype does not in itself provide insights into the physiological mechanisms affected by the genetic variant, the authors elegantly tested the functional significance of these results with gene reporter assays. Under hypoxic conditions, the GPx-3 promoter H2 haplotype was shown to reduce GPx-3 gene transcription, thereby attenuating the protective effect of this antioxidant enzyme.

As with most candidate gene association studies, this study is potentially limited by inadequate sample size, misclassification of stroke phenotypes and population stratification attributable to genetic admixture. However, confirmation of their findings in an independent cohort, together with the additional mechanistic studies performed to show the biological relevance of the candidate gene, strengthen the authors‘ conclusion that the GPx-3 promoter gene is causally associated with stroke in children and young adults.

The next steps will continue to involve the integration of “bench” and “bedside” research. Additional experimental data from the laboratory are needed to understand the pathways regulated by the GPx-3 gene and how these are involved in stroke. At the same time, epidemiological and patient-centered research is also needed to determine the predictive value of this newly identified genetic risk factor for nonatherogenic stroke. Only through interdisciplinary approaches, of the type this study so well illustrates, will the gaps between bench and bedside be successfully bridged.

Disclosures

None.

References


Key Words: pediatric stroke ■ risk factors ■ stroke ■ stroke in children ■ stroke in young adults ■ genetic modifiers
From Bench to Bedside and Back: The Value of Candidate Gene Association Studies in Translational Research
Carolyn Hoppe

Stroke. 2007;38:6; originally published online November 22, 2006; doi: 10.1161/01.STR.0000252121.56643.4a
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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