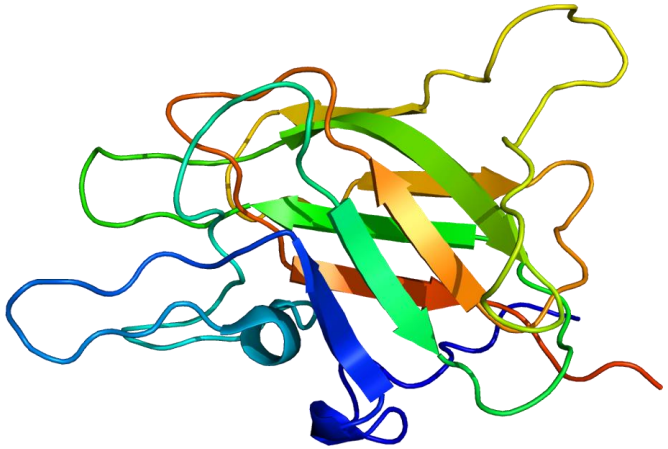


Basics of Factor V, Combined FV, & FVIII- FV-Short Deficiency

Sweta Gupta, MD, MS
Indiana Hemophilia & Thrombosis Center

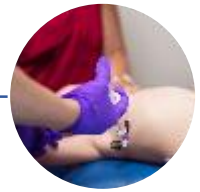
NATIONAL HEMOPHILIA FOUNDATION

No financial disclosures

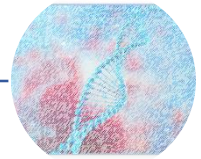
Care of Patients With Bleeding Disorders

Role in clotting

Diagnosis



Treatment



Future

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FV--Role in clotting

- First reported in 1947 by Owren
- Primarily made in the liver
- 20% of FV in platelets
- Half life 12-36 hrs

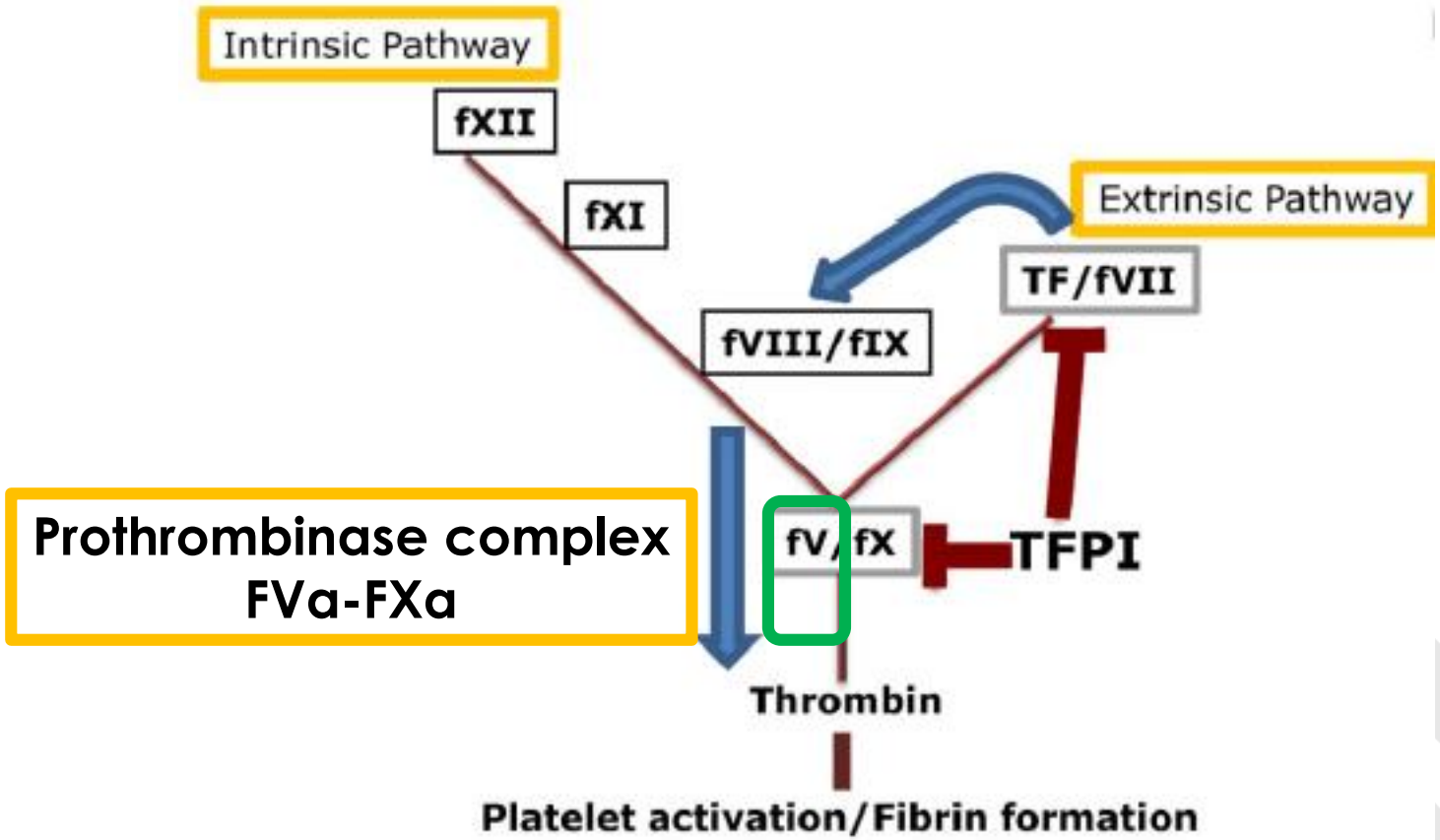

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Image: Alan E. Mast , Arterioscler Thromb Vasc Biol. 2016 January ; 36(1): 9–14.

FV deficiency--Diagnosis

Inheritance

- Rare bleeding disorder: 1 in 1,000,000
- 56 mutations published to date
  - Majority are null mutations for severe FV deficiency
- Autosomal Recessive
  - Males = females
  - More common in Iran & southern India where it is ten times more frequent than in western countries
- Genetic counselling important

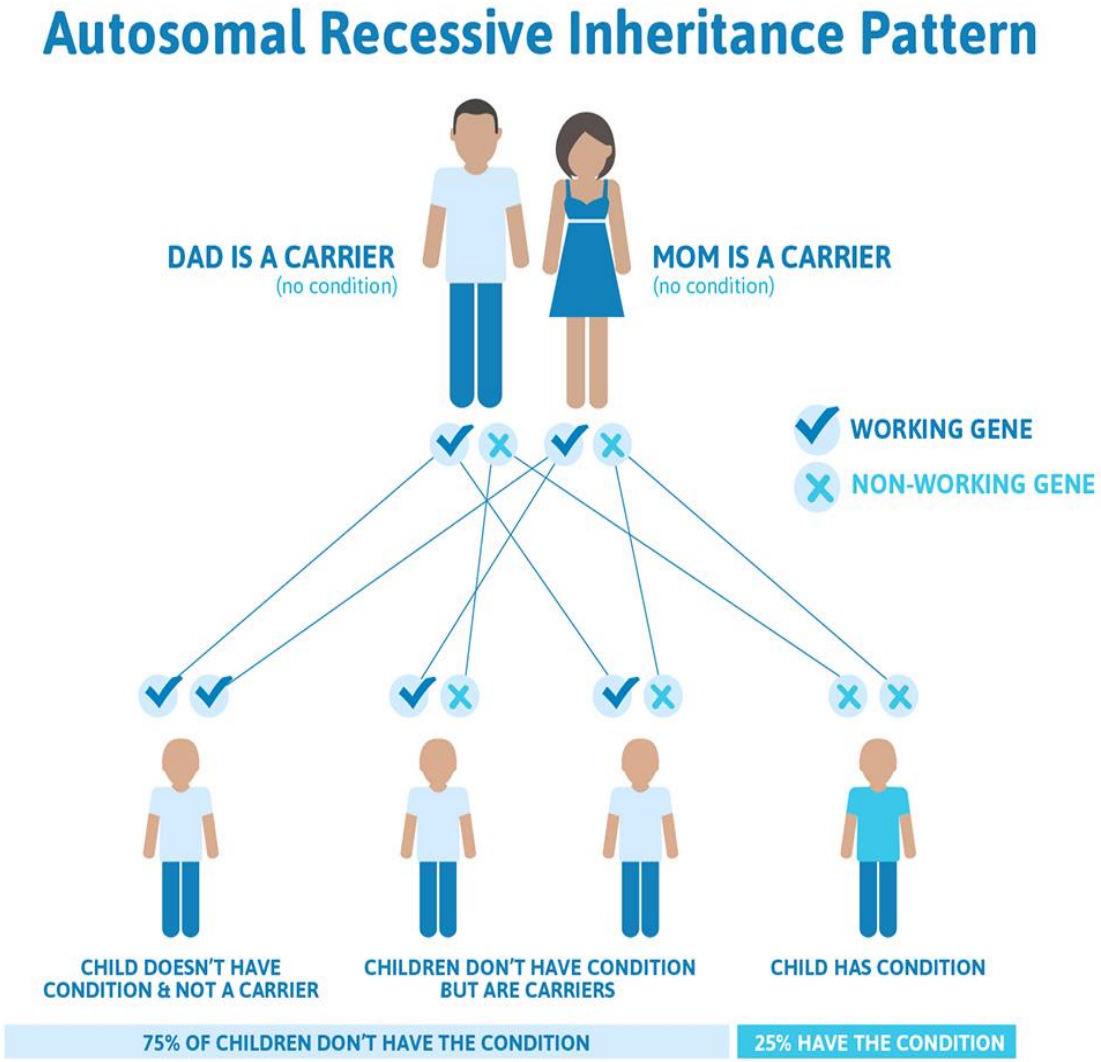

*Image in the public domain**

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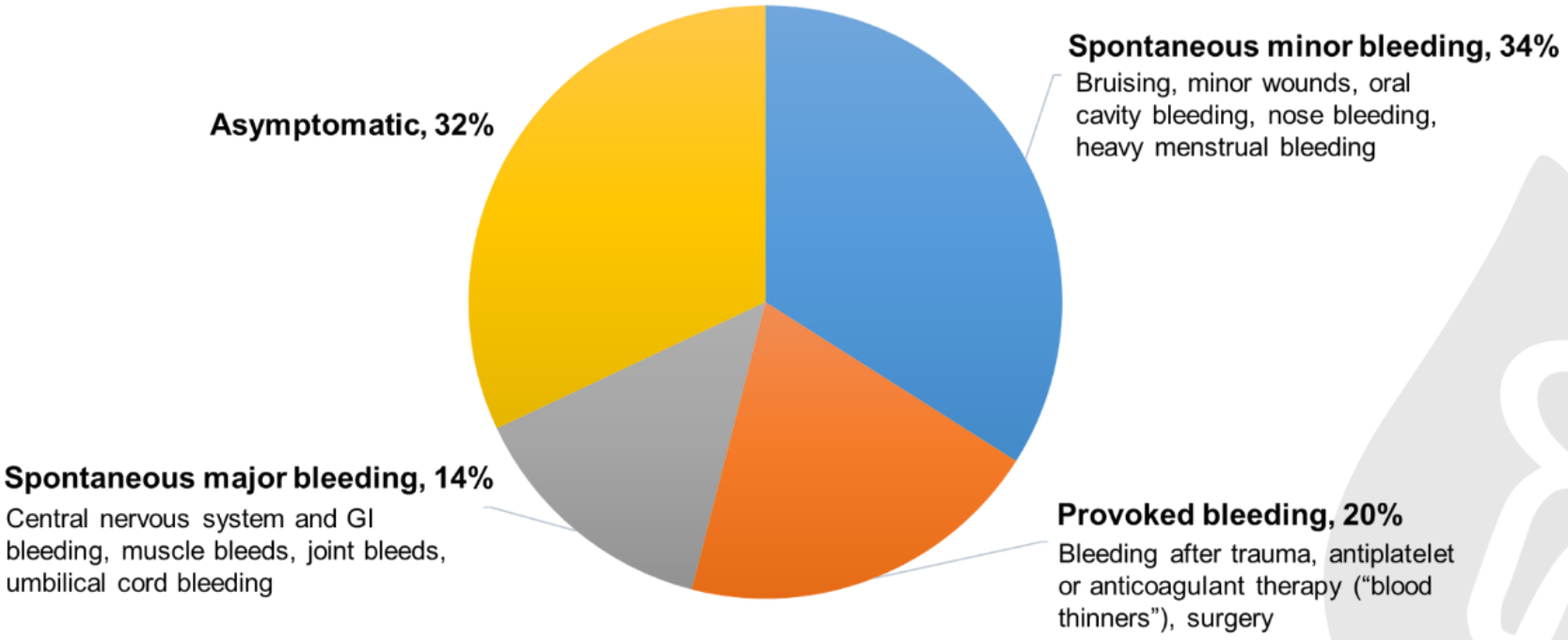
Thalji N et al, Semin Thromb Hemost. 2013;39(6):607

Clinical Features

Deficiency--Severe <20%, Mild ≥20%
Bleeding might not correlate with levels



Adapted from: Thalji N, Camire RM. Semin Thromb Hemost 2013;39:p.610.

- In the Iranian cohort, 50% women had menorrhagia, 43% postpartum bleeding
- Some cases of recurrent miscarriages, premature births and/or fetal losses (level 1-10%)

Thalji N et al, Semin Thromb Hemost. 2013;39(6):607-612.; Lak M et al, Br J Haematol 1998;103:1067-9; Bolton-Maggs et al, Haemophilia 2004; 10: 593-628; Younesi et al, Haemophilia (2013), 19, e296--e323

Laboratory Diagnosis

- Abnormal blood clotting tests: PT & aPTT
- Check FV *and* FVIII level
  - Combined F5F8 deficiency may exist

- Acquired factor V deficiency
  - Development of anti-factor V antibodies
    - Use of bovine thrombin during surgery
    - Underlying rheumatologic conditions or malignancies
    - Use of some antibiotics

Asselta et al, Semin Thromb Hemost 2009; 35: 382-389; Girolami et al, Haemophilia 2005; 11: 26-30; Bolton-Maggs et al, Haemophilia 2004; 10: 593-628;Younesi et al, Haemophilia (2013), 19, e296--e323

FV deficiency--Treatment

Main Replacement Product: Fresh Frozen Plasma (FFP)

Spontaneous Minor Bleeding: Mucocutaneous	Spontaneous Major Bleeding: CNS, GI, MSK	Provoked Bleeding: Post trauma and surgery
Heavy menstrual bleeding: • Oral contraceptives • Progestin IUDs • Endometrial ablation or hysterectomy Other bleeding: Antifibrinolytics	FFP prophylaxis* to maintain FV levels >20% of normal Platelet transfusions and rFVIIa in patients with FV inhibitors Monitor volume status in at-risk patients	FFP prophylaxis prior to surgery to raise FV levels to >25% of normal
* Prophylaxis: treatment to prevent bleeding		

- **FV level of 20-25% should prevent most bleeding**
- **Rare need for prophylaxis: Prophylaxis based on bleeding symptom severity rather than baseline FV level**
- **If poor clinical response to treatment with FFP, think of inhibitor development**

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Thalji N et al, Semin Thromb Hemost 2013;39:607-12

Treatment & Dosing

- **FFP:** Initial dose ~ 20cc/kg; subsequent doses ~ 5cc/kg every 12 hours and adjusted based on FV levels and bleeding severity

- **Pregnancy:** levels > 15 U/dl are generally accepted for prevention of pregnancy loss
  - Regular prophylactic FFP started in patients at 33 weeks, 3–4 times per week during pregnancy and until wound healing after delivery

- **Platelets:** Provide alternate option as contain ~20% of circulating FV supply

- **Antifibrinolytics:** Aminocaproic acid and Tranexamic acid

- **Recombinant FVIIa:** Patients rarely develop inhibitors to FV after receiving exogenous FV, such as with FFP; can be measured with Bethesda assay

Asselta et al, Semin Thromb Hemost 2009; 35: 382-389; Girolami et al, Haemophilia 2005; 11: 26-30; Bolton-Maggs et al, Haemophilia 2004; 10: 593-628;Younesi et al, Haemophilia (2013), 19, e296--e323

FV deficiency—Future

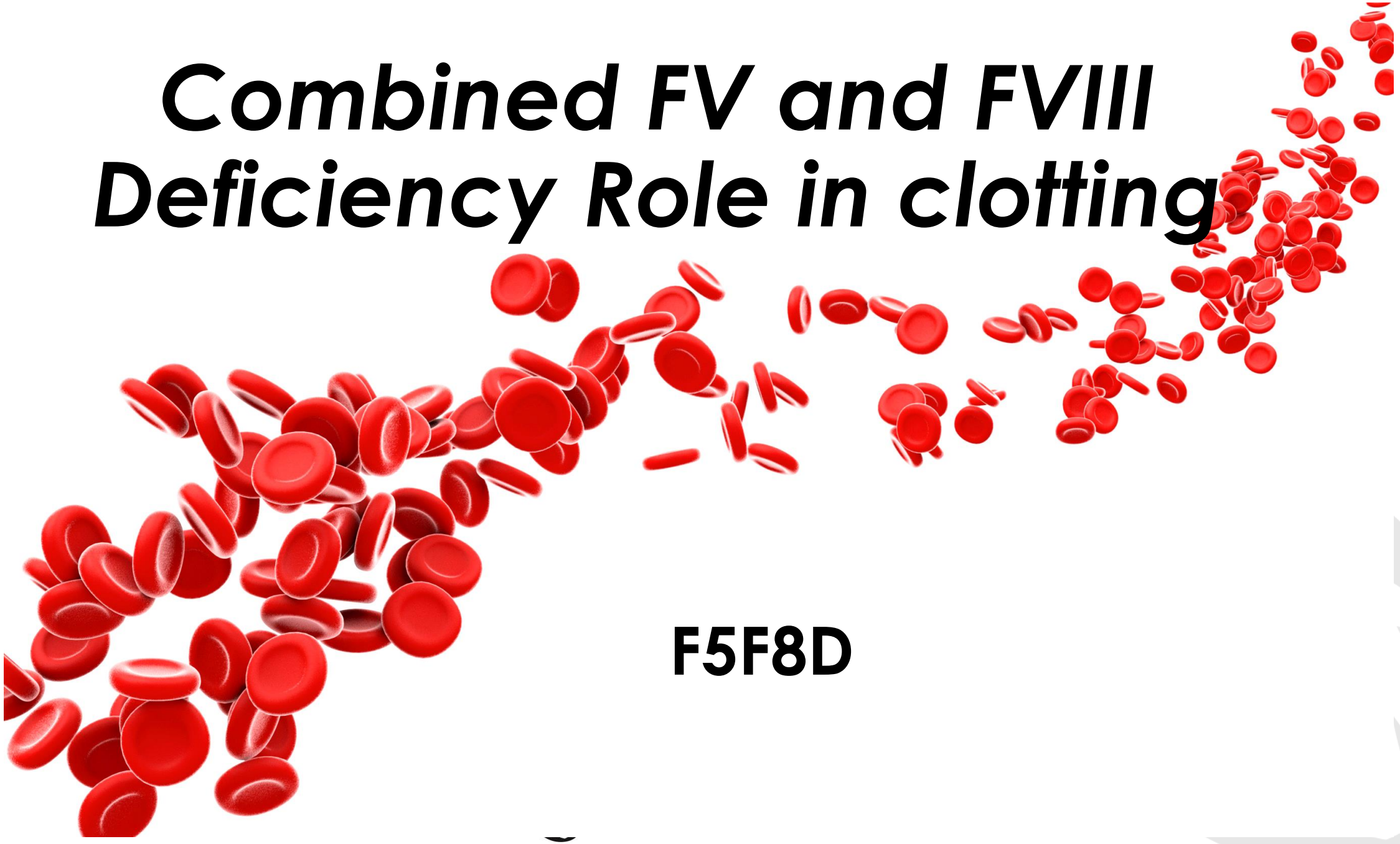
- Resources for ongoing research and registries http://www.rarecoagulationdisorders.org/diseases/factor-v-deficiency/disease-overview
- Global Treatment Centre Directory https://www.wfh.org/en/page.aspx?pid=1264
- Patient organizations may also be found by searching the Orphanet website http://www.orpha.net/consor/cgi-bin/index.php
- Future needs in the field
  - Development of FV specific replacement products: Developed by Kedrion (Italy); not commercially available and outcomes in FV deficient patients need to be clarified
  - Gene replacement therapy

Individuals conducting research in pathophysiology, molecular basis, and registries:

Country	Investigator	Contact Information
Italy	Dr. Flora Peyvandi University of Milan Hemophilia Center	flora.peyvandi@unimi.it
The Netherlands	Dr. Elisabetta Castoldi Maastricht University	https://www.maastrichtuniversity.nl/e.castoldi/research
United States	Dr Rodney Camire Children's Hospital of Philadelphia	https://www.research.chop.edu/people/rodney-m-camire
	Dr. David Ginsburg University of Michigan and Howard Hughes Medical Institute	www.lsi.umich.edu/labs/david-ginsburg-lab
	Dr. Kenneth Mann University of Vermont	https://www.med.uvm.edu/biochemistry/lab_mann_research
	Dr. James Zehnder Stanford University Medical Center	http://med.stanford.edu/profiles/James_Zehnder
	The American Thrombosis and Hemostasis Network (ATHN)	http://www.athn.org/

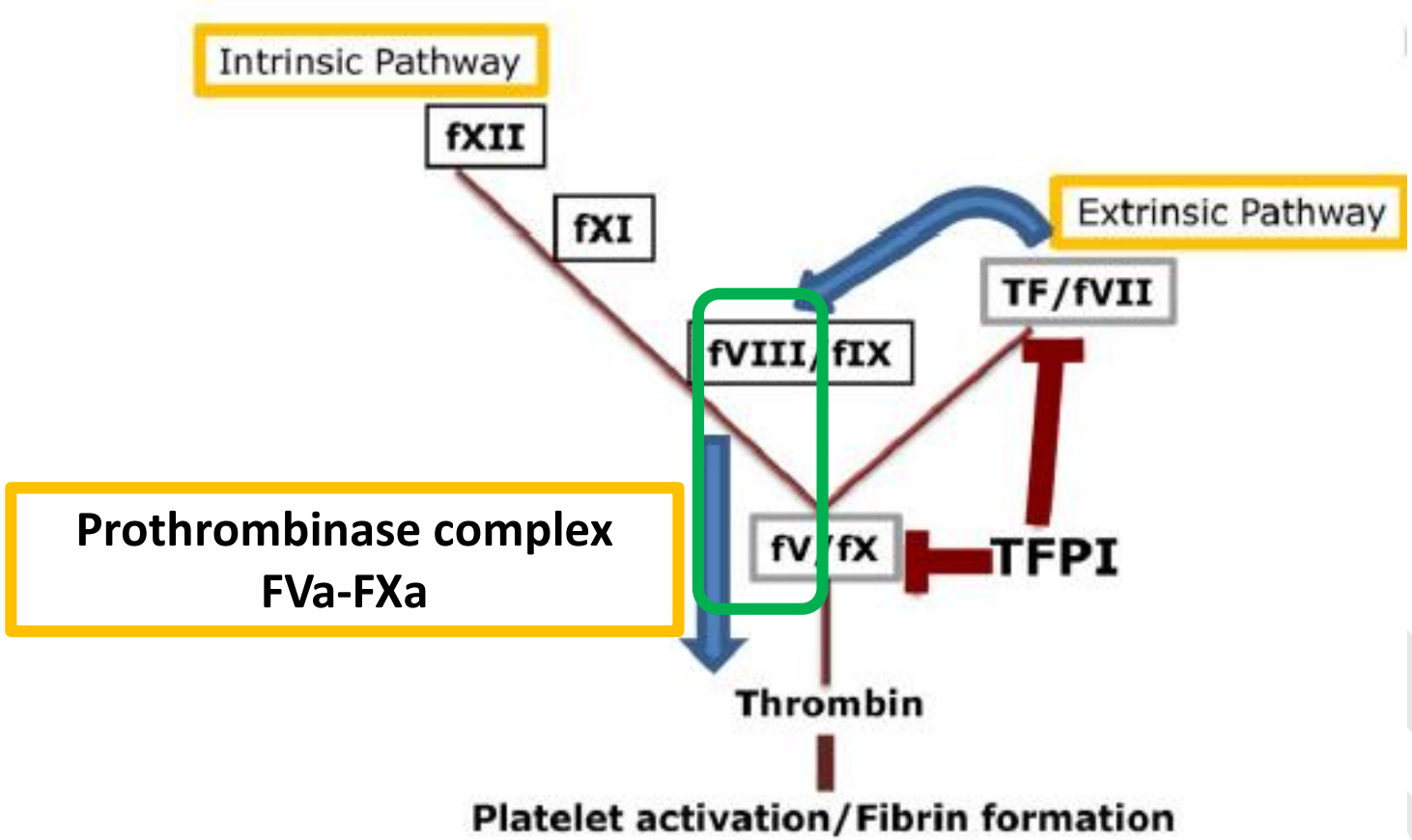
Bulato C et al, Haemophilia. 2018;24:648-56

Combined FV and FVIII Deficiency Role in clotting



F5F8D

- First reported by Oeri in 1954
- Low levels of both coagulation factors: Between 5% – 20%



Marta S et al, Semin Thromb Hemost. 2009 Jun;35(4):390-9 ; Image: Alan E. Mast , Arterioscler Thromb Vasc Biol. 2016 January ; 36(1): 9–14.

F5F8D – Diagnosis

Inheritance

- Rare bleeding disorder: 1 in 1,000,000
- Due to a single gene defect
  - Mutations in *LMAN1* gene (70%) and *MCFD2* (15%) cause F5F8D
- Low levels of both coagulation factors; usually between 5% to 20%
- Genetic counselling important
- Autosomal Recessive
  - Males = females

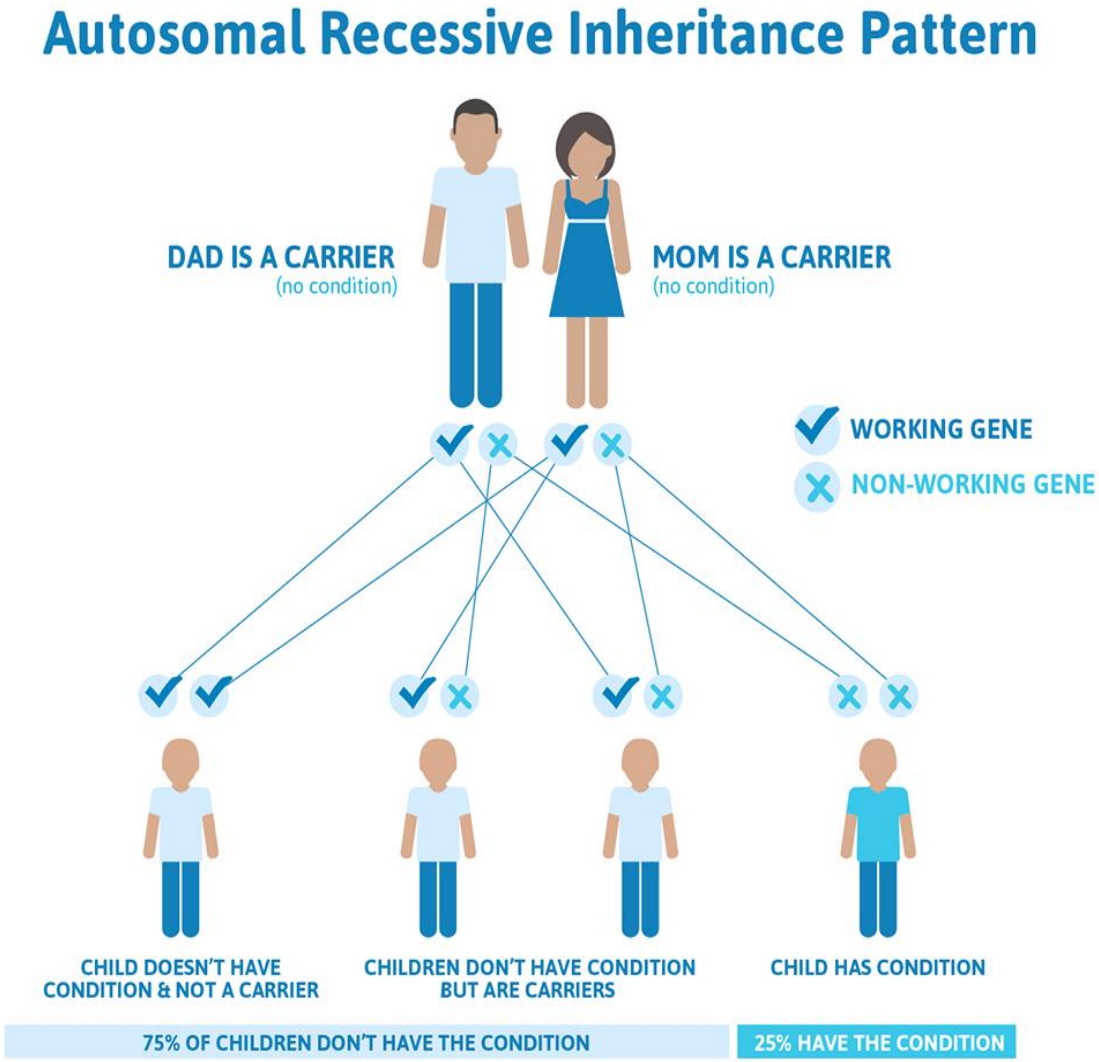


*Image in the public domain**

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Marta S et al, Semin Thromb Hemost. 2009 Jun;35(4):390-9

Clinical Features

- **Symptoms:**
  - Mucocutanoeus bleeding
  - HMB > 50% of affected women; bleeding after delivery not much known
  - Excessive bleeding after circumcision was also reported in a high number of male patients
  - Rare – GI/CNS bleeding
  - Neonatal intracranial hemorrhage has not been described in this condition

Severity Category	Levels	Symptoms
Mild	>40%	Asymptomatic, but might have problems with bleeding during trauma, a surgical procedure or with pregnancy/delivery
Moderate	20 – 40%	Mild spontaneous bleeding, or bleeding triggered by trauma, surgery, or pregnancy/delivery
Severe	<20%	May have spontaneous, severe, and even life-threatening bleeding

Peyvandi F et al, Br J Haematol. 1998;100:773-6; Seligsohn U et al, N Engl J Med. 1982;307:1191-5; .Peyvandi F et al, Haemophilia. 2002;8:308-21.; Mansouritorgabeh H et al, Haemophilia. 2004;10:271-5.

Laboratory Diagnosis

- Abnormal blood clotting test: PT and aPTT
  - PTT is disproportionately prolonged
- Perform both V+VIII levels when FV deficiency present
- FVIII deficiency (hemophilia A) can be distinguished from F5F8D by
  - X-linked inheritance
  - Normal PT among individuals with hemophilia A
- FV deficiency can be confused with F5F8D as both
  - Autosomal recessive disorders
  - Prolonged PT and PTT assays.
- FV deficiency associated with mild hemophilia A → requires genetic analysis

F5F8D--Treatment

Main Treatment Products: Fresh Frozen Plasma & FVIII Concentrate /DDAVP

Minor Bleeding: Mucocutaneous	Major Bleeding: CNS, GI, MSK	Surgery	Pregnancy
Goal **FVIII ≥ 30 IU/dl** FVIII concentrate/DDAVP **FV ≥ 25 IU/dl** FFP- 15-25 ml/kg	**Goal** **FVIII ≥ 50 IU/dl** FVIII concentrate/DDAVP **FV ≥ 25 IU/dl** FFP- 15-25 ml/kg	**Goal:** Infusions Q 12 hours to achieve **FVIII ≥ 50 IU/dl** FVIII concentrate/DDAVP **FV ≥ 25 IU/dl** FFP- 15-25 ml/kg	• FVIII levels increase in pregnancy • FV remains same: Levels linked to risk of bleeding • Measure both factors during third trimester • In labor: Maintain FV levels >15%, FVIII levels >50% • Epidurals can be performed • Administer FFP (15–25 mL/kg) during labor, with additional FFP (10 mL/kg q12h) for ≥3 days

- **Antifibrinolytics are adjunctive treatment**
- **Rare need for prophylaxis as mild to moderate bleeding severity**

Bolton-Maggs et al, Haemophilia 2004; 10: 593-628; Spreafico et al, Haemophilia 2008; 14: 1201-1208; Mumford et al, Br J Haematol 2014; 167(3):304-326 ; Mansouritorghabeh et al, J Thromb Haemost 2016; 14: 336-339; Peyvandi et al, Br J Haematol 1998; 100: 773-776; Spreafico et al, Haemophilia 2008; 14: 1201-1208

F5F8D—Future

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- No clinical trials currently ongoing for F5F8D
- No FV concentrate available
- Products for treatment of FVIII deficiency have improved substantially

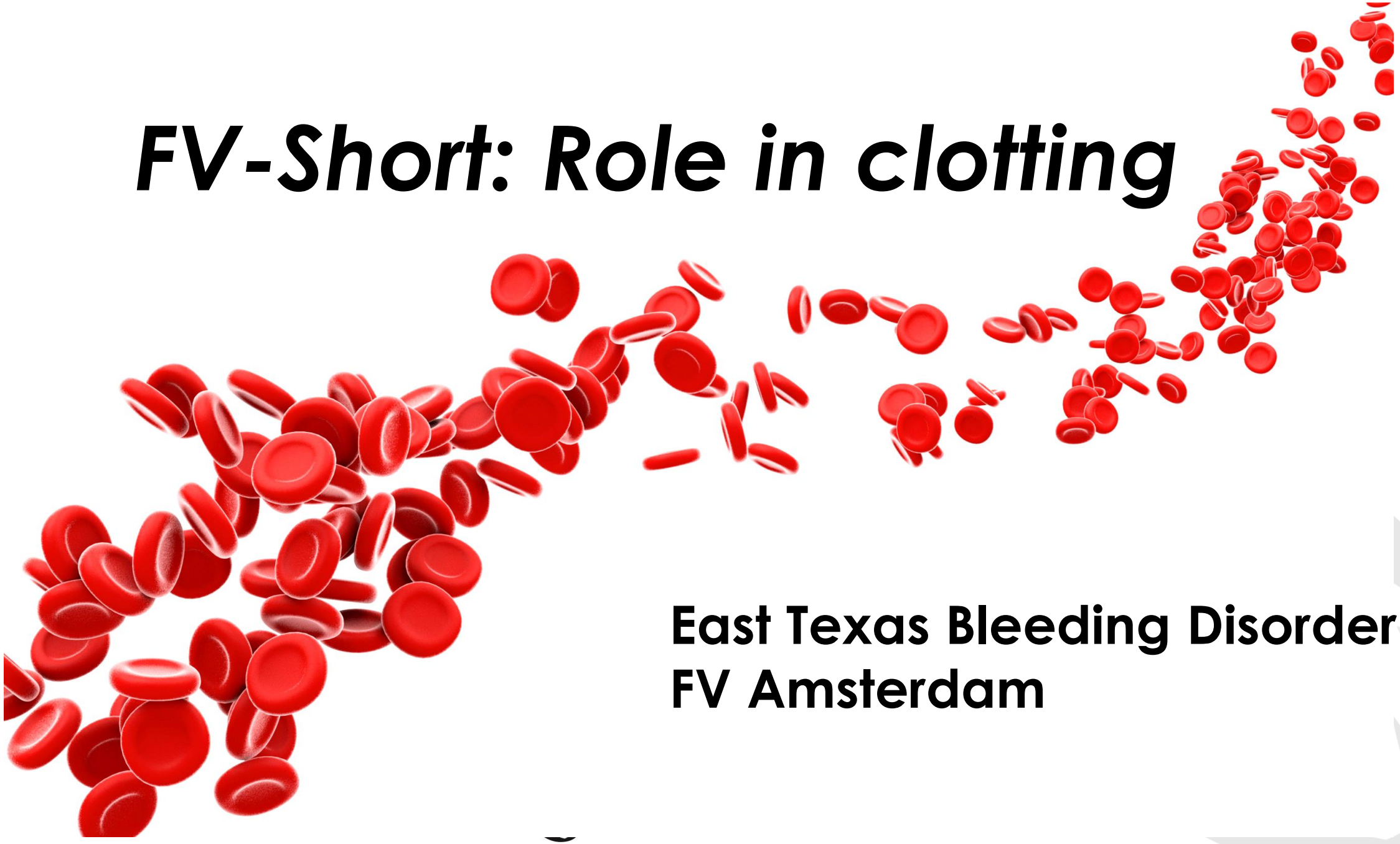
Registries and Databases

- FranceCoagNetwork http://francecoag.org/SiteWebPublic/public/Welcome.action?request_locale=en)
- Mutations causing RBDs: ISTH website http://www.isth.org/?page=RegistriesDatabases
- National Center for Biotechnology Information https://www.ncbi.nlm.nih.gov/
- PROspective Rare Bleeding Disorders Database http://eu.rbdd.org/

Resources for Information

- http://www.rarecoagulationdisorders.org/diseases/combined-factor-v-and-factor-viii-deficiency/disease-overview
- A map of the Certification of European Haemophilia Centres can be retrieved at http://www.euhanet.org/MappedCentres.aspx.

FV-Short: Role in clotting

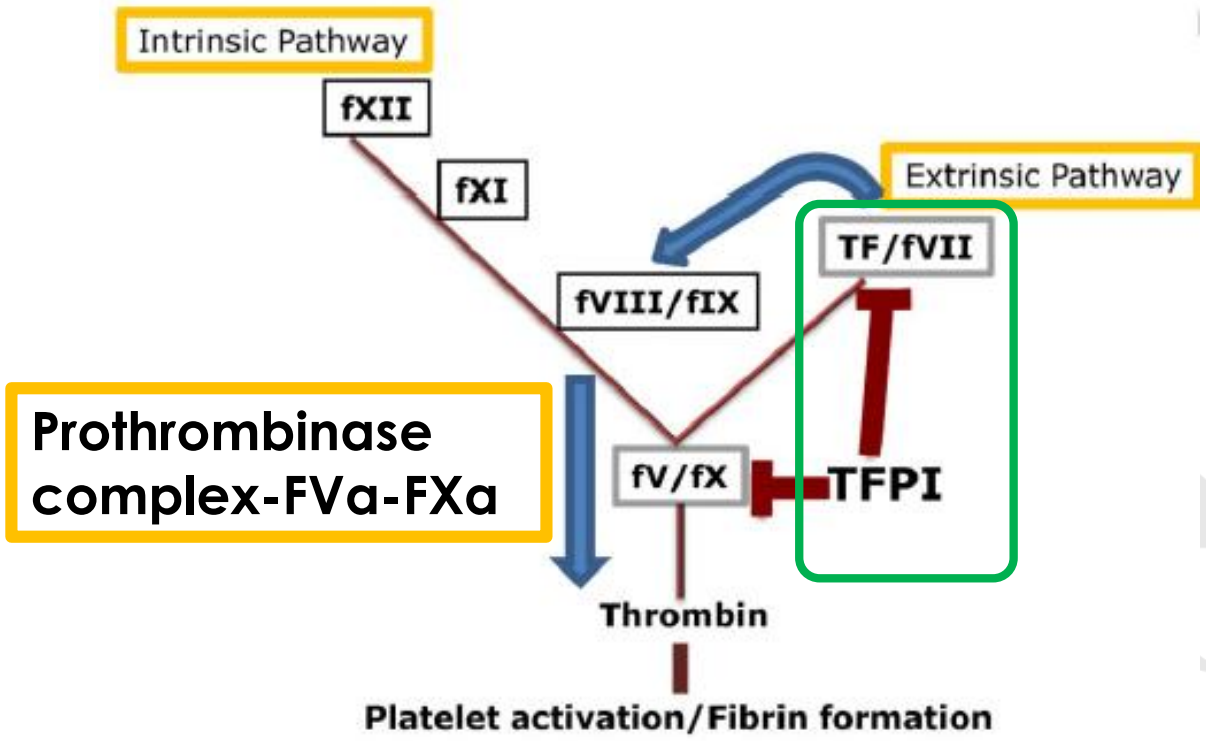


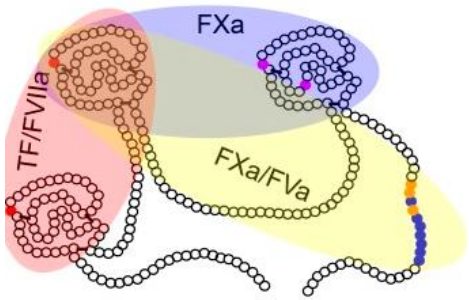
East Texas Bleeding Disorder
FV Amsterdam

- **Increase in levels of Tissue Factor Pathways Inhibitor (TFPI) a due to a mutation in FV**

- **EAST TEXAS BLEEDING DISORDER:**
  - **First described in 2001**

- **FACTOR V AMSTERDAM :**
  - **First described in 2015**



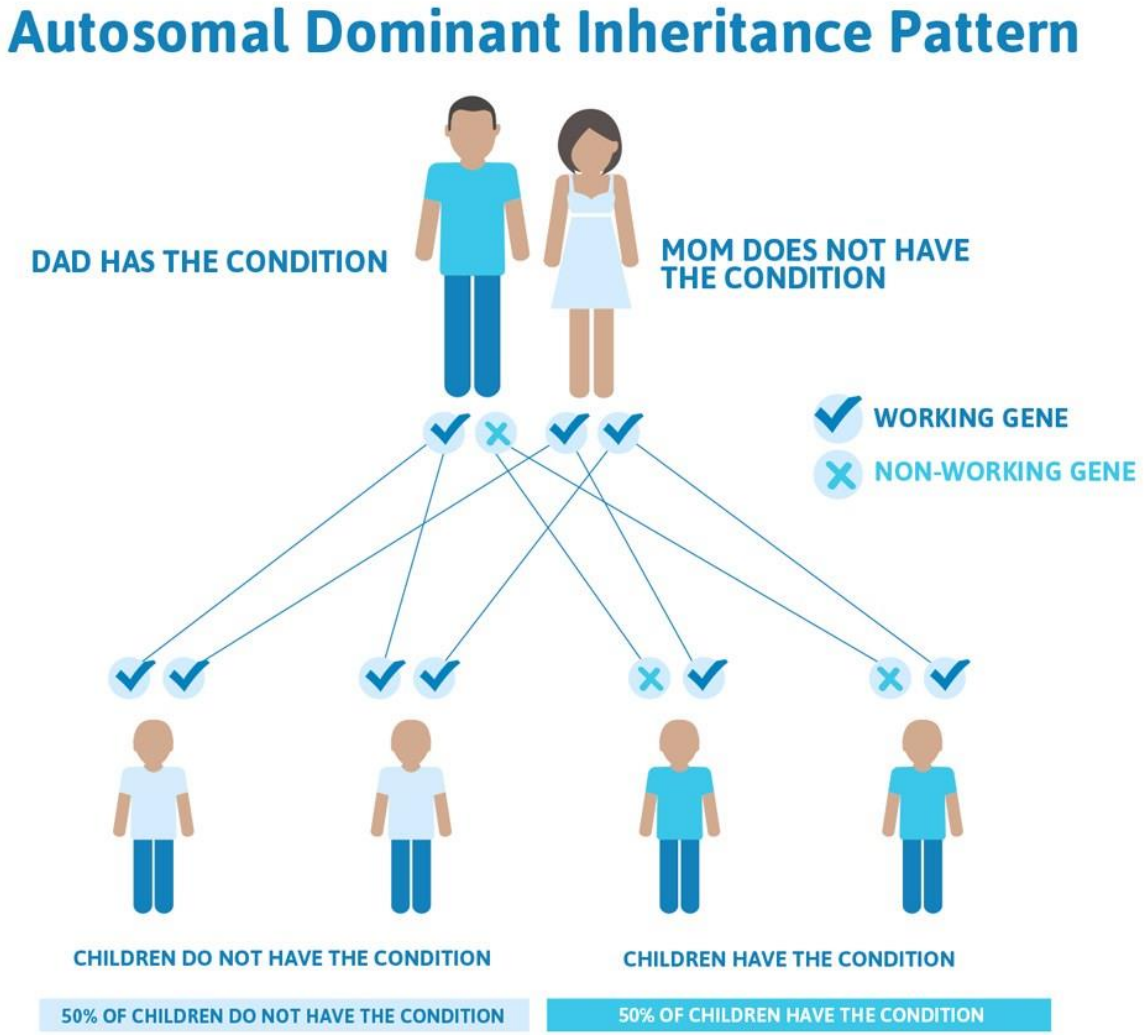


Alan E. Mast , Arterioscler Thromb Vasc Biol. 2016 January ; 36(1): 9–14.; Kuang SQ et al Blood 2001; 97:1549–1554; Vincent LM et al . J Clin Invest 2013 123:3777–3787; Cunha ML, et al Blood 2015 125:1822–1825

FV-Short bleeding disorders-Diagnosis

Inheritance

- Rare bleeding disorder
- Prevalence not known
- Autosomal Dominant
  - Males = females
- Genetic counselling important



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Kuang SQ, et al Blood 2001; 97:1549–1554; Cunha ML et al, Blood 2015 125:1822–1825

East Texas Bleeding Disorder: Clinical Features

Patient Age in years / sex	Bleeding symptoms	Labs	Treatment
Proband 35years / Male	Bruising, epistaxis, gingival oozing, bleeding post trauma and surgery	**PT prolonged: 18.4 [11.1–13.1]** **aPTT prolonged: 48.7 [25–34]** Modest variability in tests from day to day	2 PRBC* transfusions: After laceration & tooth extraction
19 years / Sister 1	Bruising, HMB, gingival oozing with loss of primary teeth needing packing, bleeding post removal of ingrown toe nail and post tooth extraction	**PT prolonged: 13.7 [9.5–12]** **aPTT prolonged: 51.1 [29–39]**	After tonsillectomy bleeding after 3 days: PRBC* and **plasma transfusion** **Hemorrhagic ovarian cyst** After appendectomy: PRBC* transfusion *** No bleeding with L & D#**
Sister 2	Epistaxis		Delivery of 2nd child: Excessive bleeding needing a PRBC* * No bleeding with L & D# of 1st child and after appendectomy
Brother	Bruising, Epistaxis, gingival oozing,	**PT & aPTT prolonged**	

*PRBC: Packed red blood cells
#L & D: Labor and delivery

Several patients followed: Males tend to be asymptomatic, women have more reproductive tract bleeding, have used FEIBA 10-20 U/Kg

Kuang SQ et al, Blood 2001; 97:1549–1554

East Texas Bleeding Disorder: Identified in Indiana

Patient Age in years /sex	Symptoms	Labs	Treatment so far
Proband 19 / Male	• Bruising • Epistaxis • Gingival oozing • Bleeding after trauma & surgery • **Delayed exfoliation of umbilical cord, delayed wound healing**	• **PT prolonged** • **aPTT prolonged** • Modest variability in these tests • FVII normal • VWF normal	• **Subgaleal hemorrhage at 7 years** • PRBC, DDAVP, Humate P → No response • NovoSeven 100 mcg/kg with good response, Amicar • **Periorbital hematoma at 11 years** • 3 doses of Stimate, Amicar for 14 days

4 other family members diagnosed, one with normal PT/aPTT

Indiana patient – unpublished data

FV Amsterdam: Clinical Features

Patient Age in years / sex	Bleeding symptoms	Labs	Treatment
Proband 59 / Female	Bleeding after trauma & surgery, after tooth extraction, surgery for ovarian cyst	**aPTT mildly prolonged:** 32 [22–30] **PT significantly prolonged:** 24.9 [9.7–11.6] FVII 46%	Blood transfusions after adenoidectomy **PCC*** after removal of skin lesion, bled after a week After PPH: Blood + FFP + PCC+**TXA**
25 / Son	**Prolonged bleeding from umbilical stump**, bleeding of gums after minor trauma, and easy bruising	**aPTT mildly prolonged** 32 [22–30] **PT prolonged** 17.9 [9.7–11.6]	PCC: Prolonged and delayed bleeding for more than a week after removal of a wart on foot

PCC: Prothrombin complex concentrate
**** TXA: Tranexamic acid**

Cunha ML et al, Blood 2015 125:1822–1825

Laboratory Diagnosis

- Abnormal blood clotting tests
  - PT *and/or* aPTT
  - In some cases normal coagulation screen
- Perform TFPIa levels: Currently a research based test
- Genetic analysis
  - East Texas: *F5* Heterozygous at nucleotide *A2440G*
  - FV Amsterdam: *F5* Heterozygous at nucleotide *A2350G*

FV-Short bleeding disorders- Treatment

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Treatment Options

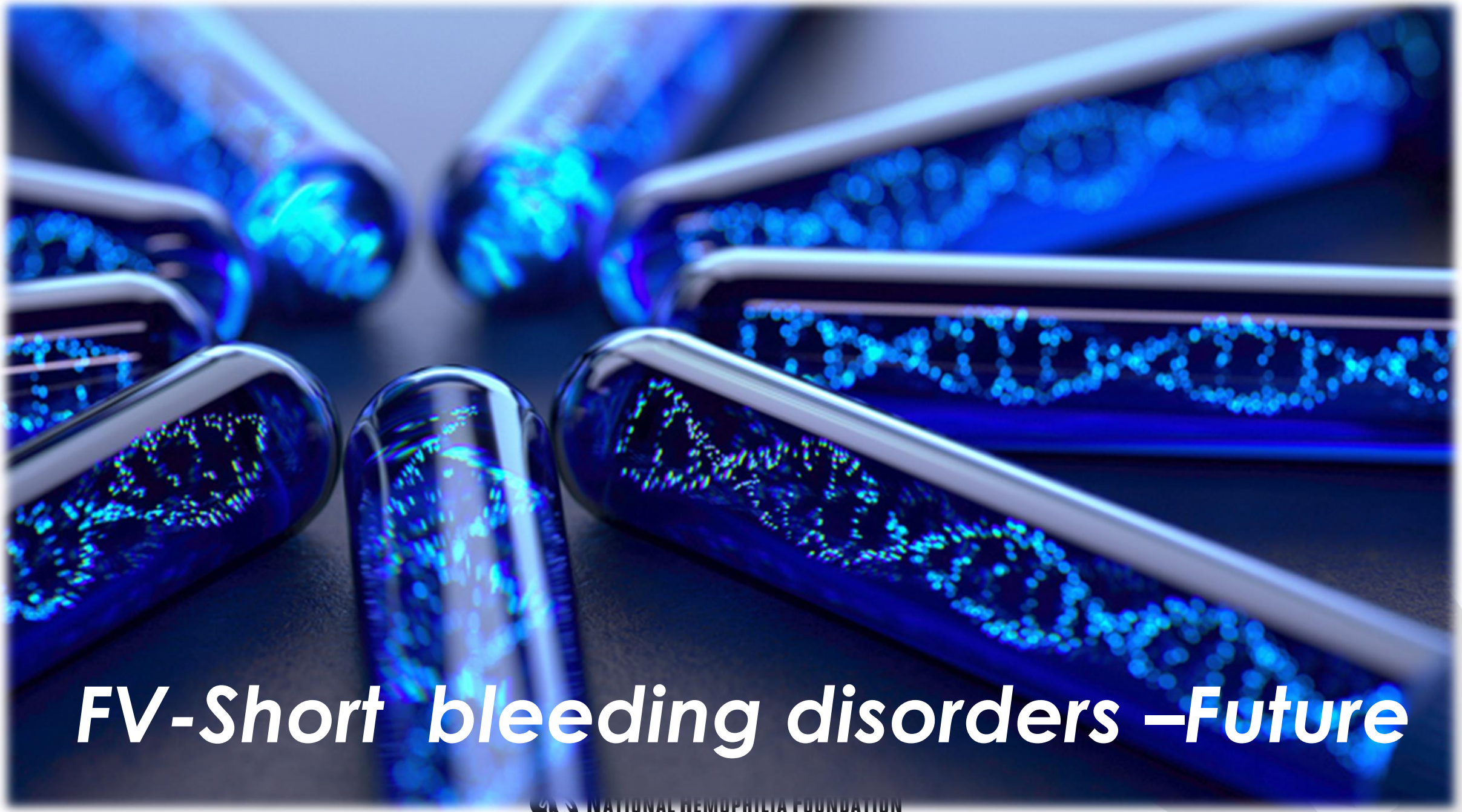
Various treatments utilized

- rFVIIa (90-200 µg/kg) for acute major bleeding: Dose based on bleed
- FEIBA 10-20 U/Kg
- Prothrombin complex concentrate
- Antifibrinolytics: Aminocaproic acid or Tranexamic acid
  - Oral for minor bleeds and mucosal bleeds
  - IV for major bleeds
- As needed PRBC and FFP

Long-Term Prophylaxis

- East Texas BD extremely rare: No details of long-term prophylactic regimens
- High variability in bleeding phenotype
- Severe bleeding events most likely associated with trauma or surgery

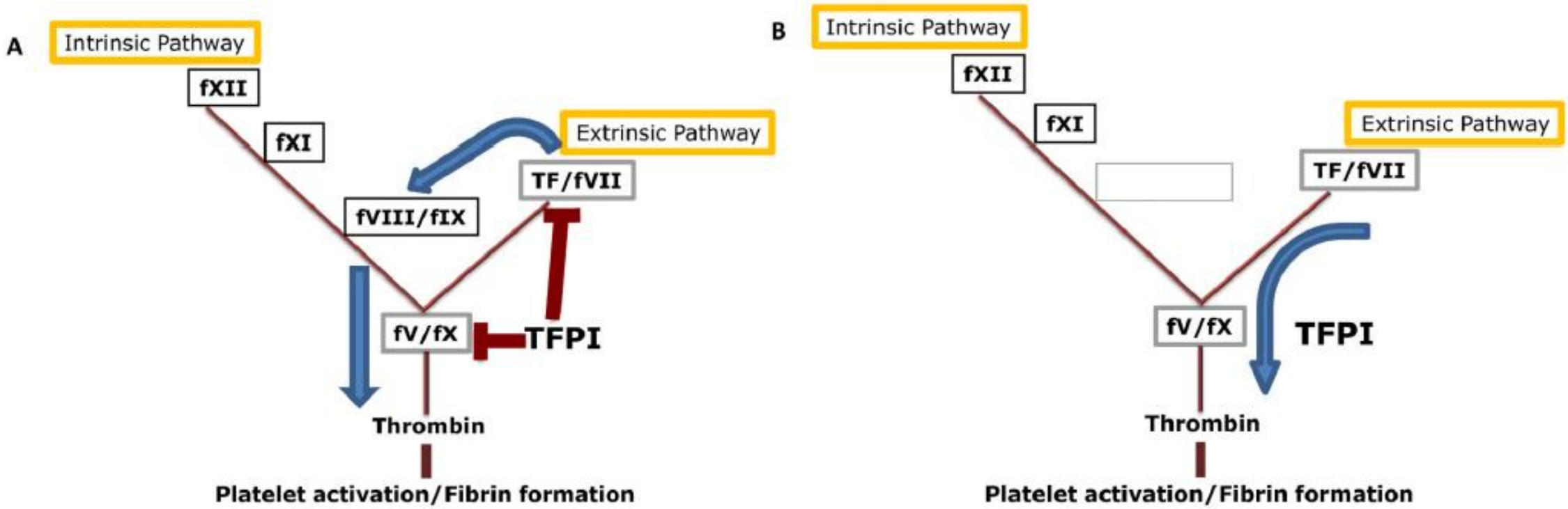
Mast, Arterioscler Thromb Vasc Biol 2016; 36(1): 9-14; Wood et al, Blood 2014; 123(19): 2934-2943; Vincent et al, J Clin Invest 2013; 123: 3777-3787; Kuang et al, Blood 2001; 97: 1549-1554; Cunha et al, Blood 2015; 125: 1822-1825; Broze et al, J Clin Invest 2013; 123(9): 3710-3712; van Doorn et al, J Thromb Haemost 2017; 15(1): 140-149; van Doorn et al, J Thromb Haemost 2019; 17(7):1195



FV-Short bleeding disorders –Future

- TFPI levels need to become available commercially

- Concizumab, a humanized monoclonal antibody against TFPI is administered subcutaneously and is under development treatment for hemophilia
  - This agent could theoretically be useful as prophylactic treatment of



Alan E. Mast , Arterioscler Thromb Vasc Biol. 2016 January ; 36(1): 9–14

SUMMARY

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All Things 5

	FV DEFICIENCY	F5F8D	SHORT FV-SHORT BLEEDING DISORDERS
Inheritance	Autosomal Recessive	Autosomal Recessive	Autosomal Dominant
Severity	Mild to severe Bleeding phenotype might not correlate with levels	Mild to moderate	Mild to severe
Treatment	FFP Antifibrinolytics	FFP + FVIII/DDAVP Antifibrinolytics	Recombinant FVIIa / FEIBA Antifibrinolytics

Summary

- Rare bleeding disorders
- Mild to severe bleeding symptoms
- Complete family history and laboratory work up for diagnosis
- Genetic counselling important for future generations
- Treatment products need to be developed for FV
- Future research needed


Thank
You

Session Evaluation

Take a few minutes now to fill out the session evaluation:

Rate this session

- Meaningful?
- Learned new ideas/skills?
- Will implement new ideas/skills?

How could this session be improved?

Comments?