Received: 28 January 2025 | Revised: 4 February 2025 | Accepted: 10 February 2025

https://doi.org/10.1016/j.rpth.2025.102703

BRIEF REPORT

Identification and characterization of factor XI autoantibodies in 2 patients with systemic lupus erythematosus: insights into mechanisms of acquired factor XI deficiency

Priyanka Srivastava[1] | Amy Zhou[2] | Christine Fuja[3] | Charles S. Eby[3] | Gail Baxter[1] | Anton Matafonov[1] | Serena Fedorov[1] | Miriam Brown[1] | Michael Pettit[1] | Benjamin F. Tillman[1,4] | David Gailani[1] | Jeremy W. Jacobs[1]

[1]Department of Pathology, Microbiology and Immunology, Vanderbilt University Medical Center, Nashville, Tennessee, USA

[2]Division of Hematology, Washington University School of Medicine, St Louis, Missouri, USA

[3]Department of Pathology and Immunology, Washington University School of Medicine, St. Louis, Missouri, USA

[4]Division of Hematology and Oncology, Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee, USA

Correspondence
Jeremy W. Jacobs, Department of Pathology, Microbiology and Immunology, Vanderbilt University Medical Center, Room C2318-C, Medical Center North, 1161 21st Ave S, Nashville, TN 37232, USA.
Email: Jeremy.w.jacobs@vumc.org

Handling Editor: Professor Michael Markis

Abstract

Background: Factor (F)XI is a zymogen that contributes to thrombin generation through activation of FIX. Patients with a complete absence of FXI are prone to developing alloantibody inhibitors after replacement therapy. Acquired FXI autoantibodies are less common, and data regarding their mechanisms of action are lacking.

Objectives: We describe 2 patients with severe acquired FXI deficiency and identify the FXI domains to which the autoantibodies bind.

Methods: FXI and prekallikrein (PK) are homologs with similar structures. We prepared recombinant human FXI and PK, as well as chimeric molecules in which individual domains within FXI or PK are replaced with the corresponding domain from the other protein. Patient plasma and normal plasma were used as antibody sources, and their capacities to recognize recombinant proteins on Western blots were compared.

Results: Patients 1 and 2 were females with systemic lupus erythematous and no bleeding history. FXI activity in both cases was undetectable by one-stage clotting assay, with autoantibody titers of 64 Bethesda Units and 11.4 Bethesda Units, respectively. In both cases, the autoantibody appeared to clear FXI protein from plasma. Immunoglobulin G in patient 1 targeted the FXI catalytic domain, while the autoantibody in patient 2 was likely oligoclonal with components that recognized the FXI apple 2 and apple 3 domains.

Conclusion: These autoantibodies inhibited FXI function and promoted its clearance. The inhibitors targeted the 2 most important FXIa domains for FIX activation and demonstrated properties similar to those described in patients with FXI alloantibody inhibitors.

KEYWORDS
blood coagulation factor, blood coagulation factor inhibitors, factor XI, hemostasis

The senior authors David Gailani and Jeremy W. Jacobs contributed equally to this study.

Essentials

- Data regarding the mechanisms of action of FXI autoantibodies are lacking.
- We identified the FXI binding domains in 2 patients with severe acquired FXI deficiency.
- The autoantibody in patient 1 targeted the FXI catalytic domain.
- The autoantibody in patient 2 was likely oligoclonal and recognized the FXI A2 and A3 domains.

1 | INTRODUCTION

Factor (F)XI is the zymogen of a trypsin-like protease (FXIa) that contributes to thrombin generation through the activation of FIX [1,2]. Severe inherited FXI deficiency (plasma level < 15% of normal) may be associated with excessive trauma-induced bleeding, particularly when tissues with high fibrinolytic activity (eg, nasopharynx, oral cavity, and genitourinary tract) are involved [3,4]. However, spontaneous hemorrhage in individuals with severe FXI deficiency is rare. Severe congenital FXI deficiency is primarily an autosomal recessive condition that is particularly prevalent in people of Ashkenazi Jewish ancestry (1 in 450 individuals) [3–5]. Two single nucleotide variants (SNVs) in the FXI gene (*F11*), each with an allele frequency of 2% to 2.5%, are responsible for most cases of FXI deficiency in this population [5,6]. The type II SNV (Glu117Stop) prevents protein production, while the type III SNV (Phe283Leu) reduces protein secretion from hepatocytes [5,6].

Patients with a complete absence of FXI in their plasma are prone to developing alloantibody inhibitors [7–9]. Salomon et al. [7] observed that one-third of patients homozygous for the Glu117Stop SNV formed neutralizing anti-FXI antibodies after plasma infusion, often after a single exposure. Acquired FXI deficiency caused by an autoantibody appears to be less common than replacement therapy-related alloantibodies to FXI, although there may be underreporting given the relatively mild clinical phenotype. Most cases are described in patients with autoimmune or neoplastic disorders [10–18]. Given their rarity, there is a paucity of data regarding their mechanisms of action. Here, we describe 2 patients with severe acquired FXI deficiency and identify the FXI domains to which the autoantibodies bind.

2 | METHODS

2.1 | Coagulation assays

For patient 1, prothrombin time (PT) and activated partial thromboplastin time (aPTT) assays, plasma mixing studies, measurements of coagulation factor levels, Bethesda inhibitor titer assays, and the dilute Russell's viper venom time (dRVVT) were performed on plasma anticoagulated with 0.32% sodium citrate with Werfen reagents on the ACL TOP (Werfen). Lupus-sensitive aPTT results were performed using Silica Clotting Time (Werfen) and StaClot LA (Diagnostica Stago), and both assays were performed on the ACL TOP. For patient 2, PT and aPTT assays, plasma mixing studies, measurements of coagulation factor levels, and Bethesda inhibitor titer assays were performed on patient plasma anticoagulated with 0.32% sodium citrate on a Sta-R Max analyzer (Diagnostica Stago). We adhered to guidelines pertaining to ethical standards and informed consent.

2.2 | Recombinant proteins

Production of recombinant human FXI [19,20], FXI with prekallikrein (PK) domain substitutions [19,20], and human PK [21] have been described. The complementary (c)DNA for human PK was modified by exchanging the sequence encoding the PK apple (A)1, A2, A3, or A4 domain with the corresponding sequence from human FXI to create the chimeras PK/FXIA1, PK/FXIA2, PK/FXIA3, and PK/FXIA4. Each cDNA was modified to include a 9-amino acid hemagglutinin tag sequence (YPYDVPDYA) at the C-terminus to facilitate purification [21]. The cDNAs were introduced into the mammalian expression vector pJVCMV and expressed in human embryonic kidney (HEK)293 cells [19,21,22]. Proteins were purified by affinity chromatography using antihemagglutinin immunoglobulin (Ig) G agarose [21].

2.3 | Western blots

Samples were size-fractionated on nonreducing 7.5% polyacrylamide-sodium dodecyl sulfate gels and transferred to nitrocellulose membranes. Samples contained 1 μL of pooled normal or patient plasma or 0.4 μg recombinant protein in 20 μL of 25 mM Tris-HCL, 100 mM NaCl, pH 7.4 (Tris-buffered saline [TBS]). The primary detection IgGs were a polyclonal goat antihuman FXI IgG (5 μg/mL in TBS), patient plasma diluted 1:50 in TBS, or pooled normal plasma diluted 1:50 in TBS. The secondary antibodies were Alexa Fluor 680 conjugated donkey antigoat IgG (∼1:15,000 dilution) or goat antihuman IgG (1:5000 dilution). Proteins on membranes were visualized using a LI-COR Odyssey Imager.

3 | RESULTS AND DISCUSSION

3.1 | Patient 1

A 38-year-old female with systemic lupus erythematosus (SLE) was referred to the hematology clinic for a persistently prolonged aPTT. She did not have signs or symptoms of abnormal hemostasis and tolerated hysterectomy, multiple paracenteses, and pleural catheter placement without excessive bleeding. She was receiving treatment

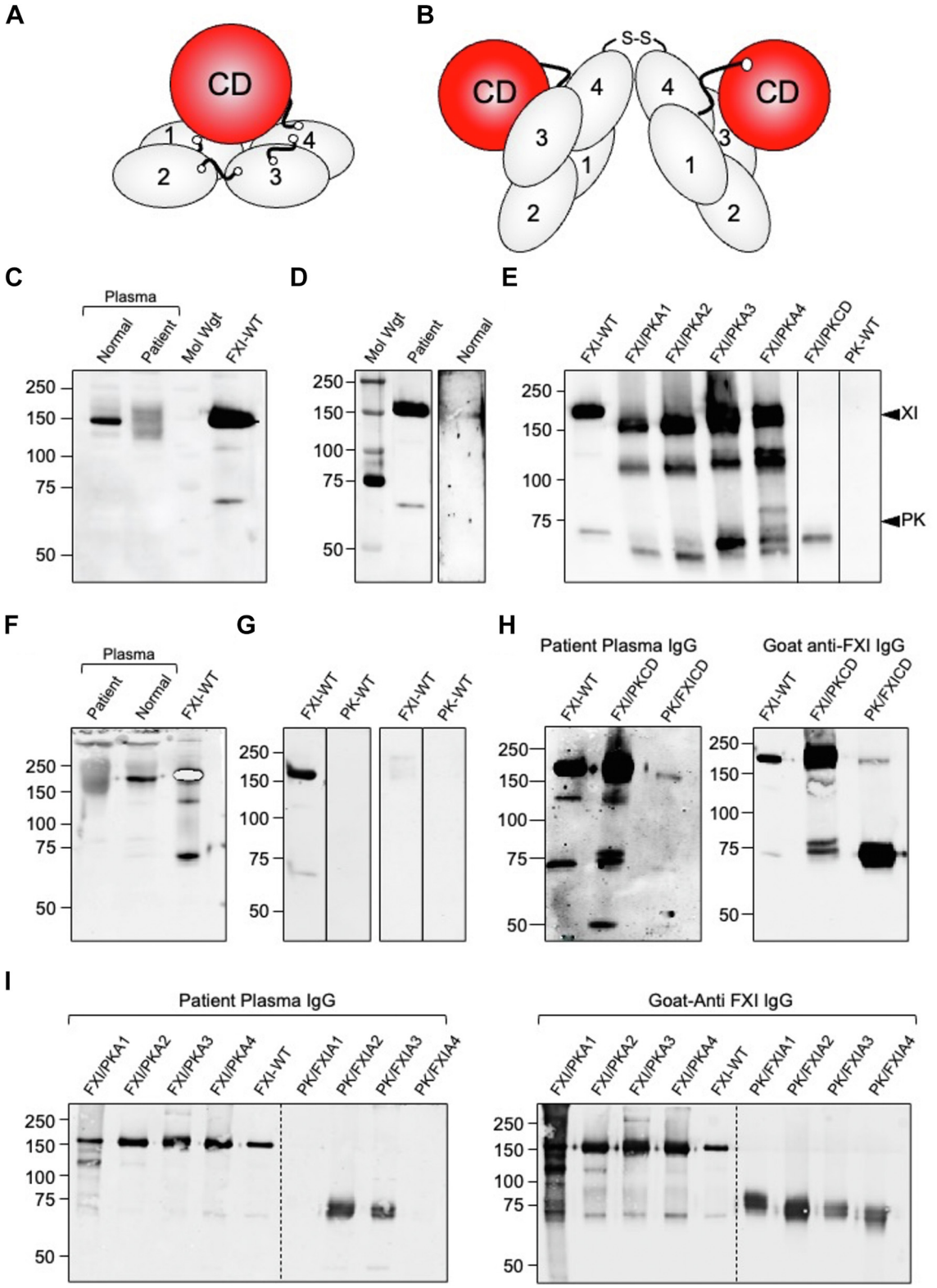

FIGURE 1 Protein models (A and B). Models for (A) prekallikrein (PK) and a subunit of factor (F)XI and (B) the FXI dimer. PK and the FXI subunit contain 4 apple (A) domains (gray ovals 1-4) and a C-terminal catalytic domain (CD). Conversion to the active proteases PKa and FXIa involves single proteolytic cleavages between A4 and the CD. The A4 domain of the FXI subunit forms an interface with another subunit to form a homodimer held together with a single disulfide bond. On nonreducing sodium dodecyl sulfate–polyacrylamide gel electrophoresis, the apparent molecular mass of FXI will be about twice that of PK because it is a dimer. (C–I) Western blots. (C) Blot of normal plasma, patient plasma for case 1, and 0.4 μg of wild-type (WT) FXI (FXI-WT). The detection antibody was polyclonal goat antihuman FXI immunoglobulin (Ig) G. (D) Blots of FXI-WT. The detection IgG source was patient plasma for case 1 (left) or normal plasma (right). (E) Blot of FXI-WT, FXI/PK chimeras

with hydroxychloroquine, mycophenolate mofetil, and prednisone at the time of presentation and had received rituximab in the past. Her aPTT was normal at the time of her SLE diagnosis 15 years earlier but had been prolonged for the past 10 years. The aPTT was 104.3 seconds (normal 25-37 seconds) on the day of the clinic visit and did not correct on mixing with pooled normal plasma. The PT (10.7 seconds, normal 9.2-14.0 seconds) and dRVVT were normal. The StaClot LA (Diagnostica Stago) was technically positive for a lupus anticoagulant, but the delta of the screen and confirmed clotting times was barely above the normal reference range (14 seconds, normal < 10 seconds). FVIII (112%, normal 45%-160%) and FIX (58%, normal 55%-160%) activities were normal, although both demonstrated inhibitor patterns and required dilution to reach a "normal" activity. Cumulatively, these findings raised the possibility of a nonspecific inhibitor such as a lupus anticoagulant; however, FXI activity was undetectable (<1%, normal 60%-140%) and did not increase upon serial dilution, consistent with a specific FXI inhibitor. The FXI inhibitor titer was subsequently determined to be 64 Bethesda Units.

3.2 | Patient 2

An 18-year-old female with SLE and lupus nephritis presented to the rheumatology clinic for a routine visit. At the time of diagnosis 4 years earlier, methylprednisolone, mycophenolate mofetil, and hydroxychloroquine were initiated. There were no new clinical concerns, and she had no features suggestive of a bleeding diathesis. The aPTT was prolonged (74.7 seconds, normal 23.5-33.5 seconds) and did not correct upon mixing with pooled normal plasma (66.5 seconds at 0 hours; 71.4 seconds at 1 hour; 72.0 seconds at 2 hours). There were no aPTT values available prior to her SLE diagnosis. The PT (14.1 seconds, normal 11.9-14.5 seconds) was normal, and the dRVVT and StaClot LA tests for a lupus anticoagulant were negative. FVIII (191%, normal 50%-150%), FIX (161%, normal 50%-150%), and FXII (151%, normal 50%-150%) activities were modestly elevated, but the FXI activity was markedly reduced (<3%, normal 50%-150%). The titer of the FXI inhibitor was 11.4 Bethesda Units. She had not been pregnant or exposed to blood products prior to her initial prolonged aPTT.

Western blotting was used to identify IgGs in patient plasma that recognized FXI. The *F11* gene encodes an 80 kDa polypeptide containing 4 A domains (designated A1 to A4 from the N-terminus) and a C-terminal catalytic domain (CD; Figure 1A) [1]. FXI in plasma is a 160 kDa protein comprised 2 of these polypeptides connected through the A4 domains (Figure 1B) [1,23]. Figure 1C shows a Western blot of normal plasma, and patient 1 plasma was probed with a goat IgG to human FXI. The sharp FXI band in normal plasma is missing from patient plasma, indicating the FXI protein has been removed from plasma. Consistent with this, an enzyme-linked immunosorbent assay for FXI did not detect FXI protein in the patient's plasma. In the blot in Figure 1D, patient (left) and normal (right) plasma were used as sources of IgG to detect pure FXI. Patient 1 plasma contains an IgG that recognizes FXI, while normal plasma does not. FXI and its paralog PK have similar domain organization (Figure 1A), except that PK is monomeric [1,24]. We took advantage of the homology to prepare FXI molecules in which individual A domains (FXI/PKA1, FXI/PKA2, FXI/PKA3, and FXI/PKA4) or the CD (FXI/PKCD) were replaced with the corresponding PK domain. The blot in Figure 1E contains samples of wild-type (WT) FXI (FXI-WT) and PK-WT, as well as FXI/PK chimeras. The IgG in patient 1 plasma recognized FXI-WT and the FXI/PKA1, FXI/PKA2, FXI/PKA3, and FXI/PKA4 chimeras, but did not recognize FXI/PKCD or PK-WT, indicating the FXI inhibitor targets the FXICD.

Like patient 1 plasma, patient 2 plasma lacked FXI protein (Figure 1F) and contained an IgG that recognized FXI-WT (Figure 1G). In contrast to patient 1, patient 2 plasma recognized FXI/PKCD but not a chimera containing PK A domains and the PK/FXICD (Figure 1H). While these results imply that the IgG in patient 2 targeted a FXI A domain, the antibody recognized all FXI proteins with individual PK A domain replacements (Figure 1I, left side of the panel). This suggests the inhibitor may be comprised of more than 1 antibody (ie, oligoclonal). Consistent with this, when using a panel of PK molecules in which individual A domains were replaced with FXI A domains, patient 2 plasma recognized chimeras with the FXIA2 and FXIA3 domains. A monoclonal IgG that recognized a shared epitope between FXIA2 and FXIA3 is possible but not likely, as it would likely not bind to a protein in which either FXIA2 or FXIA3 was replaced with the PKA2 or PKA3 domains (FXI/PKA2 or FXI/PKA3).

Autoantibodies to a clotting factor may compromise blood coagulation by inhibiting the function of the targeted factor, by inducing clearance of the factor from plasma, or by a combination of the 2 processes. Previously, we described a young child with membranoproliferative glomerulonephritis who developed an autoantibody to FXI, rendering the patient refractory to plasma infusions [25]. Mixing patient plasma with normal plasma corrected the abnormal aPTT in this case, indicating that the autoantibody acted primarily by inducing FXI clearance from plasma *in vivo*. The inhibitors characterized in the current study also appear to be IgGs that reduce FXI antigen in plasma. However, unlike our prior case, mixing studies

with individual A domain replacements (FXI/PKA1, FXI/PKA2, FXI/PKA3, and FXI/PKA4), a chimera with FXIA1 to FXIA4 and the PK CD (FXI/PKCD), and PK-WT. The detection IgG was plasma for case 1. FXI/PKA4 is a dimer despite the replacement of the FXI A4 domain because of a serine substitution for Cys326 that frees Cys321 for dimerization. The positions of FXI and PK standards are shown on the right side of the blot. (F) As in panel C, except that the patient's plasma is from case 2. (G) As in panel D, except that the patient's plasma is from case 2. (H) Blots with FXI-WT, FXI/PKCD, and chimeras with PK A1 to A4 and FXI-CD (PK/FXICD). The blot on the left was developed with patient plasma from case 2, while the blot on the right was developed with polyclonal goat antihuman FXI IgG. (I) Blots of FXI/PK chimeras and FXI-WT (left part of the blot) and PK/FXI chimeras (right part of the blot). The blot on the left was developed with patient plasma from case 2, while the blot on the right was developed with polyclonal goat antihuman FXI IgG. For all blots, positions of molecular mass standards are shown on the left of each panel. Mol Wgt, molecular weight.

utilizing pooled normal plasma indicate these antibodies also neutralize FXI or FXIa activity *in vitro*.

The locations of the binding sites for the inhibitors on the FXI protein are worth noting. We would expect an inhibitor that binds to the FXIa CD to neutralize protease activity toward its macromolecular substrate FIX. However, the FXIA3 domain is also required for normal FIX activation. There is a FIX binding exosite on FXIA3 that becomes exposed upon the conversion of FXI to FXIa [22,26]. The exosite positions FIX properly for efficient activation, and loss or inhibition of the exosite results in a marked decrease in FXIa catalytic efficiency toward FIX (<1% of normal) [22,26]. Thus, the 2 most important FXIa domains for protease function are the targets of the antibodies identified in our 2 patients. These autoantibodies may have similar inhibitory activities to those described for alloantibody inhibitors in FXI-deficient patients by Salomon et al. [7]. Alloantibodies or autoantibodies to parts of FXI other than the catalytic or A3 domain may occur, but unless they clear FXI from plasma, they may not affect FXI function sufficiently to be detected by an aPTT assay.

A review of the literature indicates that FXI autoantibodies are rare and predominantly occur in patients with rheumatologic conditions, particularly SLE [10,27–31]. Despite their marked effects on the aPTT, the FXI inhibitors in our patients appear to have been present for years without compromising hemostasis. However, there are reports of significant hemorrhage associated with FXI autoantibodies [10]. It is possible that the antibodies in such cases have specific functional properties that are not common to other FXI inhibitors. Alternatively, given the mild and variable bleeding diathesis associated with inherited FXI deficiency, hemostasis in certain individuals may be more dependent on FXI activity, rendering them more susceptible to bleeding if they develop a FXI inhibitor. Finally, our patient 2 had a prolonged aPTT that was assumed, erroneously for several years, to be due to a lupus anticoagulant. This highlights the need to fully investigate the etiology of a prolonged aPTT, particularly in patients with autoinflammatory conditions associated with nonspecific inhibitors such as lupus anticoagulants, to exclude coexisting specific autoantibodies to coagulation factors that could potentially compromise hemostasis.

FUNDING

This work was supported the National Heart, Lung, and Blood Institute of the National Institutes of Health (award HL140025), and by the Ernest W. Goodpasture Chair in Experimental Pathology for Translational Research from Vanderbilt University.

AUTHOR CONTRIBUTIONS

P.S. performed the laboratory analysis and critically revised the manuscript. J.W.J. provided supervision, performed a literature review, and drafted the manuscript. D.G. provided supervision and funding and critically revised the manuscript. A.Z., C.F., and C.S.E. provided clinical data and critically revised the manuscript. G.B., A.M., S.F., M.B., M.P., and B.F.T. critically revised the manuscript. All authors approved the final version.

RELATIONSHIP DISCLOSURE

D.G. is a consultant for several pharmaceutical companies with interests in developing drugs that target factor XI and prekallikrein. All other authors report no potential conflicts of interest related to this study.

ORCID

Christine Fuja https://orcid.org/0000-0001-8044-5314
Miriam Brown https://orcid.org/0000-0001-5006-7068
David Gailani https://orcid.org/0000-0001-8142-8014
Jeremy W. Jacobs https://orcid.org/0000-0002-5719-9685

X

Jeremy W. Jacobs @jwjacobs12

REFERENCES

[1] Mohammed BM, Matafonov A, Ivanov I, Sun MF, Cheng Q, Dickeson SK, et al. An update on factor XI structure and function. *Thromb Res*. 2018;161:94–105.
[2] Moellmer SA, Puy C, McCarty OJT. Biology of factor XI. *Blood*. 2024;143:1445–54.
[3] Barg AA, Livnat T, Kenet G. Factor XI deficiency: phenotypic age-related considerations and clinical approach towards bleeding risk assessment. *Blood*. 2024;143:1455–64.
[4] Sharman Moser S, Chodick G, Ni YG, Chalothorn D, Wang MD, Shuldiner AR, et al. The association between factor XI deficiency and the risk of bleeding, cardiovascular, and venous thromboembolic events. *Thromb Haemost*. 2022;122:808–17.
[5] Asselta R, Paraboschi EM, Rimoldi V, Menegatti M, Peyvandi F, Salomon O, et al. Exploring the global landscape of genetic variation in coagulation factor XI deficiency. *Blood*. 2017;130:e1–6. https://doi.org/10.1182/blood-2017-04-780148
[6] Peretz H, Mulai A, Usher S, Zivelin A, Segal A, Weisman Z, et al. The two common mutations causing factor XI deficiency in Jews stem from distinct founders: one of ancient Middle Eastern origin and another of more recent European origin. *Blood*. 1997;90:2654–9.
[7] Salomon O, Zivelin A, Livnat T, Dardik R, Loewenthal R, Avishai O, et al. Prevalence, causes, and characterization of factor XI inhibitors in patients with inherited factor XI deficiency. *Blood*. 2003;101:4783–8.
[8] Schnall SF, Duffy TP, Clyne LP. Acquired factor XI inhibitors in congenitally deficient patients. *Am J Hematol*. 1987;26:323–8.
[9] Zucker M, Zivelin A, Teitel J, Seligsohn U. Induction of an inhibitor antibody to factor XI in a patient with severe inherited factor XI deficiency by Rh immune globulin. *Blood*. 2008;111:1306–8.
[10] Bortoli R, Monticielo OA, Chakr RM, Palominos PE, Rohsig LM, Kohem CL, et al. Acquired factor XI inhibitor in systemic lupus erythematosus–case report and literature review. *Semin Arthritis Rheum*. 2009;39:61–5.
[11] Castaman G, Ruggeri M, Rodeghiero F. Acquired transitory factor XI inhibitor after gynaecological surgery. *Haemophilia*. 2008;14:643–4.
[12] Mi J, Liu C, Huang X, Ling L, Zhou J. Acquired factor XI inhibitor with immune system disorder: a case report. *Med Case Rep Stud Protoc*. 2021;2:e0079. https://doi.org/10.1097/MD9.0000000000000079
[13] Goodrick MJ, Prentice AG, Copplestone JA, Pamphilon DH, Boon RJ. Acquired factor XI inhibitor in chronic lymphocytic leukaemia. *J Clin Pathol*. 1992;45:352–3.
[14] Kyriakou DS, Alexandrakis MG, Passam FH, Foundouli K, Matalliotakis E, Koutroubakis IE, et al. Acquired inhibitors to coagulation factors in patients with gastrointestinal diseases. *Eur J Gastroenterol Hepatol*. 2002;14:1383–7.

[15] Reece EA, Clyne LP, Romero R, Hobbins JC. Spontaneous factor XI inhibitors. Seven additional cases and a review of the literature. *Arch Intern Med*. 1984;144:525–9.
[16] Segalen I, Siohan P, Podeur L, Wehbe B, Hutin P, Lellouche F. [Acquired factor XI inhibitor and chronic lymphocytic leukemia]. *Rev Med Interne*. 2008;29:832–3.
[17] Zucker S, Zarrabi MH, Romano GS, Miller F. IgM inhibitors of the contact activation phase of coagulation in chlorpromazine-treated patients. *Br J Haematol*. 1978;40:447–57.
[18] Uwingabiye J, Zahid H, El Amrani M, Labrini F, Elkhazraji A, El Kabbaj D, et al. Rare and unusual case of anti-factor XI antibodies in patient with plasma cell leukemia. *BMC Hematol*. 2018;18:18. https://doi.org/10.1186/s12878-018-0100-9
[19] Cheng Q, Sun MF, Kravtsov DV, Aktimur A, Gailani D. Factor XI apple domains and protein dimerization. *J Thromb Haemost*. 2003;1:2340–7.
[20] Ivanov I, Verhamme IM, Sun MF, Mohammed B, Cheng Q, Matafonov A, et al. Protease activity in single-chain prekallikrein. *Blood*. 2020;135:558–67.
[21] Mohammed BM, Sun MF, Cheng Q, Litvak M, McCrae KR, Emsley J, et al. High molecular weight kininogen interactions with the homologs prekallikrein and factor XI: importance to surface-induced coagulation. *J Thromb Haemost*. 2024;22:225–37.
[22] Sun Y, Gailani D. Identification of a factor IX binding site on the third apple domain of activated factor XI. *J Biol Chem*. 1996;271:29023–8.
[23] Papagrigoriou E, McEwan PA, Walsh PN, Emsley J. Crystal structure of the factor XI zymogen reveals a pathway for transactivation. *Nat Struct Mol Biol*. 2006;13:557–8.
[24] Li C, Voos KM, Pathak M, Hall G, McCrae KR, Dreveny I, et al. Plasma kallikrein structure reveals apple domain disc rotated conformation compared to factor XI. *J Thromb Haemost*. 2019;17:759–70.
[25] McManus MP, Frantz C, Gailani D. Acquired factor XI deficiency in a child with membranoproliferative glomerulonephritis. *Pediatr Blood Cancer*. 2012;59:173–5.
[26] Geng Y, Verhamme IM, Sun MF, Bajaj SP, Emsley J, Gailani D. Analysis of the factor XI variant Arg184Gly suggests a structural basis for factor IX binding to factor XIa. *J Thromb Haemost*. 2013;11:1374–84.
[27] Madan B, McCormick A, Polgrean R. Diagnosis and management of acquired factor XI deficiency in systemic lupus erythematosus [abstract]. *Haemophilia*. 2021;27:153–4.
[28] Martinuzzo M, Seehaus CM, López MS, Barrera LH, Garrott LF, Maffassanti PQ, et al. Acquired FXI deficiency in a systemic lupus erythematosus patient: evolution and coagulation phenotypic changed to lupus anticoagulant during immunosuppressive therapy. *Int J Lab Hematol*. 2022;44:e269–74. https://doi.org/10.1111/ijlh.13937
[29] Seehaus CM, Lopez MS, Barrera LH, Quinones Maffassanti P, Ferreyra Garrott L, Privitera V, et al. Acquired factor XI deficiency: diagnosis and evolution. A case report. *Res Pract Thromb Haemost*. 2019;3(Supp 1):373–4.
[30] Vercellotti GM, Mosher DF. Acquired factor XI deficiency in systemic lupus erythematosus. *Thromb Haemost*. 1982;48:250–2.
[31] Wool GD, Treml A, Miller JL. Acquired factor XI deficiency and therapeutic plasma exchange. *J Clin Apher*. 2018;33:427–30.