

Fig. S1. The domain organization of teneurin-1 and the sequences that were expressed or purified in this study. The amino acid sequence of human teneurin-1 with the various domains indicated. The expressed protein is underlined, the furin cleavage site is indicated in red, and the GHH toxin domain is in italics. The amino acid sequences of the two human and two chicken CTDs are also shown, with the furin cleavage sites in red and the region corresponding to the GHH toxin domain in italics.

Intracellular domain

MEQTDCPKYQPLPKVKHEMDLAYTSSSDESEDGRKPRQSYNSRETLHEYNOELRM
 NYSQSRKRKEVEKSTQEMEFCESTHTLCSGYQTDMSVSRHGYLEMGSDVDTE
 TEGAASPDHALRMWIRGMKSEHSSCLSSRANSALS LTD DHERKSDGENGFKFS P
 VCCDMEAQAGSTQDVQSSPHNQFTFRPLPPPPPPHACTCARKPPPAADSLQRRS
 MTTRSQPSPAAPAPTSTQDSVHLHNSWVLSNIPLRTRHFLFKHSGSSAIFSA
 ASQNYPLTSNTVYSPPPRPLPRSTFSRPAFTFNKPYRCCNWK

Transmembrane domain

CTALSATAITVTLALLLAYVIAV

Beginning of extracellular domain

HLFGLTWQLQPVEGELYANGVSKGNRGTESMDTTYSPIGGKVSDKSEKKVFQKGR
 AIDTGEVDIGAQMOTIPPLGLFWRWFQITIHHPHYLKFNISLAKDSSLGIYGRNI
 PPTHQFDFVKLMDGKQLVKQDSKGSDDTQHSPRNLIILTSLQETGFIEYMDQGPW
 YLAFYNDGKKMEQVFVLTTAIEIM

EGF-like domains

DDCSTNCNGNGECISGHCHCFPGFLGPDCARDSCPVLCGGNGEYKGGHCVCRHW
 KGPECDVPEEQCIDPTCFGHGTCIMGVCICVPGYKGEICEEEDCLDPMCSNHGIC
 VKGECHCSTGWGGVNCETPLPVCQEQC SGHGTFLLDAGVCS CDPKWTGSDCSTEL
 CTMECGSHGVCSRIGICQCEEGWVGPTCEERSCHSHCTEHGQCKDGKCECSPGWE
 GHCTIAHYLDAVRDGCPLCFGNGRCTL DQNGWHCV CQVGVSGTGCV

C-rich domain

VMEMLCGDNLDNDGDGLTDCVDPDCCQQSNCYISPLCQ

GSPDPLDLIQQSQTLFSQHTSRLFYDRIKFLIGKDSTHVIPPEVSFDSRRACVIR
 GQVVAIDGTPLVGVNVSFLHHSYDGTISRQDGSFDLVAIGGISVILIFDRSPFL
 PEKRTLWLPWNQFIVVEKVTMQRVVS DPPSCDISNFISPNIIVLPSPLTSFGGSC
 PERGTIVPELQVVQEEIPIPSFVRLSYLSSRTPGYKTLRILLTHSTIPVGMK

VHLTVAVEGRRLTQKWFPAAINLVYTFAWNKTDIYGQKVGWGLAEALVSVGYEYETC
PDFILWEQRTVVVLQGFEMDASNLGGWSLNKHHILNPQSGIIHKNGENMFISQQP
PV

6-bladed beta propeller

ISTIMGNGHQRSVACTNCNGPAHNNKLFAPVALASGPDGSVYVGDVFNFVRRIFPS
GNSVSI LELSTSPAHKYYLAMDPVSESLYLSDTNTRKVYKLSLVETKDLSKNFE
VVAGTGDQCLPFDQSHCGDGRASEASLNSPRGITVDRHGFIYFVDGTMIRKIDE
NAVITTVIGSNGLTSTQPLSCDSGMDITQVRLEWPTDLAVNPMDNSLYVLDNNIV
LQISENRRVRIIAGRPIHCQ

YD-repeats and first half of the RHS-domain

VPGIDHFLVSKVAIHSTLESARAI SVSHSGLLFIAETDERKVNRIQQVTTNGEIIY
IIAGAPTDCCDKIDPNCDCFSGDGGYAKDAKMKAPSSLAVSPDGTLYVADLGNVR
IRTI SRNQAHLNDMNIYEI ASPADQELYQFTVNGTHLHTLNLITRDYVYNFTYNS
EGDLGAITSSNGNSVHIRRDAGGMPLWLVPVGGQVYWLTISSNGVLKRVSAQGYN
LALMTYPGNTGLLATKSNENGWTTVY EYDPEGHLTNATFPTGEVSSFHS DLEKLT
KVELDTSNRENVLMSTNL TATSTIYILKQENTQSTYRVNPDGSLRVTFASGMEIG
LSSEPHILAGAVNPTLGKCNISLPGEHNANLIEWRQRKEQNKGNVSAFERRLRAH
NRNLLSIDFDHITRTGKIYDDHRKF TLRILYDQTGRPI LWSPVSRYNEVNITYSP
SGLVTFIQRTWNEKMEYDQSGKII SRTWADGKIWSYTYLEKSVMLLLHSQRRYI
FEYDQPDCLLSVTMPMSMRHSLQTML SVGYRNIYTPPDSSTSF IQDYSRDGRL
QTLHLGTGRRVLYKYTKQARLSEVLYD TTQVTLTYEESSGVIKTIHLMHDGFICT
IRYRQTGPLIGRQIFRFSEGLVNARFDYSYNNFRV TSMQAVINETPLPIDLYRY
VDVSGRTEQFGKFSVINYDLNQVITTTVMKHTKIF SANGQVIEVQYEILKAIAYW
MTIQYDNVGRMVICDIRVGV DANITRYFY EYDADGQLQTVSVNDKTQWRYSYDLN
GNINLLSHGKSARLTPLRYDLRDRITRLGEIQYKMD EDGFLRQRGNDIFEYNSNG
LLQKAYNKASGWTVQY YDGLGRRVASKSSLGQHLQFFYADLTNPIRVTHLYNHT
SSEITSLYYDLQGH LIAMELSSGEEYYVACDNTGTPLAVFSSRGQVIKEILYTPY
GDIYHDTYPDFQVIIGFHGGLYDFLTKLVHLGQRDYDVVAGRWTTPNH HIWKQLN
LLPKPFNLYSFENNYPVGKIQDVAKYTTDIRSWLELEFGFQLHNVLPGF PKPELEN
LELTYELLRLQTKTQEWDPGKTILGIQCELOKQLRNFI SLDQLPMTPRYNDGRCL
EGGKQPRFAAVPSVFGGKIKFAIKDGIVTADIIGVANEDSRRLAAI LNNAHYLEN
LHFTIEGRDTHYFIKLGSL EEDLV LIGNTGGRRILENGVNVTVS QMTSVLNG

Furin-cleavage site within the RHS-domain (red**) and C-terminal domain (GHH Tox domain) in *italics***

RTRRFADIQLQHGALCFNIRYGTTVVEEK~~NHVLEIARQRAVAQAWTKEQRRLOEG~~
EEGIRAWTEGEKQQLLSTGRVQGYDGYFVLSVEQYLELSDSANNIHFMRQSEIGR
R

Expressed human Teneurin-1 C-terminal domain (CTD) sequence (furin cleavage site in **red, GHH toxin domain in *italics*):**

VTVSQMTSVLNG**RTRR**FADIQLQHGALCFNIRYGTTVVEEK~~NHVLEIARQRAVAQ~~
~~AWTKEQRRLOEG~~EEGIRAWTEGEKQQLLSTGRVQGYDGYFVLSVEQYLELSDSAN
NIHFMRQSEIGRR

Expressed human Teneurin-2 C-terminal domain (CTD) sequence (furin cleavage site in **red, GHH toxin domain in *italics*):**

TVSQPTLLVNG**RTRR**FTNIEFQYSTLLLSIRYGLTPDTLDEEKARVLDQARQRAL
GTAWAKEQQKARDGREGSRLWTEGEKQQLLSTGRVQGYEGYYVLPVEQYPELADS
SSNIQFLRQNEMGKR

Purified chicken Teneurin-1 C-terminal domain (CTD) sequence (GHH toxin domain in *italics*):

FADIQLQHGALCFNVRYGTTVVEEK~~NHVLEVARQRAVAQAWTKEQRRLOEG~~EEGI
RAWTDGEKQQLLNTGRVQGYDGYFVLSVEQYLELSDSANNIHFMRQSEIGRR

Purified chicken Teneurin-2 C-terminal domain (CTD) sequence (GHH toxin domain in *italics*):

FTNIEFQYSTLLINIRYGLTADTLDEEKARVLDQARQRALGSAWAKEQQKARDGR
EGSRVWTDGEKQQLLNTGRVQGYEGYYVLPVEQYPELADSSSNIQFLRQNEMGKR

Fig. S2. Amino acid identity and similarity between teneurin C-terminal domains and the bacterial GHH toxins. The GHH domains from three bacterial toxins were aligned with the corresponding amino acids from the C-terminal domains (CTDs) of representative teneurins (TOX) to illustrate the possibility that the teneurin CTD is an endonuclease.

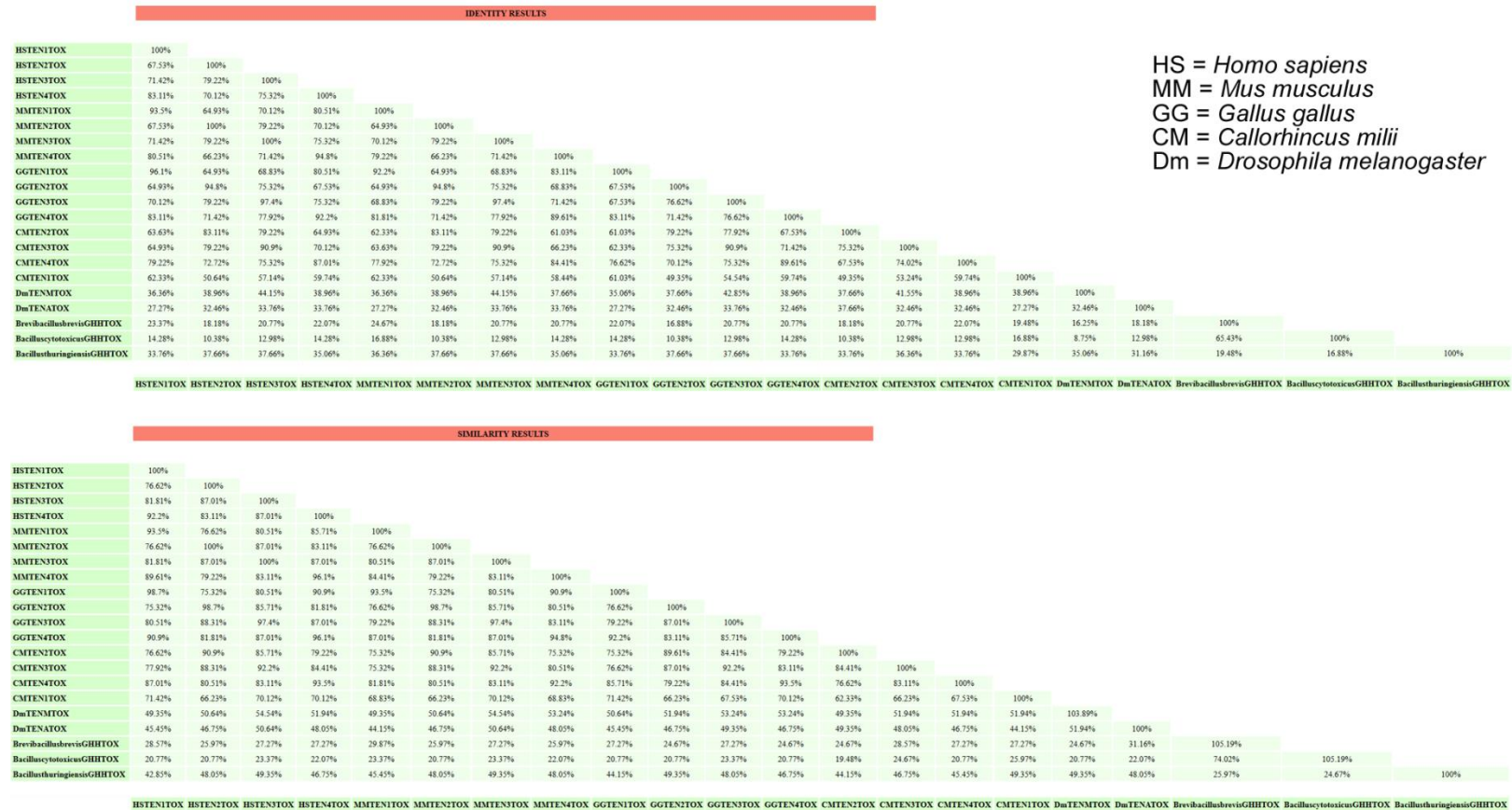


Fig. S3. Purification of recombinant proteins. Lanes from Coomassie blue-stained polyacrylamide gels showing the purified CTDs of chicken teneurin-1 and teneurin-2 used for cell culture and nuclease activity studies. The size ladder indicates apparent molecular weights in kDa.

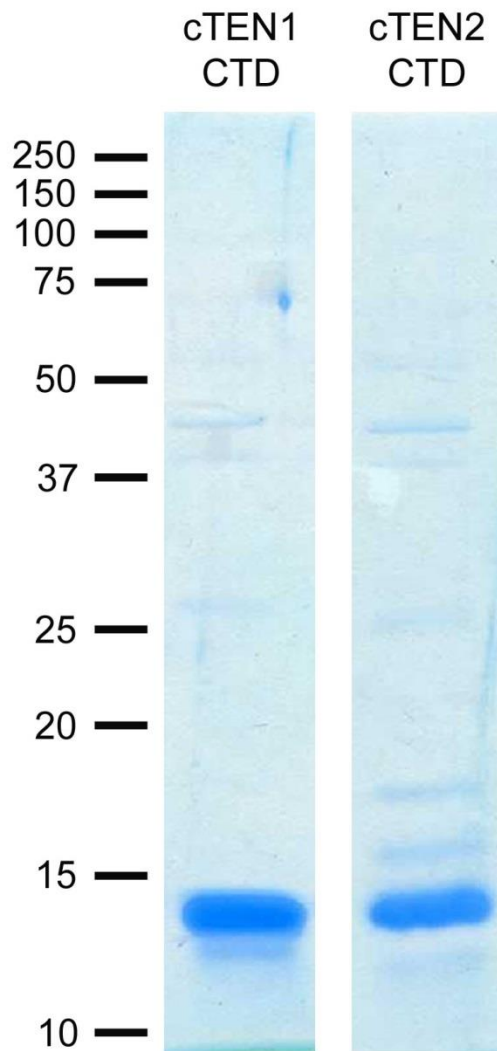


Table S1. Transcriptional profiling of HEK293 cells expressing the teneurin-2 CTD.

Affyprobes	logFC	FC	AveExpr	t	P.Value	adj.P.Val	geneID	Gene name
7903592	-0.72145	0.606487	7.354426	-12.5757	5.03E-08	8.33E-05	NM_020775	KIAA1324
7906878	-0.67236	0.627478	7.214012	-9.72767	7.41E-07	0.000403	NM_001014796	DDR2
7909610	-0.6658	0.630338	7.822956	-10.525	3.29E-07	0.000272	NM_001040619	ATF3
7914923	-0.67225	0.627527	8.664322	-8.30028	3.67E-06	0.000768	NM_145047	OSCP1
7918504	-0.76381	0.588938	8.79511	-8.34036	3.50E-06	0.000768	NM_002557	OVPG1
7919606	-0.69246	0.618796	9.119708	-5.54779	0.000153	0.004596	NM_001024599	HIST2H2BF
7921916	-0.59982	0.659835	7.830591	-9.63692	8.16E-07	0.000406	NM_003617	RGS5
7927305	1.503777	2.835841	9.252199	3.594072	0.003997	0.027026	NM_001144000	AGAP5
7934979	-1.16012	0.447475	8.087316	-15.8307	4.18E-09	1.38E-05	NM_014391	ANKRD1
7937257	-0.71473	0.609319	9.36582	-3.5064	0.004675	0.029707	NM_145651	SCGB1C1
7937696	-1.17705	0.442256	8.674062	-19.0097	5.59E-10	2.78E-06	NM_001004325	KRTAP5-2
7938263	-0.87302	0.546001	8.173645	-6.09672	6.72E-05	0.002971	NM_003754	EIF3F
7948332	-0.5969	0.661171	8.843283	-7.0881	1.69E-05	0.001556	NM_004811	LPXN
7949124	-0.71169	0.610605	8.297349	-7.01971	1.85E-05	0.001598	NM_005609	PYGM
7959102	-0.7667	0.587759	6.783417	-8.20601	4.10E-06	0.000801	NM_014365	HSPB8
7985450	-0.65561	0.634809	8.042572	-3.68078	0.003425	0.024381	NM_198181	GOLGA6L9
7986250	-0.64639	0.638877	10.61057	-9.15753	1.37E-06	0.000593	NM_001271	CHD2
7990391	-0.93391	0.523439	7.239254	-12.1247	7.42E-08	9.41E-05	NM_000499	CYP1A1
8012951	-0.97986	0.50703	8.099792	-8.85831	1.92E-06	0.000709	NM_006382	CDRT1
8018902	-1.63346	0.322315	8.372967	-26.4478	1.41E-11	1.40E-07	NM_173628	DNAH17
8034512	-0.66339	0.631394	12.72709	-3.14155	0.009025	0.043986	NR_002751	SNORD41
8044450	-0.64022	0.641617	8.976154	-9.88059	6.31E-07	0.000376	NM_198581	ZC3H6
8044669	-0.74997	0.594617	6.139221	-3.92222	0.002236	0.018966	NM_013412	RABL2A
8073015	0.590598	1.505871	8.841807	8.056205	4.92E-06	0.000858	NM_006855	KDEL3
8076612	-0.76622	0.587957	7.321342	-10.2007	4.55E-07	0.000337	NM_022785	EFCAB6
8087145	-0.67592	0.625934	7.738101	-8.44067	3.11E-06	0.000768	NM_001407	CELSR3
8090509	0.621983	1.538989	8.029379	3.589539	0.004029	0.027123	NM_004637	RAB7A
8110032	-0.59103	0.663869	8.910183	-7.19709	1.46E-05	0.001474	NM_153607	CREBRF
8113103	-0.77638	0.583831	7.527023	-10.8112	2.48E-07	0.000247	NM_001145678	KIAA0825
8113483	-0.92081	0.528211	8.496886	-10.5983	3.06E-07	0.000272	NM_001039763	TMEM232
8116532	-0.58961	0.664521	9.988008	-4.7771	0.000522	0.008636	NR_002591	SNORD95
8124448	-0.80405	0.572738	11.50295	-12.6511	4.72E-08	8.33E-05	NM_003543	HIST1H4H

Table S1. Transcriptional profiling of HEK293 cells expressing the teneurin-2 CTD. (cont.)

Affyprobes	logFC	FC	AveExpr	t	P.Value	adj.P.Val	geneID	Gene name
8128001	-0.81901	0.566831	6.542142	-14.1864	1.38E-08	3.42E-05	NM_000735	CGA
8133314	-0.78137	0.581813	6.560076	-4.64017	0.000655	0.009589	NM_000265	NCF1
8140211	-0.66516	0.630617	9.648513	-4.05341	0.001778	0.016774	NR_003664	SPDYE8P
8156160	-1.61451	0.326575	7.891629	-7.61267	8.53E-06	0.001162	NM_017576	KIF27
8159259	-0.65752	0.633968	8.34969	-8.54771	2.74E-06	0.000757	NM_014582	OBP2A
8163505	0.634357	1.552246	9.225563	7.482806	1.01E-05	0.001236	NM_031219	HDHD3
8164766	-0.72428	0.605298	8.047926	-12.1016	7.57E-08	9.41E-05	NM_152572	AK8
8165496	0.649239	1.568341	10.8664	4.995579	0.000366	0.006937	NM_006088	TUBB4B
8165672	-1.20723	0.433099	6.809187	-3.32621	0.006464	0.036244	L23320	RFC

Table S2. FASTA files used for sequence analyses.

>HSTEN1TOX
EKNHVLEIARQRAVAQAWTKEQRRLLQEGEEGIRAWTEGEKQQLLSTGRVQGYDGYFVLSVEQYL
ELSDSANNIHFM

>HSTEN2TOX
EKARVLDQARQRALGTAWAKEQQKARDGREGSRLWTEGEKQQLLSTGRVQGYEGYYVLPVEQYP
ELADSSSNIQFLR

>HSTEN3TOX
EKARILEQARQRALARAWAREQQRVRDGEEGARLWTEGEKRQLLSAGKVQGYDGYVLSVEQYP
ELADSANNIQFLR

>HSTEN4TOX
EKARVLELARQRAVRQAWAREQQRLREGEGLRAWTEGEKQQVLSTGRVQGYDGGFFVISVEQYP
ELSDSANNIHFM

>MMTEN1TOX
EKNHVLEMARQRAVAQAWTQEQRRLQEGEEGTRVWTEGEKQQLLGTGRVQGYDGYFVLSVEQYL
ELSDSANNIHFM

>MMTEN2TOX
EKARVLDQARQRALGTAWAKEQQKARDGREGSRLWTEGEKQQLLSTGRVQGYEGYYVLPVEQYP
ELADSSSNIQFLR

>MMTEN3TOX
EKARILEQARQRALARAWAREQQRVRDGEEGARLWTEGEKRQLLSAGKVQGYDGYVLSVEQYP
ELADSANNIQFLR

>MMTEN4TOX
EKVRVLELARQRAVRQAWAREQQRLREGEGLRAWTDGEKQQVLNTGRVQGYDGGFFVTSVEQYP
ELSDSANNIHFM

>GGTEN1TOX
EKNHVLEVARQRAVAQAWTKEQRRLLQEGEEGIRAWTDGEKQQLLNTGRVQGYDGYFVLSVEQYL
ELSDSANNIHFM

>GGTEN2TOX
EKARVLDQARQRALGSAWAKEQQKARDGREGSRVWTDGEKQQLLNTGRVQGYEGYYVLPVEQYP
ELADSSSNIQFLR

>GGTEN3TOX
EKARILEQARQRALSSAWAREQQRVRDGEEGARLWTEGEKRQLLSAGKVQGYDGYVLSVEQYP
ELADSANNIQFLR

>GGTEN4TOX

EKARVLELARQRAVAQAWAREQQRLRDGEEGIRSWTEGEKQQVLNTGRVQGYDGYFVISVEQYP
ELSDSANNIHFM

>CMTEN2TOX

EQARLLEQARLRALANAWTREQQKARDGKEGGRLWTEGEKQQLLSAGRIQGYEGYYVLPVEQYP
ELADSSTNIQFLR

>CMTEN3TOX

EKARILEQARQRALGCAWAREQQRVRDGEDGVRLWTEGEKQQLLSAAKVQGYDGYVLSVEQYP
ELADSVSNIQFLR

>CMTEN4TOX

EKARVLELARQRAVTQAWAREDQRLRDGEEGVRSWTEGEKQQLLSTGRVQGYDGYFVTTVEQYP
ELSDSVNNIHFM

>CMTEN1TOX

ERRHVLELAGQRAVARAWARERRRLGRGERGTRAWTEAERRQLLAGGRVPGYDGRAVLPPEQFA
ELSDSPGNVRFVR

>DmTENMTOX

ERHRILKHAHKRAVERAWELEKQLVAAGFQGRGDWTEEEKEELVQHGDVDGWNGIDIHSIHKYP
QLADDPGNVAFQRDAK

>DmTENATOX

EQQRLMHAKLTAVRKAWHREKEALRSGLTTALEWSQQETDEILKQSYANNYEGEYIHDVNLYP
ELAEDPYNIKFVK

>BrevibacillusbrevisGHHTOX

EWNRRLLAKRRDAGVKEFWKQEKRRIKNGEPTTRNWTQEQKDAILSNQVPTFNGKPIIGHHAYSV
SKYPHLANRGEIIPVT

>BacilluscytotoxicusGHHTOX

EWNKKFAKRWDKGVKEFWYQEQQRILNNEPLTREWSQEQDKDILAGKTPKFDGKPIAGHHSYSA
AKYPHLADKGEIIPVT

>BacillusthuringiensisGHHTOX

LTDKQFSALRQKAVRHAWRQEKELIKKTGKGRDWTPEAKLELLQTGKVKGYEGQHMKSANEYP
DFAGEPDNIQFLK