



Review

Supplementary materials: High Molecular Weight Kininogen: A review of the structural literature

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D5 domain His rich domain is important in contact activation
D6 domain interacts with prekallikrein and Factor XI

***Amino acid** numbering is according to human factor **HK**.

Human	MKLITILFL---C	SRLLSLTQE	-SQSEEIDCND	KDLFKAVDAA	LKKYNSQNQSN	NQFVLYRITE
Dog	MKLLAMFL---C	SRLLPSTQE	-SLSEEIDCND	EDLFKAVDTA	LKKYNSRNQSG	NQFVLYRVTE
Siberian Tiger	MKLIIVLFL---C	SRLLPSTTEE	-SFSQDIDCND	EDLFKAVDTA	LKKYNSRNQSG	NQFVLYRVTE
Grizzly Bear	MRLALLFL---C	SRLLPVSQE	-SSQE-IDCDD	EDLFKAVDTA	LKKYNSRNQIG	NQFVLHRVTE
Hippopotamus	MKLITILFL---C	SRLLPSTQD	-SLQE-IDCND	QDVFEAVDTA	LKKYNSGNKSG	NQFVLYRVTE
BN Dolphin	MKLITILFL---C	SRLLPSTQD	-SSQE-IDCND	PDVFQAADTA	LKKYNSGNKSG	NQFVLYRVTE
Opossum	MKLAVVL-L-L-V	TSQL-NVQGE	-S--E-VSCQD	NDVFRAMDA	LTEYNNQKTSG	NQFVLHQIMA
Koala	MELAAIL-L-L-V	A-IQLNVQV	-SQVKDVACDD	NDVFQAVDVA	LTKYNNQKSSG	PQFVLYRIIT
Wombat	MELAVIL-L-L-V	AS-QLNVQVE	-SQVKDVACDD	NDVFRADVDA	LTKYNNQKSSG	PQFVLYRIIT
Platypus	MKLLGVL-L-F-L	GSSLLPSRTA	-PVPQDVDCND	SDVFKAVDRA	LRWYNEHLKDG	NQFLLYRVTE
Kiwi	MKPFLAI--VL-C	CSFFSSRATP	-LPFEFSDCDD	PDVLEAVDTA	LKKYNGGRTTG	NQFALYMVME
Pigeon	MKPFLVL--AL-C	CSFLSSRATP	-LPFEFLDCDD	PDVFKAVDAA	LQEYNGDRASG	NQFALYTVVE
W-T Tropicbird	MKLFIVL--AL-C	CSFFSSRATP	-LPFEFSDCDD	PDVFKAVDTA	LKKYNGDRGTG	NQFALYMVME
Alligator	M-----L-C	CLFKSTND				DFMLL-----
Green Sea Turtle	MKLSTVL--VL-C	CSFFSSRASFP	-LPTQDADCDD	PDVFEAVDIA	LRKYNGDKTDG	NQFALYMVME
E Brown Snake	MEVFI-LLLLGIGFC	QAARDKVDR	-----ND	PEVVDVAGA	IAALNEDRSHG	NKLALGAILH
Anolis Lizard	MELFILLVLTFC	C----KQAVP	-LEGEDADCDS	PDVFSAVDLA	VKAHNEDQKHG	NLFALRVILA
Xenopus leavis	MKHLFSF--IFF-	LHLL--RG-S	ASQTIEADCND	HNIFYAVDEA	LRHHNKELIDG	NQFVLYRITE
Xenopus tropicalis	MQHLFTF IVF-	LHLL--RG-S	ATQAIEADCND	HNIFNAVDEA	LRHHNRALTDG	NKFVLYRITE
Nanorana parkeri	MVV-----VVV-	VGGDS AAVP	V-PDIGVDCDD	PNIFKAVDEA	LRYYNDAKEDG	NQFLLFRV--
Latimeria	MKVLALV--LL-C	TKLYVSWAK-	-SLLQPADCGD	PRVHQAVDAA	IKKYNEELKDG	HQFALYRITK
Zebrafish	MARDKILTVAL-M	LWLIFCGGLA	-QTDSSVPCDD	RRVEKVVNLT	LGTHNKMITEG	AQLALYEIL-
Pufferfish	MRSGLGLCVLG-L	LCLSSSVR-A	-QEPVKVSCDD	PSVEKAVSSA	VEKFEKLTTG	NKLALFQIQ-
Elephant Shark	MKLFVVLLFSSQLLH	SNARSVSDIDS	VDPIPIDCDD	PELKAVDFT	LRKFNGERRTT	HQYALDRVS-

Human	ATKT-VGSDTF	-Y-S-FKY-EIKEG	-DCPVQSGKT	WQDCDYKDAA	KAATGECTAT	VGKRSSTKFS
Dog	GTRT-DDPDTF	-Y-S-FKY-QIREG	-NCSVQSGKT	WQDCDYKEST	QAATGECTSAT	VGKRGKTKFS
Siberian Tiger	VRTT-DDPETF	-Y-S-FKY-QIREG	-DCSVQSDKT	WQDCDYKESA	QAATGECTSAT	VGKRGNTKFS
Grizzly Bear	VVRT-DDPDTF	-Y-S-FKY-QIREG	-NCSAESGKT	WQDCDYKDAA	QAATGECTSAT	VGKRGNTKFS
Hippopotamus	VTRM-DNPDTF	-Y-S-FKY-QIKEG	GDCPVQSNKT	WQDCDYKDSA	QAATGECTAT	VAKRGNMKFS
BN Dolphin	VIRT-DDPDTF	-Y-S-FKY-QIKEG	-NCPVQSDKT	WQDCDYNDSA	QAATGECTAT	VAKRGNMKFS
Opossum	VSLT-ESSQRT	-F-T-VTY-NIQEG	-DCHVRMGKN	WKECGIKKDL	NKERGQCTAI	VKSHNEFEFT
Koala	ASLT-DSSERT	-F-T-ITY-EIRES	-NCMIETGKN	WKECSYKDSA	EWKQGECTAI	VKSQNGKEFK
Wombat	TASL-TDSNER	-T-FTITYE-IRE-	SNCMETGKN	WKECSYKDSA	KWEQGECTAI	LKSQNGKEFK
Platypus	ASMT-TDSDTF	-Y-S-LKYQ-IREG	-DCPVQKDKH	WQDCDYREAA	EAATGECTAT	VKTKNKEKFT
Kiwi	GKKT-AGPDTQ	-F-Y-VKYQ-IRET	-SCAIEENKH	WKDCDYKAPA	EAKTGECTAR	VHINKAEKTS
Pigeon	AKRT-VGPVTQ	-F-H-VKYR-IRET	-TCATEENKL	WQDCDYKASA	EAQTGE CIAQ	VHLNDAEKTS
W-T Tropicbird	AKKT-ASPDTQ	-F-Y-VKYR-IQET	-TCAIEENKL	WQDCDYKVPS	EAKTGECTAR	VHMYNTEKTS
Alligator	FFSQ-AGPGAQ	-F-F-VKYR-IRES	-TCAIGEGKA	WQDCDYNAAV	EAETGECTAE	VYIDKTQKIS
Green Sea Turtle	AKRI-EGSGKQ	-F-F-VMYR-IRES	-SCAVGGDKL	WQDCDYRASA	EAESGECTAQ	VYVDKTEQIS
E Brown Snake	AYRI-ADPRKK	-FLIIYHVR--ETV	--CPIAVDKP	WQKCELLRTS	KAHSGKCTAN	IDINESEQFT
Anolis Lizard	ARRT-AGPGKN	-F-L-IKYQ-LAET	-SCPLKGSVS	WQNCDFLPPS	EGDSGECTAE	IHTDDSQVFS
Xenopus leavis	ARI-KTEN-GG	-T-HNFVSYDIREG	-SCGVKSGKV	WQNCDFKQSD	E-KVGKCSAH	IVVNKELKTS
Xenopus tropicalis	AKI-KIENDSG	-T-HNFVSYDIREG	-SCGVKSGKV	WQNCDFKQSD	E-KVGKCSAH	VLVNKELKSS
Nanorana parkeri	TDA-QQRNDEN	GQIHVFLDYEIREG	-SCTVKSMHS	WQDCQFQAHT	P-EQGKCSAH	LLINTEKKIR
Latimeria	AKTQ-LE-KE-	---THYFVTYEIRE	STCSVHDNKI	WQCNVYVSP	SATTGT CIAE	VYIDETVKTS
Zebrafish	----EATKAQN	ESGDVLLVRFSSRE	TDCPAGGEKT	WHECDYLQQA	DKALRIC HAK	VQFTEAGEEL
Pufferfish	----SASKTGS	GADAVYSLQFTSRR	SDCPAGGIKP	WTDCDYLPRR	-KSPVPCSAI	VHV TATEVNT
Elephant Shark	-----FGTVOR	KRGSRYFIKFDIOE	SNCLVESEKT	WTBCHDRPPT	VANIGHCESS	VYIHRAGRI

Supplemental Figure S1. A) Amino acid sequence alignment of vertebrate high molecular weight kininogens (continued).

	103	114					
Human	-VATQTCQITP	AEGPVVTAQY	DCLG---CVHPIS	TQSPDLEPIL	RHGIQYFNNN	TQHSSLFMLN	
Dog	-VATQTCQITP	AEGPVVTAQY	DCLG---CVHPIS	IASPELEPVL	RHAIEHFNNN	TDRSHLFALR	
Siberian Tiger	-VATQTCQITP	AEGPVVTSQY	DCLG---CVHPIS	TASLDLEPVL	RHAIQHFNNH	TGRSHLFALR	
Grizzly Bear	-VATQTCQITP	AEGPVVTAQY	DCLG---CVHPIS	TASPDLEPVL	RHAIEHFNNN	TAHSHLFAVR	
Hippopotamus	-VATQTCQITP	AEGPVVTEQY	NCLG---CMHPIS	TTHPDLEPVL	RHAIQHFNNN	TDHSHLFELR	
BN Dolphin	-VATQTCQITP	AEGPLVTAQY	DCLG---CLHPIS	TESPDLEPVL	RHAIQHFNNN	TDHSHLFDLK	
Opossum	-ITEQHCKIIP	VNDEVIADV	PCLG---CYRPIS	ANDEDLQAVL	NNAVEQFNYQ	SQSDHLYTLK	
Koala	-VIEQNCHIIIP	AHDVVVAVHS	PCLG---CFNPIS	TNHSDELEIL	KHGLQSFNEK	SKHEYLFALK	
Wombat	-VIEQNCHIIIP	AHDVVVAVHR	PCLG---CFNLIS	TNHSDELEIL	KHALQSFNEK	SKHEYLFDLK	
Platypus	-VSLQTCQITP	AEGPVITAHY	ECSG---CIHPIS	PTSTDLPIL	KHGLQHFNNR	TNHPFLFRVN	
Kiwi	-NVSQDCKTVP	ATATIIPAEA	LCLG---CYYPIS	SDSLQVSEIL	KQAIQKFNRH	SDEAALFKLV	
Pigeon	-NVSQDCKISP	ATPKVTRTEA	TCLG---CFHPIS	SDSSEVSEIL	KQAIQKFNRH	SAESALFKLV	
W-T Tropicbird	-NVSQDCKIFP	AMPKITVTEA	TCLG---CFHPIS	SDSSGVSEIL	KQAIQKFNRH	SAEPALFKLV	
Alligator	-NVSQECCKIIP	AAGKVTLSPA	PCLG---CYHPIP	GNSLDLLPIL	RYAIRNFNKE	SQKSFLYEVG	
Green Sea Turtle	-NVTQECCKIIP	VEGKVLISHV	QCLG---CYHPIP	GDSLQLLPIL	RYAIRIFNNQ	SEQSSLFEVG	
E Brown Snake	-SISQNCCKISQ	GQQNIEQSHV	EFVGLSQCVGCWH	RIKTLSPRVL	HIVRHTVRQF	NNQSQHSSLF	
Anolis Lizard	-SVFQTCRITT	APGKVTRSHA	RCLG---CWHITIS	SKSEELVPIL	RRAIYLFNNE	SDQQPLFDAV	
Xenopus leavis	EVIIQNCSTFQ	V-EPTVSAIKQ	DCLG---CPINLD	TRNKDLLPLI	KSAIEKMKNL	ANYPFYFDLE	
Xenopus tropicalis	EVIFQNCSTFK	V-EPTVTAVEQ	GCLG---CPIKLD	TTNEELLPLI	KVAMEKMKNV	ANHPFYFNLE	
Nanorana parkeri	TVVSQTCQSVSK	VPLEPYVTAVHH	QCLG---CPYPID	TNNEEVLRV	HIAIEKMNRQ	GSHLYYFDLD	
Latimeria	-VVSQKCDLVP	-PKDPIVPSVA	QCLG---CPREIP	TNSSKVKVVL	DAALKKYNKE	SNHSFHF---	
Zebrafish	--LLHDCLEPA	-----IIASVA	PCIVTEECCHPLLE	KTEVLKCNSS	VDVAPWRHEV	PEVHVVCAGVSKTNS	
Pufferfish	--RHVECCQIDG	----HFTPEKA	PCLG---CEMEID	ENSEDLKSP	SVSITKYNM	SNLHLFTLN	
Elephant Shark	EVTMYNCTIIP	VNDPWIVPKIA	PCLG---CAISLP	HNSSRAKETL	DYSIKKFNSD	SNYPNIFGSE	
	163						
Human	EVKRAQRQVV	AGLNFRITYS	IVQTNCSKENF	LFLTPD-CKSL	-WNGDTGECT	DNAYIDIQL	
Dog	EVKKAHRQVV	TGWNYEITYS	IEQTNCSKENY	LFLTPD-CKSL	-LNGDIGECT	DHAHMDLQL	
Siberian Tiger	EVKRAHRQVV	AGWNYEITYS	IVQTNCSKEHF	LFLTPD-CKSL	-LNGDIGECT	DHAHVDLQL	
Grizzly Bear	EVKRAHRQVV	AGWNYEITYS	IAQTNCSKENF	LSLTPD-CKSL	-LNGDIGECT	DHAHMDLQL	
Hippopotamus	XXXXAQRQVV	AGWNYEITYS	IVQTNCSKENF	LFLNPD-CKSL	-PSGDVGECT	DKAYVDIQX	
BN Dolphin	EVKKAQRQVV	AGWNYEITYS	IVQTNCSKENF	LFLTPD-CKSL	-SNGNIGECT	DKAYVDIQL	
Opossum	DVLKALRQVV	RGWNYDLEFT	VVETNCKVSEV	KNVTSE-CKPL	-PQGKSMACR	ELSHVSPDM	
Koala	EVMNASRQVV	NGWNYKIQYS	IVQTDCKSKED	GQLSDK-CKPT	-PQGEISVCS	DFTYVDPQM	
Wombat	EVMNASRQVV	NGWNYKVQYS	IMQTDCKSKED	GQLSAK-CKPV	-PQGEISVCS	DFTHVDPQM	
Platypus	EVKKAQRQVV	SGWNFDVHYT	IIQTNCSKQDF	EELLPD-CKPM	-PGGDTGDCS	DKAFVDPHM	
Kiwi	EIKEAKRQVV	AGWNYIIKYE	IKETNCSKDQF	QDLSPE-CKTT	-STGRVGNCE	AKAYANLND	
Pigeon	EIKEATRQVV	AGWNYIIKYE	VEETNCSKDQF	QDLTPE-CKTT	-SRGHIGKCD	AKAYVNPQG	
W-T Tropicbird	EIKEAKRQVV	AGWNYIIKYE	IEETNCSKDQF	QDLTPE-CKTT	-SRGRVGKCD	TKAYENLHA	
Alligator	EIIKATRQVV	AGWNYAVEYM	VKETNCSKKEF	QDLSPK-CKPI	-FGGHVGNCV	AKAFVDLSN	
Green Sea Turtle	EIIKATRQVV	AGWNYAVEYE	VKETNCTKNNF	QDLSPE-CKPI	-VGGHVGRCE	AKAYVDLTN	
E Brown Snake	GFPVINEAES	QVNVGVNYRF	KYSINETNCSK	KEFLDLSPECR	PLSGGLKVFCE	AKAYVDNRG	
Anolis Lizard	GVVHAARQVV	AGWKYKFEYW	IQETNCSKADF	ADMAPE-CKIL	-PKGHVGSCH	VESYVDFRN	
Xenopus leavis	NIIETALQVV	AGWNYRLIYT	VRQTNCSKSIH	SNVPLEECDLD	-ANGQNGTCT	TQVFKNTRG	
Xenopus tropicalis	TITEATRQVV	FGWNYKLFYT	IRQTNCSKSIH	SNVPLEECNFD	-ANGQNGTCT	TQLFINTQG	
Nanorana parkeri	QIVNATRQVV	GGWDYIINC	VRKTNCSKMDF	KTGDSNECKLD	-KEGETGECE	LQVSETPDG	
Latimeria	EIKRATSQVV	AGFKYRVEFR	ITETNCSKKDF	-EELTEDC-SP	-ISATTGTCTI	AEVYIDETV	
Zebrafish K	RFKRPPGWSP	LSKESISPPK	HVPLNCPKTPW	-KEFKPIIAPP	--NATEPSEP	SADTALS	
Pufferfish	SVGYATRQVV	AGFRFKIRFD	MKKTTCAKSQH	-SDLSDLCPVD	DQNMEFANCN	STVDVAPWR	
Elephant Shark	VIFKVTSQVV	AGYLYTLKFS	LRETECTKSSN	--DVWQDCILK	PDNATTLYCN	STVLFSIRA	

Supplemental Figure S1. A) Amino acid sequence alignment of vertebrate high molecular weight kininogens (continued).

	222	235						
Human	R-IASFSQNC	IYPGKDFVQP	PTKICVGC	PRD	IPTN	SPELEE	TLTHTITKL	NAENNATFYF
Dog	R-IASFSQKCE	LFPGEDFVQP	PSRICLGCP	PKK	IPVD	SPELEV	PLTHSIAKL	NAENNGTFYF
Siberian Tiger	R-IASLSQKCE	LYPGEDFIEP	PPSICPGCP	PKE	IPVN	SPELEV	ALNHSTAKL	NAENNGTFYF
Grizzly Bear	R-IASFSQKCD	LYPAEDFVQP	-SKICSDG	PKD	IPVN	SPELEV	ALNHSIAKL	NAENNGTFYF
Hippopotamus	R-IASFSQKCN	VYPEEDFVAP	PTRICAGCP	PIR	IPVD	SPELEE	PLNHSIAKL	NAENNGTFYF
BN Dolphin	R-IASFSQKCD	LYPGEDFVQP	PTRICAGCP	PIS	IPVN	SPELEE	PLEHSIAKL	NVENNGTFYF
Opossum	K-ISSHLQTCQ	--TEADS-QF	SD	MQY	ISGY	SPELKE	SLRAALENF	NSENESDFYF
Koala	K-ISIVSQACN	--PGSDSASS	VT-----	QK	MSVY	SPELKE	PLRHSLEKI	NSENKNNFYF
Wombat	K-ISIVSQVCN	-----P	RSDSGSSVT	QK	MSIY	SPELNE	PLRYSLEKI	NSESKNNFYF
Platypus	K-ITGFVQNC	LFPGAEWIPP	PDLMCAGCP	PQN	LPVD	SPELKE	PLKHSLDKV	NSADNYTFYF
Kiwi	Q-IIDTASQCK	FPAEETVDPP	-TLICAGCP	PRP	IPKT	SPELKE	LLEVSMEKY	NLETNDDFYF
Pigeon	Q-IVDIASQCK	LPVEKTVNPD	---IRTGCTKT		IPTD	SPELKE	LLKLSMEKY	NSESNDHHYF
W-T Tropicbird	Q-IVDIASQCK	LPVEDTVVPA	-TR--TNC	PKT	IPKD	SPELKE	LLKVSMEKY	NLESDDDFYF
Alligator	T-LVDVTQCK	FPVEETVPPP	--QMCPC	PKR	IPND	SPELKE	VLKASMEKY	NSESDDDFYF
Green Sea Turtle	T-IADVAQKCK	FPVAETVSPH	-ISICAGCP	PRP	IPTN	STELEE	PLRATLEKY	NAESNDHFYF
E Brown Snake	T-LIHSEVECR	PEAEDNMRIL	-AQACPGCH	SP	LAPD	SQELKR	PLEAVVKLF	NIKSSSDFYF
Anolis Lizard	T-IVNVEQKCE	LEVDTKKN--	----CPGCP	PRT	IPSD	SQELKE	PLAAIVENY	NTKCSNGFLY
Xenopus leavis	E-IIDINLSCF	SQ-----KG	FCLSCPDA	VDV	DDPE	LLDLLR	QVMDEYSY	NNNTNLNFV
Xenopus tropicalis	E-IKDINLECF	SQ-----KG	FCLSCPDA	VDV	DDPE	LLDLLR	QVMDEYSN	NNNTNLNFV
Nanorana parkeri	Q-VNDIILKCT	SQAGVC-----	LNCPLN	VDS	DDAE	LQNLIS	QVIDEYSN	INVTNLHKLN
Latimeria	KTSEVVSQKCD	LVPPKDPIVP	SVAQCLGCP	PRE	IPTN	SSKVKV	VLDAALKKY	NKESNHSFHF
Zebrafish	DLIR							
Pufferfish	HELPQVQMECE	EGMLIMPLIK	RRPPGWTP	LRK	FEKPGSAAKE		ESSEEDTAA	AQPSASPVVD
Elephant Shark	NEIDTF-VSCS	TDPIGFQMEG	FRSQPTETIGI		LAQQRQRHRQ		HHFYQQQDS	HEQHLINKSE

	282							
Human	KIDNVKKARV	QVVAGKKYFI	DFVARETTCSK	ESNEELTESC	ETKKLGQSL	DCAEVYVVP		
Dog	KIDSVQSATV	QMVGAEKFFI	QFVARETMCSC	ESNEELAESC	QINKYGEQL	KCEAEVYVIP		
Siberian Tiger	KIDHVKSATV	QVVAGKKFSI	EFTARETTCSK	ESNEELTESC	NTNKF GKIL	DCKAEVYVIP		
Grizzly Bear	KIDS VKSATV	QMVAGKKFSI	AFTARETTCSK	ESNEELTESC	QINKYGHTL	ECKAEVFVIR		
Hippopotamus	KIDMVQKATV	QVVAGKKYSI	AFTARETTCSK	ESNEELTKSC	EIHKHGRLL	SCNADVYVVP		
BN Dolphin	KIDTVEKATV	QVVAGKKYSI	VFTARETTCSK	ESNEELTKSC	EINKHSPI L	NCKADVYVVP		
Opossum	KPSILLKAHL	-VEPEGKH SI	EIQVQETECSK	EKG-QFSEDC	EFKTDGRVL	QCIVQVPMGQ		
Koala	KMETIEKAES	PAGPGPKYII	EFLIKETEC SK	EKD-KYSEDC	AFKESGDGL	KCIANVSVED		
Wombat	KMDTIQKAES	LVGPEPKYII	EFLIKETEC SK	EKD-KYSEDC	TFKELGDGL	KCVANIPMED		
Platypus	KVETIRKATF	QLVAGQKFSI	EFLVRQTRCSK	EDNEKMPEDC	EVDSNGKVL	VCNAMVYMVP		
Kiwi	KAGDIEKATV	QVVAGKSYRI	TFTVKKTNC SK	KEFEKL NEDC	EATPNSVRL	KCEAQIYVIP		
Pigeon	KSGDIEAAAV	QVVGSKIYHL	EFAVRKTNC SK	KEFEKL NEDC	EATS DSAPL	PCEAQIHVIP		
W-T Tropicbird	K-GEIEEATV	QVVAGQNYHL	IFAVRKTNC SK	KEFEKL NEDC	EATS DSAPL	PCEAHVHVIP		
Alligator	KVESVFHSTV	QVVAGKNYEI	EFLIGKTNC SK	SEVEKL NEDC	KIVIPKISL	QCTANIYVVP		
Green Sea Turtle	KAENVLYATV	QVVAGKNYNI	RFKIRKTNC SK	TDVKKLNEDC	VTTTDSKPL	LCTAQVYVIP		
E Brown Snake	KIVDITKISG	QMLVGHVYRI	DFKAQRTNC SK	AEVEKPDKNC	HAVKG GELM	TCHALIYVKP		
Anolis Lizard	RITKVTKATV	QIVSGIMYRI	EFQITETNC SN	AEVHEL NEDC	IAMENSESL	QCYGS AWEKP		
Xenopus leavis	SVDYASKKGV	HEKTYDVTFN	---IKETNC SK	SDYAILGEEB	QFIETKNAL	NCDAKVNVT D		
Xenopus tropicalis	SVNQASKKGT	HEKTYDV KFN	---IQETNC SK	SDYSILGEEB	EFIETKEAL	NCDAKVNI TD		
Nanorana parkeri	QVIKATKHGF	QE QIYEVLF S	---MMPTVC SK	PDHTILGDEB	NNLENASPL	SCDTTIKVTD		
Latimeria	GVVEIKRATS	QVVAGFKYRV	EFRITETNC SK	KDFEELTEDC	AISEK-NPH	N CNSATT VVP		
Zebrafish	VVPDDPLHCP	SK						
Pufferfish	DPLHCSPKVV	PD						
Elephant Shark	PAVITTSAPL	ELPLSAIDOL	ADLLGPEPPVN	CPGKPKWKPL	OSN			

Supplemental Figure S1. Amino acid sequence alignment of vertebrate high molecular weight kininogens (continued).

	342	358	384	
Human	-WEKKIYPTVN	--CQPLGMIS-LM	KRPPGFSPFRS	SRIGEIKEET TVSPPHSTSM --APAQDEERDS
Dog	-WEKKIYPTVN	--CQSLGKVI-LM	RPPGFSPFRS	SFMEKTEKGT TVSSPHNSM --VPVQDEEWDS
Siberian Tiger	-WEKKIYPTVH	--CQSRGETT-LM	KRPPGFSPFRS	VQVEKTEKGT TVSPPHSTSM --ASVQDEEQDS
Grizzly Bear	-WEEKIYPTVN	--CQPLKKII-LM	KRPPGFSPFRS	VPLEKTEEGT TVSSPHISM --APVPDEERDS
Hippopotamus	-WEEKIYPTVN	--CQPLGQTS-LM	KRPPGFSPFRS	VQVEKTEKGT TVSPPHPSM --APEQDEERDS
BN Dolphin	-WEKKIYPTVN	--CQSLGQTT-LM	KRPAGFSPFRS	VPVEKTEKGT IVSPPHSTFL --APVQDEERDS
Opossum	DGEVKPVI--D	--CHEPPPELGLM	KRPSGFSPFRS	AL--RILEEK IIAAREPQN FNTTEQEEQTP
Koala	--EGTFNPTVR	--CEHPTM--LM	KRPPGFSPFRA	AAVIPEMEGA EAPSEPQTS -DMTDQEEAQGP
Wombat	--EGTFNPTVH	--CEQPTM--LM	KRPPGFSPFRA	AALIPETNGA EAPSEPQTS -DTTDQEEAQ-P
Platypus	-WKNEVFPTVT	--CQDLEMSSFL-	KRPPGFSPFRS	VQT-PAKEGS NVSPQPQPK -APDREEE-QA-
Kiwi	-WENKILPQVN	--CTEELLPVFLA	RPPGFTPFRT	AQYFAQSQPD TTS----- -SNKNETES
Pigeon	-WENKILPQVN	--CSIERSAAVLL	RPPGFTPFRT	--FVALGQPN ENSCSQNE KEMQRPGEETG
W-T Tropicbird	-WENKIFPQVN	--CSKERSMTVLL	RPPGFTPFRT	FAMLSQPS-E IL-CSDKNE EERQTPGKEMR
Alligator	-WKQEIFFQVN	--CSEVTPIIQAR	RP-PGFTPFRT	L-MLHEIYPQ TSPLQTAE E GKDPDKGPREN LGPGLENE
Green Sea Turtle	-WTKTIRPKVS	--CAEEENLLMR	PPGFT--PFRS	LAVEAKTVQY T-PQIKNEK GPREGQGRGKSGK
E Brown Snake	-WEPVSVPEVT	--CTDDQPFQAHE	LEEPNILEDGF	NIFHDYEEQK WFLWYLLGRY TLSVILKLF
Anolis Lizard	-WQPKSEVEVT	FKCMEKAFNTALL	RPPGFTPFRT	AAMATEEN-- TQVCGHRH- GHKNGHNKTKPKSSD LQE
Xenopus leavis	-TKIIVASSPI	--CNARARTMEFL	NQFLAKMGDNT	IFVVYSAMFT YKGLSPFRG VLPQGSPIRI
Xenopus tropicalis	-TKITVASSPM	--CIHRVRST---	-----PFFS	----- YKGLSPFRM VLPQANPSNK
Nanorana parkeri	-KRINVHSGPV	--CVEQQA-----	-----	-----LIMR LSGLSPLRM SKKPDQAETN
Latimeria	-WKNTTTTDVN	--CVL---EMALL	RLPAGMSPFRV	LQATPDSAK- -----
Zebrafish				
Pufferfish				
Elephant Shark				
	402			
Human	GKEQGHTRRH	-DWGHEKQRKH	NLGHGHKHE	RDQGHGHQRG HGLGHGHEQQ HGLGHGHKFKL
Dog	GKEQGPTRGH	-GRGHEKQIKH	GHKYKHDQG	YGHNRGHGLG HGHQKQHGLG HGGQRELD FDL
Siberian Tiger	GKEQGPTRGH	-GWGHGKQIKH	GFGHGHKHE	HDQGHRHNRG RGLGHGHQKQ HGFAHGHQKQH GFGHGHQQ
Grizzly Bear	GKEQGPTRGH	-GWGHEKQIKH	GFGHGHKPE	HDQGRGYHGG RGLGHGYQKQ HGLGHGHQREH
Hippopotamus	GKEQGPNRGH	-GWGHGNQIKH	GLGHGHKXX	XXXXXXXXXX XXXXXXXXXXXX XXXXXXXXXXXX
BN Dolphin	GKEQGPTRH	-GWGHGKQIKH	GLGHGHKHE	HDQGHGHQKG HDLGHGHQRG HGHQGGHGLAH
Opossum	GK-AGYP--H	-DHGHWQRGR	HPVHGTKNH	PGSGLGHKHG HNHSHGRRH HDLG-----
Koala	GKEQGLTRSF	-GPGH--QKEH	NSGHGHK--	-----DHRG LGLGHKHEHA H-----
Wombat	GKEKGLIR--	-----	SFGHGHRKE	HSSGHGHKDH PGLGLGHK---HGH-----
Platypus	GKRRGHPLGH	-DSCRGRGPQ	GRGRGCKRA	RD-----
Kiwi	QTPSTETR--	-----	-----	KDHGHGPEGE GEPGCKHRHK HGCKHGHGFKK
Pigeon	KDGGQEPE--	-----	-----	GEGEPE HKHGHKHEHK HGHKHEHKHE HKHEKDHKPDK
W-T Tropicbird	KDGGQEPEGK	GEPEKHRLMX	GRKHRHGYI	KDHESDKRHR HEIGCGHRTG YGHGHKKH SKN
Alligator	DGQGDGCDHR	VGHGNGHGHGQ	GHRFNHKPG	HGRGRGRGHD IGRGHKKH QK KDKHKDSK
Green Sea Turtle	DIRHEPA-HK	QGHRHDIGHGP	EHDHRRGHE	DEHGCRHDIG HEPEHEHRRG HGHKDEHRCRH
E Brown Snake	LSFPCSSEAQ	RSFSH		
Anolis Lizard	DADKHDESLP	TASTSNPLKLA	MEVFILLVL	SVGLCQAGPV QDDVSCDDPE XVFEAVARAIT
Xenopus leavis				
Xenopus tropicalis				
Nanorana parkeri				
Latimeria	-KEEKE----	---TELRRT-	-----DD	KPHGHERGRG RGRGQEHGR GPGHEH----
Zebrafish				
Pufferfish				
Elephant Shark				

Supplemental Figure S1. Amino acid sequence alignment of vertebrate high molecular weight kininogens (continued).

	462		503	
Human	DDdleHQGGH	VLDHGHHKHH	GHGHGKHKNKG	KK-- NGKHNGWK TEHLASSE DStT-PSA---
Dog	EHQRRHGLGH	GHQRGHGLAH	GHKYEHHGHGHE	KY-- KNKRKDNG KNGRKTEN LAGS-PED---
Siberian Tiger	QHQRHGLGH	GHQRGRGLAH	GHTHEHHGHGHE	KY-- KNKRKDNE KDNGWRIEH LASS-SED---
Grizzly Bear	-----	-----GLAH	GHIREHGGQHG	KY-- KNKRKDNG KPNDWKTEH LASS-PEE---
Hippopotamus	XXXXXXXXXX	XXXXXXXXXX	XXXXXXXXXXXXXX	XX--XXXXXXXX XXXXXXXXXXXX
BN Dolphin	-----	--GHKHGHGH	GKHKNRGKNNG	KH--DGWRTEYL ANFY----E DSTI-SSS---
Opossum	-----	---QGNKHHK	GQGHWKHEKKP	KK---NRK--SWM DEYPYSPTE EN-F-PSS---
Koala	-----SQ	GHGHRHKKHH	GEGHRKHEKKG	KK---SP--GSWT DRYLDSPAK ENS--PS-KT
Wombat	-----AHSQ	KHGHRHKPKH	GEGHQKHEKKD	KK---S--HGSWT NGYLDSPIK ENS--PSSKT
Platypus	-----	---HERSPEC	RGQKHRNKDR	PR---GKPNGGK- -KNCPEDNS NPSR-PEQ
Kiwi	DHASDKRHRQ	G--IDCGHRT	GHGCGHQKHSK	HGKHHPNPKSSE ESDERVFNH KETL-PSS
Pigeon	RHRHEIGCGH	KTGHKCGHKK	HSKNG--KHPN	PESSEESDERVFN QDETSPSST DETASPEAAV
W-T Tropicbird	GKRKYPNPKP	SDESDEGRFN	QNKTIPTASAE	TDKRHRHEIGCGH RTGYGHGKH KHSKNGKRKYPN
Alligator				
Green Sea Turtle	DIGCGSEHE	DKHGRGHGHGK	HRIKDCKKHS	TEESSEESHDKVT NQKETLLAV VAEIQSHK
E Brown Snake	AYVDNANTL	VHTQQDCQVQV	EEKVGPPVHL	CPGCPVEI
Anolis Lizard				
Xenopus leavis	RR-DTERA--	-----KG--	PAHGNKGEQKH	VKKHKKK---KD KRKKKNGHK NEDSSEES
Xenopus tropicalis	NRIDTERA		KRHA HGHGHKEEQKH	GRKHKKERKDKKD KKNKKNGHK NGDSSEES
Nanorana parkeri		LQQH	TKGKNKGQHK	RKQEQGKSDKKR KHKHDEDE ---SSEEV
Latimeria	-----	---GHGHKEKK	IHGHKQHGDDS	SE--EHSHE ETTVATTIS ESLPDNADKP-
Zebrafish				
Pufferfish				
Elephant Shark				
		519		
Human	-----	-QTQEKTEGP	TPI--P-----	--SLAKP-GVTVTFSDQSDLI--ATMMP
Dog	----STTSSA	-QTQEKTEGP	TTL--P-----	--SLAQ-P-GIAVTMPDFQSDLI--AAVMPN
Siberian Tiger	----STTSSA	-QTQEKTEGP	TPL--P-----	--PLAQ-P-GIAVTLPDFQSDLI--AAVMSN
Grizzly Bear	----STTSSA	-QTQEKTEGP	TPL-L-----	--SLAQ-P-GIAVTVPDFQSDLI--AAVN--
Hippopotamus				--SLAQ-P-GVTVTSPDFQSDLI--AT
BN Dolphin	-----	-QVQKKEGP	TPF--P-----	--SLAQ-P-SVANTFPNLQSDLI--ATVMPN
Opossum	-----	-PMQEETQGP	PPP--Q-----	--SPSQQ-GVDVTPSYFQDFDLDNPNPTNIP
Koala	-----	---QEETQGP	PPLLSSALQEV	IT-PSDF-QDLDLNLNPTNPPSEPKTDEKT
Wombat	-----	---QEETQGP	PPLLSSSLQEV	IT-PSDF-QDLDLNLNPTNPPSEPPTTKEKE
Platypus	-----	IDPEEPGTPP	SILRPTHQPRP	EGAVTLSYFRDSDLLSPDTPLAALP-----
Kiwi	-----	--NAEMVSE-	-----LVTPGA	VR-----
Pigeon	KKTSSPAECG	HKKHSHKNGKH	PNPESSEESDE	RVFNQDETSPSSDTETAS--PEAAV-----
W-T Tropicbird	GKRKYPNPKP	SDESDEGRFN	QNKTIPTASAE	TASELVNPGVARKKTSTSAEPLILPDISLNLPLD
Alligator	DKSSEESSEK	VLCERESQLP	SVDRTSENSQF	PTTPSLFQSDALTPGVTVG
Green Sea Turtle				PDLVELD
E Brown Snake	QQSALYEVRE	MKTATRQVVN	GWNYNLEYSIK	ETNCSKNEFLDLTPECRHLPPEGKEGFCVT
Anolis Lizard				
Xenopus leavis	-QEYITLPTV	HATQRMQHTT	TQTVQLITSAQ	KQESLSKTPGEQIS
Xenopus tropicalis	-QEHTILLTQ	HTTAQTVELI	TST--LTPHSI	-----S-TPGQTP
Nanorana parkeri	-DERG			
Latimeria	IPGSGLLPSS	VLIKPPSSGP	GPVVLPSHPEQ	IPAPDKPVTS TVEFPSPFD VALVSASL--
Zebrafish				
Pufferfish				
Elephant Shark				

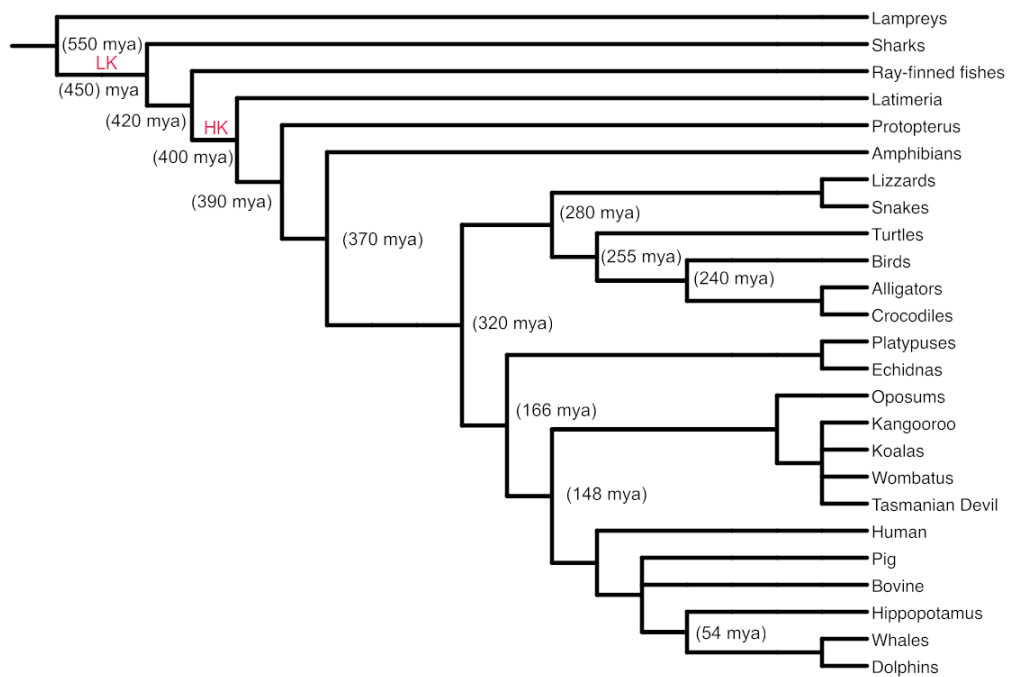
Supplemental Figure S1. Amino acid sequence alignment of vertebrate high molecular weight kininogens (continued).

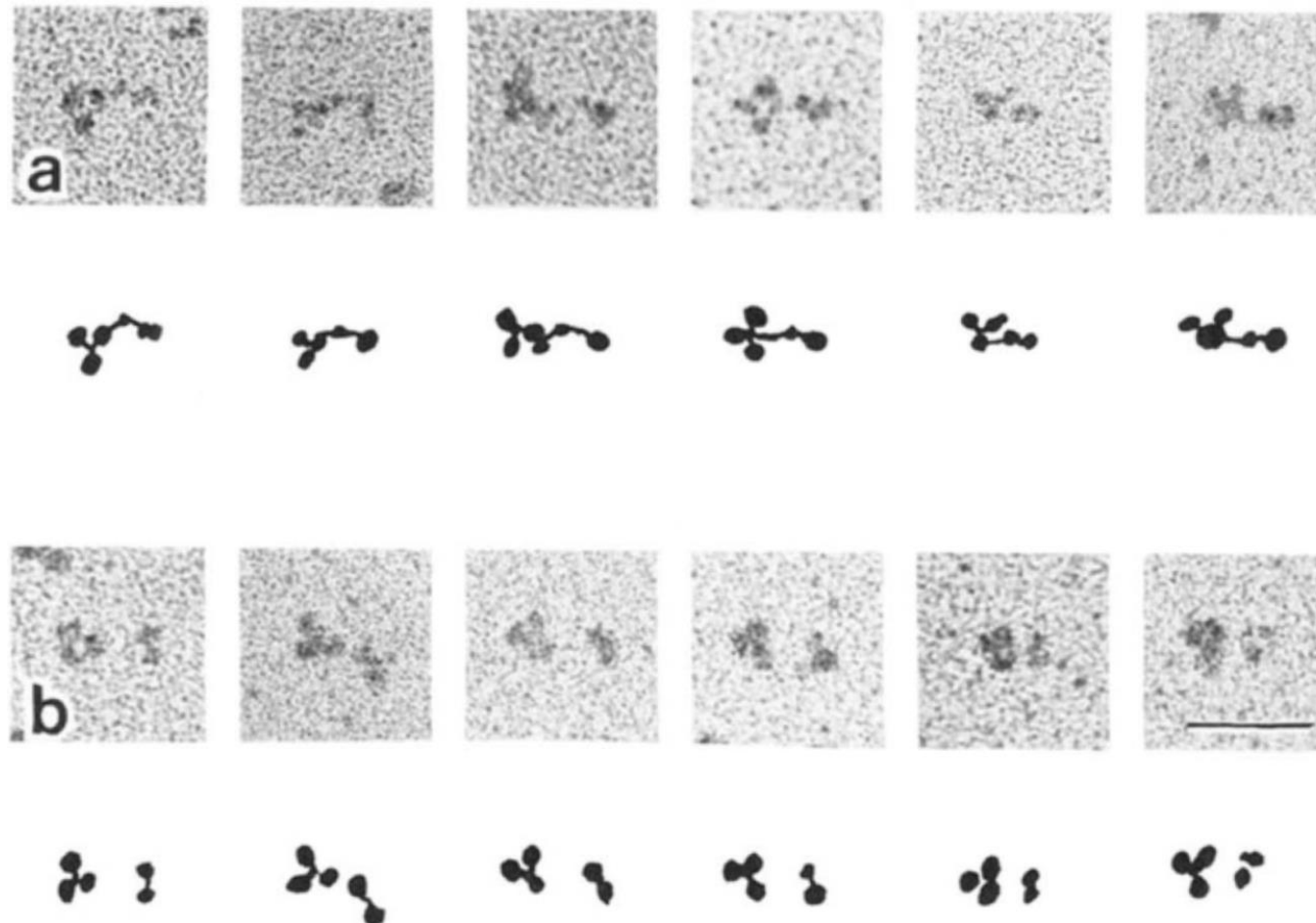
558

Human	ISPAPIQ-----	SDD	DWIPDIQIDP	NGLSFNPISDF	--PD TTSPK CPG	RPWK SVSEI	NPTTQMKE--
Dog	IPPTATE-----	SDD	DWIPDIQIKP	NSLSFNLIISDF	--PEQ TSPK CPG	RPWKPVHGM	NPTVEVKMN--
Siberian Tiger	TPPTPTE-----	IDD	DWIPDIQIEK	NSLSFNLIIPDF	--PEK TSPK CPG	RPWKPVNGM	NPTVEIKEF--
Grizzly Bear	NPSAPKE-----	SDD	DWIPDIQIEP	NSLSFNLIIPDF	--PEK TSPK CPG	RPWKPVNGM	NPAAVEVKEF--
Hippopotamus	LPPPTTE-----	SDD	DLIPDIQIEP	NSLPFELISDF	--PE TTSPK CPG	RPWKPINGV	NPTVEMKE---
BN Dolphin	TLPPPTTE-----	SDD	DLIPDIQIEP	NSLAFKLIPDF	--PE TTSPK CPG	RPWKPVNGV	NPTVEMKEFHD
Opossum	VEPTAEQKTGGEEA	EEE	VLFPDIPIVP	KSPLFTLMPDF	PEPEPIVP K CPG	SPWQPITVM	NPVTEESQNE
Koala	-----KETAGEEEY	TDD	DWIPDIPIQP	KSSLFTLVPDF	--PEPPAP K CPG	RPWKPIDVM	DPVKEESQYMD
Wombat	-----KEKAGEEED	TDD	DWIPDIPVQP	KSPLFTLVPDF	--PEPSAP K CPG	RPWKPIDAM	GPVKEESPYVD
Platypus	-----	PSD	GDLFPEIQSE	PKDFSLGLLDF	--PEPPPP K CPG	RPWKPIQGM	DPATEEKQYDD
Kiwi	-----	QET	SIPAETVTLP	DIFLVNGLPDR	--SESPLP R CPG	KPWKPIMDL	PVPPSFPPRELE
Pigeon	-----	KKT	SSPAEPLILP	DTSFSNGSPDH	--PESPLP R CPG	KPWKQIMDL	PAPDSFPREFE
W-T Tropicbird	---ASELVNPGVAR	KKT	STSAEPLILP	DISLFNGLPDR	--PESSLP R CPG	KPWKQLMDL	PVPPSLPREFK
Alligator	---PRDDSSTPDIP	EET	VSPGTAEIAP	DISLFDELPLD	--PEPPV S KCPG	KPWKSIMQF	TNPSENTILFT
Green Sea Turtle	VLPSTLTDGVTEIP	DLP	AEPDSPGIIP	DIPLFGLPLDV	--PEPSVP K CPG	KPWKPIADL	STTTNKPKVLT
E Brown Snake							
Anolis Lizard	---QEDITARSPE	ESV	GFPSPDSIVP	SLSLFERLPDL	--PEPPAP K CPG	NPWKPIILP	PTSLPDPGDFA
Xenopus leavis	KTTEKPTLGLFPHI	PSV	QEDQDNFFNF	HNNAEPDLGPG	--DDSN F KCPG	KPWEVPVKLP	STEPTYDLFDL
Xenopus tropicalis	ETTEEPTLGLFPQI	PSV	PEDQDNFFNF	HDNVEPDLGPG	--EDSN L KCPG	NPWEVPVKLP	ITEPVYNPFDL
Nanorana parkeri	INVNMKEDSHQVLD	LPS	AQPTVPSKEA	VPKDIEEKSNI	--ELPV V KCPG	KLWQPRSLT	TTVKTFTHDDL
Latimeria	-----	PSF	PDVALVSASL	PDLHKETFPDL	--PEGPEI K CPG	QPWKPI SPL	HGVTSSEFSHT
Zebrafish							
Pufferfish							
Elephant Shark							

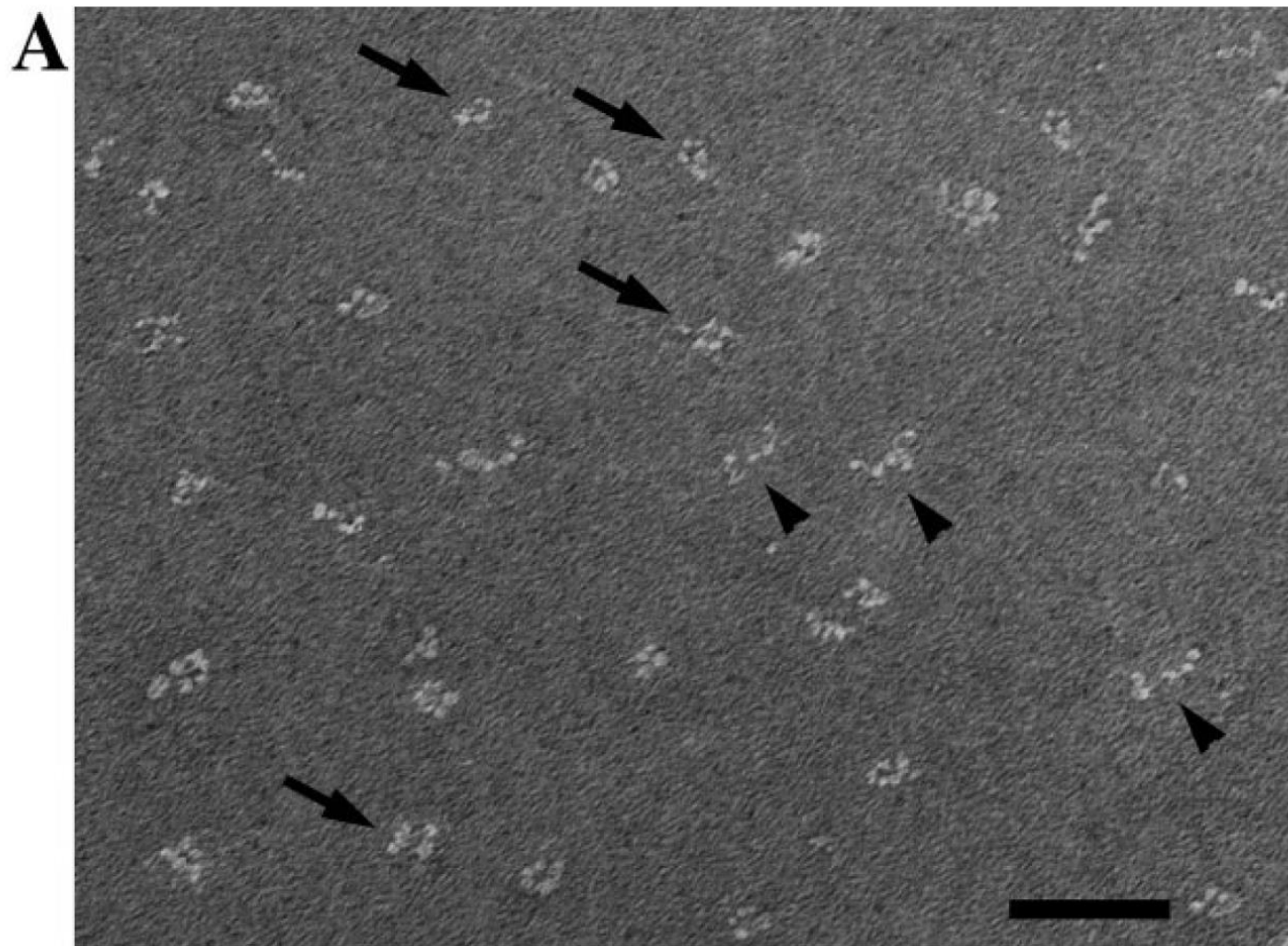
	617	626
Human	YYFDLTDGLS-----	-----
Dog	PTVEVKEFHDFDLSDALY	
Siberian Tiger	EIKEFHDFDLSDALY	
Grizzly Bear	PDFDLTDALY	
Hippopotamus		
BN Dolphin	FSLSDALY	
Opossum	FELSDALSFGKK	
Koala	FDSLDALEFGKK	
Wombat	FDSLDALEFGKK	
Platypus	FDLFDAVR	
Kiwi	DLLPSAVENINPTTENSNTQNEETS	FELSDALQ
Pigeon	NEDLLVFSLKNDPATESSTSP--QTKDL	DLSDALL
W-T Tropicbird	NEDLLTSVKENVNPD TENSTPP--QNKDF	DLLDALL
Alligator	NEDLLPNPLENLPASEKPSPI	NTDVGDFDLVDALPL
Green Sea Turtle	NEDLLPHLSED TNPETEKYTLPPQDL	DDFNLMDSLL
E Brown Snake	ATDSPELQEPLQNIIESFNANNSGDFH	FRIVEIKDATKQV
Anolis Lizard	LEDLLPSEGDVVEPKEISAVAIQ	PVAADFDLADALY
Xenopus leavis	ASAIGDATPTVAENIENKVP	GSTSQG--FNDEDLLLSFI
Xenopus tropicalis	AFAIEDTTTTTTANENIKNKEPG	SQGQPFNDEDLLLSLI
Nanorana parkeri	AFAAADFKPLPEKEEEEP	SKPYTPKQI-PFFDDEDLLL
Latimeria	SSAYEEKSMV	GGATDFKDTD LLGF
Zebrafish		
Pufferfish	PWKVFNPSPVAPT	DAPNMTADAPVLS
Elephant Shark	RHITPTDPVSETVPPPLNTAEEGEQ	PKSDGFFDFDLAGL

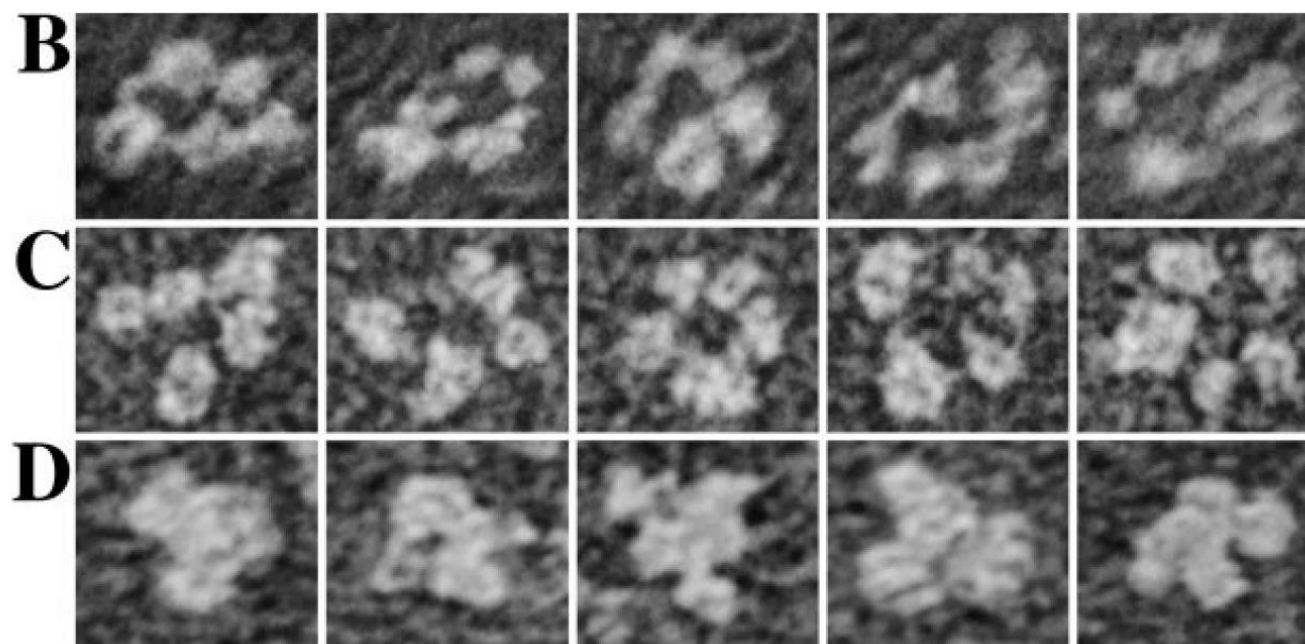
B) Cladogram depicting ancestral relationships of extant vertebrates together with **LK and **HK** emergence.**



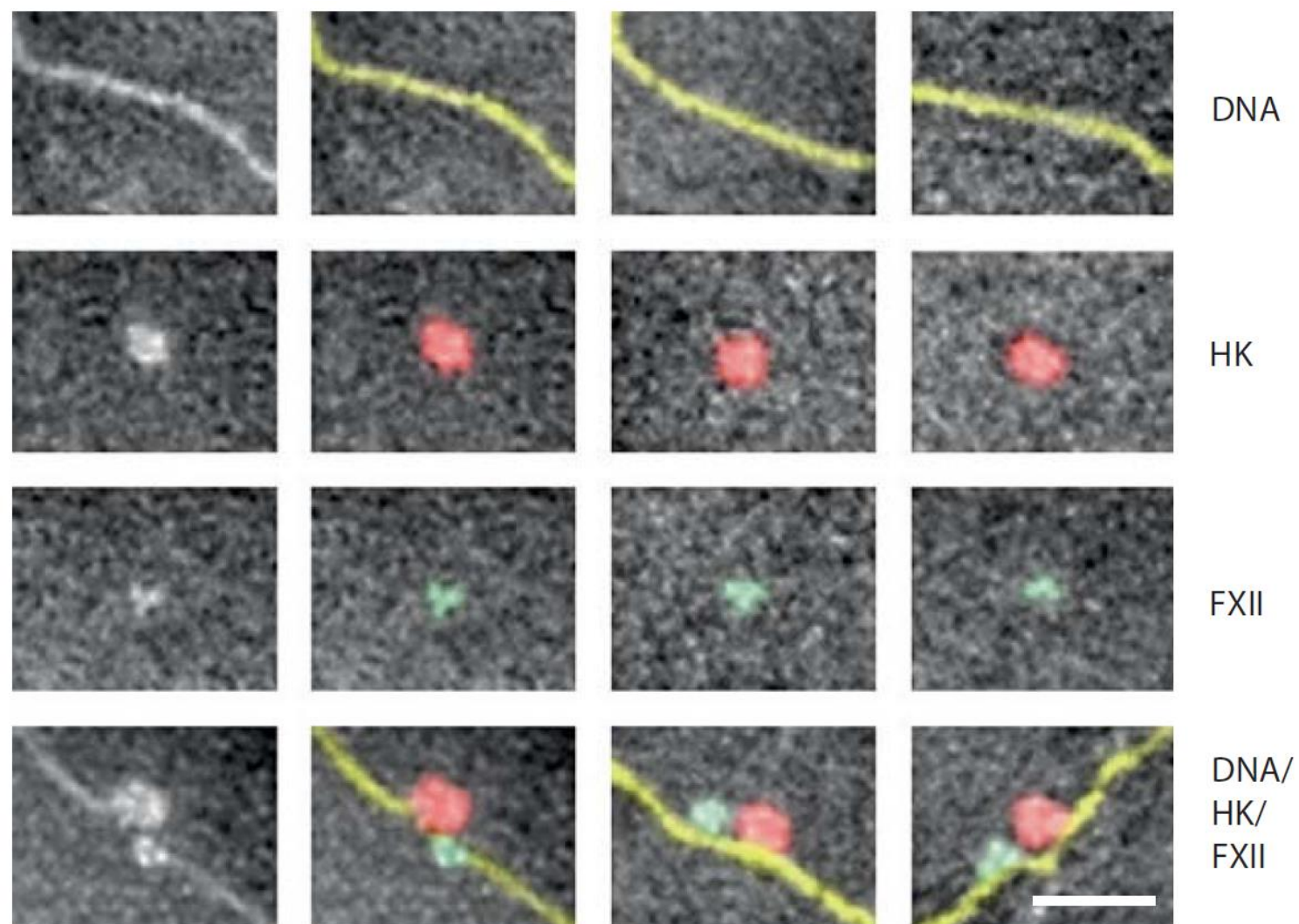


Supplementary Figure S2. Electron microscopy of rotary-shadowed complexes of monoclonal antibody 2B5 with high molecular weight kininogen according to Weisel *et al.* 1994 figure 3 (a) and with cleaved high molecular weight kininogen (b). (Weisel, J.W.; Nagaswami, C.; Woodhead, J.L.; dela Cadena, R.A.; Page, J.D.; Colman, R.W. The Shape of High Molecular Weight Kininogen. Organization into Structural Domains, Changes with Activation, and Interactions with Prekallikrein, as Determined by Electron Microscopy. *Journal of Biological Chemistry* 1994, 269, doi:10.1016/s0021-9258(17)36995-8.) The reproduction is presented according to JBC CC-BY license <https://www.asbmb.org/journals-news/copyright-and-reproduction>.





Supplementary Figure S3. Negative staining transmission electron microscopy according to Herwald *et al.* 2001 figure 9 A-D. (Herwald, H.; Mörgelin, M.; Svensson, H.G.; Sjöbring, U. Zinc-Dependent Conformational Changes in Domain D5 of High Molecular Mass Kininogen Modulate Contact Activation. *European Journal of Biochemistry* 2001, 268, doi:10.1046/j.1432-1033.2001.01888.x.). The reproduction is presented according to FEBS letters Creative Commons License.



Supplementary Figure S4. Negative staining transmission electron microscopy of DNA and HK figure 1a according to Oehmcke, Mörgelin and Herwald 2009 (Oehmcke, S.; Mörgelin, M.; Herwald, H. Activation of the Human Contact System on Neutrophil Extracellular Traps. *Journal of Innate Immunity* 2009, 1, doi:10.1159/000203700.). The reproduction is presented according to reuse permission of the figure as MDPI and Karger, are signatories of the STM permission guidelines.