

Novel missense mutation C106R in the *PROC* gene associated with type I protein C deficiency in a young Polish man with high-risk pulmonary embolism

To the Editor Protein C is a vitamin K-dependent plasma glycoprotein precursor of the serine protease, activated protein C, which is a natural anticoagulant protein.¹ Protein-C deficiency is classified as type I (quantitative defects of protein C: low antigen levels, reduced activity) and type II (qualitative defects of protein C: normal antigen concentrations, reduced activity).² The prevalence of protein C deficiency is estimated at 0.5% in the general population.³

Protein C is encoded by the protein C gene (*PROC*) located on chromosome 2q13-q14. *PROC* is approximately 11kb-long and comprises 9 exons.¹ Heterozygous protein C deficiency is associated with deep vein thrombosis (DVT) and/or pulmonary embolism (PE), occurring spontaneously or triggered, for example, by trauma.⁴

Here we report a case of protein C deficiency resulting from *PROC* C106R (HGVS numbering system) missense mutation diagnosed in a young Polish man with provoked DVT and PE.

A 29-year-old man experienced first-ever proximal DVT of the left leg following trauma and subsequent high-risk PE with hypotonia that was successfully treated with tenecteplase. The patient started therapy with acenocoumarol with a target international normalized ratio value of 2 to 3. His family history of DVT and PE was negative. The patient was obese (97 kg, 178 cm). No other risk factors for DVT were observed. An 18-month follow-up while on anticoagulant therapy was uneventful.

While taking enoxaparin for 2 weeks, the patient was screened for thrombophilia. Plasma protein C activity was quantified using the HemosIL Protein C chromogenic assay (Instrumentation Laboratory, Milan, Italy) and protein C antigen was measured by an enzyme-linked immunosorbent assay (Asserachrome Protein C, Diagnostica Stago, Asnieres, France). On 2 separate occasions, protein C activity was 42% (reference range, 70%–140%), while protein C antigen was 44% and 41%, respectively (reference range, 65%–140%). Transient causes of low protein C concentrations

were excluded. Type I protein C deficiency was established. Other thrombophilic factors were absent.

After obtaining written informed consent from the patient, genomic DNA was extracted from whole blood collected in EDTA. All exons and the exon–intron boundaries of the *PROC* gene were subjected to direct sequencing.⁵

A heterozygous nucleotide substitution T>C was found in codon 106 resulting in the replacement of cysteine by arginine (C106R) at the protein level. This mutation is predicted to be detrimental given its position and the amino acid change (PolyPhen2 score 1; genetics.bwh.harvard.edu/pph2). There was no other mutation in the exons or flanking introns of the *PROC* gene. Other family members were unavailable for analysis.

To the best of our knowledge, a missense C106R mutation in the *PROC* gene has not been reported in the literature. Another missense mutation at the same position, cysteine-to-tryptophan substitution (C106W, designated as PC Shanghai), was detected in a 32-year-old woman diagnosed with DVT.⁶ The current Polish patient with protein C deficiency had massive DVT complicated by PE requiring fibrinolytic therapy, which was likely due to the combined effect of genetic and transient risk factors. To our knowledge, this case is the second genetically characterized protein C deficiency in a Polish patient.⁷

Molecular modeling studies suggested that the consequences of single nucleotide substitutions leading to amino acid changes within the coding region of *PROC* are improper folding of the mutant proteins² as well as their impaired secretion and partial intracellular degradation through the proteasome pathway.⁸ In some populations, i.e., Finnish, Dutch, or Japan, characteristic missense mutations have been described, suggesting the presence of the founder effect.²

Our report supports the view that screening for inherited thrombophilia should be conducted in young patients with extensive venous

thromboembolism, in particular high-risk PE, even if a family history is negative.

Author names and affiliations Ewa Wypasek, Daniel P. Potaczek, Martine Alhenc-Gelas, Anetta Undas (E.W., D.P.P, A.U.: The John Paul II Hospital, Kraków, Poland; E.W., A.U.: Institute of Cardiology, Jagiellonian University Medical College, Kraków, Poland; M.A.G.: Hématologie biologique, AP-HP Hôpital Européen G. Pompidou, Paris, France)

Corresponding author Prof. Anetta Undas, MD, PhD, Instytut Kardiologii, Uniwersytet Jagielloński, Collegium Medicum, ul. Prądnicka 80, 31-202 Kraków, Poland, phone: +48-12-614-30-04, fax: +48-12-423-39-00, e-mail: mmundas@cyf-kr.edu.pl

Conflict of interest The authors declare no conflict of interest.

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