HEMOFİLİ A ve B’NİN

GENETİK HETEROJENİTESİ

HEMOFİLİ A

- FVIII eksikliği
- ~5000-10.000:1 erkek
- Xq28

HEMOFİLİ B

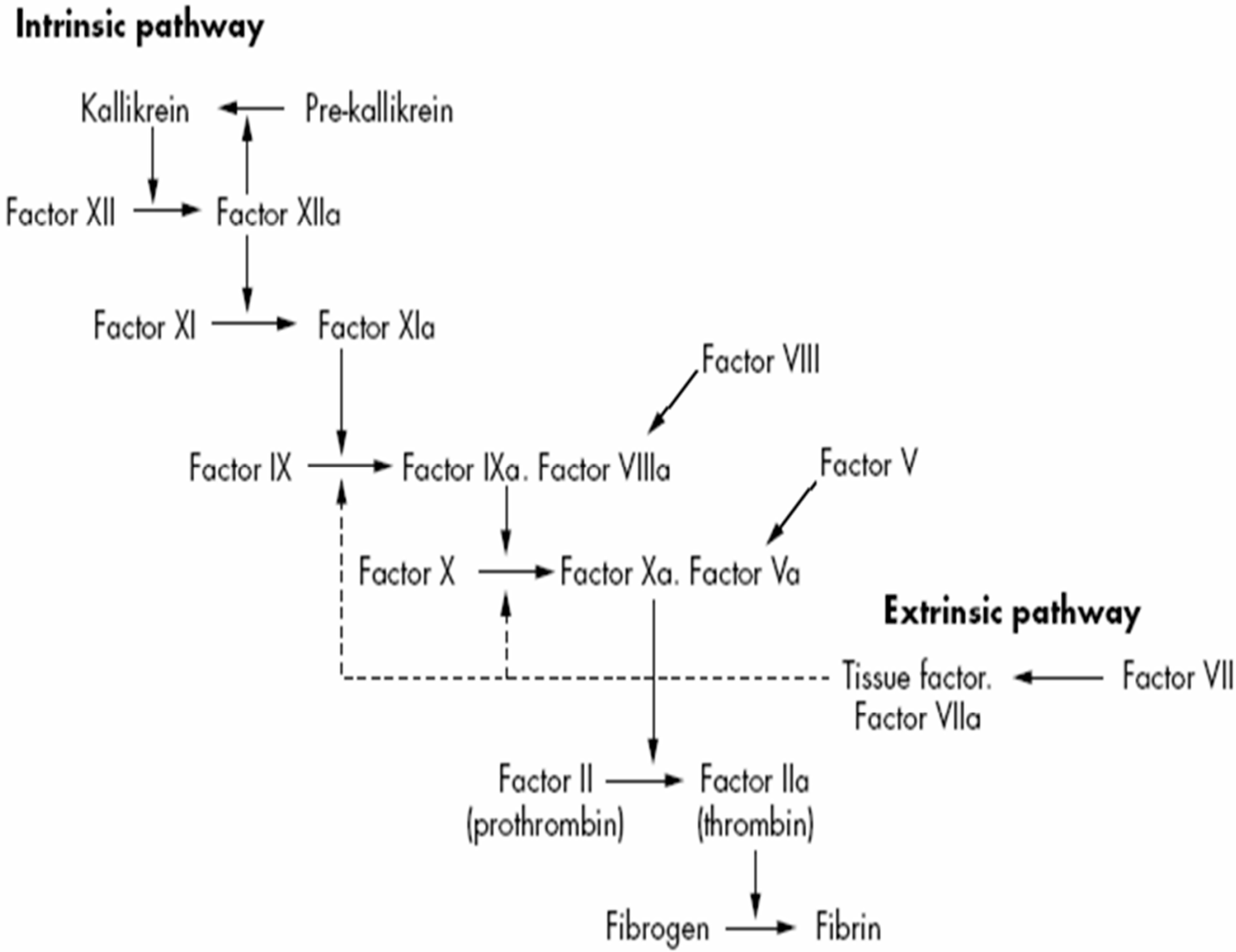
- FIX eksikliği
- ~30.000:1 erkek
- Xq26.3-q27.1

F VIII

- Enzim aktivitesi yok
- 186 kb
- mRNA ~ 9 kb
- Mature proteini 2332 aa

F IX

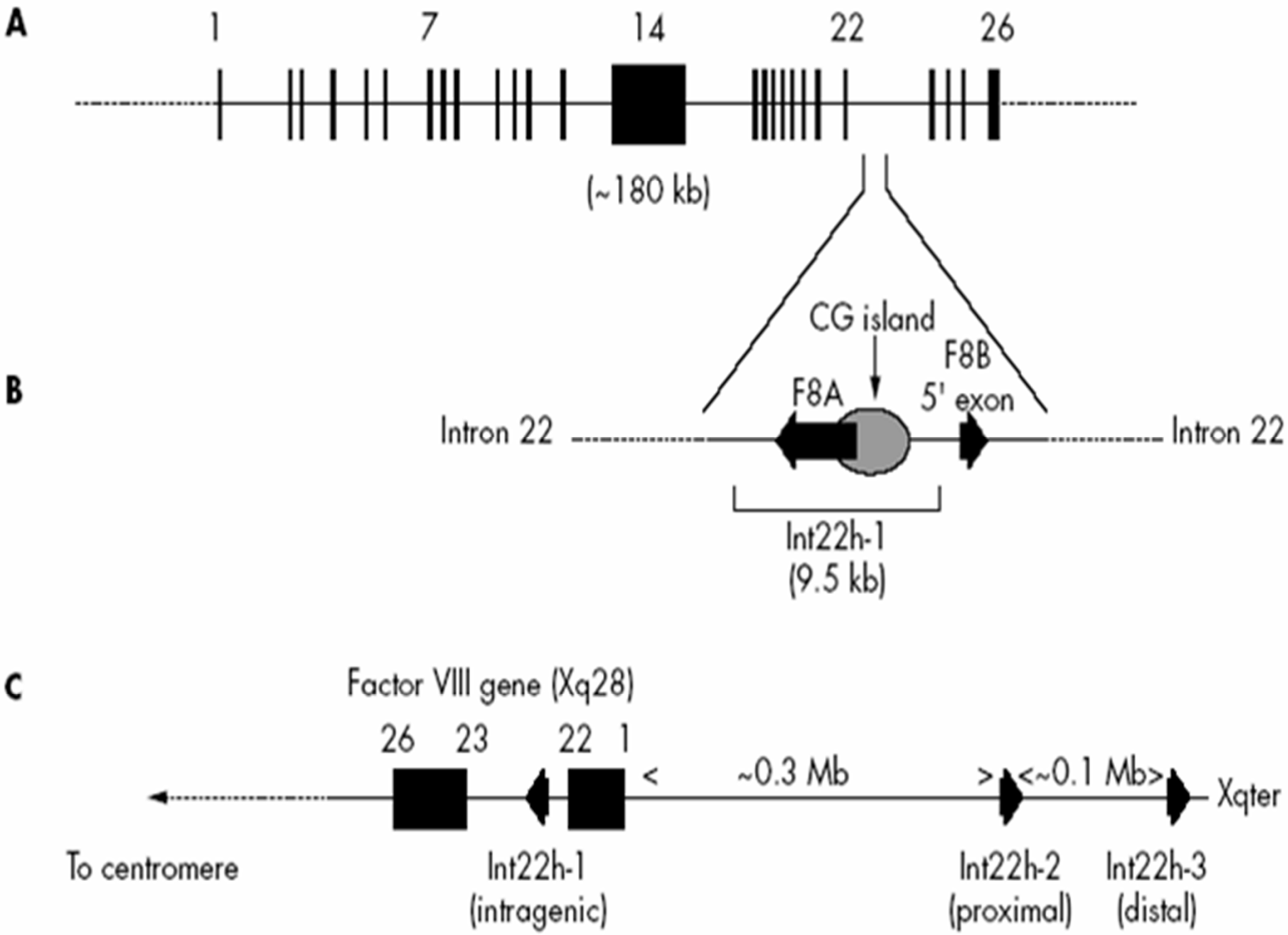
- Kofaktör olarak F VIII'e ihtiyaç duyan serin proteaz
- 34 kb
- mRNA 3 kb
- Mature proteini 415 aa


Intrinsic pathway
Kallikrein
Pre-kallikrein
Factor XII
Factor XIIa
Factor XI
Factor XIa
Factor VIII
Factor IX
Factor IXa. Factor VIIIa
Factor V
Factor X
Factor Xa. Factor Va
Extrinsic pathway
Tissue factor.
Factor VIIa
Factor VII
Factor II
(prothrombin)
Factor IIa
(thrombin)
Fibrogen
Fibrin

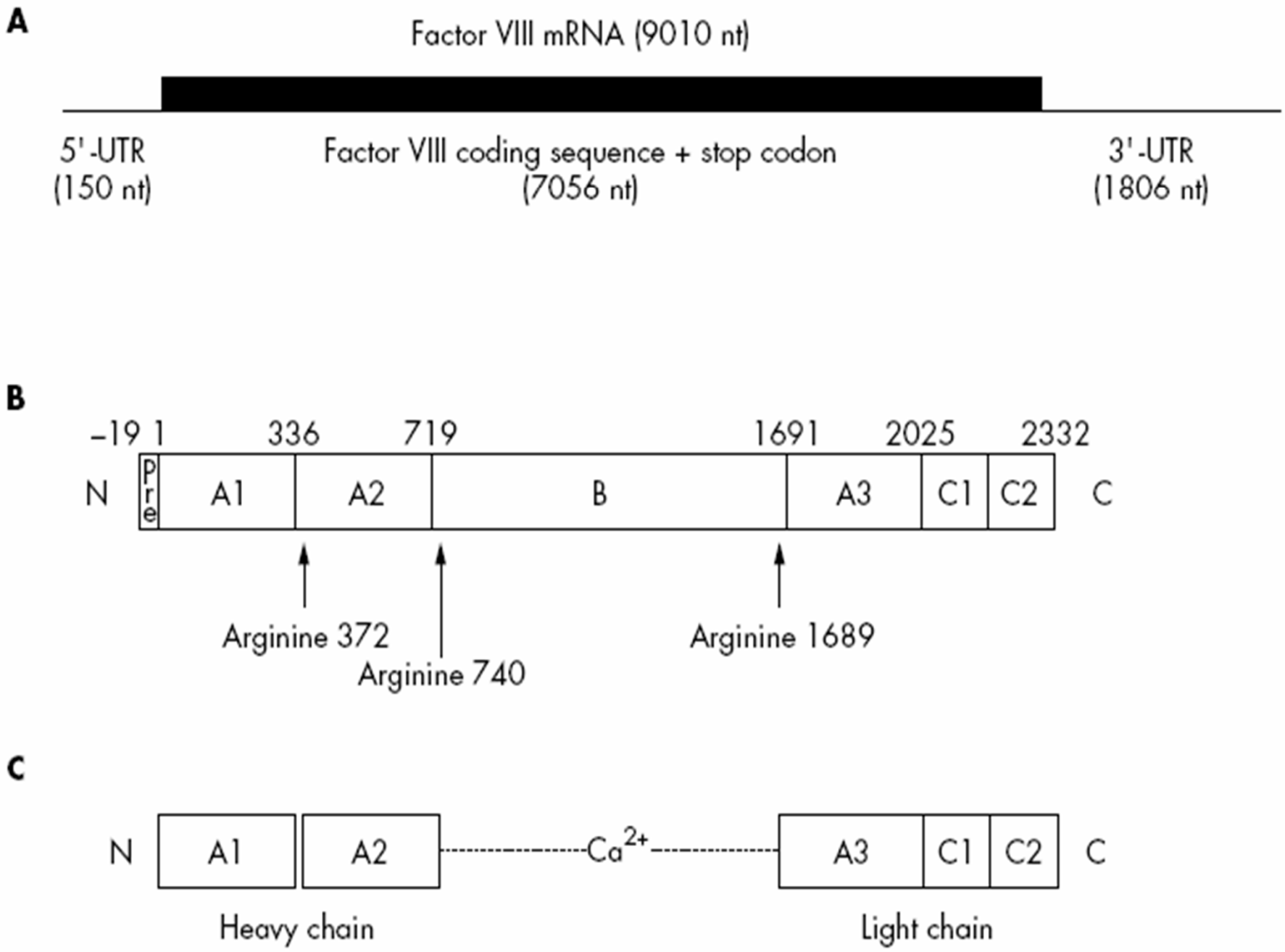
Klinik

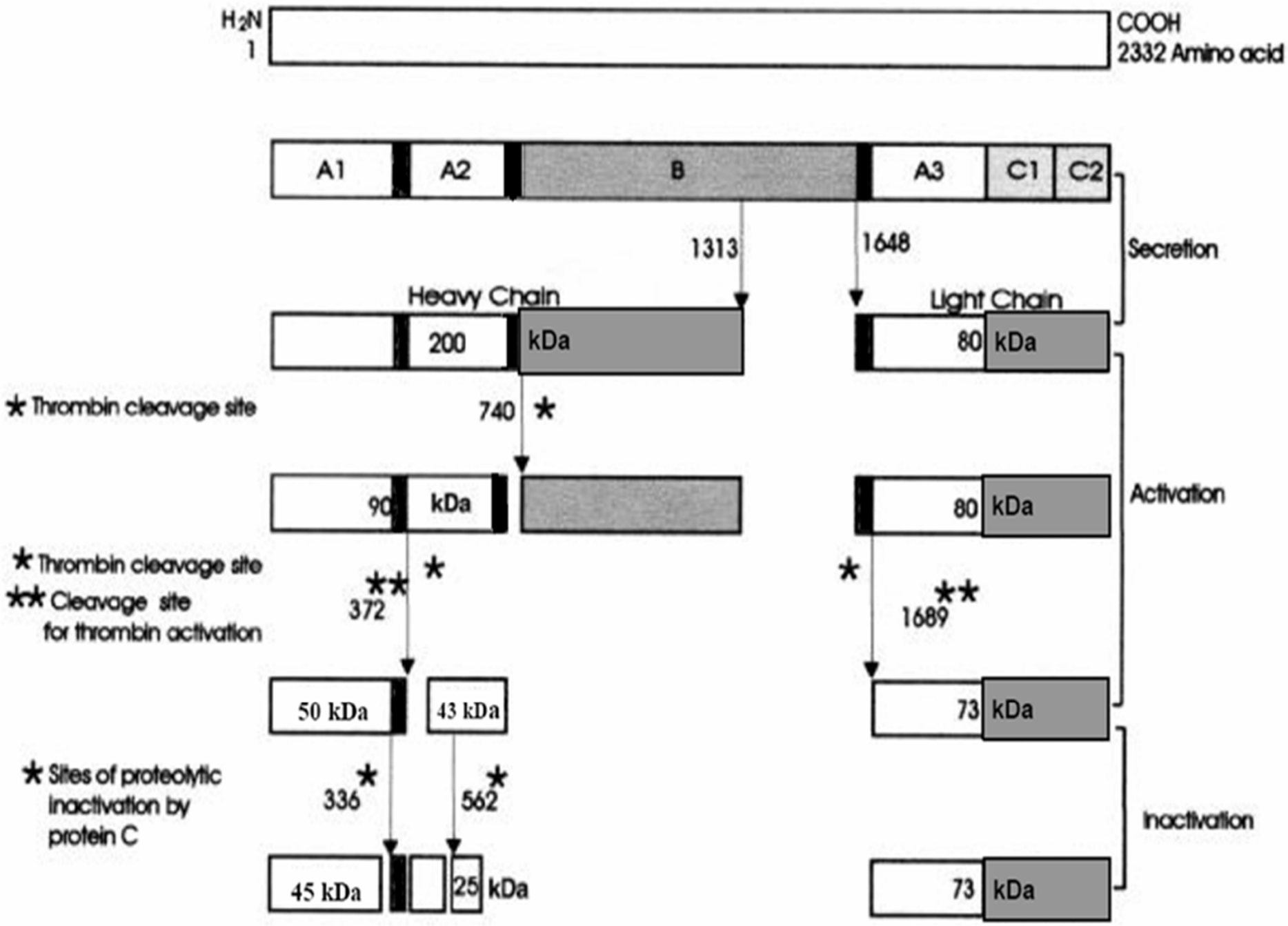
- Fleksiyon deformiteleri
- Psödotümör
- Kas içi kanamalar,
- Nadiren hematuri,
- Nadiren MSS kanamaları
- Kanama sıklığı ve şiddeti faktör düzeyine bağlıdır

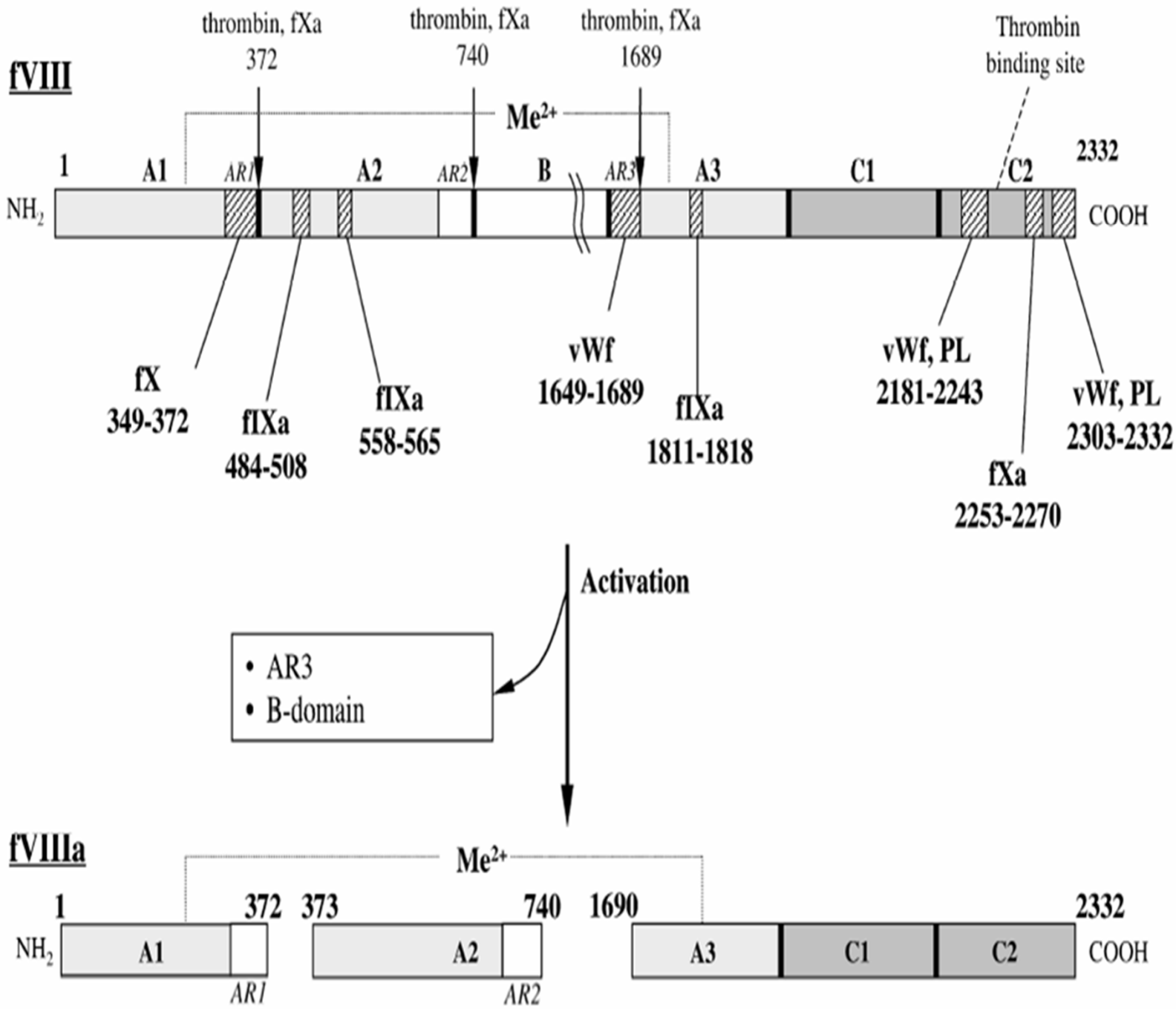
- Eksik olan faktörün aktivitesi;
  - % 1< ise (<0.01 IU mL^{-1}) ağır tip hemofili
  - % 1-4 (0.01–0.05 IU mL^{-1}) orta tip hemofili
  - % 5-30 (>0.05 IU mL^{-1}) ise hafif tip hemofili

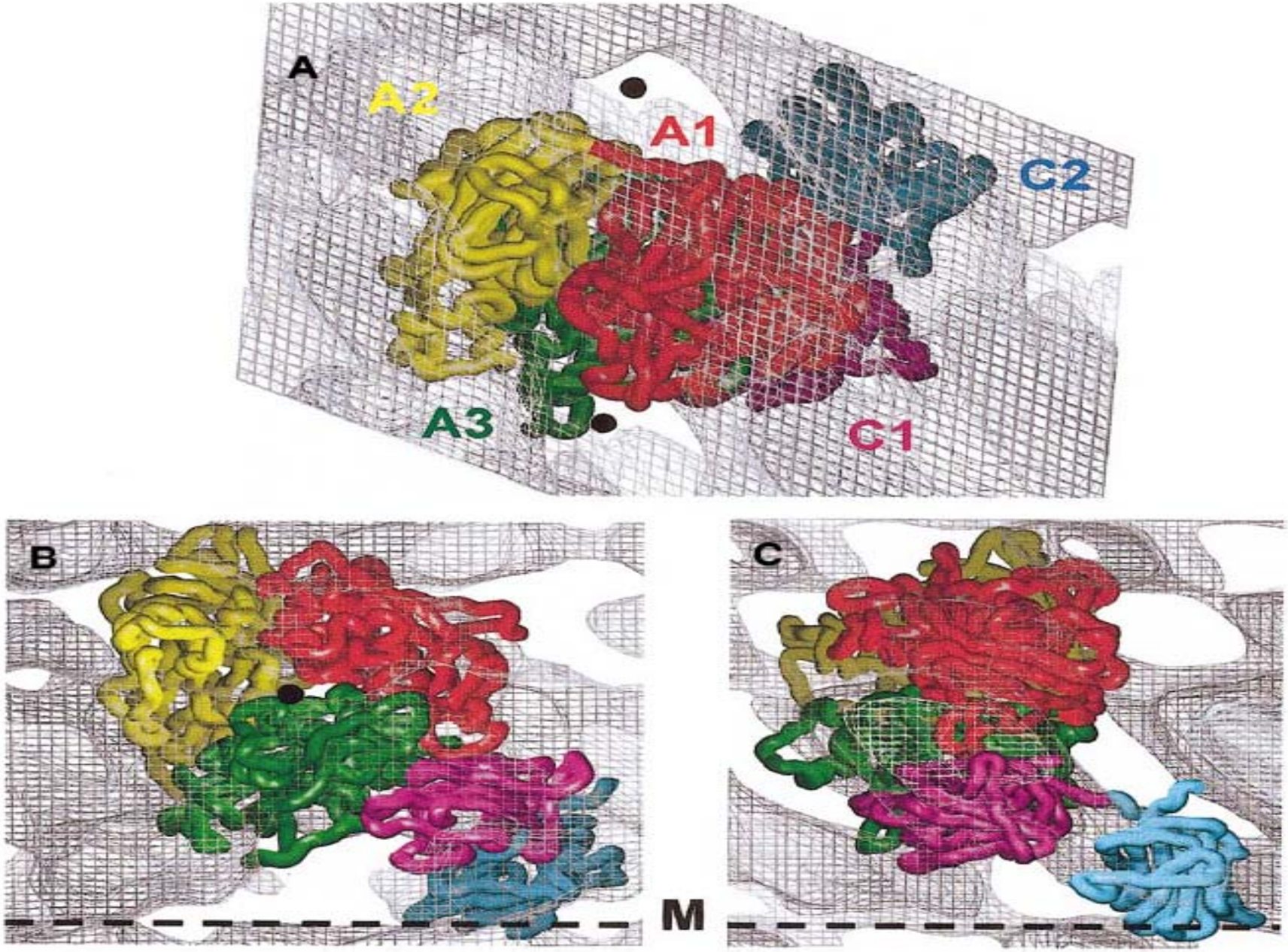

A
1
7
14
22
26
(~180 kb)
B
CG island
F8B
F8A
5' exon
Intron 22
Intron 22
Int22h-1
(9.5 kb)
C
Factor VIII gene (Xq28)
26
23
22
1
<
~0.3 Mb
>
<~0.1 Mb>
Xqter
To centromere
Int22h-1
(intragenic)
Int22h-2
(proximal)
Int22h-3
(distal)

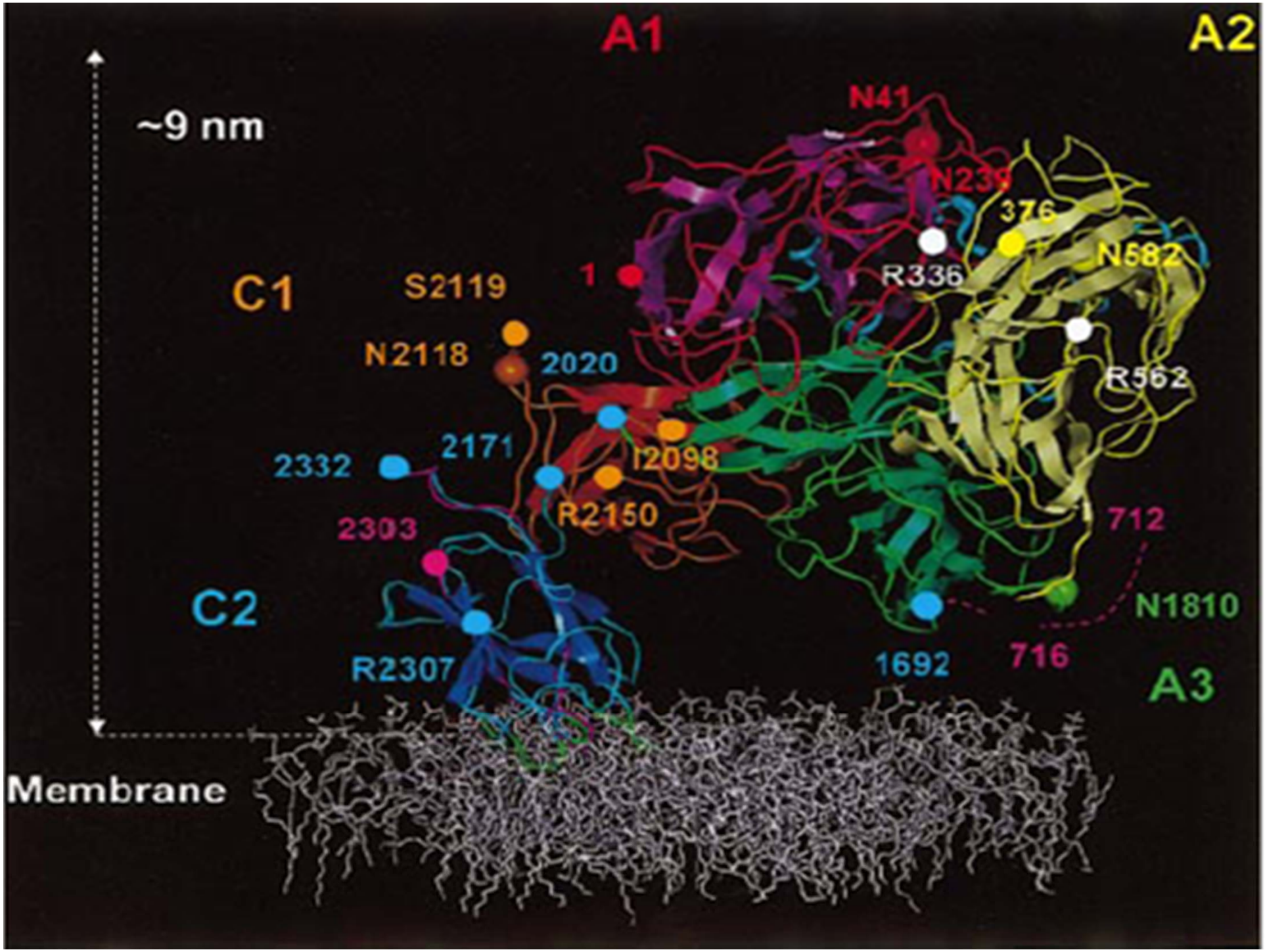
Exon	Length (bp)	Intron	Length (kb)
1	313	1	22.9
2	122	2	2.6
3	123	3	3.9
4	213	4	5.4
5	69 ↓	5	2.4
6	117	6	14.2
7	222	7	2.6
8	262	8	0.3
9	172	9	4.8
10	94	10	3.8
11	215	11	2.8
12	151	12	6.3
13	210	13	16.0
14	3106 ↑	14	22.7
15	154	15	1.3
16	213	16	0.3
17	229	17	0.2
18	183	18	1.8
19	117	19	0.6
20	72 ↓	20	1.6
21	86	21	3.4
22	156	22	32.4 ↑
23	145	23	1.4
24	149	24	1.0
25	177	25	22.4
26	1958 ↑		

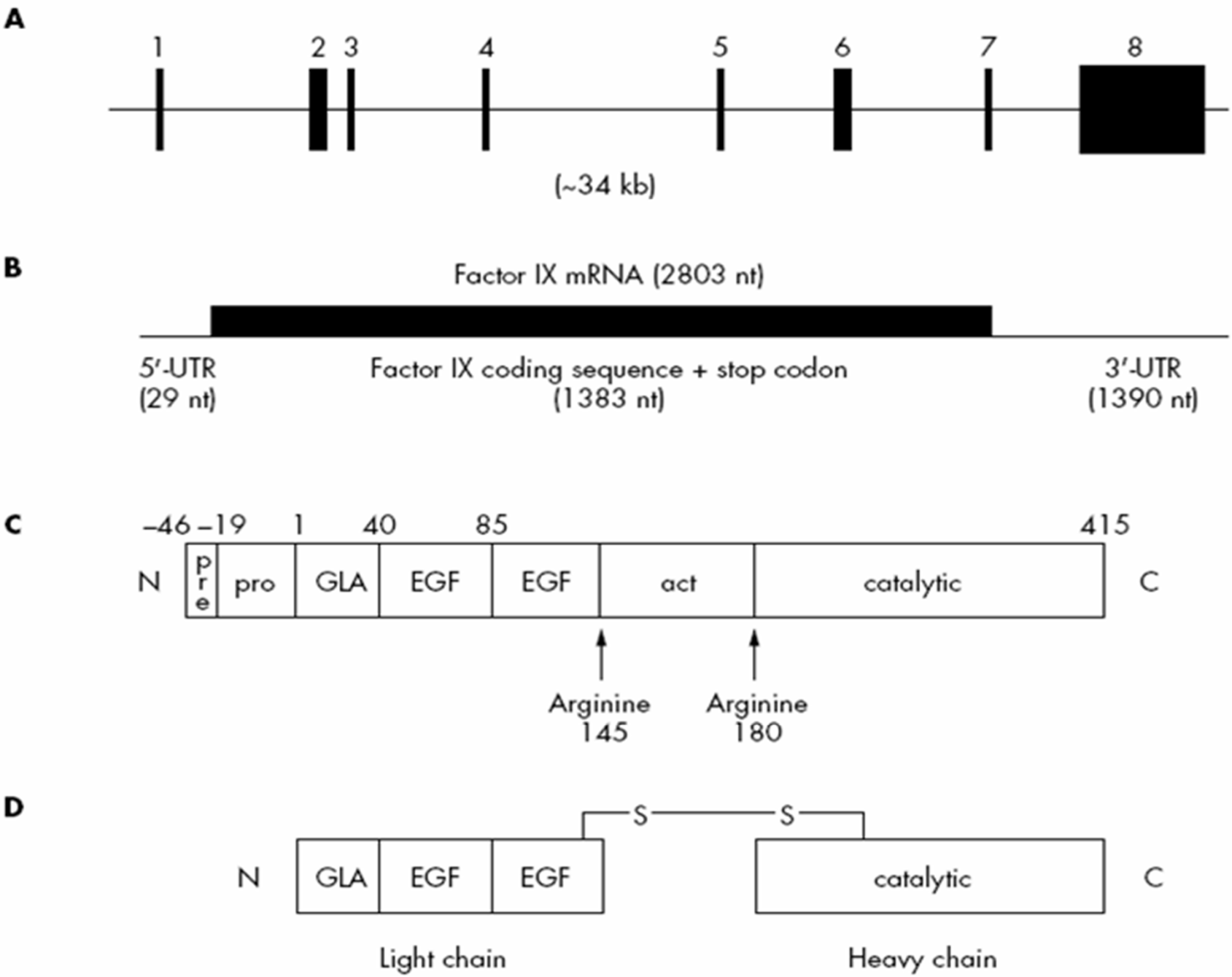

A
Factor VIII mRNA (9010 nt)
5'-UTR
(150 nt)
Factor VIII coding sequence + stop codon
(7056 nt)
3'-UTR
(1806 nt)
B
–19 1
336
719
1691
2025
2332
N
pre
A1
A2
B
A3
C1
C2
C
Arginine 372
Arginine 740
Arginine 1689
C
N
A1
A2
Ca2+
A3
C1
C2
C
Heavy chain
Light chain


H2N
1
COOH
2332 Amino acid
A1
A2
B
A3
C1
C2
1313
1648
Secretion
Heavy Chain
Light Chain
200
kDa
80
kDa
* Thrombin cleavage site
740
*
90
kDa
80
kDa
Activation
* Thrombin cleavage site
** Cleavage site
for thrombin activation
**
*
372
*
**
1689
50 kDa
43 kDa
73
kDa
* Sites of proteolytic
inactivation by
protein C
*
336
*
562
Inactivation
45 kDa
25
kDa
73
kDa

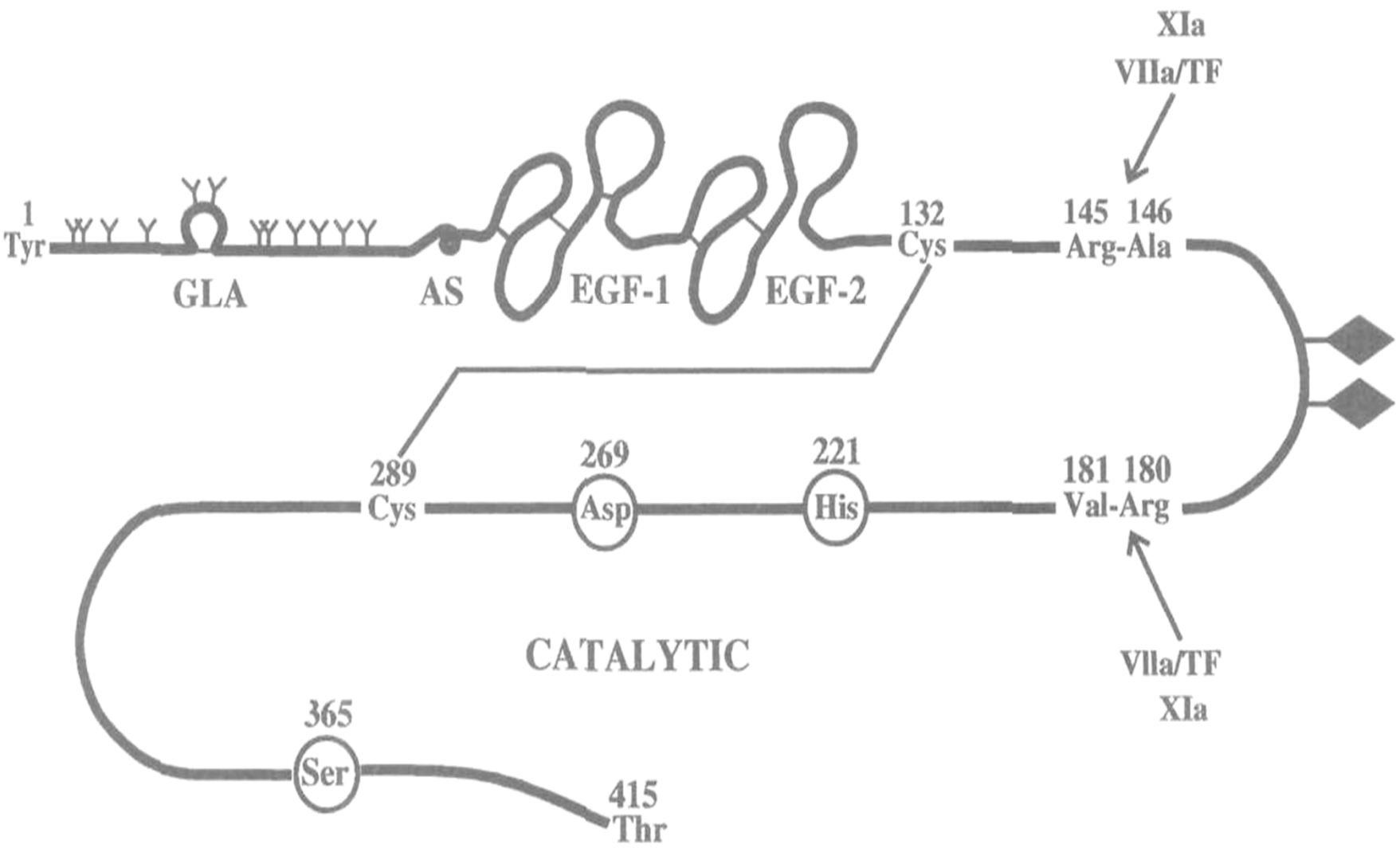

fVIII
thrombin, fXa
372
thrombin, fXa
740
thrombin, fXa
1689
Thrombin
binding site
Me2+
1
A1
AR1
A2
AR2
B
AR3
A3
C1
C2
2332
NH2
COOH
fX
349-372
fIXa
484-508
fIXa
558-565
vWf
1649-1689
fIXa
1811-1818
vWf, PL
2181-2243
vWf, PL
2303-2332
fXa
2253-2270
Activation
• AR3
• B-domain
fVIIIa
Me2+
1
372
373
740
1690
2332
NH2
A1
A2
A3
C1
C2
COOH
AR1
AR2


A
A2
A1
C2
A3
C1
B
C
M


A1
A2
~9 nm
N41
N239
376
N582
R336
C1
S2119
1
N2118
2020
R562
2171
2332
I2098
R2150
2303
712
C2
N1810
R2307
1692
716
A3
Membrane

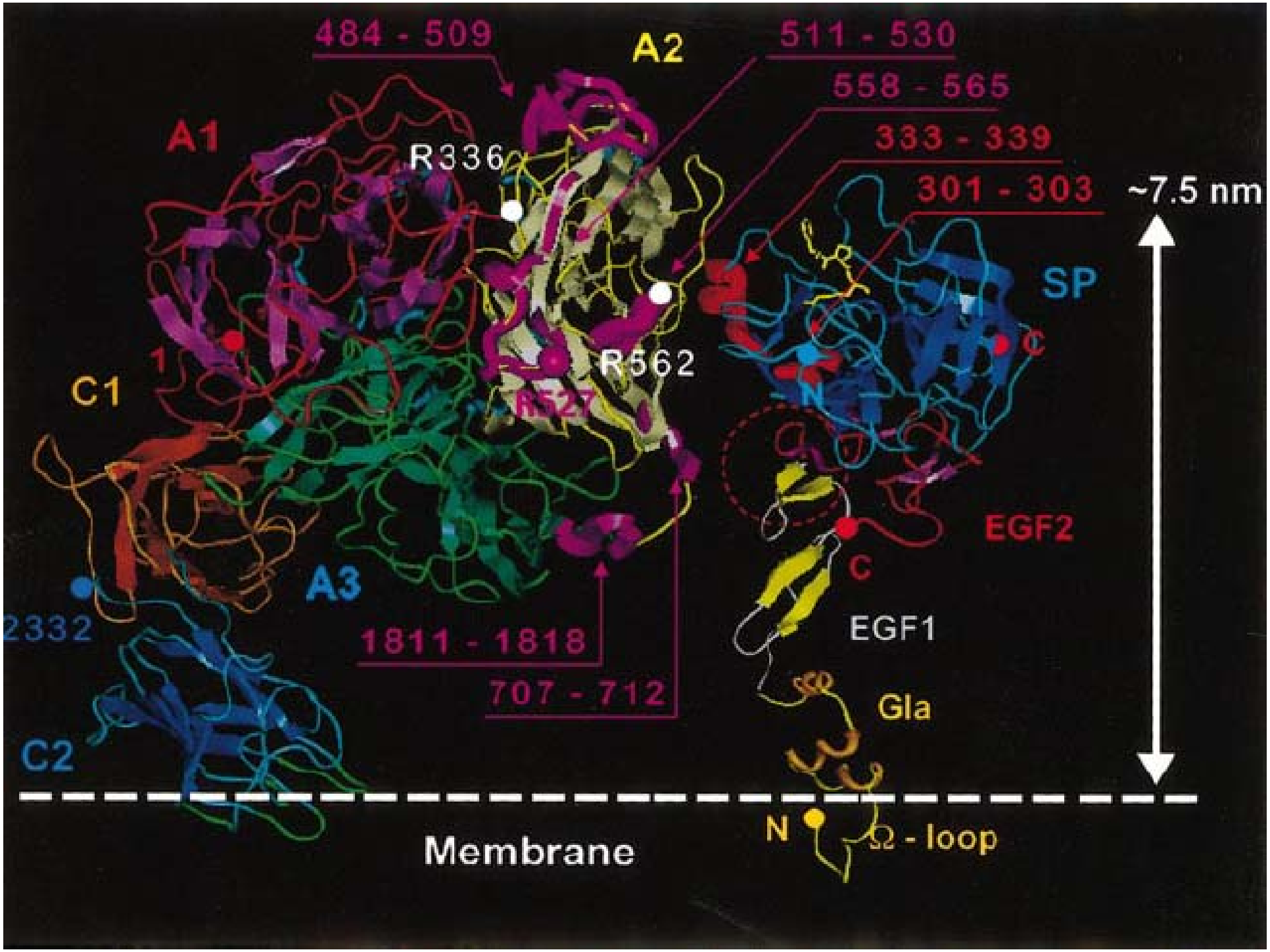

A
1
2
3
4
5
6
7
8
(~34 kb)
B
Factor IX mRNA (2803 nt)
5′-UTR
(29 nt)
Factor IX coding sequence + stop codon
(1383 nt)
3′-UTR
(1390 nt)
C
–46
–19
1
40
85
415
N
pre
pro
GLA
EGF
EGF
act
catalytic
C
Arginine
145
Arginine
180
D
S
S
N
GLA
EGF
EGF
catalytic
C
Light chain
Heavy chain

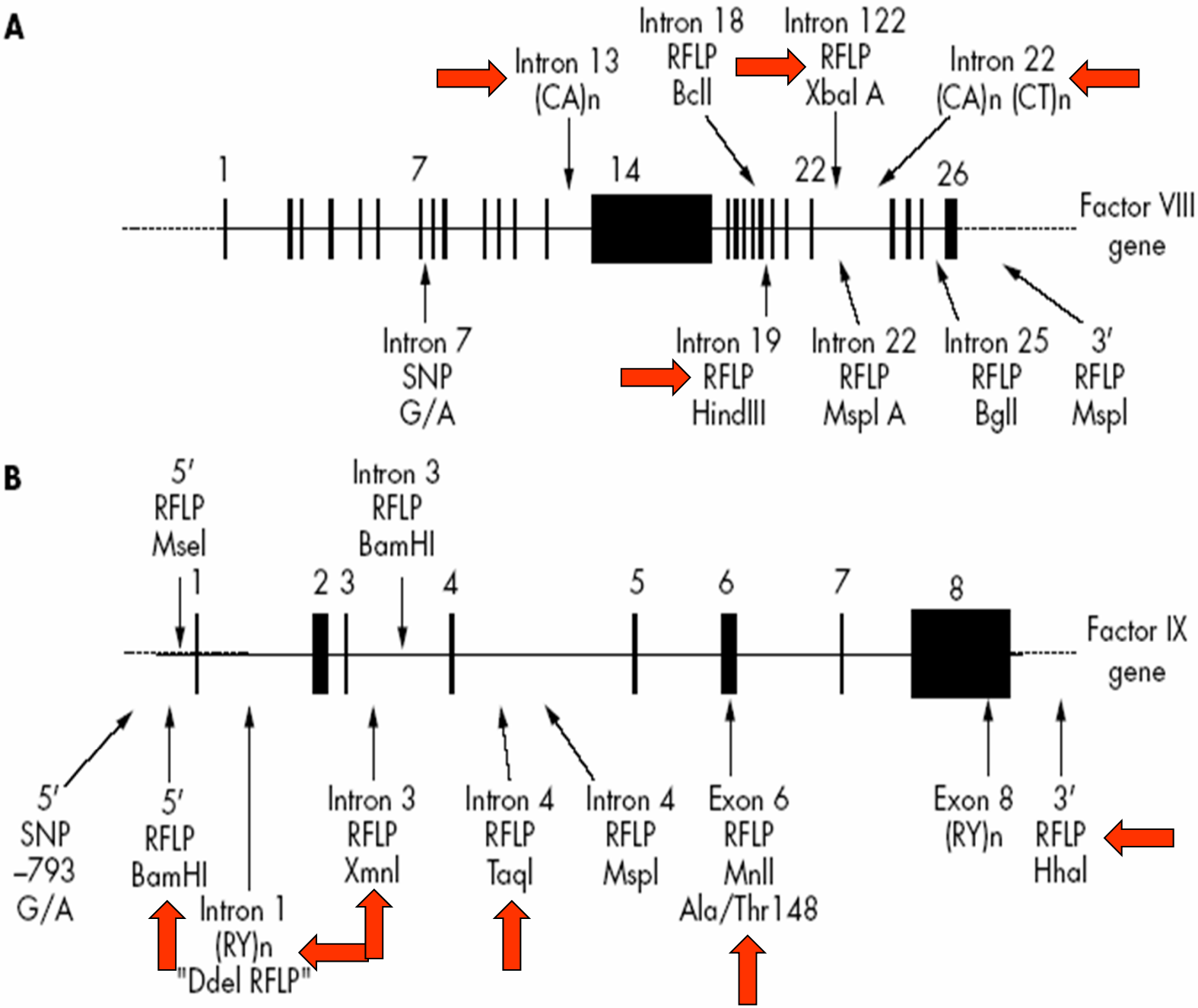
Matur FIX PROTEİNİ



F IX'un ekson ve intron uzunlukları

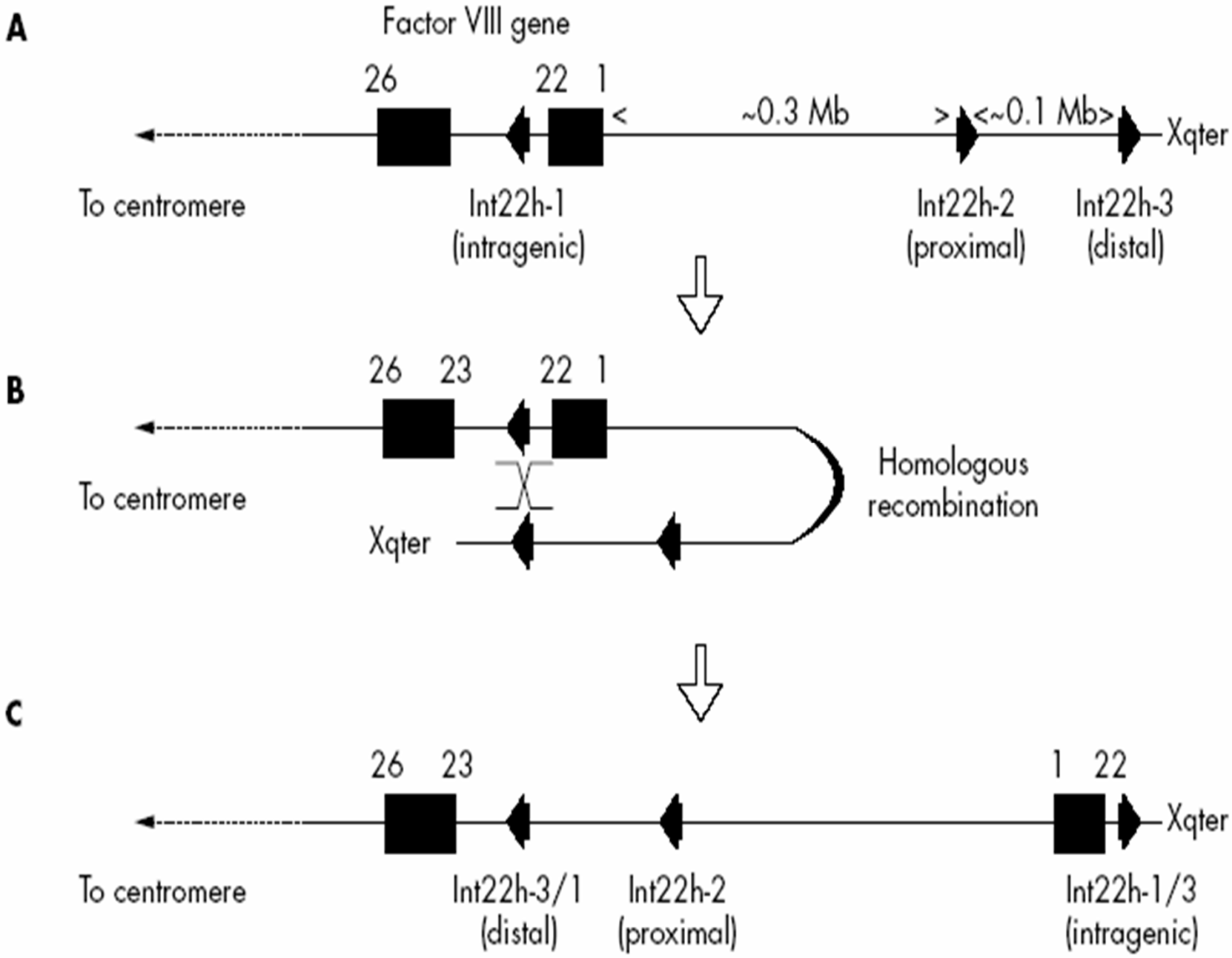
Exon	Length (bp)	Intron	Length (bp)
1	117	1	6206
2	164	2	188 ↓
3	25 ↓	3	3689
4	114	4	7163
5	129	5	2565
6	203	6	9473 ↑
7	115	7	668
8	1935 ↑		

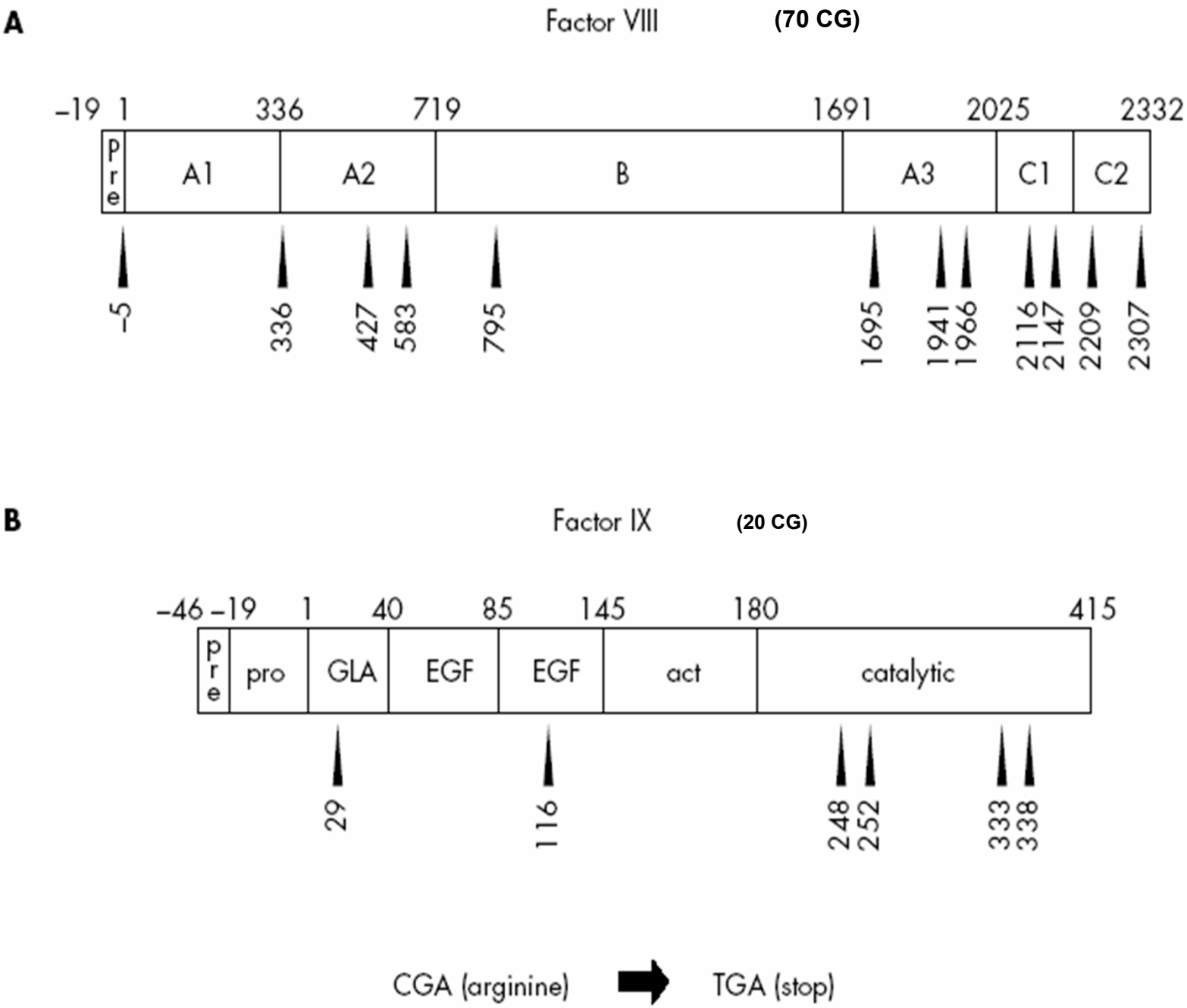

484 - 509
A2
511 - 530
558 - 565
A1
R336
333 - 339
301 - 303
~7.5 nm
SP
R562
C1
EGF2
A3
2332
EGF1
1811 - 1818
707 - 712
Gla
C2
N
Ω - loop
Membrane


A
Intron 13
(CA)n
Intron 18
RFLP
BclI
Intron 122
RFLP
XbaI A
Intron 22
(CA)n (CT)n
1
7
14
22
26
Factor VIII
gene
Intron 7
SNP
G/A
Intron 19
RFLP
HindIII
Intron 22
RFLP
MspI A
Intron 25
RFLP
BglI
3′
RFLP
MspI
B
5′
RFLP
MseI
Intron 3
RFLP
BamHI
1
2 3
4
5
6
7
8
Factor IX
gene
5′
SNP
–793
G/A
5′
RFLP
BamHI
Intron 1
(RY)n
"DdeI RFLP"
Intron 3
RFLP
XmnI
Intron 4
RFLP
TaqI
Intron 4
RFLP
MspI
Exon 6
RFLP
MnlI
Ala/Thr148
Exon 8
(RY)n
3′
RFLP
HhaI

MUTASYONLAR

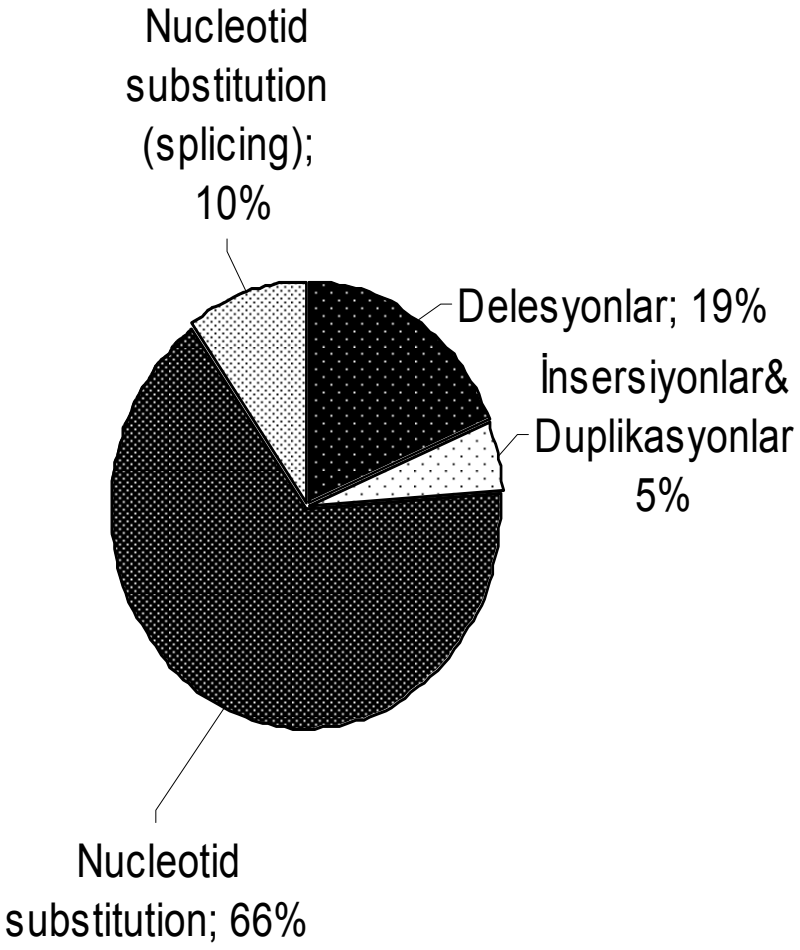
- Point
- Nonsense
- Missense
- mRNA splice site
- Delesyonlar
- İnseryonlar
- İnversiyonlar


A
Factor VIII gene
26
22
1
~0.3 Mb
~0.1 Mb
Xqter
To centromere
Int22h-1
(intragenic)
Int22h-2
(proximal)
Int22h-3
(distal)
B
26
23
22
1
To centromere
Xqter
Homologous
recombination
C
26
23
1
22
Xqter
To centromere
Int22h-3/1
(distal)
Int22h-2
(proximal)
Int22h-1/3
(intragenic)


A
Factor VIII
(70 CG)
–19
1
336
719
1691
2025
2332
pre
A1
A2
B
A3
C1
C2
–5
336
427
583
795
1695
1941
1966
2116
2147
2209
2307
B
Factor IX
(20 CG)
–46
–19
1
40
85
145
180
415
pre
pro
GLA
EGF
EGF
act
catalytic
29
116
248
252
333
338
CGA (arginine)
TGA (stop)

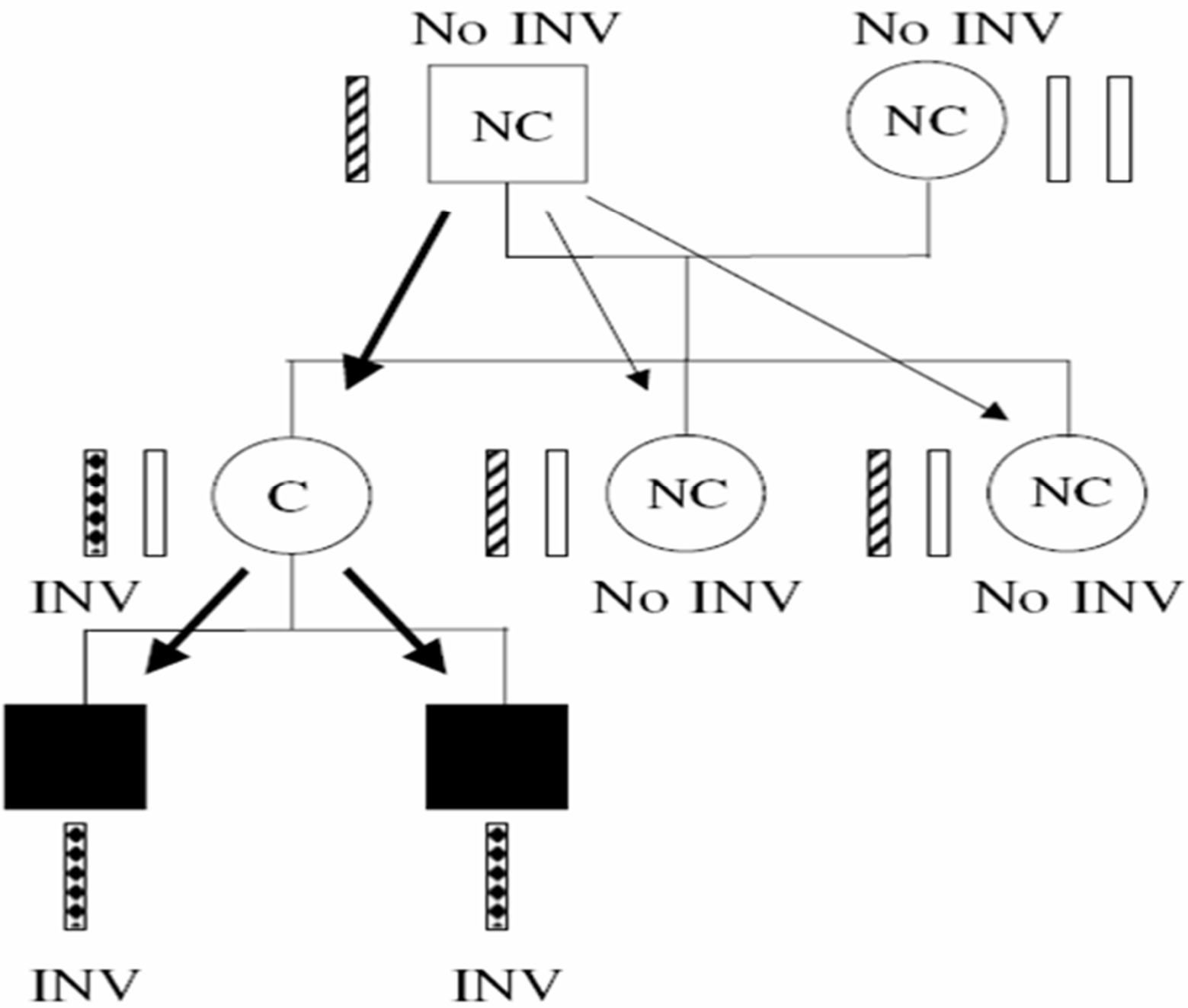
	Point Mutations			Deletions		Insertions
Exon	Missense [1]	Nonsense (Stop)	Splicing [2]	Small	Large	
1	14	1	4	2	na	0
2	5	1	5	6	na	2
3	24	0	3	4	na	0
4	24	5	2	1	na	1
5	11	1	7	3	na	1
6	6	0	3	4	na	2
7	32	4	0	6	na	0
8	21	4	1	8	na	1
9	22	3	1	5	na	1
10	10	1	0	4	na	0
11	27	1	3	1	na	1
12	20	5	2	0	na	1
13	23	3	2	4	na	1
14	37	39	3	63	na	31
15	13	1	4	2	na	0
16	18	4	2	5	na	0
17	24	3	1	5	na	4
18	26	4	1	3	na	3
19	14	1	5	3	na	1
20	5	1	0	0	na	1
21	5	4	0	0	na	1
22	16	5	5	3	na	1
23	25	1	4	6	na	0
24	10	3	3	3	na	2
25	11	2	1	4	na	2
26	19	3	0	7	na	0
TOTAL	**462**	**100**	**62**	**152**	**119**	**57**

Hemofili B Mutasyonları



MOZAİZM

- F VIII geninde;
  - Sperm veya oositte (de novo mutasyonu)
  - Embriyogenezde germ hücrelerinin gelişim evresinde
  - Germinal veya somatik mozaizm


No INV
No INV
NC
NC
C
NC
NC
INV
No INV
No INV
INV
INV

HA'da inversiyonların kökeni

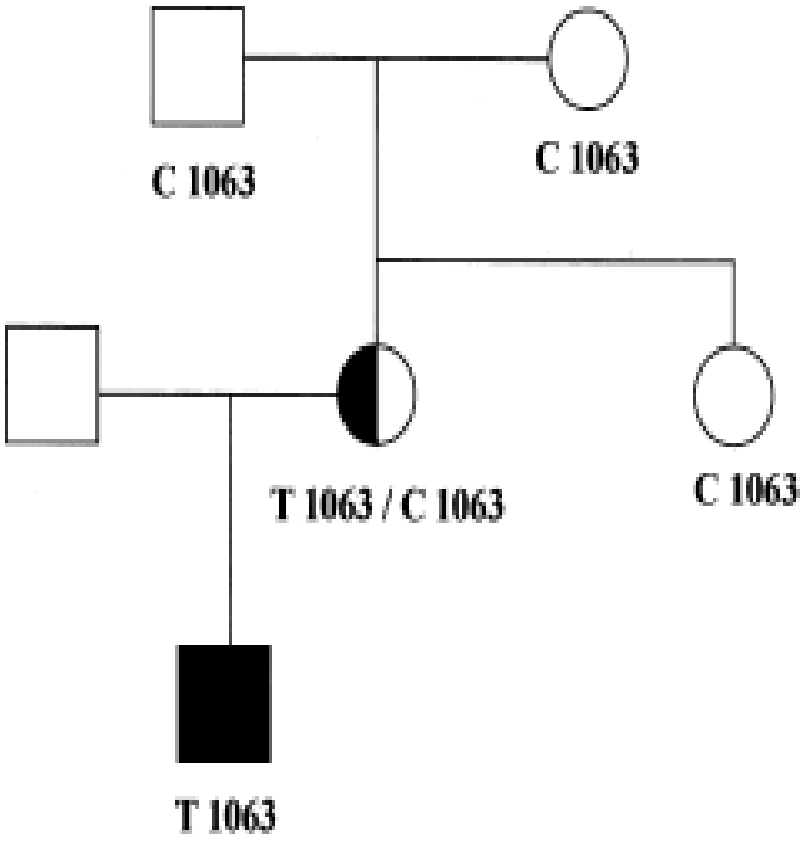
(İspanya)

- 3 generasyonu mevcut olan inversiyon taşıyıcısı olan 22 ailede haplotip analizler;
  - Vakaların % 91'inde ***de novo*** mutasyonu grandpaternal kökenli
  - Bu erkeklerde bir X kr olması

HA mutasyonların kökeni

(İsveç)

Mutasyon	n
İnversiyon Tip 1	11
İnversiyon Tip 2	3
İnversiyon Tip 3	1
Delesyon	6
İnsersiyon	2
Nonsense	4
Missense	2
TOPLAM	29



29 proband

- 8/29'i ***de novo*** mutasyonu taşımakta
- 21/29 taşıyıcı annenin;
  - 16'sı *de novo* mutasyonu taşımakta
  - 1'i maternal grandmother taşıyıcı
  - 4'ünün grandparent durumları incelenememiş
- Polimorfizmlerinden yararlanılarak;
  - 15/21'nin mutasyonun kökeni paternal
  - 1/21'nin mutasyonun kökeni maternal
  - 5/21'nin mutasyonun kökeni ise tespit edilememiş

Erkeklerde X faktörü mü?

- Mayozda erkek X kr eşleşmeyeceğinden inversiyonlar oluşmakta
- Ama 8 ***de novo*** mutasyonu taşıyan propand
  - 3 inversiyon
  - 2 nonsense
  - 1 missense
  - 1 insersiyon
  - 1 delesyon

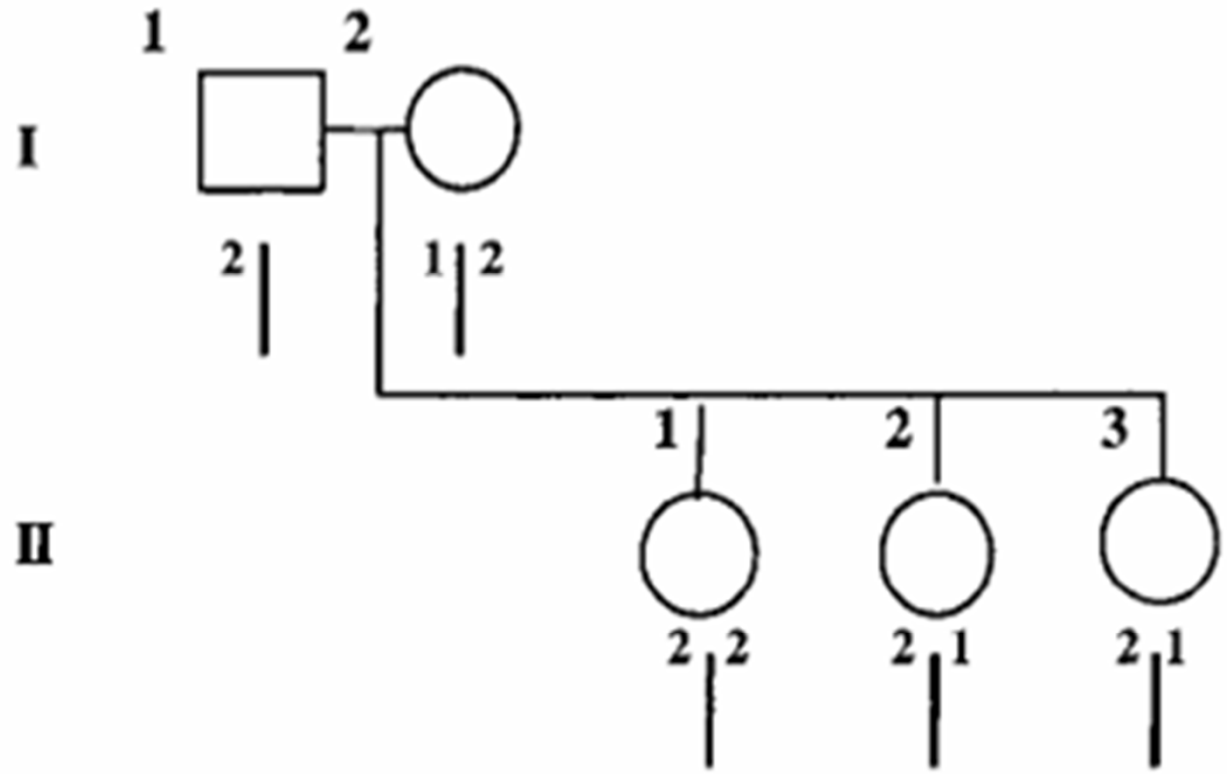
Bu Çalışmada

- Paternal yaş?
  - Bu çalışmada aynı yaşlardaki erkek ve kadınlar incelenmiş
- Somatik veya germinal mozaizm
- Mutasyon çeşidine bakılmaksızın E/K: 6/1

Bayanlarda HB

- Oldukça nadir

- Farklı mekanizmalar söz konusudur.
  - En çok heterozigot kızlarda normal X kr inaktivasyonu
    - X kr da translokasyon varsa veya
    - Genetik farklılığı içeren X'in inaktivasyonu



F.IXC (U/dL)	110	92	74	7	1
F.IXAg (U/dL)	110	93	70	7	28
Mutation T6704C	(-)	(+) Mosaic	(-)	(+)	(+)
Mutation T31152C	(-)	(-)	(-)	(-)	(+)

KOMŞULARIMIZDA

HA ve HB

BULGARİSTAN

2004

- İnsidans 1:18.000
- 36 HA'lı bireylerde yapılan çalışmada;
  - 23 ağır tip (FVIII:C<%1)
  - 8 orta tip (FVIII:C%1-5)
  - 5 hafif tip (FVIII:C>%5
- Ağır tip hastalarda inversiyon % 45

PT

- 14 prenatal tanı;
  - 5 kız
    - 2 taşıyıcı
    - 2 taşıyıcı olmadığı
    - 1'i cinsiyet analizinden sonra DNA bitmiş
  - 5 sağlam erkek
    - 1 fetüsün FVIII geninde ekstragenik ve intragenik polimorfizm saptanmış ama DNA bittiğinden mutasyon taraması tamamlanamamış
  - 2 fetus HA hasta
  - 1 CVS'te yeterince DNA elde edilememiş, II. girişimde fetüs kaybedilmiş

YUNANİSTAN

2002

- 1986’dan itibaren:
  - 214 aile
  - 338 hasta, 578 akraba incelenmiş

- **HA**'da hastaların %40'ının mutasyonu tanımlanmış
  - Ağır tip hastaların %35'inde inversiyon
  - Asn280Ile (A→T) (71 hafif tip hastada)
  - 27 kb del (3 hastada)
  - C6977T prematur terminasyon (98 ailede)
- 27 **HB** hasta taramasında
  - Frameshift T delesyonu (de novo)
  - Cd44 ve Cd252 nonsense mutasyonu
  - Missense mutasyonu
    - Arg-4 substitution Trp veya Gln
    - His221Arg
    - Arg248Gln
  - Promotor bölgede 1 nokta mutasyonu (FIX Leyden)

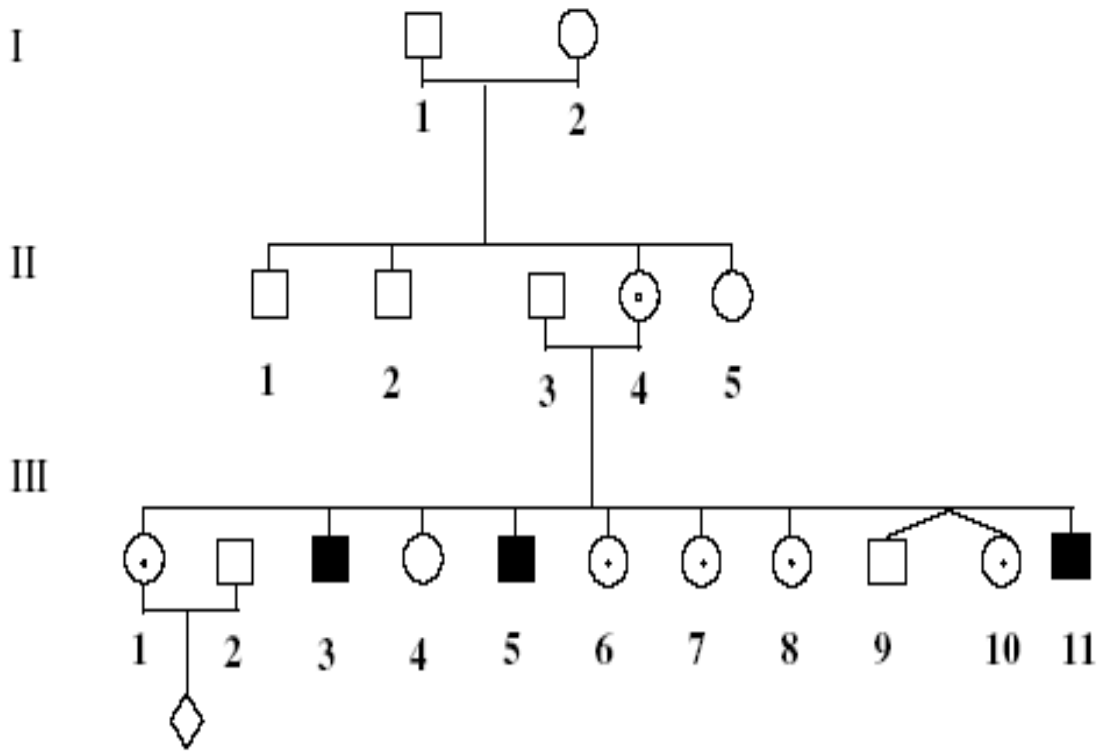
PT

- 230 HA ve HB taşıyıcında
  - %96 başarıyla
  - Vakaların % 87’sinin tanısı konmuş
  - 69/69 cinsiyet analizi yapılmış

İRAN

- FVIII ~3000
- FIX ~900
- HB'nin PT'sı RFLP-SSCP analizi ile yapılmıştır.

G20519A



Family no.	FIX:C level in the index (IU mL^{-1})	Nucleotide change codon number	Location in exon	Amino acid change
1	<0.01	G30073A	g	207G→E
2	<0.01	G30073A	g	207G→E
3*	<0.01			
4	<0.01	T10418 C	d	56C→R
5	<0.01	20382–3ΔAG†	f	Frame shift
6	<0.01	T6427C	b	18C→R
7	<0.01	T10482G	d	77F→C
		G6365A	b	−4R→Q
8	<0.01	G30864A	h_1	248R→Q
9	<0.01	T10482G	d	77F→C
10	0.018	G6365A	b	−4R→Q
11	0.11	G31276C†	h_2	385W→C
12	0.015	10502 or 3ΔT†	d	Frame shift
13	0.26	T10449A†	d	66I→N
14	<0.01	G17692A	e	93G→S
		G17701A†	e	96E→K
15	0.07	C31326A†	h_2	402S→Y
16	<0.01	G6472A†	b	33E→K
17	<0.01	T20374C	f	132C→R

ÜLKEMİZDE

Molecular pathology of haemophilia A in Turkish patients: identification of 36 independent mutations

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59 HA

- 24 ağır tip
- 15 orta tip
- 16 hafif tip

- 22 yeni mutasyon tanımlanmıştır

Family number	Domain/ exon–intron	Base change	Amino acid change	(%)	FVIII:C Severity	Comments
1	A1/IVS1	IVS1–1G→A		2.2	Severe	Acceptor splice site
2	A1/Exon2	c.201G→C	Lys48 Asn	?	?	3° structure,[e] new *N*-glycosylation site
3	A1/Exon 3	c.349C→T	Leu98 Phe	20	Mild	Cyclic side chain effects His99; metal^{2+}-binding?
4	A1/Exon 4	c.409 A→G	Thr118 Ala	0.2	Severe	3° structure, reduced glycosylation?
5	A1/Exon 4	c.514–515 insTCAAGATA	–	0.5		Severe frameshift and premature termination at codon 154
6	A1/Exon 7	c.800G→A	Cys248 Tyr	3	Moderate	Loss of a disulphide bond; 3° structure
7	A1/Exon 7	c.901C→T	Arg282 Cys	0	Severe	
8	A1/Exon 7	c.902G→A	Arg282 His	2.5	Severe	
9	A1/Exon 8	c.1043G→A	Cys329 Tyr	7	Mild	
10	A1/Exon 8	c.1063C→T	Arg336 Ter	2.1	Severe	
11	A1/Exon 8	c.1063C→T	Arg336 Ter	1	Severe	
12	A2/Exon 9	c.1423G→A	Glu456 Lys	3	Moderate	3° structure; FIXa and thrombin binding?
13	A2/Exon 11	c.1736 A→C	Asp560 Ala	7	Mild	3° structure; FIXa binding
14	A2/Exon 12	c.1804C→T	Arg583 Ter	?	?	
15	A2/Exon 12	c.1834C→T	Arg593 Cys	1.5	Moderate	
16	A2/Exon 13	c.2048 A→G	Tyr664 Cys	2.6	Severe	Extra disulphide bond; 3° structure, binding to FIXa, thrombin, and other A ddomains?
17	A2/Exon 13;	c.2092T→C	Phe679 Leu	?	?	
	C2/Exon 25	c.6745C→T	Leu2230 Leu			Variant?
18	A2/Exon 13	c.2099C→A	Ser681 Ter	< 2	Severe–Moderate	Premature termination
19	A2-A3/Exon 14 del→2.8kb	?	–	1.2	Severe	
20	A2/Exon 14a	c.2128G→T	Gly691 Trp	?	?	3° structure?
21	A3/Exon 14b	c.5122C→T	Arg1689 Cys	6	Mild	
22	A3/Exon 15	c.5362G→C	Asp1769 His	7	Mild	3° structure; FIXa and metal^{2+}-binding?
23	A3/Exon 17;	c.5626G→C;	Val1857 Leu	31	Mild	
	A1/IVS3	IVS3–9C→T				Variant?
24	A3/Exon 19	c.6046C→T	Arg1997 Trp	2.9	Moderate	
25	A3/Exon 20	c.6120T→A	Cys2021 Ter	2	Severe	Premature termination
26	C1/Exon 20	c.6134G→A	Gly2026 Glu	7.5	Mild	3° structure
27	C1/Exon 22	c.6394C→T	Gln2113 Ter	?	Severe	Premature termination
28	C1/Exon 23	c.6532C→T	Arg2159 Cys	5	Mild	
29	C1/Exon 23	c.6544C→T	Arg2163 Cys	1	Severe	
30	C1/Exon 23	c.6545G→A	Arg2163 His	1.5	Moderate	
31	C1/Exon 23	c.6545G→A	Arg2163 His	1.5	Moderate	
32	C1/Exon 23	c.6545G→C	Arg2163 Pro	3	Moderate	3° structure
33	C1/Exon 23	c.6545G→A	Arg2163 His	1	Severe	
34	C2/Exon 25	c.6882 del T		2.5	Severe–Moderate	Frameshift and premature termination at codon 2286
35	C2/Exon 26	c.6920 A→C	Asp2288 Ala	4	Mild	3° structure; phospholipid binding?
36	C2/Exon 26	c.6968G→T	Arg2304 Leu	4.9	Mild	3 structure; phospholipid binding

Family number	Mutation type	Generation number	Mother's carrier status	Mutation origin	Allele origin
1	Splicing	2	Non-carrier	Mother	Mother
3	Missense	2	Carrier	?	?
5	Insertion	2	Carrier	?	?
10	Nonsense (CpG)	2	Non-carrier	Mother	Mother
11	Nonsense (CpG)	2	Carrier	?	?
15	Missense (CpG)	2	Carrier	?	?
13	Missense	3	Carrier	MGF	MGF
16	Missense	2	Carrier	?	?
25	Nonsense	3	Carrier	MGM	MGM
29	Missense (CpG)	2	Non-carrier	Mother	Mother
31	Missense (CpG)	2	Carrier	?	
32	Missense (CpG)*	3	Carrier	MGF	MGF
34	Small deletion	3	Carrier	MGF	MGF
35	Missense	3	Carrier	MGF	MGF

Molecular pathology of haemophilia B in Turkish patients: identification of a large deletion and 33 independent point mutations

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	FIX:C (%)	Nucleotide change	Amino acid change	FIX Domain	CpG
1		Δ (−84,4780)*	–	–	–
2	3·9	112G > A	Cys-19Tyr	Signal pep.	N
3	1·3	6365G > T	Arg-4Leu	Gla	N
4	2	6365G > A	Arg-4Gln	Gla	Y
5	1·7	6392T > C*	Leu6Ser	Gla	N
6	3	10431G > A	Gly60Asp	EGF1	N
7	< 1	10468 G > A	Trp72Stop	EGF1	N
8	0·1	10484G > A	Glu78Lys	EGF1	N
9		17678G > A	Cys88Tyr	EGF2	N
10	12·2	20518C > G	Arg180Gly	Activation peptide	N
11	Moderate	20518C > G	Arg180Gly	Activation peptide	N
12	< 1	20518C > T	Arg180Trp	Activation peptide	Y
13		20519G > A	Arg180Gln	Activation peptide	Y
14	1	20563C > A	Gln195Lys	Catalytic	N
15	7·8	30070G > A	Cys206Tyr	Catalytic	N
16	1	30104insAA*	Ile251Stop	Catalytic	N
17		30845G > T*	Glu242Stop	Catalytic	N
18		30863C > T	Arg348Stop	Catalytic	Y
19	4	30864G > A	Arg248Gln	Catalytic	Y
20	0·2	30864G > A	Arg248Gln	Catalytic	Y
21	1	30875C > T	Arg252Stop	Catalytic	Y
22		30929 A > T	Ile270Phe	Catalytic	N
23		30936T > G	Leu272Arg	Catalytic	N
24		31118C > T	Arg333Stop	Catalytic	Y
25		31119G > A	Arg333Gly	Catalytic	Y
26	3·8	31130C > A	Leu337Ile	Catalytic	N
27	2	31130C > T	Leu337Phe	Catalytic	N
28		31133C > T	Arg338Stop	Catalytic	Y
29		31166T > A*	Phe349Ile	Catalytic	N
30	7·8	31170G > T	Cys350Phe	Catalytic	N
31	0·4	31171T > A*	Cys350Stop	Catalytic	N
32	5	31202T > C	Cys361Arg	Catalytic	N
33	2·2	31218G > A	Gly366Glu	Catalytic	N
34	0·5	31218G > A	Gly366Glu	Catalytic	N

Mutations Associated With Hemophilia B in Turkish Patients

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HUMAN MUTATION 10:76–79 (1997)

Patient	FIX activity[a]	Clinical severity[b]	Nucleotide Change	Nucleotide No.[c]	At CpG	Structural change
HB367	0	S	del.			Deletion of exons d–f
HB364 (Istanbul1)	<3	S	G→C	6707	No	donor splice I3
HB298 (Antalya)	12	Mi	T→A	10453	No	Asn^{67}→Lys
HB363	11	Mi	C→T	31008	Yes	Thr^{296}→Met
HB365	1.5	Mo	G→A	31220	No	Gly^{367}→Arg
HB369 (Istanbul2)	<1	S	T→G	31253	No	Phe^{378}→Val

Intron 22 inversions in the Turkish haemophilia A patients: prevalence and haplotype analysis

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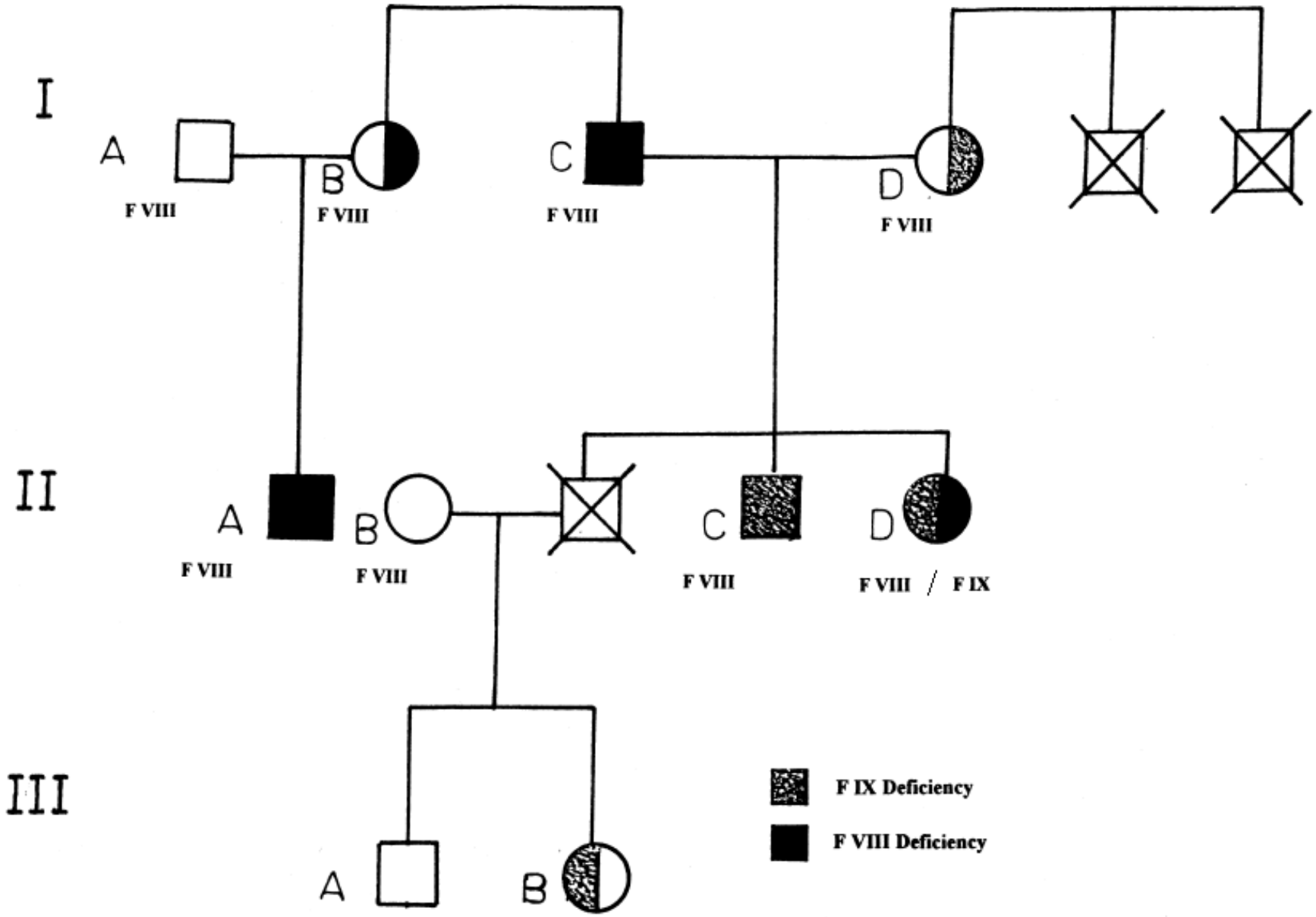
- 141 HA vakasında

Genel olarak % 29 oranda inversiyon

ağır tip hastaların % 42'si inversiyon taşımaktadır.


I
A
F VIII
B
F VIII
C
F VIII
D
F VIII
II
A
F VIII
B
F VIII
C
F VIII
D
F VIII / F IX
III
A
B
F IX Deficiency
F VIII Deficiency

teşekkürler....