frontiers in Medicine

MINI REVIEW
published: 15 April 2021
doi: 10.3389/fmed.2021.654197

The Possible Non-Mutational Causes of FVIII Deficiency: Non-Coding RNAs and Acquired Hemophilia A

Alina-Andreea Zimta[1†], Ionut Hotea[2,3†], Melen Brinza[4,5], Cristina Blag[6,7], Sabina Iluta[2], Catalin Constantinescu[2,8], Atamyrat Bashimov[1], Elisabeth-Antonia Marchis-Hund[1], Alexandra Coudsy[1], Laetitia Muller-Mohnssen[1], Noemi Dirzu[1], Diana Gulei[1], Delia Dima[2], Margit Serban[9,10,11], Daniel Coriu[4,5] and Ciprian Tomuleasa[1,2,3]*

[1] Medfuture Research Center for Advanced Medicine, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj Napoca, Romania, [2] Department of Hematology, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj Napoca, Romania, [3] Department of Hematology, Ion Chiricuta Clinical Cancer Center, Cluj Napoca, Romania, [4] Department of Hematology, Fundeni Clinical Institute, Bucharest, Romania, [5] Department of Hematology, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania, [6] Department of Pediatrics, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj Napoca, Romania, [7] Department of Hematology, Emergency Clinical Children's Hospital, Cluj Napoca, Romania, [8] Intensive Care Unit, Clinical Hospital for Infectious Diseases, Cluj Napoca, Romania, [9] Louis Turcanu Emergency Children's Hospital, Timisoara, Romania, [10] European Hemophilia Treatment Center, Timisoara, Romania, [11] Department of Pediatrics, Victor Babes University of Medicine and Pharmacy, Timisoara, Romania*

Hemophilia type A (HA) is the most common type of blood coagulation disorder. While the vast majority of cases are inherited and caused by mutations in the *F8* gene, recent data raises new questions regarding the non-heritability of this disease, as well as how other molecular mechanisms might lead to the development of HA or increase the severity of the disease. Some data suggest that miRNAs may affect the severity of HA, but for some patients, miRNA-based interference might cause HA, in the absence of an *F8* mutation. A mechanism in HA installation that is also worth investigating and which could be identified in the future is the epigenetic silencing of the *F8* gene that might be only temporarily. Acquired HA is increasingly reported and as more cases are identified, the description of the disease might become challenging, as cases without FVIII autoantibodies might be identified.

Keywords: hemophilia, non-coding RNAs, epigenetics, hypothesis, acquired bleeding disorder

OPEN ACCESS

Edited by:
Robert Campbell,
The University of Utah, United States

Reviewed by:
Bipin P. Kulkarni,
Indian Council of Medical Research, India
Zuben E. Sauna,
United States Food and Drug Administration, United States
Chava Kimchi-sarfaty,
United States Food and Drug Administration, United States
Katarzyna Jankowska,
Center for Biologics Evaluation and Research (CBER), FDA, United States, in collaboration with reviewer CK-s

**Correspondence:*
Ciprian Tomuleasa
ciprian.tomuleasa@umfcluj.ro

†These authors have contributed equally to this work and share first authorship

Specialty section:
This article was submitted to Hematology, a section of the journal Frontiers in Medicine

Received: 15 January 2021
Accepted: 11 March 2021
Published: 15 April 2021

Citation:
Zimta A-A, Hotea I, Brinza M, Blag C, Iluta S, Constantinescu C, Bashimov A, Marchis-Hund E-A, Coudsy A, Muller-Mohnssen L, Dirzu N, Gulei D, Dima D, Serban M, Coriu D and Tomuleasa C (2021) The Possible Non-Mutational Causes of FVIII Deficiency: Non-Coding RNAs and Acquired Hemophilia A. Front. Med. 8:654197. doi: 10.3389/fmed.2021.654197

INTRODUCTION—"CLASSICAL" VIEW OF HEMOPHILIA TYPE A AND THE STILL UNANSWERED QUESTIONS

Hemophilia type A (HA) is a blood coagulation disorder described as an inherited condition caused by mutations in the *F8* gene. Two mutations are found the most often in HA: intron 22 inversion (inv 22) and intron 1 inversion. Inv 22 is the most frequent mutation with different reported frequency, depending on the population: 35% (1), 45% of severe HA cases (2). Inv1 is the second most common mutation of HA in severe HA, with a different reported frequency of between 5 (3) and 7% (1). One large populational study from the US, the My Life, Our Future (MLOF) project concluded that the inv22 is found in 42% of severe HA cases and 3.7% of mild/moderate cases. Inv1 was found in 1.2% of severe HA cases and 0.2% of mild/moderate HA cases. In the majority of HA cases, which account for around 79.5% of patients, the most common type of mutation is the missense mutation (4).