No Association of the Plasma Glutathione Peroxidase (GPx-3) Gene With Cerebral Venous Thrombosis in the German Population

To the Editor:

In a recent publication in Stroke, cerebral venous thrombosis (CVT) was found to be associated with a variant of the plasma glutathione peroxidase (GPx-3) gene (promoter haplotype H2).1 The observed association was strong (OR >10) and highly significant (P<0.0001). However, the number of analyzed patients was small (n=23) and the findings were not confirmed in an independent study population. We analyzed 79 patients with nonseptic CVT and 203 healthy control subjects and sought to confirm the association between GPx-3 and CVT. Our study groups were characterized in detail elsewhere.2 We tagged haplotype H2 with SNP rs1946235 (this is polymorphism −927 T/C in the study of Voetsch et al1) as described before.3 The C allele of rs1946235 identifies haplotype H2, as well as the rare (<1% in our population) haplotypes H1 and H4.

In our series of healthy control subjects, we found 3 homozygous and 52 heterozygous carriers of haplotype H2. The frequency of H2 in this control series is therefore 14.3%. In the patients group we found one homozygous and 17 heterozygous carriers of haplotype H2 (estimated frequency of H2=12.0%). Comparison of the H2 frequencies in the 2 study groups by χ² testing revealed that the difference was not significant (P=0.48).

In an additional series of 500 healthy German control persons, we genotyped SNP rs1946235 and found 11 CC, 112 CT and 377 TT, which corresponds to an estimated H2 frequency of 13.4%.

Our findings do not confirm the recently published findings of a strong association between a GPx-3 promoter variant and CVT. We tagged the same haplotype of the GPx-3 gene, but we did not find different frequencies of this genetic variant in patients and control subjects. Moreover, to increase the power of our study we analyzed the GPx-3 promoter also in an additional large (n=500) control series from the same population.

The causes of the discrepancies between our plain findings and the impressive results of a recent study by Voetsch et al1 are unclear. The diagnosis of CVT in our patients was restricted to pathognomonic findings on either MRI angiography or conventional angiography, and the control series was randomly selected from the region from which most patients were recruited.3 With these same study samples we could detect a significant association of CVT with inherited variants in Factor XII and Factor II and confirmed the association with the factor V Leiden mutation4 that was described by others before.5

At an earlier occasion we pointed out that the genotypes found in the control population by Voetsch et al4 are different from those reported by others for other white samples.3 The use of these population data might have introduced a bias in their study. Moreover, because of the small size of the patients group (n=23) the study by Voetsch et al was probably victim of statistical error. The analysis of adequate sample sizes and the replication of positive associations in independent populations were strongly recommended in genetic case control studies.6 By analyzing a larger series of patients and controls from another population we followed these recommendations.

Disclosures

None.

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