Letters to the Editor

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GPx-3 Gene Promoter Variation and the Risk of Arterial Ischemic Stroke

To the Editor:

The recently published association of a particular promoter variant of the GPx-3 (plasma glutathione peroxidase) gene with increased risk for arterial ischemic stroke in this journal1 was the result of a long-duration research project. A set of linked polymorphisms in the promoter of the GPx-3 gene was described previously, and it was shown that carriers of a particular haplotype (H2) had a 2-fold increase in risk of ischemic stroke compared with noncarriers.2 The authors had, furthermore, analyzed the regulation of GPx-3 expression in a cultured cell system, identified a novel transcription start site and demonstrated that hypoxia was a strong transcriptional regulator of GPx-3 expression.3 The interest of the research group in GPx-3 was raised by their initial discovery of decreased plasma glutathione peroxidase activity in familial childhood stroke.4

The novel investigations extended these findings in several ways: 8 single nucleotide polymorphisms (SNP) were identified in the 5'end flanking region as well as 8 promoter haplotypes. The association of the H2 haplotype with an increased risk of arterial ischemic stroke (AIS) was demonstrated in an enlarged series of 123 young adults, compared with 123 control subjects. The association was confirmed in a second independent population with childhood stroke (82 patients and 82 control subjects).1

These promising results lead us to analyze the GPx-3 promoter in 2 populations of young stroke patients (<50 years) in order to confirm these results in a replica study. The H2 haplotype was tagged with the −65 T/C SNP as well as with the −927 T/C variant (the combination of −65C and −927C identifies the H2 haplotype as well as the very rare H7 and H8 haplotypes). In contrast to the findings of Voetsch et al, our observations (Table) did not show an elevated prevalence of H2 among patients.

Further subclassification of the patients according to stroke etiology yielded haplotype frequencies (H2+H7+H8) of 12.1% (Heidelberg) and 10.4% (Brescia) for large vessel atherosclerosis and 12.5% and 9.8% for cardioembolism. Our data revealed higher prevalences of H2 (H7+H8) haplotypes in the control samples from both populations, as compared with the adult and childhood controls studied by Voetsch et al. Our findings are in line with other estimated allele frequencies in healthy populations. Some of the GPx-3 promoter SNPs were also studied in the HapMap project. The T allele of rs8177409 (−302A/T) was found in 11% of 156 CEPH parent chromosomes and in 16% of 180 chromosomes from the National Institutes of Health Polymorphism Discovery Resource (NIHPDR) 90 individual screening subset. These frequencies (albeit varying between populations and based on rather small samples) are in good agreement with the observed frequencies in the Heidelberg and Brescia control populations. HapMap estimated allele frequencies of rs6888961 (−284T/A) and rs8177412 (−65T/C) similarly do not suggest heterogeneity between the HapMap samples and the control samples from Heidelberg and Brescia.

Our analysis of young stroke patients from 2 further populations did not confirm the finding of Voetsch et al that patients carry more often than healthy control subjects the GPx-3 promoter haplotype H2. Because of ethnic differences and differences in age at first stroke the populations are not perfectly comparable. Sample error might be a further reason for the discrepancy between our data and the published findings. Further studies of the GPx-3 promoter in larger populations of young stroke patients are warranted.

Disclosures

None.

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<table>
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<th>Analysis of GPx-3 Promoter Haplotypes in Young Stroke Patients</th>
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<tr>
<td>Heidelberg</td>
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<td>Controls, n = 203</td>
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<td>H2 + H7 + H8</td>
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(Stroke. 2007;38:e23.)
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Stroke is available at http://www.strokeaha.org

DOI: 10.1161/STROKEAHA.106.479444
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Stroke. 2007;38:e23; originally published online April 26, 2007;
doi: 10.1161/STR0KEAHA.106.479444
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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World Wide Web at:
http://stroke.ahajournals.org/content/38/6/e23