SUPPLEMENTAL DATA

SUPPLEMENTAL TABLE 1. *Clinical and laboratory data of HAEIII family members. Numbers correspond to the pedigree in Figure 1B.*

No.	Gender	Age	C1INH antigen [mg/l]	C1INH function [U/ml]	C4 antigen [mg/l]	ACE activity [U/ml]	Mutation		Symptomatic
							c.DNA‡	Protein§	
1	F	62	308	26.3	191	46	c.1032C>A	p.Thr309Lys	Yes
2	F	28	291	23.5	*	35	c.1032C>A	p.Thr309Lys	Yes
3	F	67	287	18.5	114	*	c.1032C>A	p.Thr309Lys	Yes
4	F	38	293	20.6	294	54	c.1032C>A	p.Thr309Lys	Yes
5	F	34	272	22.7	286	52	c.1032C	p.Thr309	No
6	F	29	261	21.0	153	49	c.1032C>A	p.Thr309Lys	No
7	M	94	*	*	*	*	c.1032C>A	p.Thr309Lys	No
8	M	31	280	24.5	225	*	c.1032C>A	p.Thr309Lys	No

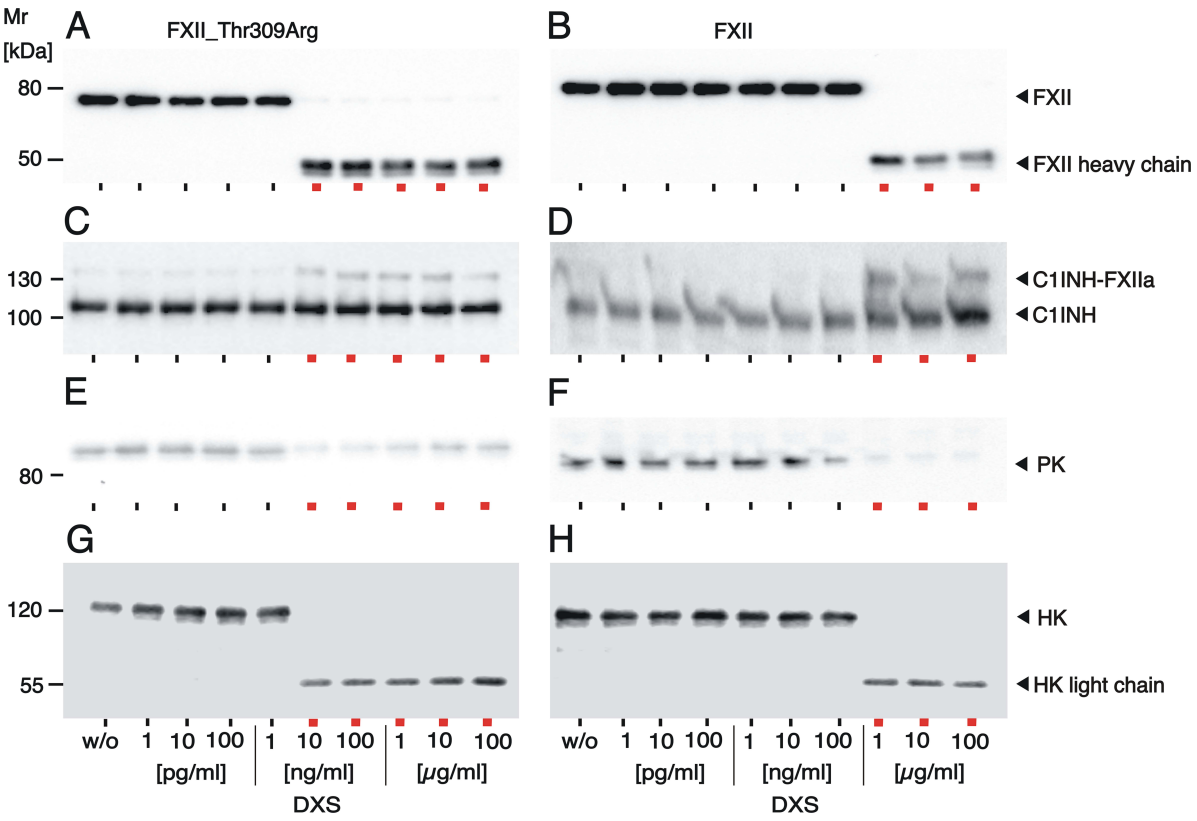
*: not determined

ACE: angiotensin converting enzyme

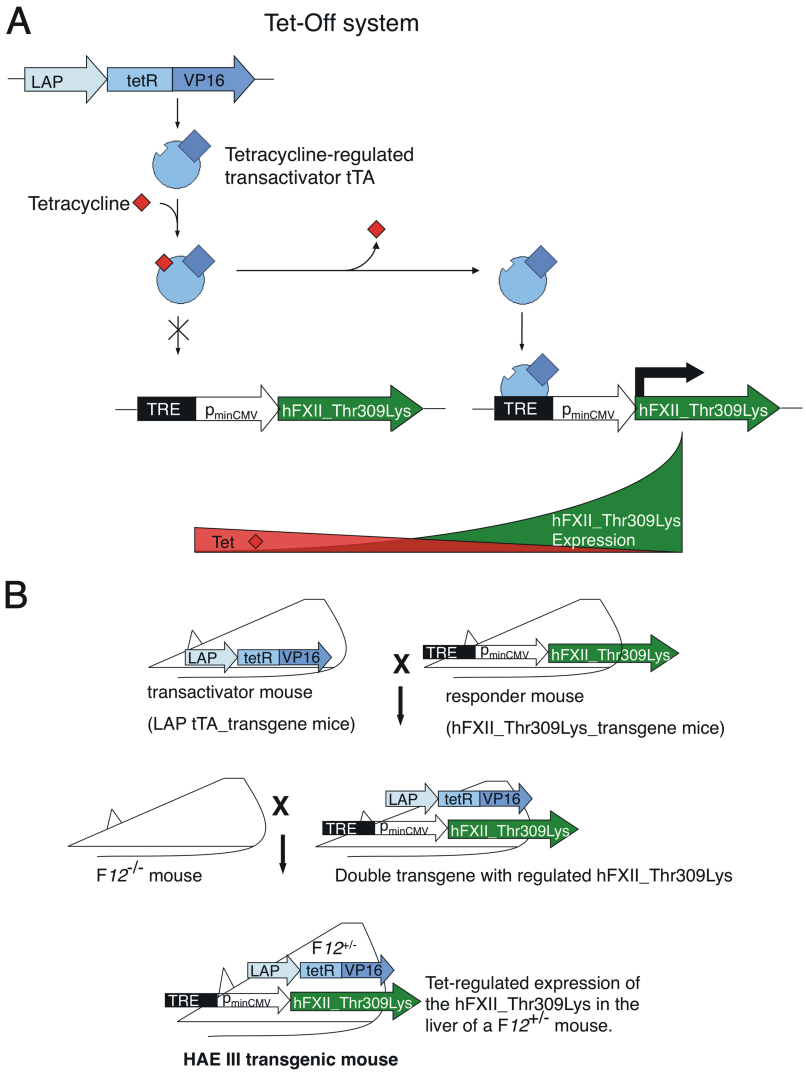
‡ Nucleotide numbering according to cDNA sequence of *F12* (gi:9961354).

§ Amino acid numbering omitting signal peptide.

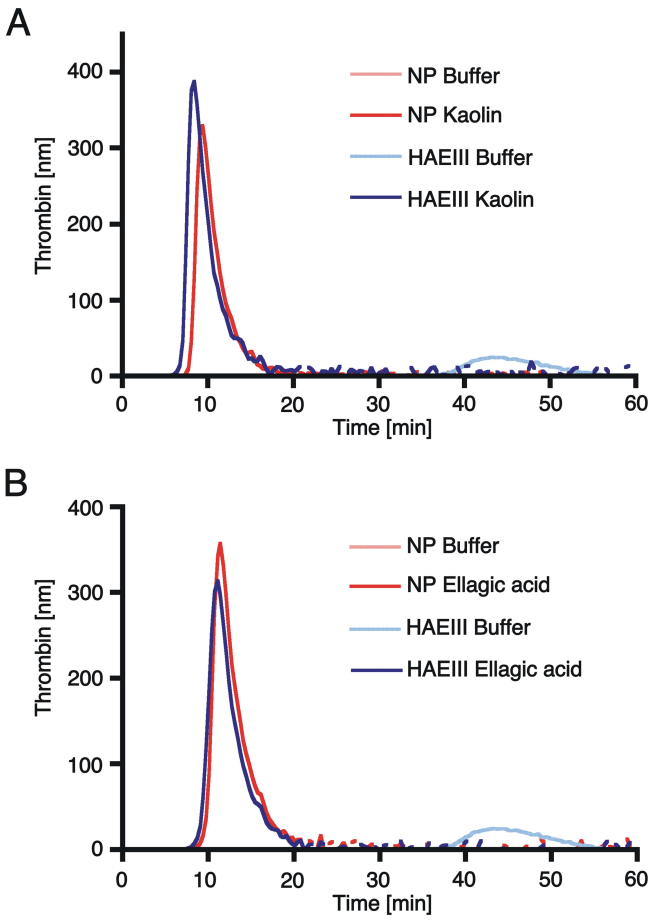
Normal range: C1INH antigen [210-390 mg/l], C1INH function [17.2-27.4 U/ml], C4 antigen [100-400 mg/l] and ACE activity [23-57 U/ml].



SUPPLEMENTAL FIGURE 1. *Increased FXII_Thr309Arg zymogen activation triggers excess KK-mediated HK cleavage in a purified system.* (A) Purified recombinant FXII or FXII_Thr309Arg was added to PK, HK and C1INH, all at normal plasma concentrations. Protein mixtures were incubated with a concentration series of dextran sulfate (DXS, 1 pg/ml-100 µg/ml) or buffer (w/o). Contact factors were analyzed by Western blotting with (A, B) anti-FXII, (C, D) anti-C1INH, (E, F) anti-PK and (G, H) anti-HK antibodies. A representative photographic film of a series of n=3 is shown.



SUPPLEMENTAL FIGURE 2. *Generation of HAEIII transgene mice.* Liver specific inducible expression of Thr309Lys mutated human FXII (hFXII_Thr309Lys) by a tetracycline (Tet)-regulated system. (A) Schematic outline of the tetracycline-controlled transactivator system used in this study. The LAP promoter restricts expression of the regulatory protein tTA to the liver. In the absence of tetracycline (or its analog doxycycline), tTA binds to TRE-sequence and activates the expression of Thr309Lys mutated human FXII protein. (B) Breeding scheme of HAEIII transgene mice. HAEIII transgene mice were generated by breeding Tg(Cebpb-tTA)5Bjd (LAP-tTA) mice to hFXII_Thr309Lys responder mice. Double transgenic animals were further crossbreed to FXII knockout animals ($F12^{-/-}$) to obtain a heterozygous *F12* background ($F12^{+/-}$). When tetracycline (or doxycycline) is removed, tTA binds to the TRE-sequence and allows for the expression of the mutated hFXII_Thr309Lys (Tet-Off System).



SUPPLEMENTAL FIGURE 3. *Procoagulant activity in HAEIII plasma*. Real time thrombin generation in HAEIII patient and healthy control plasma (NP) (A) stimulated with kaolin (1 µg/mL) or (B) ellagic acid (100 ng/ml). A representative thrombin generation curve of a series of n=3 is plotted.