Dear Sir,

Tissue factor (TF) is a key initiator of blood coagulation in vivo. Its –1812C>T (rs958587) polymorphism, completely concordant with the other three TF variants (–1322C>T, –1208D>I and –603A>G) (5), was inconsistently associated with clinical outcomes of ischaemic heart disease (5,6). Another TF polymorphism, +5466A>G (rs3917643), was reported to be a predictor of cardiovascular death in patients with acute coronary syndrome (6). Recently, we have shown that the thrombin-lowering effects of simvastatin are at least partly determined by TF+5466A>G polymorphism (7).

Although data on the links between genetic thrombophilic factors and cryptogenic stroke are discordant (8–10), search for novel risk factors might have practical implications given the fact that cryptogenic stroke represents one third of all strokes (11). We sought to investigate the impact of TF –1812C>T and +5466A>G polymorphisms on TF regulation in subjects who survived cryptogenic ischaemic stroke.

We studied 94 patients (42.6 ± 1.4 years; 26 men; 6 diabetics; 33 subjects with arterial hypertension) following documented cryptogenic ischaemic stroke 2–5 years before enrollment and 33 subjects with arterial hypertension) following documented cryptogenic ischaemic stroke. In patients, but not in controls, there were correlations between age, sex, glucose, lipids, smoking, diabetes, arterial hypertension and TFPI or TF.

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0.3 ng/ml, p=0.0002) and lower HDL-C (AA vs. AG+GG, 1.45 ± 0.04 vs. 1.22 ± 0.10 mM, p=0.02). Minor allele of –1812C>T polymorphism was associated only with lower TF levels (Fig. 1B). No genotype-related associations were observed in controls.

Haplotypic analysis of TF concentrations demonstrated that +5466A>G polymorphism was the major predictor of TF levels, while the contribution of –1812C>T variant was comparatively low (Fig. 1C). It might be assumed that an association between –1812C>T polymorphism and TF levels in stroke patients was largely determined by its haplotypic relationship with +5466A>G variant, which is consistent with previous findings (6).

The observation that, under lipopolysaccharide stimulation, +5466G allele-carrying monocytes demonstrated higher increase in TF activity compared to cells with +5466AA genotype (6) might also explain our findings regarding higher TF levels in stroke patients carrying the +5466G allele. A weak “own” positive effect of –1812C allele on TF levels in the current study might be supported by observations that, being associated with higher TF expression, –1208D (completely concordant with –1812C) allele demonstrated variant transcription factor binding (6). The observation that, under lipopolysaccharide stimulation, –1812G allele-carrying monocytes demonstrated higher increase in TF activity compared to cells with +5466AA genotype (6) might also explain our findings regarding higher TF levels in stroke patients carrying the +5466G allele. A weak “own” positive effect of –1812C allele on TF levels in the current study might be supported by observations that, being associated with higher TF expression, –1208D (completely concordant with –1812C) allele demonstrated variant transcription factor binding (6).

To our knowledge, we are the first to study TF genetic variants in subjects with cryptogenic ischaemic stroke. It might be hypothesised that elevated plasma TF levels may be a risk factor for recurrent ischaemic cerebrovascular events in patients with a history of cryptogenic stroke. Large studies are needed to confirm this hypothesis.

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References
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