Published in final edited form as:

Am J Hematol. 2009 November ; 84(11): 775–776. doi:10.1002/ajh.21542.

Venous thrombosis associated with gene deletion of tissue factor pathway inhibitor

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To the editor

Tissue factor pathway inhibitor (TFPI) is an anticoagulant that acts by directly inhibiting factor Xa and inactivating the factor VIIa/TF catalytic complex responsible for the initiation of coagulation [1]. In addition, TFPI activity is potentiated by protein S, essential component of the protein C pathway that downregulates thrombin formation and is associated with the most common genetic cause of thrombophilia, activated protein C resistance due to factor V Leiden mutation [2]. It has been proposed that the prothrombotic tendency of patients with protein S deficiency, in part, may be due to concomitant TFPI deficiency, but this is yet to be demonstrated [3]. The effects of TFPI loss in humans have not been described, but studies of mice with *TFPI* gene deletion suggest that it may contribute to thrombosis [4].

Here, we describe a patient with a chromosomal deletion, including the *TFPI* gene, who developed deep venous thrombosis. The patient is an 18-year-old male with developmental delay, blindness, microcephaly, foot syndactyly, spastic paresis and scoliosis, and interstitial deletion of chromosome 2q32. He underwent an uncomplicated surgical fusion of his thoracolumbar spine, without prophylactic anticoagulation, and on postoperative day 15 was noted to have right extremity swelling. Ultrasonography and venography revealed extensive deep venous thrombosis of the right external iliac and femoral veins, with extension to the inferior vena cava, without evidence of abnormalities of vascular anatomy. The patient has tolerated numerous episodes of postsurgical immobilization in the past without anticoagulation and thrombotic complications. No family history of thromboembolic disease, stroke, myocardial infarction, or recurrent miscarriage was identified. Evaluation for possible thrombophilia revealed normal prothrombin and activated partial thromboplastin times, fibrinogen level, and antithrombin activity, as well as the absence of activated protein C resistance, prothrombin gene G20210A mutation, antiphospholipid antibodies, and hyperhomocysteinemia (Table I). Testing for possible inherited deficiencies of protein C and S revealed normal protein C and S activities in both of his parents (Table I).

Because the human *TFPI* gene resides at chromosome 2q32, this patient offered a unique opportunity to study the association of thrombosis and *TFPI* gene deletion. The chromosomal deletion was identified using DNA isolated from peripheral blood leukocytes by using oligonucleotide comparative genomic hybridization array (G4411B, Agilent Technologies), which extends from 2q31.1 to q32.3 (chr 2: 173394141-191869063; NCBI build 36.1; hg18). This deletion is approximately 18 Mb in size and includes the *TFPI* gene, as well as 86 other genes, but none among the latter that have been reported to be associated with thrombosis, hemostasis, or coagulation, as assessed using text mining of Medline (<http://twease.org>) [5]. Contrary to expectations, the patient's TFPI level in plasma collected before administration of heparin was found to be within normal limits at 30 ng/ml, as assessed using ELISA that detects both full-length and truncated isoforms (normal range of 13–45 ng/ml; R&D Systems). Repeat measurement after 8 weeks of treatment with heparin was 28 ng/ml.

Mice homozygous for the deletion of the *TFPI* gene die from disseminated intravascular thrombosis in utero [4]. Mice with heterozygous *TFPI* gene deletion that have 50% reduced plasma TFPI levels, which in the background of thrombophilia associated with homozygous murine homolog of factor V Leiden, also develop disseminated thrombosis early in life [6]. Several *TFPI* gene polymorphisms have been described in humans, but their association with thrombosis remains controversial [7]. Several patients with similar chromosomal deletion and phenotype have been reported, but none had thrombotic complications [8]. The finding of normal plasma TFPI level in the reported patient with *TFPI* gene deletion suggests that haploinsufficient or hypomorphic *TFPI* gene variants may not be prothrombotic in humans by themselves, but may act cooperatively with other causes of thrombophilia. The latter is not the case for the reported patient, whose normal plasma TFPI level and absence of established thrombophilic predisposition suggest that in his case the relationship between genotype and phenotype appears to be incidental.

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TABLE I

Patient Laboratory Data

Prothrombin time	11.3 sec
Activated partial thromboplastin time	25.9 sec
Thrombin time	17.2 sec
Fibrinogen	449 mg/dl
Antithrombin activity	83%
Activated protein C resistance	1.03
<i>Prothrombin</i> gene G20210A mutation	Negative
Maternal protein C activity	161%
Maternal protein S activity	145%
Paternal protein C activity	103%
Paternal protein S activity	108%
Anti- β 2-glycoprotein 1 antibodies	Negative
Anti-cardiolipin antibodies	Negative
Homocysteine	10 μ M
Total plasma TFPI level	30 ng/ml