Role of Promoter Polymorphisms in the Plasma Glutathione Peroxidase (GPx-3) Gene as a Risk Factor for Cerebral Venous Thrombosis

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Background and Purpose—Plasma glutathione peroxidase (GPx-3) is a major antioxidant enzyme in plasma and the extracellular space that scavenges reactive oxygen species produced during normal metabolism or after oxidative insult. A deficiency of this enzyme increases extracellular oxidant stress, promotes platelet activation, and may promote oxidative posttranslational modification of fibrinogen. We recently identified a haplotype (H2) in the GPx-3 gene promoter that increases the risk of arterial ischemic stroke among children and young adults.

Methods—The aim of this study is to identify possible relationships between promoter haplotypes in the GPx-3 gene and cerebral venous thrombosis (CVT). We studied the GPx-3 gene promoter from 23 patients with CVT and 123 young controls (18 to 45 years) by single-stranded conformational polymorphism and sequencing analysis.

Results—Over half of CVT patients (52.1%) were heterozygous (H1H2) or homozygous (H2H2) carriers of the H2 haplotype compared with 12.2% of controls, yielding a more than 10-fold independent increase in the risk of CVT (OR 10.7; 95% CI, 2.70 to 42.36; P = 0.0001). Among women, the interaction of the H2 haplotype with hormonal risk factors increased the OR of CVT to almost 70 (P < 0.0001).

Conclusions—These findings show that a novel GPx-3 promoter haplotype is a strong, independent risk factor for CVT. As we have previously shown that this haplotype is associated with a reduction in transcriptional activity, which compromises antioxidant activity and antithrombotic benefits of the enzyme, these results suggest that a deficiency of GPx-3 leads to a cerebral venous thrombophilic state. (Stroke. 2008;39:303-307.)

Key Words: cerebral venous thrombosis ■ genetic risk factors ■ glutathione peroxidase ■ oxidant stress ■ thromboembolic disease

Cerebral venous thrombosis (CVT) is an uncommon, yet potentially devastating, condition with a peak incidence in the third decade of life. It is characterized by a wide spectrum of etiologies and predisposing factors, in particular, local infections, autoimmune diseases, and acquired or inherited hypercoagulable states.1 Factor V Leiden and the prothrombin G20210A mutation are the most frequent genetic risk factors involved in CVT, being reported in up to one-fourth of cases.2-5 Among women, the use of oral contraceptives, pregnancy and the postpartum period, and hyperhomocysteinemia6,7 are further relevant predisposing factors for CVT. Despite the wide range of known causes, the etiology of CVT remains undetermined in approximately 15% to 35% of cases.8

Plasma glutathione peroxidase (GPx-3), a member of the selenocysteine-containing GPx family, is a major antioxidant enzyme in plasma that scavenges reactive oxygen species (ROS) arising from normal metabolism or after oxidative insult, thereby maintaining the vasorelaxant and antithrombotic effects of nitric oxide (NO) in the vasculature.9-11 In addition, this decrease in oxidant stress protects against posttranslational modifications of fibrinogen by ROS and NO-derived oxidants that promote thrombosis.12,13 Freedman and colleagues demonstrated that GPx-3 deficiency impairs bioavailable NO and leads to platelet hyperreactivity and an increased risk of thrombosis.14 In clinical studies, GPx-3 deficiency has been associated with coronary artery disease15-17 and familial arterial ischemic stroke.14,18
We recently identified a novel functional transcription start site of the GPx-3 gene and demonstrated that oxygen tension and redox state regulate GPx-3 gene transcription.\(^9\) In addition, we recently described novel polymorphisms defining a unique haplotype in the promoter region of the GPx-3 gene associated with an approximate 2-fold increase in the risk of arterial ischemic stroke in young adults and children.\(^22\) The association of GPx-3 deficiency or polymorphisms with venous thrombosis has not been studied. As there is evidence suggesting a role for oxidative stress in the pathobiology of venous thrombosis,\(^21\) we sought to investigate the possible association of the GPx-3 promoter polymorphisms, and, particularly, the H2 haplotype, with the risk of venous thrombosis in a population of young adults with idiopathic CVT.

### Subjects and Methods

#### Study Subjects

Between January 1996 and June 2001, we studied 30 young (18 to 45 years) survivors of a first episode of CVT consecutively referred to the Neurology or Hematology Clinics of the State University of Campinas and the University of São Paulo Medical School Hospitals in Brazil. The diagnosis of CVT was based on findings of history and physical examination, and confirmed when computed tomography showed the typical empty-delta and cord signs or when MRI or cerebral angiography of the brain showed a complete or partial lack of filling of 1 or several venous sinuses. After undergoing extensive work-up, 7 patients were excluded owing to the presence of antiphospholipid antibodies in 3, Behçet’s disease in 1, a dural arteriovenous malformation at the site of thrombosis in 1, a dural fistula after head trauma in 1, and otitis media complicated by mastoiditis in 1. The remaining 23 patients were enrolled in a research study for the evaluation of inherited risk factors for idiopathic venous thrombosis in the young. This study was approved by the Medical Ethics Committee of the State University of Campinas and the University of São Paulo, and the Institutional Review Board at Boston University Medical Center. Participation was voluntary, and all study subjects gave informed consent.

Unrelated blood donors and volunteers from the same age group and geographical area without a clinical history of coronary, peripheral, cerebrovascular, or thromboembolic disease were invited to participate in the study as control subjects. These same control subjects were included in our prior study of arterial ischemic stroke.\(^20\) All controls were interviewed to obtain information on past medical history, family history of thromboembolism, conventional vascular risk factors, predisposing factors for CVT (infections, head injury, or trauma), and the use of medications and illicit drugs. Among women, oral contraceptive use, pregnancy, and the puerperium were assessed and grouped as hormonal risk factors. Use of oral contraceptives (OCP) was considered positive if a woman had taken OCP for at least 2 weeks at any time in the 3 months before the thrombotic event. The puerperium was defined as the 30-day postpartum or postabortion period. Differences in demographic and vascular risk factor profile between patients and controls were first determined by univariate analysis using Student t test for age and the χ² test for all categorical variables. When cell counts were sparse, the Fisher exact test was used. Haplotypes were estimated from unphased genotypes by an expectation-maximization (EM) algorithm that assumes Hardy-Weinberg equilibrium, as previously described.\(^20–23\) We used the HelixTree Genetics Analysis Software, version 2.4.0 (Golden Helix Inc), to perform this analysis, as well as to determine Hardy-Weinberg equilibrium; allele, genotype, and haplotype frequencies; and linkage disequilibrium (LD) between polymorphism pairs. To test the association of GPx-3 haplotypes with the risk of CVT, we determined the most likely haplotype phase for each study subject using the EM procedure. We then performed multivariate analysis with logistic regression at the diplotype level for the GPx-3 haplotypes significantly associated with the risk of CVT by univariate analysis, adjusting for age, gender, ethnicity, and vascular, hormonal, and inherited prothrombotic risk factors. Statistical analyses were performed using Sigmastat version 3.0.1 (SPSS Inc).

### Results

Table 1 shows the demographic characteristics and risk factors of all study subjects. CVT patients were significantly younger than controls and more frequently female. Of the 16 female patients, 10 (62.5%) had a hormonal risk factor (OR=8.67, 95% CI, 2.22 – 35.49; ) 2 patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Controls (n=123)</th>
<th>CVT Patients (n=23)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y(^1)</td>
<td>36.8±6.8</td>
<td>30.0±6.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male</td>
<td>57 (46.3%)</td>
<td>7 (30.4%)</td>
<td>0.16</td>
</tr>
<tr>
<td>Ethnic background</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>100 (81.3%)</td>
<td>17 (73.9%)</td>
<td></td>
</tr>
<tr>
<td>African</td>
<td>22 (17.9%)</td>
<td>6 (26.1%)</td>
<td>0.61</td>
</tr>
<tr>
<td>Asian</td>
<td>1 (0.8%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Conventional vascular risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>10 (8.1%)</td>
<td>4 (17.4%)</td>
<td>0.24</td>
</tr>
<tr>
<td>Smoking</td>
<td>45 (36.6%)</td>
<td>7 (30.4%)</td>
<td>0.57</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>35 (28.5%)</td>
<td>4 (17.4%)</td>
<td>0.27</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>3 (2.4%)</td>
<td>1 (4.3%)</td>
<td>0.50</td>
</tr>
<tr>
<td>No vascular risk factors</td>
<td>52 (42.3%)</td>
<td>14 (60.9%)</td>
<td>0.10</td>
</tr>
<tr>
<td>Hormonal risk factors(^2)</td>
<td>10 (16.1%)</td>
<td>6 (37.5%)</td>
<td></td>
</tr>
<tr>
<td>Oral contraceptive use</td>
<td></td>
<td></td>
<td>0.00048</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>0</td>
<td>1 (6.3%)</td>
<td></td>
</tr>
<tr>
<td>Postpartum period</td>
<td>0</td>
<td>5 (31.3%)</td>
<td></td>
</tr>
<tr>
<td>Inherited prothrombotic risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Factor V Leiden(^3)</td>
<td>4 (3.3%)</td>
<td>2 (8.7%)</td>
<td>0.24</td>
</tr>
<tr>
<td>Prothrombin G20210A(^2)</td>
<td>3 (2.4%)</td>
<td>4 (17.4%)</td>
<td>0.012</td>
</tr>
<tr>
<td>MTHFR C677T(^1)</td>
<td>14 (15.5%)</td>
<td>1 (4.3%)</td>
<td>0.47</td>
</tr>
</tbody>
</table>

\(^{1}\)Plus-minus values are means±SD.

\(^{2}\)Among 62 female controls (4 postmenopausal controls were excluded from this analysis) and 16 female CVT patients.

\(^{3}\)In heterozygosity; \^{4} in homozygosity.
were taking oral contraceptives while still in the postpartum period. Factor V Leiden and heterozygosity for the prothrombin G20210A mutation were more prevalent among patients with CVT, yet only the latter reached statistical significance with an OR of 8.42 (95% CI, 1.43 to 52.54; P=0.012). One CVT patient carried both factor V Leiden and the prothrombin 20210A allele.

Analysis by SSCP and direct sequencing of GPx-3 promoter fragments obtained from CVT patients and controls revealed the presence of 8 promoter polymorphisms previously described by us: −942 A→C, −927 T→C, −861 A→T, −302 A→T, −284 T→A, −568 T→C, −518 T→C, and −65 T→C. Numbering of the nucleotides was performed relative to the transcription start point of the GPx-3 gene we recently identified, defined as +1. All GPx-3 promoter polymorphisms were in Hardy-Weinberg equilibrium, the distribution of each SNP in patients and controls is shown in Table 2, and the distribution of each SNP in adults and children is shown in supplemental Table II; with the exception of the SNP at position −284, the rare polymorphic alleles were significantly more frequent in patients than controls. As previously demonstrated, a high degree of linkage between polymorphism pairs was evidenced on the LD map, with R² values ranging from 0.93 to 1.0. The 3 most 5′ SNPs (positions −942, −927, −861), as well as the −568, −518, and −302 polymorphisms, were in complete LD and formed 2 blocks which, in turn, were linked (R²=0.95), ultimately yielding 7 haplotypes (Table 3). Haplotype frequencies were calculated from the EM algorithm in the patient and control groups (Table 3; haplotype pairs are listed in supplemental Table III). Haplotypes H₁ and H₂ accounted for ≈95% of the observed haplotypes; haplotypes H₃ through H₇ were, therefore, not included in further analyses given their low frequency in the population. The GPx-3 H₁ haplotype was almost 4 times more prevalent among CVT patients (26.1%) than controls (7.0%), yielding an odds ratio (OR) of 4.61 (95% CI, 1.86 to 11.37; P=0.00054). Over half of CVT patients (52.1%) were heterozygous (H₁H₂) or homozygous (H₁H₁) for the H₁ haplotype compared with 12.2% of controls, yielding an almost 8-fold increase in risk associated with carriahership of the GPx-3 H₁ haplotype by univariate analysis (OR=7.91, 95% CI, 2.55 to 25.07; P<0.0001). The H₂ haplotype remained independently associated with the risk of CVT after adjustment for age, gender, ethnicity, and hormonal and inherited prothrombotic risk factors, with an OR of 10.7 (95% CI, 2.70 to 42.36; P<0.0001). Among women, the presence of the GPx-3 H₂ haplotype in combination with a hormonal risk factor potentiated the risk of CVT almost 70-fold (OR=69.0, CI, 5.47 to >2000; P<0.0001; Table 4); however, the sample size for this analysis was very small (as indicated by the wide confidence interval). In addition, owing to the limited number of study subjects carrying conventional prothrombotic risk factors, we were unable to assess valid interactions between the latter and the GPx-3 polymorphisms. A multiple logistic regression model including the H₁ haplotype, demographic characteristics, and vascular and prothrombotic risk factors is presented in supplemental Table IV.

### Table 2. Genotypic Distribution of GPx-3 Promoter Polymorphisms Among Study Subjects

<table>
<thead>
<tr>
<th>Polymorphism</th>
<th>Controls (n=123)</th>
<th>CVT Patients (n=23)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>−942 AA</td>
<td>104 (84.6%)</td>
<td>11 (47.8%)</td>
<td></td>
</tr>
<tr>
<td>−942 AC</td>
<td>18 (14.6%)</td>
<td>11 (47.8%)</td>
<td></td>
</tr>
<tr>
<td>−942 CC</td>
<td>1 (0.8%)</td>
<td>1 (4.4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>−927 TT</td>
<td>104 (84.6%)</td>
<td>11 (47.8%)</td>
<td></td>
</tr>
<tr>
<td>−927 TC</td>
<td>18 (14.6%)</td>
<td>11 (47.8%)</td>
<td></td>
</tr>
<tr>
<td>−927 CC</td>
<td>1 (0.8%)</td>
<td>1 (4.4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>−861 AA</td>
<td>104 (84.6%)</td>
<td>11 (47.8%)</td>
<td></td>
</tr>
<tr>
<td>−861 AT</td>
<td>18 (14.6%)</td>
<td>11 (47.8%)</td>
<td></td>
</tr>
<tr>
<td>−861 TT</td>
<td>1 (0.8%)</td>
<td>1 (4.4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>−568 TT</td>
<td>105 (85.4%)</td>
<td>11 (47.8%)</td>
<td></td>
</tr>
<tr>
<td>−568 TC</td>
<td>17 (13.8%)</td>
<td>11 (47.8%)</td>
<td></td>
</tr>
<tr>
<td>−568 CC</td>
<td>1 (0.8%)</td>
<td>1 (4.4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>−518 TT</td>
<td>105 (85.4%)</td>
<td>11 (47.8%)</td>
<td></td>
</tr>
<tr>
<td>−518 TC</td>
<td>17 (13.8%)</td>
<td>11 (47.8%)</td>
<td></td>
</tr>
<tr>
<td>−518 CC</td>
<td>1 (0.8%)</td>
<td>1 (4.4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>−302 AA</td>
<td>105 (85.4%)</td>
<td>11 (47.8%)</td>
<td></td>
</tr>
<tr>
<td>−302 AT</td>
<td>17 (13.8%)</td>
<td>11 (47.8%)</td>
<td></td>
</tr>
<tr>
<td>−302 TT</td>
<td>1 (0.8%)</td>
<td>1 (4.4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>−284 TT</td>
<td>108 (87.8%)</td>
<td>21 (91.3%)</td>
<td></td>
</tr>
<tr>
<td>−284 TA</td>
<td>14 (11.4%)</td>
<td>2 (8.7%)</td>
<td></td>
</tr>
<tr>
<td>−284 AA</td>
<td>1 (0.8%)</td>
<td>0</td>
<td>0.63</td>
</tr>
<tr>
<td>−65 TT</td>
<td>104 (84.6%)</td>
<td>11 (47.8%)</td>
<td></td>
</tr>
<tr>
<td>−65 TC</td>
<td>18 (14.6%)</td>
<td>11 (47.8%)</td>
<td></td>
</tr>
<tr>
<td>−65 CC</td>
<td>1 (0.8%)</td>
<td>1 (4.4%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

P values were calculated assuming a dominant genetic model.

### Discussion

Cerebral venous thrombosis is multifactorial in etiology and occurs in the context of complex interactions between environmental and genetic predisposing factors. In addition, CVT is a good model to investigate the role of genetic risk factors, as cerebral sinuses lack valves and are susceptible to stasis. As several prothrombotic risk factors, such as factor V Leiden and the prothrombin G20210A mutation, are not major arterial vascular risk factors but assume increased importance in patients with CVT, we hypothesized that the GPx-3 gene polymorphisms may behave in a similar way.

The enzymes in the GPx family reduce ROS in the vasculature and maintain the bioavailability of NO, thereby preserving normal endothelial function and an antithrombotic vascular environment. In addition, these antioxidant enzymes protect against free radical–induced cerebral injury. A
deficiency of GPx-3 has been associated with an increased risk of familial childhood stroke; recently, we also reported that a GPX-3 promoter haplotype with decreased transcriptional activity is associated with arterial ischemic stroke in young individuals. Furthermore, 3 reports have demonstrated decreased GPx-3 activity among patients with coronary artery disease, suggesting a more extensive effect of this defect in the vascular system. Taken together, these data suggest that the GPx-3 gene is a compelling candidate gene for the risk of cerebrovascular thrombosis; however, its role in CVT had never been studied. In this study, we have found that the novel GPx-3 promoter haplotype recently described by us in association with arterial ischemic stroke is also strongly associated with the risk of CVT.

The polymorphisms we identified are in accordance with variations recently described by Rieder and colleagues in GenBank (accession number AY310878). Haplotype H2, formed by the combination of the rare alleles of each of the linked polymorphisms, was associated with a 10.7-fold independent increase in the risk of CVT when compared with carriers of the H1H1 haplotype pair. This risk estimate has to be interpreted with caution owing to the small sample size of our CVT population; nevertheless, it is striking that more than 50% of the patients with CVT carried the GPx-3 H2 haplotype in either the heterozygous or homozygous form. Increased oxidant stress has been shown to predispose to venooclusive disease, and the posttranslational modifications of fibrinogen caused by oxidant conditions may be particularly important in the venous bed. In the small group of women with CVT, the simultaneous presence of the GPx-3 H2 haplotype with an hormonal risk factor strongly potentiated the risk, yielding an OR of 69.0; however, the confidence interval for this analysis was very wide owing to the sample size. Consistent with this observation, Martinelli and colleagues have previously found that other prothrombotic inherited risk factors interact with oral contraceptive use, increasing the risk of CVT up to 150-fold.

We have previously performed reporter gene studies with the 2 most common haplotypes in our population, and found that the transcriptional activity of the H2 risk haplotype was significantly less than that of the H1 haplotype under normoxic, but especially under hypoxic, conditions. The lower basal expression levels of the GPx-3 H2 haplotype and its compromised ability to upregulate gene expression in hypoxia yield less peroxidase potential, thereby compromising neuroprotective and antithrombotic function. We have not determined which specific polymorphism(s) is (are) functionally relevant and responsible for the altered transcriptional response. The SNP at position /H11002/943, located within an AP-1 transcription factor consensus binding site, suggests that it may affect the ability of the GPx-3 promoter to interact with hormonal risk factors.

The position of each polymorphism is based on the transcription start site being +1.

<table>
<thead>
<tr>
<th>Haplotype</th>
<th>Controls</th>
<th>CVT Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>H1</td>
<td>84.9%</td>
<td>69.6%</td>
</tr>
<tr>
<td>H2</td>
<td>7.0%</td>
<td>26.1%</td>
</tr>
<tr>
<td>H3</td>
<td>6.2%</td>
<td>4.3%</td>
</tr>
<tr>
<td>H4</td>
<td>0.8%</td>
<td>0.0%</td>
</tr>
<tr>
<td>H5</td>
<td>0.4%</td>
<td>0.0%</td>
</tr>
<tr>
<td>H6</td>
<td>0.4%</td>
<td>0.0%</td>
</tr>
<tr>
<td>H7</td>
<td>0.3%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

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<tr>
<th>Haplotype pairs</th>
<th>Controls</th>
<th>CVT Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>H1/H1</td>
<td>89 (72.4%)</td>
<td>9 (39.1%)</td>
</tr>
<tr>
<td>H1/H2</td>
<td>14 (11.4%)</td>
<td>11 (47.8%)</td>
</tr>
<tr>
<td>H1/H3</td>
<td>12 (9.8%)</td>
<td>2 (8.7%)</td>
</tr>
<tr>
<td>H1/H4</td>
<td>2 (1.6%)</td>
<td>0</td>
</tr>
<tr>
<td>H1/H5</td>
<td>1 (0.8%)</td>
<td>0</td>
</tr>
<tr>
<td>H2/H2</td>
<td>2 (1.6%)</td>
<td>0</td>
</tr>
<tr>
<td>H2/H3</td>
<td>1 (0.8%)</td>
<td>1 (4.3%)</td>
</tr>
<tr>
<td>H2/H4</td>
<td>2 (1.6%)</td>
<td>0</td>
</tr>
<tr>
<td>H2/H5</td>
<td>1 (0.8%)</td>
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<table>
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<tr>
<th>Hormonal Risk Factor*</th>
<th>Patients</th>
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<th>OR</th>
<th>95% CI</th>
<th>P Value</th>
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<td>No</td>
<td>4</td>
<td>46</td>
<td>1</td>
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<tr>
<td>No</td>
<td>4</td>
<td>7</td>
<td>6.57</td>
<td>1.05–43.37</td>
<td>0.029</td>
</tr>
<tr>
<td>Yes</td>
<td>2</td>
<td>8</td>
<td>2.88</td>
<td>0.30–23.97</td>
<td>0.259</td>
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<tr>
<td>Yes</td>
<td>6</td>
<td>1</td>
<td>69.0</td>
<td>5.47–2003.04</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Defined as oral contraceptive use, pregnancy, or puerperium (30-day postpartum or postabortion period).
to respond to changes in oxidant stress. The AP-1 transcription factor is sensitive to redox state and regulates antioxidant and proinflammatory genes.27

Some limitations of our study should be recognized. We did not correlate the GPx-3 haplotypes with GPx-3 activity levels in vivo owing to the lack of available plasma samples from our study population. In addition, this study includes only survivors of CVT, and the possibility of survival bias must be considered. As discussed above, the sample size for some of the analyses was very small. Lastly, we have not conducted a prospective analysis in a validation set owing to the rarity of the disease.

Conclusion

In conclusion, we have identified novel GPx-3 promoter polymorphisms that form a haplotype associated with a significant increase in the risk of CVT. These findings, in combination with prior work from our group on arterial ischemic stroke,11,15,17 support a novel mechanism for thrombotic cerebrovascular disease. This mechanism involves the antioxidant enzyme GPx-3 and its role in eliminating reactive oxygen species that limit the bioavailability of NO, and, consequently, its antiplatelet and antioxidant effects; especially in the case of CVT, the loss of antioxidant effects may also promote oxidative modification of fibrinogen, thereby facilitating fibrin thrombus formation.12,13 This genetic variant strongly interacts with conventional and hormonal vascular risk factors to potentiate the risk of CVT. Studies involving a larger number of subjects and patient populations with thrombotic disease in other vascular beds, as well as efforts to correlate the GPx-3 H1 haplotype with enzyme activity in plasma, are necessary to confirm these results and determine the generalizability of this relationship to disease mechanism and vascular risk.

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Disclosures

None.

References

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