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Multilocus genetic risk score predictive for inherited venous thrombophilia: A family description from the magister-study

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Abstract

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)5-18 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).

Speaker Publications:

1. “Maternal Haplotypes in DHFR Promoter and MTHFR Gene in Tuning Childhood Acute Lymphoblastic Leukemia Onset-Latency: Genetic/Epigenetic Mother/Child Dyad Study (GEMCDS) August 2019Genes 10(9):634 DOI: 10.3390/genes10090634

2. “Profiling the mutational landscape of coagulation factor V deficiency“
August 2019Haematologica 105(4):haematol.2019.232587

3. "Crosstalk Between Adipokines and Paraoxonase 1: A New Potential Axis Linking Oxidative Stress and Inflammation August 2019Antioxidants 8(8):287
DOI: 10.3390/antiox8080287
4. "Genotype-phenotype correlation in von Willebrand disease by automated von Willebrand multimer analyzer [Hydrasys 2] and UK-NEQAS validation"
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