Supplemental Methods

Materials

DMEM and Opti-MEM cell culture media, HBSS, and Geneticin were purchased from Gibco Life Technologies (Waltham MA). Fetal Bovine serum was purchased from VWR (Radner, PA). Cell culture plates, flasks, and ELISA costar 96-well plates were purchased from Corning (Corning, NY) and conical tubes were purchased from Sarstedt (Nümbrecht, Germany). Restriction enzymes NheI, AgeI, NotI, and BssHII were purchased from New England Biolabs (Ipswich, MA). Heparin-Sepharose 6 Fast Flow, "VIIISelect" resin, HiTrap SPHP columns, and SFM4HEK293 media was purchased from GE Healthcare (Chicago, IL) and Poly-Prep columns were purchased from Bio-Rad (Hercules, CA). HEK cell lines were purchased from ATCC (Manassas, VA) with the exception of Expi293™F and HEK293-H cells purchased from Thermo Fisher Scientific (Waltham, MA). Polyethylenimine, o-phenylenediamine dihydrochloride, RNAlater, bovine serum albumin, and M2 anti-FLAG antibody were purchased from Sigma-Aldrich (St. Louis, MO). TransIT-EE hydrodynamic buffer and TransIT-X2 transfection reagent were purchased from Mirus Bio (Madison, WI). DNA and RNA purification kits were purchased from Qiagen (Germantown, MD) and Omega Bio-Tek (Norcross, GA). Amicon 50K NMWL filters were purchased from EMD Millipore (Burlington, MA). Immunohistochemistry DAKO protein block, DAKO mounting medium, isotype antibody X0936, polyclonal rabbit anti-human VWF antibodies A0082 and P0226 were purchased from Agilent (Santa Clara, CA). Factor VIII chromogenic SP4 assay was purchased from Diapharma (Chester, OH). WHO standard human plasma, and the INNOVANCE VWF:Ac kit were purchased from Siemens (Munich, Germany). RNase Inhibitor RiboLock, Power SYBR™ Green PCR master mix, and Multiscribe™ reverse transcriptase were purchased from Thermo Fisher Scientific (Waltham, MA). The ExpiFectamine293™ transfection reagents and Expi293™ expression media was also purchased from Thermo Fisher Scientific. Human collagen type I was purchased from StemCell Technologies (Vancouver, Canada) and human collagen type III was purchased from Sigma-Aldrich (St. Louis, MO). Maleic anhydride activated plates were purchased from Thermo Scientific (Waltham, MA). Recombinant B-domain deleted human FVIII was provided by Octapharma Biopharmaceuticals GmbH (Berlin, Germany).

Ancestral FVIII expression and purification

Production clones for An63-, 70-, 84-, and 88-FVIII were generated in HEK293-H cells. Monoclonal populations were isolated under Geneticin selection and expanded as suspension cultures in FreeStyle™ 293 media without serum. Adherent populations were cultured in triple flasks in SFM4HEK293 medium. An101-FVIII protein was collected from a polyclonal population of HEK293-H cells transduced with lentivirus encoding the An101-FVIII cDNA. Lentiviral vectors were produced as previously described[1]. All ancestral FVIII was purified initially with the 'VIIISelect' resin according to the manufacturer's instructions and followed by a 5-mL SPHP cation exchange HiTrap column. FVIII was eluted with a NaCl gradient as previously described[2].

Collagen Binding

Collagen binding assays were performed as previously reported [3,4] using human collagen type I and III. Briefly, maleic anhydride activated plates were coated with 10 µg/mL human collagen (95% type I, 5% type III) for 2 hours at room temperature. Plate was washed three times with 75 mM NaCl, 5 mM Tris, 0.1% Tween-20, pH 9.1 and blocked overnight in phosphate buffered saline with 5% BSA. Recombinant AnVWF protein curves were diluted in PBS with 1% BSA, 0.1% Tween-20 and applied to the collagen coated plates. VWF was detected with DAKO anti-human VWF polyclonal antibody P0226 at a dilution of 1:1000 in diluent. Absorbance of HRP mediated catalysis of OPD was conducted at 492 nm. Ancestral VWF curves were compared to human recombinant VWF and reference human plasma was also included.

Kinetic SPR Measurements

Kinetic SPR SCK was run with five sequential 60 s injections with increasing concentrations of each FVIII-variant (0.185 – 15 nM) followed by a final 300 second dissociation phase. The sensorgrams were fitted globally by using a 1:1 binding model and setting RI = 0. Goodness of the fits were evaluated by visual inspection of the fit, the residual plot, T values, $\chi 2$ value and U-value. Because a clear differentiation only by means of T values, $\chi 2$ value and U-value was insufficient we introduced a classification for the fit quality with a visual inspection of the fit and the residual plot (1 ≙ good fit, residuals within 3x SE and minor systemic deviations; 2 ≙ weak fit mainly in the last injections, residuals within 3x SE and clear systemic deviations; 3 ≙ bad fit overall, residuals higher than 3x SE and clear systemic deviations).

Supplemental Tables

Supplemental Table 1. Kinetic SPR Affinity determinations with 1:1 binding model (nM)

K_D (nM)	coh-VWF	An101-VWF	An84-VWF	An63-VWF	An70-VWF	An88-VWF
hFVIII	0.48 (± 0.06)	0.45 (± 0.02)	1.4 (± 0.53)	0.88 (± 0.24)	0.27 (± 0.03)	0.42 (± 0.08)
An101-FVIII	0.49 (± 0.08)	0.49 (± 0.03)	1.2 (± 0.36)	0.83 (± 0.19)	0.30 (± 0.02)	0.44 (± 0.07)
An84-FVIII	0.59 (± 0.07)	0.56 (± 0.07)	1.1 (± 0.22)	0.60 (± 0.1)	0.38 (± 0.01)	0.53 (± 0.07)
An63-FVIII	0.63 (± 0.07)	0.57 (± 0.08)	1.5 (± 0.29)	0.88 (± 0.21)	0.35 (± 0.03)	0.64 (± 0.06)
An70-FVIII	0.72 (± 0.06)	0.52 (± 0.1)	2.1 (± 0.58)	0.85 (± 0.14)	0.41 (± 0.03)	0.66 (± 0.05)
An88-FVIII	0.37 (± 0.07)	0.54 (± 0.11)	0.65 (± 0.12)	0.57 (± 0.03)	0.85 (± 0.09)	0.61 (± 0.03)
	n=6	n=3	n=4	n=4	n=3	n=3

Classification of fit quality 1; good fit

Classification of fit quality 2; weak fit

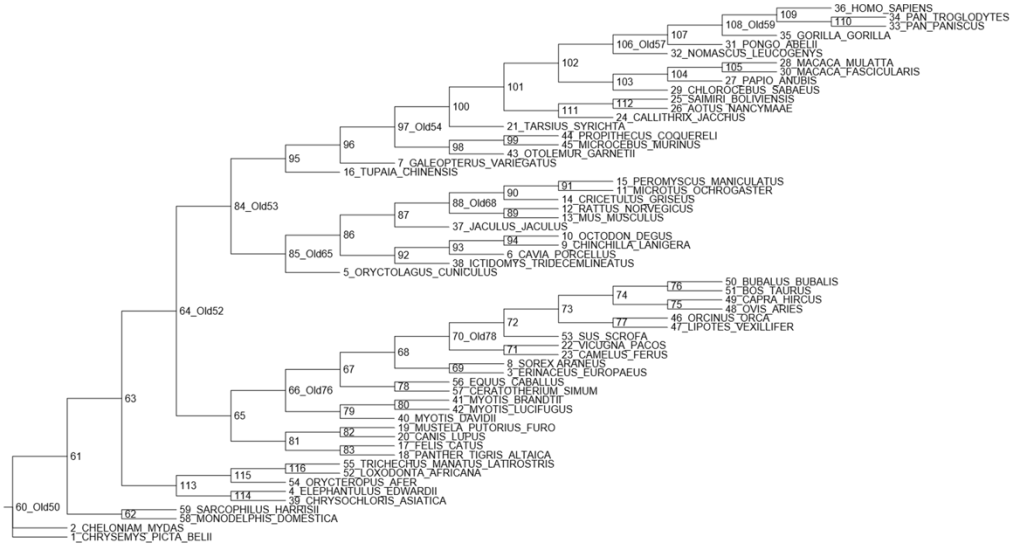
Classification of fit quality 3; bad fit

Supplemental Table 2. *P*-values of steady state affinity determinations (Dunnett's ANOVA)

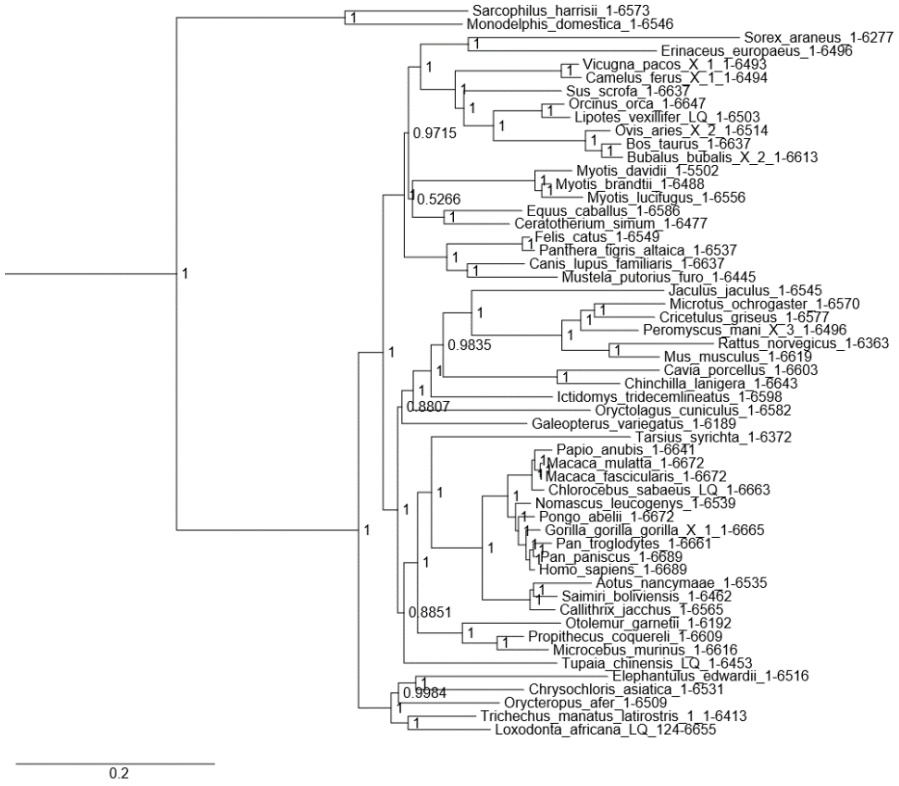
	coh-VWF	**An101-VWF**	**An84-VWF**	**An63-VWF**	**An70-VWF**	**An88-VWF**
hFVIII		0.5871	< 0.0001	< 0.0001	0.0013	0.1707
An101-FVIII	0.9991	0.9988	< 0.0001	< 0.0001	0.0154	0.1602
An84-FVIII	0.993	0.9999	0.1502	0.0047	0.112	0.0647
An63-FVIII	0.9855	0.0883	< 0.0001	< 0.0001	0.0331	0.9994
An70-FVIII	0.9787	0.0539	< 0.0001	< 0.0001	0.0422	> 0.9999
An88-FVIII	0.0354	0.0575	0.3199	0.2186	0.4592	0.0045

Supplemental Figures

S.Figure 1A

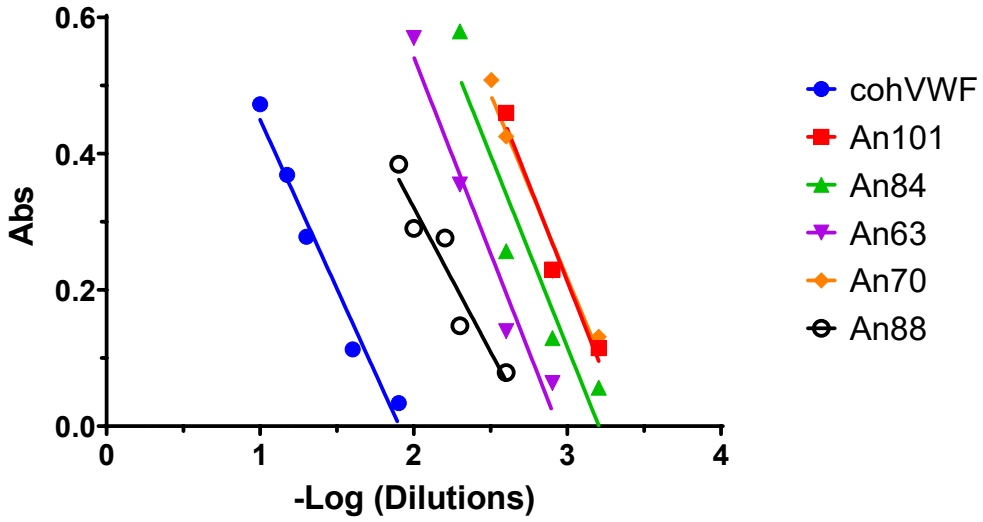


S.Figure 1B

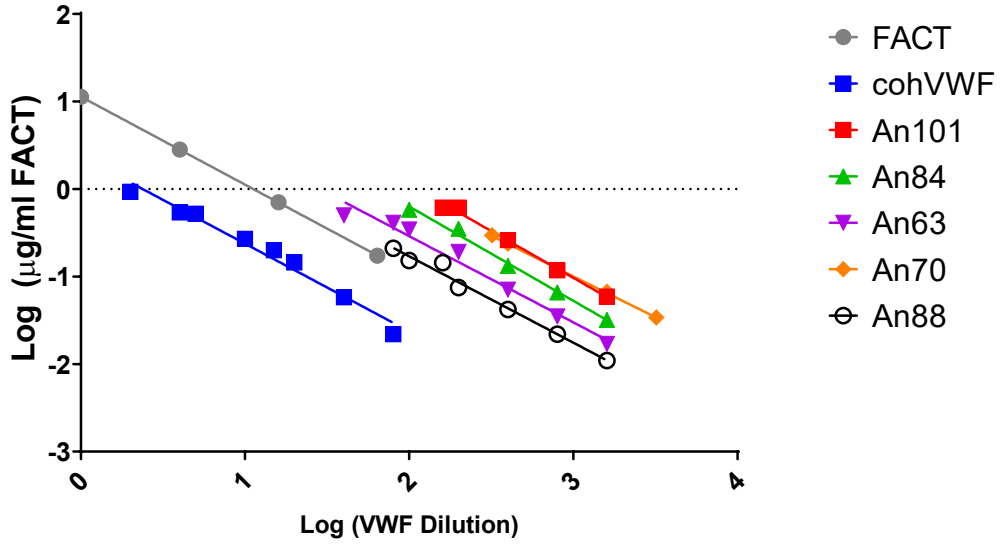


Supplemental Figure 1. **a**, Representative cladogram and species distribution for VWF as well as coagulation factors V, VII, VIII, IX, and X. Node numbers correspond to the identities of extant (1-59) or ancestral sequences (60-112). **b**, Representative phylogram for VWF as well as coagulation factors V, VII, VIII, IX, and X. Scale bar represents amino acid replacements per site per unit evolutionary time. Numbers next to nodes represent the Bayesian support for that particular node.

S. Figure 2A

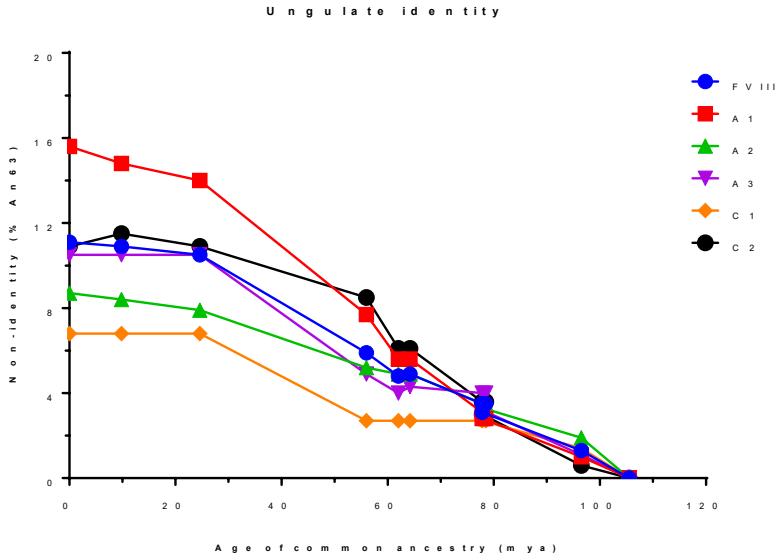


S. Figure 2B

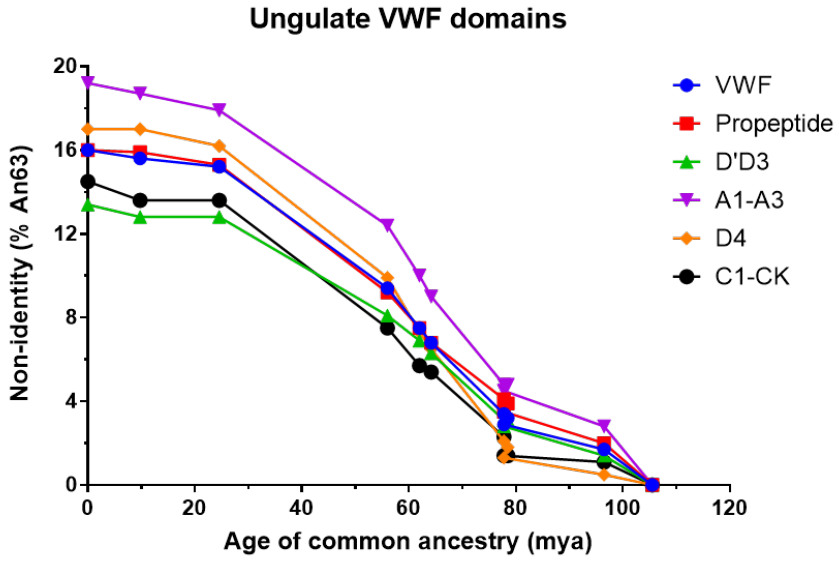


Supplemental Figure 2. Quantification of ancestral VWF:Ag was performed by ELISA using polyclonal antibodies across a range of dilutions to identify maximum and minimum detection limits, **a**. Antibody concentrations were maintained in excess and parallel OD values were observed. Using pooled normal human plasma (FACT), concentrations of VWF antigen at each dilution were elucidated, **b**.

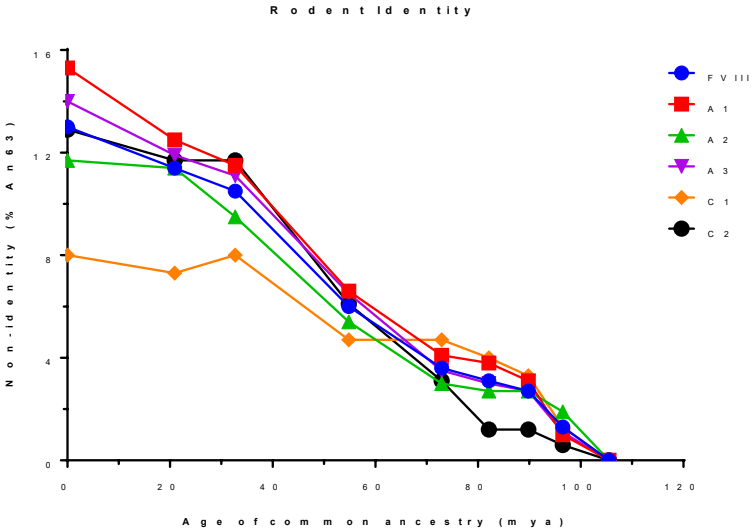
S. Figure 3A



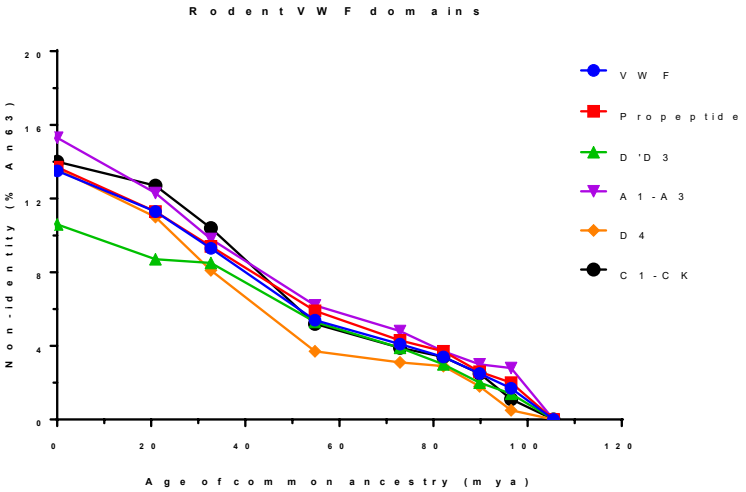
S. Figure 3B



S. Figure 3C

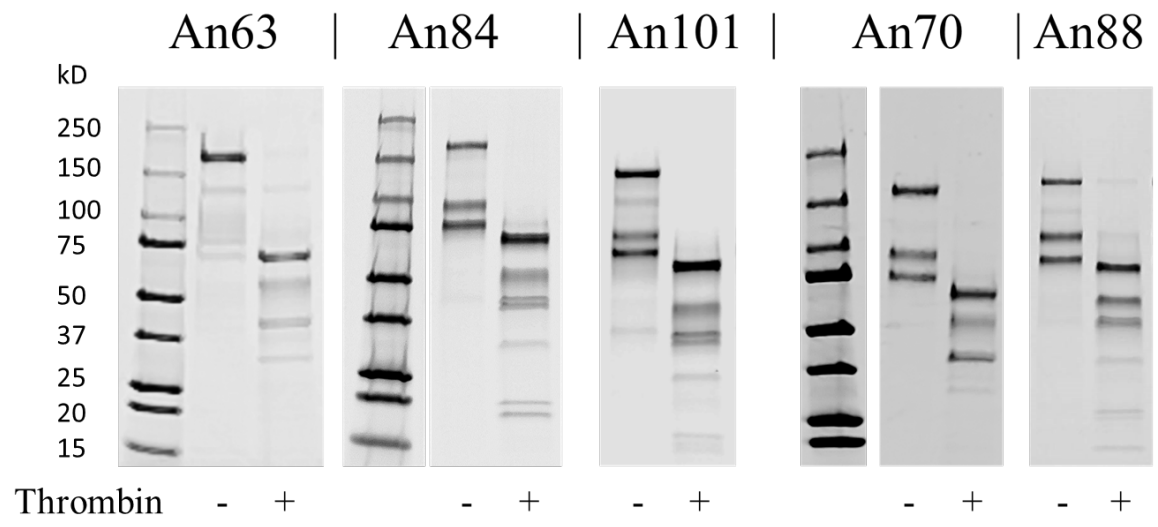


S. Figure 3D



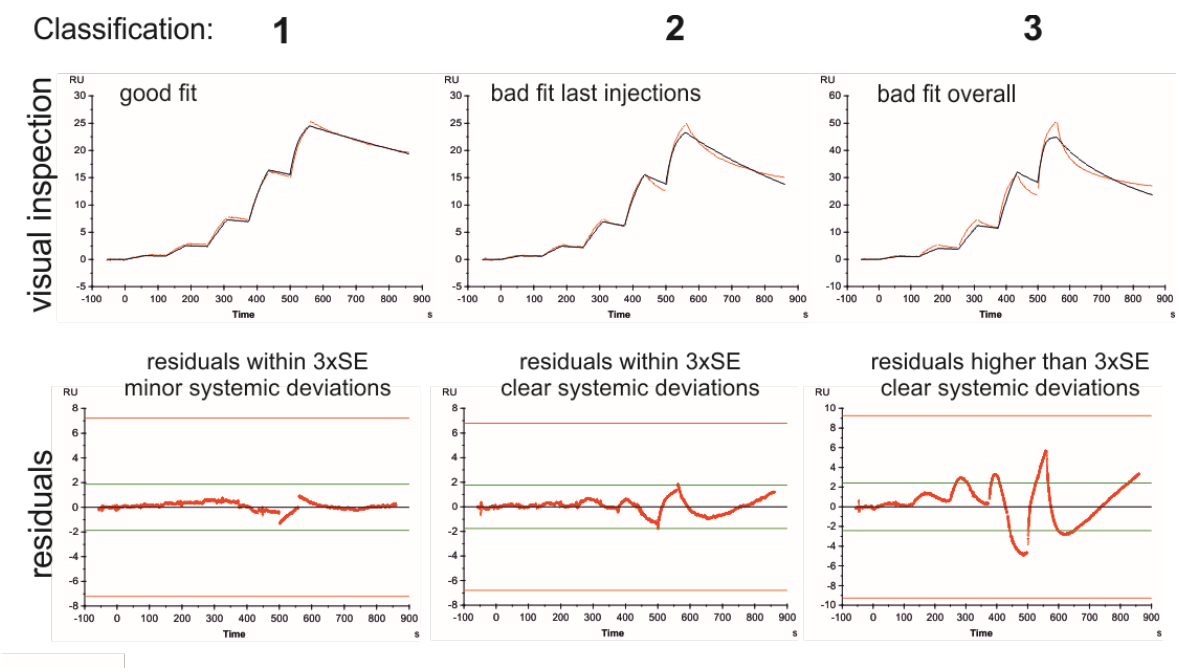
Supplemental Figure 3. Total accumulation of mutations within specific subdomains of FVIII **a**, **c** or VWF **b**, **d** are shown as percent non-identity relative to the size of each domain across ungulate **a**, **b** and rodent, **c**, **d**, lineages. The common ancestor An-63 VWF and FVIII sequences serve as the reference.

S. Figure 4



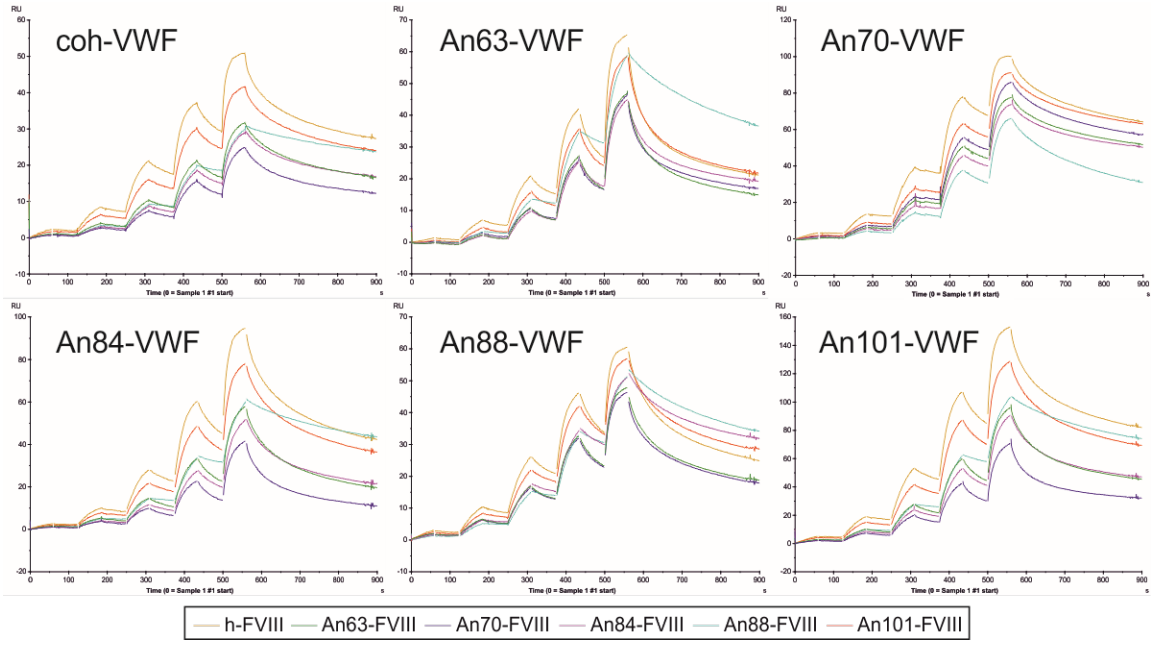
Supplemental Figure 4. AnFVIII protein was purified using affinity and ion exchange chromatography and analyzed via SDS-PAGE and Coomassie stain before and after thrombin activation. Specific activities for An63, An84, An101, An70, and An88 are 20522, 15964, 7809, 19918, and 4233 U/mg, respectively. Specific activities were determined by one-stage coagulation and normalized to absorbance after extinction coefficient correction.

S. Figure 5



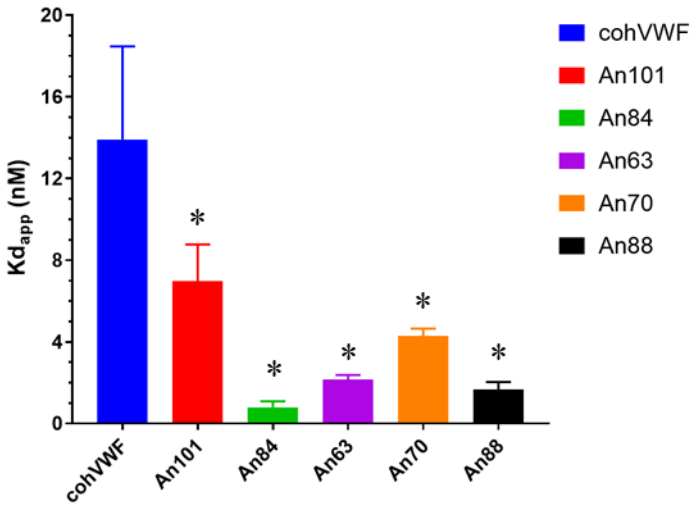
Supplemental Figure 5. Classification for inspection of 1:1 Binding fits to SPR sensorgrams. Each single sensorgram was fitted globally and RI=0 with the 1:1 Binding model with the BiaEvaluation software. The fits were separately evaluated according to the parameters shown in the figure and a classification for the visual inspection of the fit and the residual plot was assigned.

S. Figure 6



Supplemental Figure 6. 88-FVIII has a lower dissociation rate. Exemplary comparison of double reference subtracted sensorgrams on different VWF molecules. 88-FVIII shows a slower dissociation suggesting a different type of binding mode compared to the other FVIII variants.

S. Figure 7



Supplemental Figure 7. Human collagen type I (95%) and type III (5%) at 10 µg/ml was coated to maleic anhydride activated plates. Dilutions of recombinant VWF were captured and detected using polyclonal antibodies. Shown are the mean ± SD Kd_{app} values of three independent experiments. Kd_{app} values for cohVWF, An101, An84, An63, An70, and An88 are 13.9, 7.0, 0.79, 2.2, 4.3, and 1.7 nM, respectively ($P < 0.005$ for all ancestral VWF, One-way ANOVA, Dunnetts).

Amino Acid Sequences:

Human VWF:

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An101-VWF

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An84-VWF

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CVALERCPCFHQGREYAPGETVKIDCNTCVCRDRKWNCTDHVCDATCSAIGMAHYLTF
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CGNFDGIQNNDFTSSNLQVEEDPVDFGNSWKVSSQCADTRKVPLDSSPATCHNNIMKQT
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CHAHCPPGKILDELLQTCVDPEDCPVCEVAGRRLAPGKKVTLNPSDPKHCQICHCDGVN
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FEVLKAFVVGMMERLHISQKRIRVAVVEYHDGSHAYIELKDRKRPSELRRIASQVKYAG
SQVASTSEVLKYTLFQIFGKIDRPEASRIALLLTASQEPPRMARNLVRYVQGLKKKKVIVI
PVGIGPHANLKQIRLIEKQAPENKAFVLSGVDELEQRRDEIINYLCDLAPEAPAPTQPPQM
AQVTVGPGLLGVSPPGPKRNSMVLDVVFVLEGSDKIGEANFNRSKEFMEEVIQRMDVG
QDGIHVTVLQYSYMVTVEYTFSEAQSKGDVLQRVREIRYQGGNRTNTGLALQYLSEHS
FSASQGDREQAPNLVYMVTGNPASDEIKRLPGDIQVVPIGVGPHANVQELERIGWPNAPI
LIQDFETLPREAPDLVLQRCCSGEGLQIPTLSPAPDCSQPLDVVLLLDGSSSSPASYFDEM
KSFAKAFISKANIGPHLTQVSVLQYGSITTIDVPWNVAQEKAHLLSLVDLMQREGGPSQI
GDALGFAVRYITSEVHGARPGASKAVVILVTDVSTDSVDAAADAARSNRVTVFPIGIGD
RYDEAQLRILAGPEASSNVVKLQRIEDLPTMVTLGNSFLHKLCSGFVRICMDEDGNEKR
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NFTCACRKEECRRESPPSCPPHRTPTLRKTQCCDEYECACNCVNSTVSCPLGYLASATTN
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CVRVKEEVFVQQRNVSCPQLDVPTCPTGFQLSCKTSECCPSCRCEPVEACMLNGTIIGPG
KSVMIDVCTTCHCTVQVGAISGFKLECRKTTCEACPLGYKEEKNQGECCGRCLPTACTI
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KIPGTCCDTCEEPECKDITARLQYVKVGDCKSEEEVDIHYCQGKCASKAVYSIDTEDVQ
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An63-VWF

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VGIGPHASLKQIRLIEKQAPENKAFVLSGVDELEQRRDEIINYLCDLAPEAPAPTQPPQMA
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KAFISKANIGPHLTQVSVLQYGSITTIDVPWNVAQEKAHLLSLVDLMQREGGPSQIGDAL
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SQLRILAGPEASSNVVKLQRIEDLPTMVTLDNSFLHKLCSGFVRVCMDEDGNEKRPGDV
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GSCVPEEACTQCISEDGVRHQFLETWVPDHQPCQICMCLSGRKVNCTSQPCPTARAPTC
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KEECRRESPPSCPPHRTPTLRKTQCCDEYECACNCVNSTVSCPLGYLASAVTNDCGCTTT
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An70-VWF

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PAGMEYKECVSPCTRTCQSLHINEVCQEQCVDGCSCPEGQLLDEGRCVESAECSCVHSG
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PVGIGPHASLKQIRLIEKQAPENKAFVLSGVDELEQRRDEIISYLCDLAPEVPAPTQRPLV
AQVTVAPELLGVSTLGPKRSSMVLDVVFVLEGSDKVGEANFNRSTEFVEEVIRRMDVG
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FSASQGDREQAPNLVYMVTGNPASDEIRRMPGDIQVVPIGVGPHVDVQELERIGWPNAP
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GDRYDEAQLRTLAGPGASSNVVKLQRIEDLPTMVTLGNSFLHKLCSGFVRVCVDEDGN
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SIEVKHNGLSVELHSDMEVVVNGRLVSVPYVGGNMEVSIYGTIMYEVRFNHLGHIFTFT
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RPNFTCACRKEECPRGPPPSCPPHRTPALRKTQCCDEYECACNCVNSTVSCPLGYLASTV
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GKSLMIDVCTTCRCTVQEGVVSGFKLECRKTTCEACPLGYKEEKMQGECCGRCLPTAC

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An88-VWF

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QVVAWRTPTLCPQSCEERNVRENGYECEWRYNSCAPACPVTCQHPEPLACPVQCVEGC
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TCEACQEPGGLVVPPTDAPVSSTTPYVEDTPEPPLHNFYCSKLLDLVFLLDGSSRLSEAEF
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FAVRYVTSQIHGARPGASKAVVILIMDTSLDSVDTAADAARSNRVAVFPIGVGDRYDEA
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VPEEQCPVSDSSHCQVLLSALFAECHKVLAPATFHAICQQDSCHQERVCEVIASYAHLC
RTNGVCVDWRTTDFCAMSCPPSLVYNHCERGCPRHCDGNTSSCGDHPSEGCFCPQHQV
MLEGSCVPEEACTQCVGEDGVRHQFLETWVPDHQPCQICVCLSGRKINCTAQPCPTARA
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ACRKEECKRVSPPSCPPHRTPTLRKTQCCDEYECACSCVNSTVSCPLGYLASATTNDCG
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VEEAVFVQQRNISCPQLAVPTCPTGFQLSCETSECCPSCRCEPVEACLLNGTIIGPGKSVM
VDLCTTCRCIVQTGAISRFKLECRKTTCEACPMGYREEKNQGECCGRCLPTACTIQLRG
GQIMTLKRDETLQDGCDSHFCKVNERGEYIWEKRVTGCPPFDEHKCLAEGGKIMKIPGT
CCDTCEEPDCKDITAKLQYVKVGDCKSQEEVDIHYCQGKCASKAVYSIDIEDVQEQCSC
CWPSRTEPMRVPLHCTNGSVVYHEVINAMQCRCSPRKCSK

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