

# Title: Multilocus Genetic Risk Score predictive for inherited Venous Thrombophilia: A family description from the MaGiSTER-Study

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Inherited thrombophilia (i.e. venous thromboembolism, VTE) is due to rare genetic loss-of-function mutations, common genetic risk factors and acquired risk conditions, modulating onset age, severity, recurrence and penetrance of the main gene defect also within the same kindred. GWAS recently recognized about 1000 genes associated to VTE thought some gene defects may unpredictably remain asymptomatic, so calculating the individual genetic predisposition is a challenging task. Uncommon loss-of-function mutations in *SERPINC1, PROC or PROS1* genes and common gain-of-function mutations in *F5* (rs6025) or *F2* (rs1799963) genes, are the key genetic risk factors. By multilocus genetic approach, we investigated a large family (68 members) characterized by severe VTE despite of life-long anticoagulant treatment. The main defects found were a common missense mutation (c.G1691A) in the exon_10 of *F5* gene (p.R506Q, i.e. FV Leiden) and a type 1 antithrombin (AT) deficiency caused by a nonsense mutation (CGA>TGA) responsible for a premature stop codon (c.1171C>T; p.R391X) in the exon_6 of *SERPINC1* gene. Cosegregation of both mutations was found in the propositus and in 18 (26.4%) family members, and the mutations never appeared as single-defect. *SERPINC1* (1q25.1) and *F5* (1q24.2) genes are very close in the long arm of chromosome 1, and the hypothesized cis-segregation was confirmed in all the carriers by linkage analysis of STR-$(ATT)_{5\text{-}18}$ in the *SERPINC1* IVS_5. Detailed studies in a branch of this family, revealed that the proposita had VTE after surgery (20y); one of her brothers had spontaneous VTE (21y) as well one of his sons after surgery (14y). Both his daughters had early VTE episodes and complicated pregnancies: ì. the older had bilateral VTE (29y) and perinatal renal thrombosis in the newborn characterized by in-utero origin; ìì. the younger had massive VTE and cerebral ictus (23y) requiring premature life-saving pregnancy-interruption. Molecular analyses performed in the newborn of the first daughter and in the aborted tissues from the second daughter confirmed the *SERPINC1-F5* combined defect in both progenies. A multilocus-genetic approach performed in this branch of the family also included: *F5* (rs1800595); *F12* rs1801020; *F13A1* rs5985; *SERPINC1* rs121909548; *SERPINA10* rs2232698; *ABO* rs8176719; *F11* rs2036914; *FGG* rs2066865; *KNG1* rs710446; *F11* rs2289252. We found early VTE onset and recurrence being associated to *FGG* rs2066865 and *F5* rs4524; whilst *F5* (rs1800595) was fond in trans with *F5* (rs6025) in the post-mortem analysis of the in-utero thrombosis material. The common *F5* rs1800595 strongly synergizes with *F5* rs6025 becoming a life-threatening condition when combined with *SERPINC1* mutations. Merging classic and newly GWAS-identified genetic markers is mandatory for a complete and accurate VTE risk estimation and patient management in the clinical practice to avoid partial risk score estimation in unrecognized at risk patients.

**Biography**

Donato Gemmati is professor in Medical Genetics, Section of Medical Biochemistry, Molecular Biology & Genetics, University of Ferrara, Italy and Director of the Interdepartmental Research Center of Haemostasis & Thrombosis, University of Ferrara, Italy. He was born in Rome, Italy (12 Jan 1963), Specialized in Medical Genetics (2006) and PhD in Biomedical Sciences (2009), University of Ferrara, Italy. Board member of the Molecular Medicine PhD Course, University of Ferrara, Italy. Editorial board member: ì. *International Journal of Molecular Sciences* (Molecular Genetics and Genomics section); ìì. *Genes* (Human Genomics and Genetic Diseases section).

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