

Hemophilia A

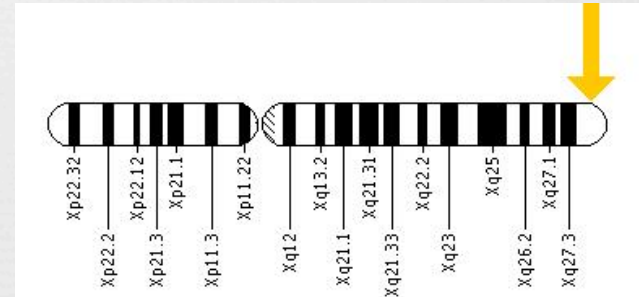


Lila Neahrng

What is hemophilia A?



- ⌘ Prolonged bleeding after injury and surgery
- ⌘ Impaired blood clotting: factor VIII deficiency
- ⌘ Mutation on *F8* gene

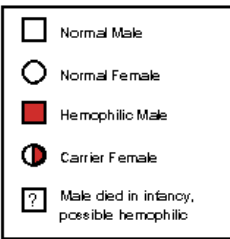
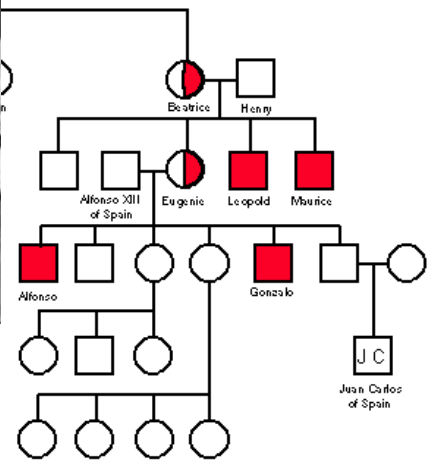
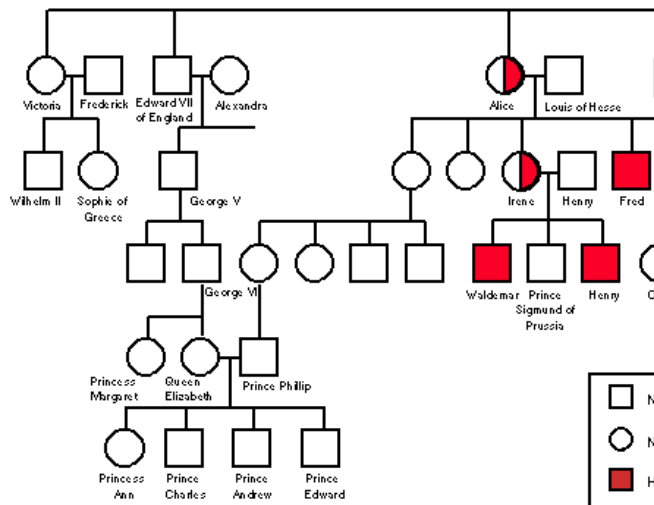


- ⌘ Intracranial bleeding, bleeding into joints
- ⌘ Well-known from European monarchy



Duke
(1767)

Albert
(1819-1861)



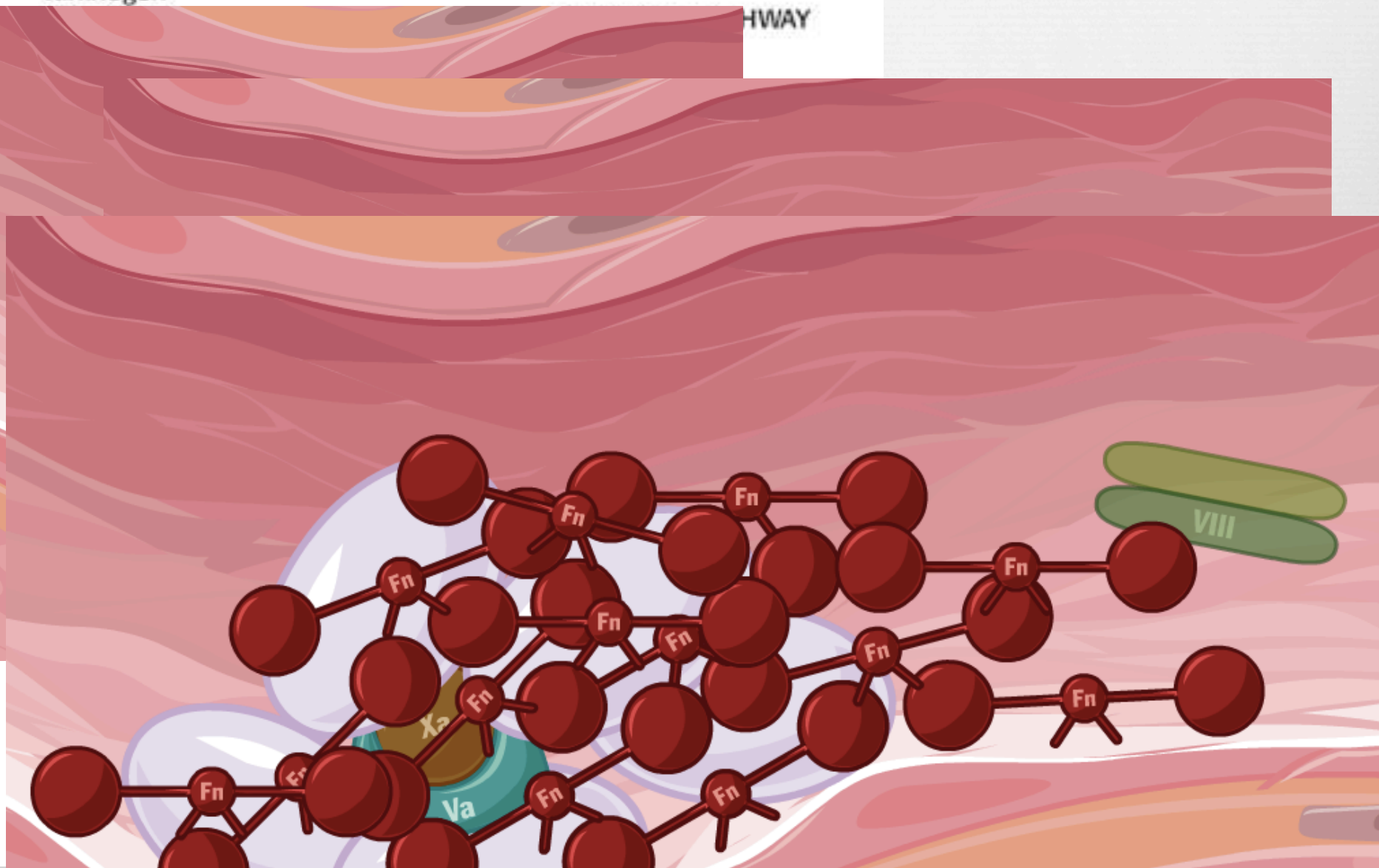
INTRINSIC PATHWAY

Damaged surface



Kininogen

HWAY



Classical Diagnosis



- ❧ Bleeding into joints, bruising, prolonged/spontaneous bleeding, GI bleeding
- ❧ Blood tests for low levels of factor VIII with normal von Willebrand factor
 - ❧ Activated partial thromboplastin time
 - ❧ Prothrombin time

Classical Treatment



- ❧ Factor VIII concentrates
 - ❧ Plasma
 - ❧ Monoclonal antibody purified factor VIII
 - ❧ Recombinant factor VIII
 - ❧ Antibodies

- ❧ Desmopressin for mild hemophilia

Diagnosics Influenced by Genomics



Gene Symbol	Test Method	Mutations Detected	Mutation Detection Frequency by Test Method ¹			
			Severe Hemophilia A		Moderate or Mild Hemophilia A	
			Affected Males	Carrier Females	Affected Males	Carrier Females
F8	Targeted mutation analysis	Intron 22-A inversion ²	48% ³	48% ³	0% ³	0% ³
		Intron 1 inversion	2-3% ⁴	2-3% ⁴	0% ⁴	0% ⁴
	Sequence analysis / mutation scanning ⁵	Sequence variants ⁶	49% ^{7,8}	43% ⁸	76%-99% ^{7,8}	76%-98% ⁹
	Deletion / duplication analysis ¹⁰	Deletion / duplication of one or more exons or the whole gene	6%	6%	<1%	<1%

Haemophilia A - Summary of Unique Mutations Reported

status at 1 June 2012

Total of all individual records in the database: 3089

Total of all unique mutations: 1492

Exon	Point Mutations			Deletions		Insertions
	Missense	Nonsense (Stop)	Splicing	Small	Large	
1	17	2	5	2	na	1
2	11	1	5	9	na	4
3	42	0	6	5	na	1
4	44	7	5	3	na	2
5	13	1	10	5	na	1
6	14	2	6	5	na	2
7	40	5	5	9	na	1
8	29	6	1	8	na	2
9	34	3	5	9	na	6
10	13	3	3	6	na	0
11	40	1	4	4	na	1
12	21	7	4	3	na	1
13	37	4	4	11	na	4
14	50	63	7	114	na	54
15	26	3	5	6	na	0
16	31	9	2	7	na	0
17	33	3	2	7	na	5
18	40	5	2	8	na	8
19	17	2	8	5	na	4
20	8	1	0	3	na	2
21	11	7	1	0	na	1
22	19	5	4	3	na	4
23	36	3	4	10	na	0
24	13	5	4	5	na	2
25	20	3	2	9	na	3
26	29	3	0	10	na	0
TOTAL	688	154	104*	266	171	109

*NB: some splice mutations are also listed as missense mutations, leading to a small over-estimate (c.2%) in the total number of unique variants.

Status of Genomics-Based Therapies



- ❧ Gene replacement therapy was in clinical trials
 - ❧ Ataluren
 - ❧ Put on hold for safety concerns
- ❧ Current research focuses on factor VIII sources
- ❧ Severe hemophilia diagnosed before the age of 2

References



- ⌘ <http://www.ncbi.nlm.nih.gov/books/NBK22260/>
- ⌘ <http://www.nlm.nih.gov/medlineplus/ency/article/000538.htm>
- ⌘ <http://www.nhlbi.nih.gov/health/health-topics/topics/hemophilia/treatment.html>
- ⌘ <http://www.ncbi.nlm.nih.gov/books/NBK1404/>
- ⌘ <http://omim.org/entry/306700>
- ⌘ <http://www.hopkinsmedicine.org/hematology/coagulation.swf>
- ⌘ <http://cancergrace.org/cancer-101/2009/12/22/cancer-and-clotting-protect/> (image on slide 4)