Plasminogen Activator Inhibitor Genotype and Brain Infarction
To the Editor:
Roest et al. \(^1\) reported a nested case-control study that assessed the relation between 4G/5G polymorphism in the plasminogen activator inhibitor (PAI-1) gene and cardiovascular and cerebrovascular mortality in women. The authors found that 4G/4G homozygotes had a decreased risk of dying from stroke compared with 5G/5G homozygotes (relative risk, 0.4; 95% confidence interval [CI], 0.2 to 0.7); the relative risk was 0.7 (95% CI, 0.4 to 1.1) for 4G/5G heterozygotes.

The authors raised 2 important issues. First, because the diagnosis was not always confirmed by CT scan or MRI, they could not distinguish brain infarcts (BIs) from hemorrhages, which are very different from a pathophysiological perspective. Thus, the possibility that misclassification may have introduced some bias cannot be discarded. The authors think that this is unlikely because the incidence of brain hemorrhages was lower than that of BIs; however, it is also true that the case fatality of hemorrhages was higher than that of BIs. Because it is likely that any gene associated with stroke will have small effects, it is difficult to draw any conclusions about the impact of misclassification. Second, these findings are somewhat unexpected because the 4G allele is associated with increased PAI-1 transcription. They concluded that PAI-1 may contribute to hemorrhages was higher than that of BIs. Because it is likely that any gene associated with stroke will have small effects, it is difficult to draw any conclusions about the impact of misclassification. The findings by Elbaz et al confirm our observations.\(^1\) Moreover, a comparable but nonsignificant reduced stroke incidence in relation to the plasminogen activator inhibitor (PAI-1) 4G polymorphism was reported previously by Catto et al.\(^2\) In a pooled analysis of the results of all published studies on the relationship between PAI-1 4G5G genotype and stroke, the genotype distribution in stroke incidence cases is as follows: 4G4G, 296 (26.1%); 4G5G, 559 (49.3%); and 5G5G, 278 (24.5%). The distribution in controls is as follows: 4G4G, 344 (30.1%); 4G5G, 587 (51.3%); and 5G5G, 213 (18.6%). Using 5G5G as the reference group, the odds ratios (ORs) are 0.66 (95% CI, 0.52 to 0.84) for 4G4G homozygotes and 0.73 (95% CI, 0.59 to 0.90) for 4G5G heterozygotes. The findings of this pooled analysis are suggestive of a protective role of plasminogen activation inhibition in cerebrovascular morbidity and mortality.

The 4G polymorphism is located in the promoter region of the PAI-1 gene and is responsible for increased transcription. They concluded that PAI-1 may contribute to cerebrovascular disease via pathways other than fibrinolysis, and that additional studies are needed.

We studied the relationship between 4G/5G polymorphism and BI in the Etude du profil Génétique de l’Infarctus Cérébral (GÉNIC) case-control study, which examined 461 cases with and 504 controls. The median age, 69 years; range, 20 to 85 years).\(^2\) The distributions of genotypes in cases were as follows: 4G/4G, 27.1%; 4G/5G, 48.4%; and 5G/5G, 24.5%. The distribution in controls was as follows: 4G4G, 344 (30.1%); 4G5G, 587 (51.3%); and 5G5G, 213 (18.6%). Using 5G5G as the reference group, the odds ratios (ORs) were 0.7 (95% CI, 0.5 to 1.0) for 4G/4G homozygotes and 0.7 (95% CI, 0.5 to 1.0) for 4G/5G heterozygotes. Carrying at least one 4G allele was associated with an OR of 0.7 (95% CI, 0.5 to 1.0); adjustment for hypertension, diabetes, smoking, and cholesterol did not modify these findings. This association was not modified by sex (P=0.25), although it was stronger in men (OR, 0.6; 95% CI, 0.4 to 0.9) than women (OR, 0.9; 95% CI, 0.6 to 1.4). After stratification by median age, the relation was stronger for younger subjects (OR, 0.5; 95% CI, 0.3 to 0.8) than for older subjects (OR, 0.9; 95% CI, 0.6 to 1.4; interaction, P=0.05).

Only patients with ischemic cerebrovascular disease were studied in the GÉNIC study, and we also found that 4G carriers were at decreased risk of BI (lethal or nonlethal). These results are similar to those reported by Roest et al.\(^1\) and this association remains to be understood.

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Response
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The mechanism that relates plasminogen activation to cerebrovascular disease probably reflects a nonfibrinolytic function of plasmin. Increased plasminogen activation may lead to increased laminin degradation in extracellular brain tissue and, hence, a reduced resistance of the brain against both ischemic and hemorrhagic damage.\(^5\)

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