Novel Fibrinogen βbeta Chain Mutation as an Underlying Mechanism of Afibrinogenemia?

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We report on the first results of genetic analysis of DNA of the only patient suffering from afibrinogenemia in Slovakia. A 26-year-old man experienced most of the typical clinical signs of afibrinogenemia, including umbilical cord and intracranial bleeding.1 At baseline, fibrin-dependent coagulation tests, including prothrombin time, activated partial thromboplastin time, thrombin time, and also reptilase time, were unmeasurably prolonged and fibrinogen level measured by both the Clauss functional method as well as the Laurel immunologic assay was undetectable.

With the aim to identify the exact genetic defect responsible for his bleeding disorder, we performed DNA sequencing with subsequent genetic analysis. To our knowledge, the genetic analysis revealed a previously unidentified mutation in FGB, exon 4, nucleotide position 9661, caused by the mutation C>T, leading to the switch of amino acid glutamine to stop codon (proposed mutation nomenclature: NM_005141.4:c.991A>T, NP_005132.2:p.Gln180Stop) (► Fig. 1). In addition to this novel mutation, the previously described single nucleotide polymorphism, rs6050 (NM_000508.3(FGA):c.991A>G (p.Thr331Ala), NC_000004.12:g.154586438T>C) in exon 5 of FGA with the overall frequency 0.28918, and previously reported to modulate fibrinogen level measured by both the Clauss functional method was undetectable.

As it has already been reported, the occurrence of the stop codon, caused in our patient by the mutation C9661T, could lead to the elimination of aberrant mRNA, which encodes incomplete β chain polypeptide by the mechanism of nonsense-mediated mRNA decay.4 Moreover, the β polypeptide is the major rate-limiting factor in the synthesis of fibrinogen by the...
Therefore, we presume that in this patient, the Bβ chain of fibrinogen is not synthesized at all. We suppose that further synthesis of Bβ-γ intermediate product, as well as the addition of Bβ to form the AαBβγ half-molecule is not possible. The final consequence could be the failure of the dimerization into functional fibrinogen. Our hypothesis correlates well with the results of laboratory tests, revealing an absolute deficiency of fibrinogen in the plasma and also with life-threatening clinical manifestations of afibrinogenemia in our patient.

We hope that our report of this novel mutation, and our proposal regarding the pathogenetic mechanism of afibrinogenemia in this patient, will contribute to better prediction and antenatal diagnosis of this disorder.

Conflicts of Interest
None declared.

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References

Fig. 1 The result of DNA sequencing of FGB showing the mutation C9661T.