Letter to the Editor

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

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Semin Thromb Hemost 2015;41:901–902.

We read with great interest the updated article written by de Moerloose et al[1] in your journal regarding congenital fibrinogen disorders, including afibrinogenemia. We wish to report a novel mutation in fibrinogen β chain, and furthermore, propose a new underlying mechanism of this rare bleeding disorder. To our knowledge, the variant has not been previously described.

Fibrinogen is produced by the liver and comprises two sets of three polypeptides (Aα, Bβ, and γ), as encoded by the genes, *FGA*, *FGB*, and *FGG*, all localized within 50 kb on 4q31. Mutations in these genes can cause a deficiency of fibrinogen by the following mechanisms: they may affect production at the level of DNA, RNA influencing mRNA splicing or its stability, or interacting with the protein synthesis, as well as assembly and secretion.[1,2]

FGA, *FGB*, and *FGG* are transcribed and translated to polypeptides independent of each other: *FGA* (7.6 kb) comprises 6 exons producing 3 distinct transcripts leading to the formation of polypeptide of 644 amino acids Aα; *FGB* (8 kb) contains 8 exons which encode the only 1.9 kb transcript with the 1.5 kb coding sequence leading to the production of the 491-amino acid polypeptide Bβ; *FGG* (8.5 kb) comprises 10 exons with 2 mRNA products translating to the 437-amino acid polypeptide γ. Assembly in endoplasmic reticulum contributes to the creation of the Aα-γ or Bβ-γ intermediate product. Addition of Bβ or Aα chain produces an AαBβγ molecule, dimerizing to functional hexamer undergoing posttranslational modifications in Golgi apparatus.[1,2]

Afibrinogenemia, an extraordinary rare autosomal recessive bleeding disorder, is defined by the absence of fibrinogen activity and its antigen.[1,2]

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.538C > 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 the risk of cardiovascular diseases and inflammation, was found.[3]

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 Bβ polypeptide by the mechanism of nonsense-mediated mRNA decay.[4] Moreover, the Bβ polypeptide is the major rate-limiting factor in the synthesis of fibrinogen by the

published online October 20, 2015

Issue Theme Current Issues in Hemophilia: Recognizing Clinical Heterogeneity, Replacement Therapy and Outcome Assessment; Guest Editor: Alok Srivastava, MD, FRACP, FRCPA, FRCP.

DOI http://dx.doi.org/10.1055/s-0035-1564802.
ISSN 0094-6176.

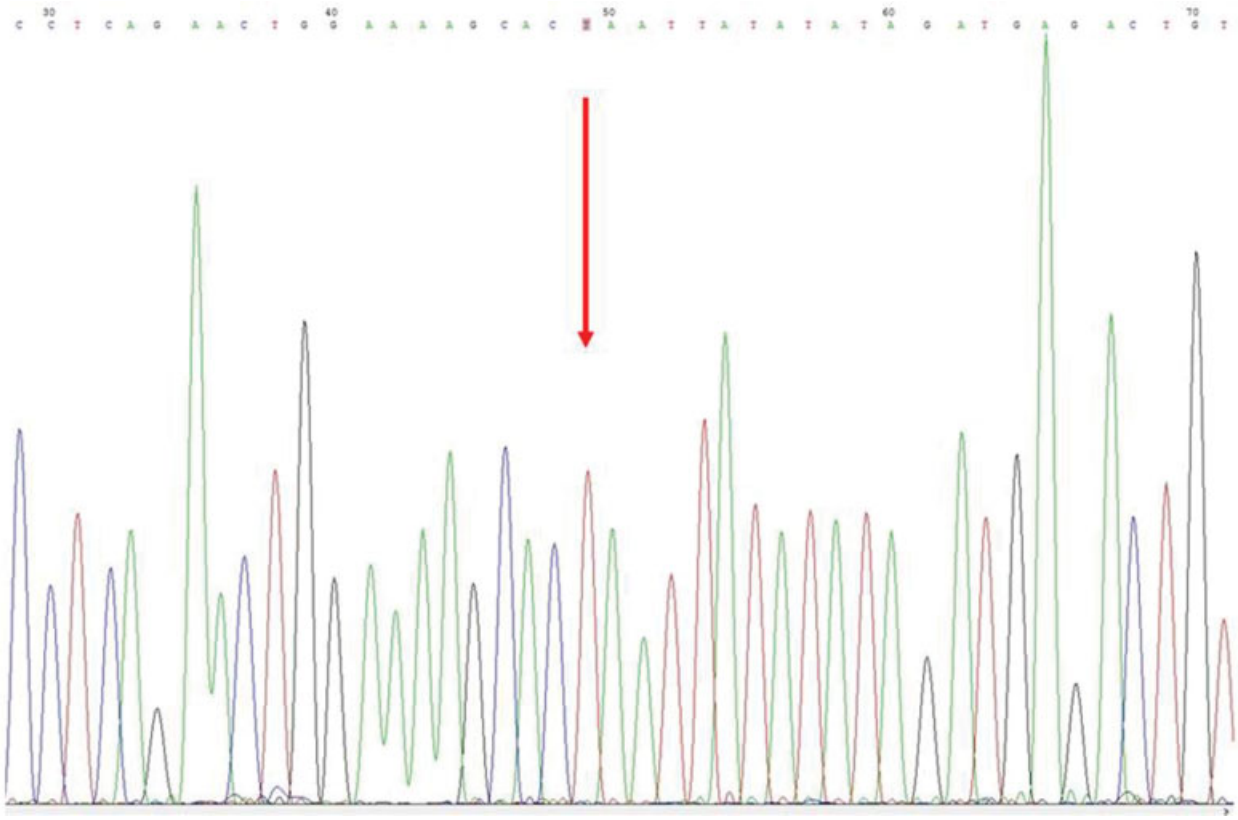

Fig. 1 The result of DNA sequencing of *FGB* showing the mutation C9661T.

liver.[5] 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.

Acknowledgments

This work has a general support by departmental chairs. We would like to thank the support of projects Virtual and Simulation Tuition as a New Form of Education at Comenius University in Bratislava, Jessenius Faculty of Medicine in Martin, operation program Education (ITMS 26110230071), Martin Center of Biomedicine (BioMed Martin, ITMS 26220220187), and Agency for the Support of Research and Development (APVV) 0222–11.

References

1 de Moerloose P, Casini A, Neerman-Arbez M. Congenital fibrinogen disorders: an update. Semin Thromb Hemost 2013;39(6): 585–595
2 Neerman-Arbez M, de Moerloose P. Mutations in the fibrinogen gene cluster accounting for congenital afibrinogenemia: an update and report of 10 novel mutations. Hum Mutat 2007;28(6): 540–553
3 Rs6050. Available at: http://www.snpedia.com/index.php/Rs6050. Accessed February 3, 2015
4 Baker KE, Parker R. Nonsense-mediated mRNA decay: terminating erroneous gene expression. Curr Opin Cell Biol 2004;16(3): 293–299
5 Casini A, Lukowski S, Quintard VL, et al. FGB mutations leading to congenital quantitative fibrinogen deficiencies: an update and report of four novel mutations. Thromb Res 2014;133(5): 868–874