RESEARCH ARTICLE



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Filling out the structural map of the NTF2-like superfamily

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Abstract

Background: The NTF2-like superfamily is a versatile group of protein domains sharing a common fold. The sequences of these domains are very diverse and they share no common sequence motif. These domains serve a range of different functions within the proteins in which they are found, including both catalytic and non-catalytic versions. Clues to the function of protein domains belonging to such a diverse superfamily can be gleaned from analysis of the proteins and organisms in which they are found.

Results: Here we describe three protein domains of unknown function found mainly in bacteria: DUF3828, DUF3887 and DUF4878. Structures of representatives of each of these domains: BT_3511 from *Bacteroides thetaiotaomicron* (strain VPI-5482) [PDB:3KZT], Cj0202c from *Campylobacter jejuni* subsp. jejuni serotype O:2 (strain NCTC 11168) [PDB:3K7C], rumgna_01855) and RUMGNA_01855 from *Ruminococcus gnavus* (strain ATCC 29149) [PDB:4HYZ] have been solved by X-ray crystallography. All three domains are similar in structure and all belong to the NTF2-like superfamily. Although the function of these domains remains unknown at present, our analysis enables us to present a hypothesis concerning their role.

Conclusions: Our analysis of these three protein domains suggests a potential non-catalytic ligand-binding role. This may regulate the activities of domains with which they are combined in the same polypeptide or via operonic linkages, such as signaling domains (e.g. serine/threonine protein kinase), peptidoglycan-processing hydrolases (e.g. NIpC/P60 peptidases) or nucleic acid binding domains (e.g. Zn-ribbons).

Keywords: NTF2-like superfamily, Protein function prediction, Protein structure, Ligand-binding, JCSG, 3D structure, Protein family

Background

The NTF2-like superfamily is a large group of related proteins that share a common fold, first observed in the structure of the rat NTF2 (Nuclear Transport Factor 2) protein [1]. It is a versatile fold that can accommodate very different sequences and has no characteristic sequence motif associated with it. The NTF2-like fold has a cone-like shape with a cavity inside and acts as a molecular container that can be adapted to serve a broad range of different functions.

The NTF2-like proteins can be broadly defined into two functional categories: enzymatically active and nonenzymatically active proteins. The intracellular examples of this fold include most of the enzymatic functions associated with these proteins. These include SnoaL polyketide cyclase, scytalone dehydratase, limonene-1,2epoxide hydrolase and δ 5-3-ketosteroid isomerase [2-5]. The extracellular NTF2-like proteins tend to be nonenzymatic and possess small molecule binding activity. Non-enzymatic members of this superfamily include NTF2 [1], a domain found at the C-terminus of calcium/calmodulin dependent protein kinase II which is responsible for the multimerization of these kinases [6] and Mba1, a protein which binds to ribosomes and may function as a receptor [7]. NTF2-like domains have been found in proteins involved in bacterial conjugation where a multiprotein complex, the type IV secretion



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system, mediates transfer of plasmid DNA from a donor to a recipient bacterial cell [8-10]. More recently the non-catalytic NTF2-like domains have also been shown to function as immunity proteins in the bacterial polymorphic toxin systems [11].

Release 27.0 of the Pfam database [12] includes 24 different families as part of the NTF2 superfamily. Of these families, 21 have at least one representative where the three-dimensional structure has been deposited in the PDB. To date, the PDB contains at least 170 structures with NTF2-like fold, including at least 27 structures solved by the Joint Center for Structural Genomics (JCSG). Here we describe the first crystal structures of three Pfam families with NTF2-like folds: DUF3828 [PDB:3KZT] [Pfam:PF12883], DUF 3887 [PDB:4HYZ] [Pfam:PF13026] and DUF4878 [PDB: 3K7C] [Pfam:PF12870].

Results and discussion

Domain descriptions

DUF3828 family [Pfam: PF12883] is annotated in Pfam as a domain of unknown function. It is present in 492 different UniProtKB proteins from 451 different organisms. It is found exclusively in Gram-negative bacteria, with the vast majority of the species it occurs in belonging to the Enterobacteraceae family. [Pfam: PF12870] was previously annotated in Pfam as a lumazine-binding domain, however this has since been found to be incorrect and so we have renamed this family as a domain of unknown function, DUF4878. This domain is present in 650 different UniProtKB proteins from 571 different species. Like DUF3828, DUF4878 is a bacterial family, however it is found in a wider variety of bacterial species. It is found in both Gram-negative bacteria (including Proteobacteria and Bacteroidetes) and Grampositive species (including Firmicutes and Actinobacteria). Finally, DUF3887 family [Pfam: PF13026] is another domain of unknown function. This domain is present in 364 different UniProtKB proteins from 262 different species. It is predominantly found in Firmicutes, but is also present in other phyla, including several Archaeal species.

All three of these domains are of a similar length (around 100 amino acids). The N-terminus of DUF3828 (Figure 1) contains a pair of conserved aromatic amino acids (phenylalanine and tyrosine). There is a conserved aspartic acid in the middle of the domain and close to this is a conserved glutamine. A conserved tryptophan is located near the C-terminus, closely followed by two conserved hydrophobic amino acids. DUF3887 (Figure 2) contains a highly conserved glycine in the middle of the domain and two conserved hydrophobic amino acids near the C-terminus. DUF4878 (Figure 3) contains a conserved glycine about 25 amino acids into the domain and a conserved tryptophan near the C-terminus.

Domain architectures

In Pfam, 224 of the 492 proteins (45%) containing DUF3828 also contain a DUF4878 domain at the C-terminus (Figure 4). Given the potential significance of this observation, we performed further investigation into the taxonomic distribution of these proteins. Using EvolView [14] we plotted a species tree containing members of the RP75 set of representative proteomes [15] which possess proteins containing DUF3828 and/or DUF4878 (Figure 5). Surprisingly, we found that only two of the 113 species in this tree possessed both domains, and therefore we conclude that the co-occurrence of these domains is not likely to be significant and is an artifact caused by the sequencing of a disproportionately large number of *Escherichia coli* strains compared to the other species these domains are found in.

Besides the apparent co-occurrence of DUF3828 and DUF4878, the three DUFs also occur in several other architectures in Pfam. These can be split roughly into three categories: Architectures suggestive of communication with extracellular ligand-sensing or intracellular signaling domains (Figure 4A), solo or multi-domain secreted and lipid-anchored architectures (Figure 4B) and fusions to C-terminal peptidase or other hydrolase domains (Figure 4C).

In the first category (Figure 4A), the intracellular domains to which the extrinsic DUF is linked include protein kinase domains and three distinct versions of zinc ribbons, which could potentially bind nucleic acids. These architectures are comparable to other signaling proteins where extracellular ligand domains are linked to intracellular signaling domains. This category also includes fusions of the DUF with the sodium pump associated oxaloacetate decarboxylase y chain (OAD gamma). In the third category (Figure 4C) we observed independent fusions to metallopeptidase (M23), DUF2324 (a transmembrane domain which is a member of the Peptidase U clan), a beta-lactamase and an α/β hydrolase domain (Abhydrolase). In all of these cases the DUF is present at the Nterminus and the hydrolase domain at the C-terminus. NTF2-like domains have been observed with α/β hydrolases before: both SnoaL-like domain [Pfam:PF12680] and DUF4440 [Pfam:PF14534] co-occur with α/β hydrolase domains.

Genomic context

We studied the genomic context of proteins containing DUF3828, DUF3827 and DUF4878. In doing this we hoped to glean information about the possible function of these domains. As a result we uncovered a conserved association with DUF3828, which in diverse gammaproteobacteria, betaprotebacteria and bacteroidetes is combined in an operon with a gene coding for a protein of the NlpC/P60 superfamily with a papain-like peptidase

fold (e.g. gi: 489959630 from *Enterobacter cloacae*) [17]. These domains are known to function as peptidases/amidases in that cleave amide/peptide linkages in the bacterial cell wall. Several of these proteins additionally contain further C-terminal domains such as EF-hands, metallopeptidase family M23 and glycohydrolases of the lysozyme [Pfam:PF00959] or the Chitinase Class I [Pfam: PF00182] families. Thus, domains point to catalytic activities that process both the peptide and glycosidic linkages in peptidoglycan.

Structure description

The crystal structure of a DUF3828 protein, BT_3511 protein [UniProtKB:Q8A1Z7] from *Bacteroides thetaio-taomicron* (strain VPI-5482), was determined to 2.1 Å resolution by MAD method and deposited to PDB as [PDB:3KZT]. The final model includes two molecules (residues 26–167), five 1,2-ethanediol, two sulfate ions and 118 water molecules in the asymmetric unit. The structure is mainly composed of three helices, one 3_{10} helix and 4 beta strands. Gly0 (that remained at the

N-terminus after cleavage of the expression/purification tag), the region from Lys26 to Pro34 was disordered and not modeled. All the side chains were fully modeled because of the complete electron density. The Matthews coefficient (V_M) is 2.05 Å³ Da⁻¹ and the estimated solvent content is 39.97%. The Ramachandran plot produced by MolProbity [18] shows that 96.9% of the residues are in favored regions, with no outliers.

The crystal structure of a DUF4878 protein, Cj0202c protein [UniProtKB:Q0PBT7] from *Campylobacter jejuni* subsp. jejuni serotype O:2 (strain NCTC 11168), was determined to 2.0 Å resolution by MAD method and was deposited to PDB as [PDB:3K7C]. The final model includes four molecules (residues 1–113), one chloride ion, thirteen di hydroxyethyl ether (PEG), six triethylene glycol and 134 water molecules in the asymmetric unit. The structure is mainly composed of three helices and four beta strands. Gly0 (which remained at the N-terminus after cleavage of the expression/purification tag), the region from Met1 to Ser5 was disordered and not modeled. All the side chains were fully modeled

Q8A1Z7.1/50-167	α1 <u>000000000000000</u>	20000	α2 200000000 000	α3 2.2020	. l llll
Q8A127.1/50-167 B5BCH0.1/22-143 B6ZUD2.1/40-155 Q0TDA0.1/24-145	EAIGMIEDFYEAYAASF DSTQAVKQFYTSWMTTF GPDSVAQQFYDYHIQHRS. TVEQTVRQIYQNYKSDAST	TN	OTTALMQRYVAKEV NDITALRPYLSDKL FGETGERAITSARI	I.HRLALIQS A.TLLSDASRDN Q.QALTLNDNLT	LYEQEIVG SHRELLS LPGNIGWLD
B5ZT84.1/27-141 B2SWU7.1/32-151 G9YCH0.1/55-177 C9Y2Y8.1/61-177 IOK6B0.1/55-189 B8HJZ2.1/26-146 F9MV53.1/48-167	TPKALLKALYSYNTDNSD. TPEASTKAFYTWFI.KRD EPDKFSLDFYKNYMITQDM SPEETVKQFYFAYL.TAW QKAANQIDFTDDNGPHLTL GPAATVEGFYQWYVSNQDR OIVAYLOEITSSOMPPAGE	SEDRGYALMI QSAGKPMPN GDPDIKI NQEKLERYLARFAAS LR	DKEVYRYVSRST NDFV.AENYLSHYL RSLADSEKAVSEYT SNFV.SREFIANEV DKLSQQKDLFEPVL	V.DFLRAEY A.NRMKYY T.QHLRN AFYRQCSQWWQH Y.QQLIQAFQKQ	KQNKFAER WQDENGPG LMQDNDTG EPIDDVPSCLD PQDGQRWLD
Q8A1Z7.1/50-167	η1 TT 22	ջ — ^{β1} →ττ-	β2 30	TT β3 90* *100	\rightarrow TT $\frac{\beta 4}{110}$
Q8A127.1/50-167 B5BCH0.1/22-143 B6ZUD2.1/40-155 Q0TDA0.1/24-145 B5ZT84.1/27-141 B2SWU7.1/32-151 G9YCH0.1/55-177 C9Y2Y8.1/61-177 IOK6B0.1/55-189 B8HJZ2.1/26-146 F9MV53.1/48-167	ADPIIRAQDLGENDMK ADYFMYAQDY.APEW.IP SDPFSSRTTLPDSAH.VA YDPVCDCQDF.GDLV.LE FDPVIAQDG.TAS AEYFTKVQDYDEQDW.LA YDYYIRAQDY.PSEW.VS ADYFTSAQEA.CRDW.AY ADRYFCAQEW.EPDFWLKS FDPFSDTQVRTY DDFFKEDLDKVQVE	TISVKHLNDNV QLRVGKAHPFLGC SASTIPNRDARN SVAITQPDADHAI DVRIGQ.PILLDDI HIATHPAVMLDDV HINVSRLFSDFFPDI NIFTNNLELKKN PVRIRPNGI SSKVRSVKLKED	WYEVNYTSAKG GEKVDVLL NIPLRVDL AVVRFRI.F KAEVEVQF VALVPVTF.G LSHSIITL.G PDRVTATL.VG. KAIIDIDV.YAG.	SQYERAVSIP ATESTPIHLEV KQGDQGWQDEV KDDKEKTTQTL .ENGQEVTLFY S.AEKKTIIA .D.GCNKQRFLV .Y.NRSKSVYQI .QAYGSPMERTV .QAYGSPMERTV	RVVNVDGQYLI YTRWEEGRWKI LMIQEGQCWVI KMVAENGRWVI TLVRQHGGWKV FLRKQNGVWKI NLTQEDKSWKI HLIKKQGRWLM ELKKEEGKWLI LLQRQNDKWQI
Q8A127.1/50-167 Q8A127.1/50-167 B5BCH0.1/22-143 B6ZUD2.1/40-155 Q0TDA0.1/24-145 B5ZT84.1/27-141 B2SWU7.1/32-151 G9YCH0.1/55-177 C9Y2Y8.1/61-177 T0K6B0.1/55-189 B8HJ22.1/26-146 F9MV53.1/48-167	DDIT.PEN YRVRDADR DDVRYLGG DDIVSNHG DDIANQKG TKIDDTQD LSIQLLDA DSVKLYSR ANIECDMG TNFVYRQN MDIRD.K				
5 1	ignment of DUF3828. Conserved Inment was displayed using ESPrip	5 5	l in open red boxes. Th	e secondary structure	is shown above

	α1	α2 222.2 20	α3			α4
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A0R8Q0.1/36-160	TEQTEEMKVYREV	HEKYDMKI	NKEINK <mark>A</mark> L	QLWEVAKEKGGKEI	TNATYKEDV	QKVTTNMLEDI
A0RFH7.1/37-125	AEEIVSLLNEAKY	KEV.HEKF	DSKMTA <mark>A</mark> L	S	EEKM	.KDLTPIIEKA
A4AWI0.1/19-104	ASKFQSKYNASNY					
A51K81.1/23-112	AFLFVQHLTSENF	ESA.LNMC	SNQVKAQL	S	VQSL	SNIWNSLKAQL
A7AYH7.1/40-142	SEAIVŜSFSQTP	DEV.FDQY	EEMSELQL <mark>D</mark> L	MLLNTGLPVD	SENFLSM	IEAWKAGEAEC
A7VCT0.1/40-133	ATEYFNQMMDGDF	ETF.FNAL	PPGVQD <mark>N</mark> I	S	AETI	QETWEEEVDKL
A9KL18.1/74-163	SAKLTHDLLTENF					
A9VKZ2.1/96-188	TLSFIRHMNSEDY	KSA.FDLT	SRSLQKII	S		KSYWEGLPVQL
B1I2Q6.1/43-137	AENILQAFNDDDY	DRF.FKDF	SQTEKRAA	PP	EPEF	LETNEQIKNRI
B5CV17.1/28-117	AOOILOWMKNAOS	DSI.YACF	DAKMOOAV	Ρ	LSOL	NNMWSOMEOOL
C8WGP2.1/123-216	AOKVAEVVGEGDY	DKL.RPML	DDAAAEAL	Т	EPVM	NDAHALFGDDW
D5NWE6.1/118-208	AESFLDALTAHQW					
D6E742.1/53-143	ARDAIDLFVARDY					
E0I2S6.1/137-226	VDTYINGFFSGKF					
E4LU36.1/46-137	ALQFVKDLTQRKY					
E6TOB6.1/58-147	AEEYISHLSQGDF	ETA YDFF	NEVMKAET	E	VSEL	GDIWETLESOV
F4XDN8.1/40-134	GRSVMELLNQGDW					
F6D290.1/13-102	AQNFVDQFLQADF					
F7JPH9.1/45-140	AECVVGWFNEQEY					
G2MPX0.1/64-153	TQDFLEALIAESF	DFA VDVA	SPEEDCOL	D		VOOWFANTTRI
H0KRP6.1/25-114	ASDFVDNLFTKKY	TEC VELE		т	ETVL	FMUNCOISCME
H1PIO7.1/41-134	SKNFVHNLNRGDF					
H1F1Q/.1/41-134 H3K6P6.1/35-127	AETFISGITTEKVPY					
Q8EMU8.1/26-113	SEELIDNLIAGNF					
Q0EM00.1/20-113	SEELIDNLIAGNF	EDV.RDSI	. FSPQLQELI	±		QASWREMIVNE
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A7B2S7.1/55-147 A0R8Q0.1/36-160 A0RFH7.1/37-125	GEFKEFGKCTYLG DHIRKEIRVPKSK GTFEKIEKOSIEE	QIK EQEHELYV KDG	DNKKY GFLNEAEQAI L	GGVIIVVKY.EEGN KKLQKLAKE.EDSS YTVILVAKY.SKEO	· VNYSLAY LIRDIEINF RTFIITY	STASTYYKR NDKEEIAGL
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A7B2S7.1/55-147 A0R8Q0.1/36-160 A0RFH7.1/37-125 A4AW10.1/19-104 A5IK81.1/23-112	GEFKEFGKCTYLG DHIRKEIRVPKSK .GTFEKIEKQSIEE GTIKTMEFYDVNN SDFREIAGYEKII	QIK EQEHELYV KDG SAY QAE	DNKKY GFLNEAEQAI L	GGVIIVVKY.EEGN KKLQKLAKE.EDSS YTVILVAKY.SKEQ VYRTSF.EKAI EIYNFTLKF.DRGE	VNYSLAY LIRDIEINF RTFIITY VDISFSL ISALVTM	STAST <mark>Y</mark> YKR NDKEEIAGL NKKNQIIAL DREGK <mark>V</mark> AGL
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A7B2S7.1/55-147 A0R8Q0.1/36-160 A0RFH7.1/37-125 A4AWI0.1/19-104 A5IK81.1/23-112 A7AYH7.1/40-142 A7VCT0.1/40-133 A9KL18.1/74-163 A9VKZ2.1/96-188 B1I2Q6.1/43-137	GEFKEFGKCTYLG DHIRKEIRVPKSK GTFEKIEKQSIEE GTIKTMEFYDVNN .SDFREIAGYEKII GAFKSYGEFETEM GGLPENTSPDVSC GELVDAISIKA.T QAGYFIEIGEVTQKE GDYVSKEYWQNEA	QIK EQEHELYV KDG QAE TSS YVP TTG TTG KDG	DNKKY GFLNEAEQAI 	GGVIIVVKY.EEGN KKLQKLAKE.EDSS YTVILVAKY.SKEQ VYRTSF.EKAI EIYNFTLKF.DRGE IVVSTEAEY.ENKT IRVEFVIPC.DKGN ISVDSLVEY.TENG TNVEIQLVF.EQMT VTVFYRAKFTGEDD	VNYSLAY LIRDIEINF RTFIITY VDISFSL ADIEFTF FKVFINY LKISYVY VPLLIKL VLVRAIFREV	STASTYYKR NDKEEIAGL NKKNQIIAL DEEGKVAGL DEEQQMDSL FPDGSLYNY NKDCKLVKL DPSGKIDDF DGEMKVAGF
A7B2S7.1/55-147 A0R8Q0.1/36-160 A0RFH7.1/37-125 A4AWI0.1/19-104 A5IK81.1/23-112 A7AYH7.1/40-142 A7VCT0.1/40-133 A9KL18.1/74-163 A9VKZ2.1/96-188 B1I2Q6.1/43-137 B5CV17.1/28-117	. GEFKEFGKCTYLG . DHIRKEIRVPKSK . GTFEKIEKQSIEE . GTIKTMEFYDVNN . SDFREIAGYEKII . GAFKSYGEFETEM . GGLPENTSPDVSC . GELVDAISIKA.T QAGYFIEIGEVTQKE . GDYVSKEYWQNEA . GTLVEEKEWKQ.D	QIK EQEHELYV KDG QAE TSS YVP TTG TNP KDG AIG	DNKKY GFLNEAEQAI 	GGVIIVVKY.EEGN KKLQKLAKE.EDSS YTVILVAKY.SKEQ VYRTSF.EKAI EIYNFTLKF.DRGE IVVSTEAEY.ENKT IRVEFVIPC.DKGN ISVDSLVEY.TENG TNVEIQLVF.EQMT VTVFYRAKFTGEDD IVYYSDLKF.ERAP	VNYSLAY LIRDIEINF RTFIITY VDISFSL ISALVTM ADIEFTF FKVFINY LKISYVY VP.LLIKL VP.LLIKL VLVRAIFREV IRFMVAF	STASTYYKR NDKEEIAGL NKKNQIIAL DREGKVAGL DEEQQMDSL FPDGSLYNY NKDCKLVKL DPSGKIDDF DGEMKVAGF NQERKVNGL
A7B2S7.1/55-147 A0R8Q0.1/36-160 A0RFH7.1/37-125 A4AWI0.1/19-104 A5IK81.1/23-112 A7AYH7.1/40-142 A7VCT0.1/40-133 A9KL18.1/74-163 A9VKZ2.1/96-188 B112Q6.1/43-137 B5CV17.1/28-117 C8WGP2.1/123-216	GEFKEFGKCTYLG . DHIRKEIRVPKSK GTFEKIEKQSIEE GTIKTMEFYDVNN SDFREIAGYEKII GAFKSYGEFETEM GLVDAISIKA.T QAGYFIEIGEVTQKE GDYVSKEYWQNEA GTLVEEKEWKQ.D	QIK EQEHELYV KDG SAY QAE TSS TYS TTG TNP KDG AIG	DNKKY GFLNEAEQAI L Y 	GGVIIVVKY.EEGN KKLQKLAKE.EDSS YTVILVAKY.SKEQ VYRTSF.EKAI EIYNFTLKF.DRGE IVVSTEAEY.ENKT ISVDSLVEY.TENG TNVEIQLVF.EQMT VTVFYRAKFTGEDD IVYYSDLKF.ERAP NAVNLVAIY.ENTT	VNYSLAY LIRDIEINF RTFIITY IS.ALVTM ADIEFTF FKVFINY VPLIKL VPLLIKL VLVRAIFREV IRFMVAF VTFDIGF	STASTYYKR NDKEEIAGL NKKNQIIAL DREGKVAGL DEEQQMDSL FPDGSLYNY NKDCKLVKL DPSGKIDDF DGEMKVAGF NQERKVNGL NEDLKIIGL
A7B2S7.1/55-147 AOR8Q0.1/36-160 AORFH7.1/37-125 A4AWI0.1/19-104 A5IK81.1/23-112 A7AYH7.1/40-142 A7VCT0.1/40-133 A9KL22.1/96-188 B112Q6.1/43-137 B5CV17.1/28-117 C8WG92.1/123-216 D5NWE6.1/118-208	GEFKEFGKCTYLG . DHIRKEIRVPKSK GTFEKIEKQSIEE GTIKTMEFYDVNN .SDFREIAGYEKII GAFKSYGEFETEM GGLPENTSPDVSC GELVDAISIKA.T QAGYFIEIGEVTQKE GDYVSKEYWQNEA GTLVEEKEWKQ.D GALKSFGNTYATG GELEARLKSDAIG	QIK EQEHELYV KDG SAY QAE TSS TTG TTG KDG AIG AIG VSQ. LPD	DNKKY GFLNEAEQAI 	GGVIIVVKY.EEGN KKLQKLAKE.EDSS YTVILVAKY.SKEQ VYRTSF.EKAI EIYNFTLKF.DRGE IVVSTEAEY.ENKGN ISVDSLVEY.TENG TNVEIQLVF.EQMT VTVFYRAKFTGEDD IVYYSDLKF.ERAP NAVNLVAIY.ENTT IVVEQHLAF.EAAD	VNYSLAY LIRDIEINF RTFIITY VD.ISFSL AD.IEFTF FK.VFINY LK.ISYVY VP.LLIKL VL.VRAIFREV IR.FMVAF VT.FDIGF LV.ARLSY	STASTYYKR NDKEEIAGL NKKNQIIAL DREGKVAGL DEEQQMDSL FPDGSLYNY NKDCKLVKL DPSGKIDDF DGEMKVAGF NQERKVNGL NEDLKIIGL NADGTMAGL
A7B2S7.1/55-147 AOR8Q0.1/36-160 AORFH7.1/37-125 A4AW10.1/19-104 A5IK81.1/23-112 A7AYH7.1/40-142 A7VCT0.1/40-133 A9KL18.1/74-163 A9KK22.1/96-188 B1I2Q6.1/43-137 B5CV17.1/28-117 C8WGP2.1/123-216 D5NWE6.1/118-208 D6E742.1/53-143	. GEFKEFGKCTYLG . DHIRKEIRVPKSK . GTFEKIEKQSIEE . GTIKTMEFYDVNN . SDFREIAGYEKII . GAFKSYGEFETEM . GELVDAISIKA.T QAGYFIEIGEVTQKE . GDYVSKEYWQNEA . GTLVEEKEWKQ.D . GALKSFGNTYATG . GELEARLKSDAIG . GGFESYGDVSFAH	QIK EQEHELYV KDG SAY QAE TSS YVP TTG TTG TNP KDG AIG VSQ LPD	DNKKY GFLNEAEQAI Y Y Y Y 	GGVIIVVKY.EEGN KKLQKLAKE.EDSS YTVILVAKY.SKEQ VYRTSF.EKAI EIYNFTLKF.DRGE IVVSTEAEY.ENKT IRVEFVIPC.DKGN ISVDSLVEY.TENG TNVEIQLVF.EQMT VTVFYRAKFTGEDD IVYYSDLKF.ERAP NAVNLVAIY.ENTT IVVEQHLAF.EAAD AIVVOOAHC.ENDD	VNYSLAY LIRDIEINF RTFIITY VDISFSL ALVTM ADIEFTF FKVFINY LKISYVY VPLLIKL VLVRAIFREV IRFMVAF VTFDIGF LVARLSY	STASTYYKR NDKEEIAGL NKKNQIIAL DEEGKVAGL DEEQQMDSL FPDGSLYNY NKDCKLVKL DPSGKIDDF DGEMKVAGF NQERKVNGL NEDLKIIGL NADGTMAGL AEDGRLVGF
$\begin{array}{c} {\tt A7B2S7.1/55-147}\\ {\tt A0R8Q0.1/36-160}\\ {\tt A0RFH7.1/37-125}\\ {\tt A4AWI0.1/19-104}\\ {\tt A5IK81.1/23-112}\\ {\tt A7AYH7.1/40-142}\\ {\tt A7VCT0.1/40-133}\\ {\tt A9KL18.1/74-163}\\ {\tt A9VKZ2.1/96-188}\\ {\tt B1I2Q6.1/43-137}\\ {\tt B5CV17.1/28-117}\\ {\tt C8WGP2.1/123-216}\\ {\tt D5RW46.1/118-208}\\ {\tt D6R742.1/53-143}\\ {\tt E0I2S6.1/137-226} \end{array}$. GEFKEFGKCTYLG DHIRKEIRVPKSK GTFEKIEKQSIEE GTIKTMEFYDVNN SDFREIAGYEKII GAFKSYGEFETEM GELVDAISIKA.T QAGYFIEIGEVTQKE GDYVSKEYWQNEA GTLVEEKEWKQ.D GALKSFGNTYATG GELEARLKSDAIG GEFEEVLNLES.S	QIK EQEHELYV KDG SAY TSS TTSS TTG TTG TTG TTG VSQ VSQ VSQ VSQ VSQ KDG	DNKKY GFLNEAEQAI L Y 	GGVIIVVKY.EEGN KKLQKLAKE.EDSS YTVILVAKY.SKEQ VYRTSF.EKAI EIYNFTLKF.DRGE IVVSTEAEY.ENKT ISVDSLVEY.TENG TNVEIQLVF.EQMT VTVFYRAKFTGEDD IVYYSDLKF.ERAP NAVNLVAIY.ENTT IVVEQHLAF.EAAD AIVVQQAHC.ENDD ISFVLACRF.ANGI	VNYSLAY LIRDIEINF RTFIITY IS.ALVTM ADIEFTF FK.VFINY VP.LLIKL VL.VRAIFREV IR.FMVAF VTFDIGF LV.ARLSY LV.YSVGI	STASTYYKR NDKEEIAGL NKKNQIIAL DREGKVAGL DEEQQMDSL FPDGSLYNY NKDCKLVKL DPSGKIDDF DGEMKVAGF NQERKVNGL NEDLKIIGL NADGTMAGL AEDGRLVGF DKDEKVAGF
A7B2S7.1/55-147 A0R8Q0.1/36-160 A0RFH7.1/37-125 A4AWI0.1/19-104 A5IK81.1/23-112 A7AYH7.1/40-142 A7VCT0.1/40-133 A9KL18.1/74-163 A9VKZ2.1/96-188 B1I2Q6.1/43-137 B5CV17.1/28-117 C8WGP2.1/123-216 D5NWE6.1/118-208 D6E742.1/53-143 E01226.1/137-226 E4LU36.1/46-137		QIK EQEHELYV KDG SAY TTSS TTSS TTG TTG TTG TTG VSQ LPD YDG KSD SYQ	DNKKY GFLNEAEQAI L Y 	GGVIIVVKY.EEGN KKLQKLAKE.EDSS YTVILVAKY.SKEQ VYRTSF.EKAI EIYNFTLKF.DRGE IVVSTEAEY.ENKT ISVDSLVEY.TENG TNVEIQLVF.EQMT VTVFYRAKFTGEDD VVYSDLKF.ERAP NAVNLVAIY.ENTT IVVEQHLAF.EAAD AIVVQQAHC.ENDD ISFVLACRF.ANGI TIIMIPCRM.EEQN	VNYSLAY LIRDIEINF RTFIITY IS.ALVTM ADIEFTF FK.VFINY VPLIKL VPLLIKL VL.VRAIFREV IR.FMVAF LV.ARLSY LV.YSVGI FD.ITVTL. TN.IQVSL	STASTYYKR NDKEEIAGL NKKNQIIAL DREGKVAGL DEEQQMDSL FPDGSLYNY NKDCKLVKL DPSGKIDDF DGEMKVAGF NQERKVNGL NEDLKIIGL NADGTMAGL AEDGRLVGF DKDEKVAGF NEQDQIQGL
A7B2S7.1/55-147 AOR8Q0.1/36-160 AORFH7.1/37-125 A4AWI0.1/19-104 A5IK81.1/23-112 A7AYH7.1/40-142 A7VCT0.1/40-133 A9KL22.1/96-188 B1T2Q6.1/43-137 B5CV17.1/28-117 C8WGP2.1/123-216 D5NWE6.1/118-208 D6E742.1/53-143 E0T2S6.1/45-137 E6TQB6.1/58-147		QIK EQEHELYV KDG SAY QAE TSS YVP TTG TTG KDG AIG VSQ VSQ YDG SYQ	DNKKY GFLNEAEQAI Y GT GT GT GT GT GT GT GT GT 	GGVIIVVKY.EEGN KKLQKLAKE.EDSS YTVILVAKY.SKEQ VYRTSF.EKAI EIYNFTLKF.DRGE IVVSTEAEY.ENKT IRVEFVIPC.DKGN ISVDSLVEY.TENG TNVEIQLVF.EQMT VTVFYRAKFTGEDD IVYYSDLKF.ERAP NAVNLVAIY.ENT IVVEQHLAF.EAAD AIVVQQAHC.ENDD ISFVLACRF.ANGI TIIMIPCRF.EQN	VNYSLAY LIRDIEINF RTFIITY VD.ISFSL AD.IEFTF FK.VFINY VP.LLIKL VP.LLIKL VL.VRAIFREV IR.FMVAF VT.FDIGF LV.ARLSY LV.YSVGI FD.ITVTL VV.FTVTI	STASTYYKR NDKEEIAGL NKKNQIIAL DREGKVAGL DEEQQMDSL FPDGSLYNY NKDCKLVKL DPSGKIDDF DGEMKVAGF NQERKVNGL NEDLKIIGL NADGTMAGL AEDGRLVGF DKDEKVAGF NEQDQIQGL DTNYEIAGF
$\begin{array}{c} {\tt A7B2S7.1/55-147}\\ {\tt A7B2S7.1/55-147}\\ {\tt A0R8Q0.1/36-160}\\ {\tt A0RFH7.1/37-125}\\ {\tt A4AWI0.1/19-104}\\ {\tt A5IK81.1/23-112}\\ {\tt A7AYH7.1/40-133}\\ {\tt A9YKI2.1/30-133}\\ {\tt A9YKI2.1/96-188}\\ {\tt B1I2Q6.1/43-137}\\ {\tt B5CV17.1/28-117}\\ {\tt C8WGP2.1/123-216}\\ {\tt D5ET42.1/53-143}\\ {\tt E0I2S6.1/137-226}\\ {\tt E4LU36.1/46-137}\\ {\tt E6TQB6.1/58-147}\\ {\tt F4XDN8.1/40-134}\\ \end{array}$. GEFKEFGKCTYLG . DHIRKEIRVPKSK . GTFEKIEKQSIEE . GTIKTMEFYDVNN . SDFREIAGYEKII . GAFKSYGEFETEM . GCLPENTSPDVSC . GELVDAISIKA.T QAGYFIEIGEVTQKE . GDYVSKEYWQNEA . GTLVEEKEWKQ.D . GALKSFGNTYATG . GELEARLKSDAIG . GGFESYGDVSFAH . GEFEEVLNLES.S . GSLIEAEQPYG.Q . GTYIDQDFNSTQE . GTFEKEEDSMATG	QIK EQEHELYV KDG SAY QAE TSS YVP TTG TTP KDG VSQ LPD KSD KSD KSD VSQ VQ VEN QKL	DNKKY GFLNEAEQAI Y Y GT EHSDQ EHSDQ EHSDQ GT GT GT GT GADGVA GADGVA GM GM S S 	GGVIIVVKY.EEGN KKLQKLAKE.EDSS YTVILVAKY.SKEQ VYRTSF.EKAI EIYNFTLKF.DRGE IVVSTEAEY.ENKT IRVEFVIPC.DKGN ISVDSLVEY.TENG TNVEIQLVF.EQMT VTVFYRAKFTGEDD IVYYSDLKF.ERAP NAVNLVAIY.ENTT IVVEQHLAF.EAAD AIVVQQAHC.ENDD ISFVLACRF.ANGI TIIMIPCRM.EEQN KVVLINGLF.DGAD	VNYSLAY LIRDIEINF RTFIITY VDISFSL ADIEFTF FKVFINY LKISYVY VFLIKL VLVRAIFREV IRFMVAF VTFDIGF LVARLSY LVYSVGI FDITVTL TNIQVSL VVFTVTI	STASTYYKR NDKEEIAGL NKKNQIIAL DEEGKVAGL DEEQQMDSL FPDGSLYNY NKDCKLVKL DPSGKIDDF DGEMKVAGF NQERKVNGL NEDLKIIGL NADGTMAGL AEDGRLVGF DKDEKVAGF NEQDQIQGL DTNYEIAGF DTDMVLMGL
A7B2S7.1/55-147 A0R8Q0.1/36-160 A0RFH7.1/37-125 A4AWI0.1/19-104 A5IK81.1/33-112 A7AYH7.1/40-142 A7VCT0.1/40-133 A9KL18.1/74-163 A9VKZ2.1/96-188 B1I2Q6.1/43-137 B5CV17.1/28-117 C8WGP2.1/123-216 D5NWE6.1/118-208 D6E742.1/53-143 E012S6.1/137-226 E4LU36.1/46-137 E5CQB6.1/58-147 F4XDN8.1/40-134 F6D290.1/13-102	. GEFKEFGKCTYLG . DHIRKEIRVPKSK . GTFEKIEKQSIEE . GTIKTMEFYDVNN . SDFREIAGYEKII . GAFKSYGEFETEM . GELVDAISIKA.T QAGYFIEIGEVTQKE . GDYVSKEYWQNEA . GTIVEEKEWKQ.D . GALKSFGNTYATG . GELEARLKSDAIG . GEFESYGDVSFAH . GEFEEVLNLES.S . GSLIEAEQPYG.Q . GTYIDQDFNSTQE . GTFEKEEDSMATG . GNLLRLTVVRT.A	QIK EQEHELYV KDG SAY QAE TTSS TTG TTG TTG TTG YVP KDG KDG VSQ VSQ YDG SYQ SYQ VEN EME	DNKKY GFLNEAEQAI L Y G EHSDQ EHSDQ EHSDQ EHSDQ GT GT GT GADGVA GADGVA GADGVA SY Y Y SGEEY	GGVIIVVKY.EEGN KKLQKLAKE.EDSS YTVILVAKY.SKEQ VYRTSF.EKAI EIYNFTLKF.DRGE IVVSTEAEY.ENKT IRVEFVIPC.DKGN ISVDSLVEY.TENG TNVEIQLVF.EQMT VTVFYRAKFTGEDD IVYYSDLKF.ERAP NAVNLVAIY.ENTT IVVEQHLAF.EAAD AIVVQQAHC.ENDD ISFVLACRF.ANGI TIIMIPCRM.EEQN KVVLINGLF.DGAD ATAVFYCKH.SEKD	VNYSLAY LIRDIEINF RTFIITY IS.ALVTM ADIEFTF FK.VFINY VP.LLIKL VP.LLIKL VL.VRAIFREV IR.FMVAF VTFDIGF LV.ARLSY LV.YSVGI TN.IQVSL VV.FTVTI VV.YRIAF VV.YRIAF	STASTYYKR NDKEEIAGL NKKNQIIAL DREGKVAGL DEEQQMDSL FPDGSLYNY NKDCKLVKL DPSGKIDDF DGEMKVAGF NQERKVNGL NEDLKIIGL NADGTMAGL AEDGRLVGF NKQCKGF NEQQQIQGL DTNYEIAGF DTDMVLMGL NIQGQISGL
$\begin{array}{c} {\tt A7B2S7.1/55-147}\\ {\tt A0R8Q0.1/36-160}\\ {\tt A0RFH7.1/37-125}\\ {\tt A4AWI0.1/19-104}\\ {\tt A5IK81.1/23-112}\\ {\tt A7AYH7.1/40-142}\\ {\tt A7VCT0.1/40-133}\\ {\tt A9KL18.1/74-163}\\ {\tt A9VKZ2.1/96-188}\\ {\tt B1I2Q6.1/43-137}\\ {\tt B5CV17.1/28-117}\\ {\tt C8WGP2.1/123-216}\\ {\tt D5NWE6.1/118-208}\\ {\tt D6E742.1/53-143}\\ {\tt E012S6.1/43-1226}\\ {\tt E4LU36.1/46-137}\\ {\tt E6TQB6.1/58-147}\\ {\tt F6D290.1/13-102}\\ {\tt F7JPH9.1/45-140}\\ \end{array}$. GEFKEFGKCTYLG . DHIRKEIRVPKSK . GTFEKIEKQSIEE . GTIKTMEFYDVNN . SDFREIAGYEKII . GAFKSYGEFETEM . GGLPENTSPDVSC . GELVDAISIKA.T QAGYFIEIGEVTQKE . GDYVSKEYWQNEA . GTLVEEKEWKQ.D . GALKSFGNTYATG . GELEARLKSDAIG . GEFESYGDVSFAH . GEFEVLNLES.S . GSLIEAEQPYG.Q . GTYIDQDFNSTQE . GTFEKEEDSMATG . GALLTVVRT.A	QIK EQEHELYV KDG SAY QAE TSS YVP TTG KDG AIG VSQ YDG YDG YDG SYQ VEN SYQ EME EKN	DNKKY GFLNEAEQAI Y GT GT GT GT GT GADGVA GADGVA GT GADGVA GT SY Y SY SY SY	GGVIIVVKY.EEGN KKLQKLAKE.EDSS YTVILVAKY.SKEQ VYRTSF.EKAI EIYNFTLKF.DRGE IVVSTEAEY.ENKT IRVEFVIPC.DKGN ISVDSLVEY.TENG TNVEIQLVF.EQMT VTVFYRAKFTGEDD IVYYSDLKF.ERAP NAVNLVALY.ENT IVVEQHLAF.EAAD AIVVQQAHC.ENDD ISFVLACRF.ANGI TIIMIPCRM.EEQN KVVLINGLF.DGAD ATAVFYCKH.SEKD RVVFIRCQF.ERAA GGLVLVQGAY.ENGK	VNYSLAY LIRDIEINF RTFIITY IS.ALVTM AD.IEFTF FK.VFINY VP.LLIKL VL.VRAIFREV IR.FNVAF LV.ARLSY LV.ARLSY VT.FDIGF LV.ARLSY VT.FDIGF VV.FTVTI VV.FTVTI VV.FTVTI VV.FTVTI VV.FTVTI VV.FRIAF LD.VQIIF	STASTYYKR NDKEEIAGL NKKNQIIAL DREGKVAGL DEEQQMDSL FPDGSLYNY NKDCKLVKL DPSGKIDDF DGEMKVAGF NQERKVNGL NEDLKIIGL NADGTMAGL AEDGRLVGF DKDEKVAGF DKDEKVAGF DKDEKVAGF DTDYVLMGL DTNYEIAGF DTDMVLMGL NIQGQISGL DEEMDVIOF
A7B2S7.1/55-147 AOR8Q0.1/36-160 AORFH7.1/37-125 A4AWI0.1/19-104 A5IK81.1/23-112 A7AYH7.1/40-142 A7VCT0.1/40-133 A9KL18.1/74-163 A9VKZ2.1/96-188 B112Q6.1/43-137 B5CV17.1/28-117 C8WGP2.1/123-216 D5NWE6.1/118-208 D6E742.1/53-143 E012S6.1/137-226 E4LU36.1/46-137 E6TQB6.1/58-147 F4XDN8.1/40-134 F6D290.1/13-102 F77PH9.1/45-140 G2MPX0.1/64-153	. GEFKEFGKCTYLG . DHIRKEIRVPKSK . GTFEKIEKQSIEE . GTFEKIEKQSIEE . GTFEKIEKQSIEE . GFEKEIAGYEKII . GAFKSYGEFETEM . GGLPENTSPDVSC . GELVDAISIKA.T QAGYFIEIGEVTQKE . GDYVSKEYWQNEA . GTLVEEKEWKQ.D . GALKSFGNTYATG . GELEARLKSDAIG . GEFEEVLNLES.S . GSLIEAEQPYG.Q . GTYIDQDFNSTQE . GTFEKEEDSMATG . GNLLRLTVVRT.A . GAFRKIEKTAVIS . GEFNOFTSIDYQG	QIK EQEHELYV KDG SAY QAE YVP TTG TTG TTP XDG VSQ LPD KSD KSD KSD KSD VEN QKL QKL EME EKN	DNKKY GFLNEAEQAI Y Y GT GT GT GT GADGVA GT GADGVA SY Y SY SY SY GEY	GGVIIVVKY.EEGN KKLQKLAKE.EDSS YTVILVAKY.SKEQ VYRTSF.EKAI EIYNFTLKF.DRGE IVVSTEAEY.ENKT IRVEFVIPC.DKGN ISVDSLVEY.TENG TNVEIQLVF.EQMT VTVFYRAKFTGEDD IVYYSDLKF.ERAP NAVNLVAIY.ENTT IVVEQHLAF.EAAD AIVVQQAHC.ENDD ISFVLACRF.ANGI TIIMIPCRM.EEQN KVVLINGLF.DGAD ATAVFYCKH.SEKD RVVFIRCQF.ERAA GGLVLVGACAF.ADGR	VNYSLAY LIRDIEINF RTFIITY IS.ALVTM ADIEFTF FK.VFINY LK.ISYVY VP.LLIKL VI.VRAIFREV IR.FMVAF VT.FDIGF LV.ARLSY LV.YSVGI FD.ITVTL TN.IQVSL VV.YRIAF LD.VQIIF IE.FRILF AE.FSVOF	STASTYYKR NDKEEIAGL NKKNQIIAL DREGKVAGL DEEQQMDSL FPDGSLYNY NKDCKLVKL DPSGKIDDF DGEMKVAGF NQERKVNGL NEDLKIIGL NADGTMAGL AEDGRLVGF DKDEKVAGF NEQDQIQGL DTNYEIAGF DTDMVLMGL NIQGQISGL DEEMDVIQF DEOI.IEGF
$\begin{array}{c} {\tt A7B2S7.1/55-147}\\ {\tt A0R8Q0.1/36-160}\\ {\tt A0RFH7.1/37-125}\\ {\tt A4AWI0.1/19-104}\\ {\tt A55K81.1/23-112}\\ {\tt A7VCT0.1/40-142}\\ {\tt A7VCT0.1/40-133}\\ {\tt A9KL18.1/74-163}\\ {\tt A9VKZ2.1/96-188}\\ {\tt B112Q6.1/43-137}\\ {\tt B5CV17.1/28-117}\\ {\tt C8WGP2.1/123-216}\\ {\tt D5E742.1/53-143}\\ {\tt E012S6.1/137-226}\\ {\tt E4LU36.1/46-137}\\ {\tt E6TQB6.1/58-147}\\ {\tt F4ZDN8.1/40-134}\\ {\tt F6D290.1/13-102}\\ {\tt F7JPH9.1/45-140}\\ {\tt G2MPX0.1/64-153}\\ {\tt H0KRP6.1/25-114}\\ \end{array}$. GEFKEFGKCTYLG . DHIRKEIRVPKSK . GTFEKIEKQSIEE . GTFEKIEKQSIEE . GTFEKIEKQSIEE . GFEKEIAGYEKII . GAFKSYGEFETEM . GGLPENTSPDVSC . GELVDAISIKA.T QAGYFIEIGEVTQKE . GDYVSKEYWQNEA . GTLVEEKEWKQ.D . GALKSFGNTYATG . GELEARLKSDAIG . GEFEEVLNLES.S . GSLIEAEQPYG.Q . GTYIDQDFNSTQE . GTFEKEEDSMATG . GNLLRLTVVRT.A . GAFRKIEKTAVIS . GEFNOFTSIDYQG	QIK EQEHELYV KDG SAY QAE YVP TTG TTG TTP XDG VSQ LPD KSD KSD KSD KSD VEN QKL QKL EME EKN	DNKKY GFLNEAEQAI Y Y GT GT GT GT GADGVA GT GADGVA SY Y SY SY SY GEY	GGVIIVVKY.EEGN KKLQKLAKE.EDSS YTVILVAKY.SKEQ VYRTSF.EKAI EIYNFTLKF.DRGE IVVSTEAEY.ENKT IRVEFVIPC.DKGN ISVDSLVEY.TENG TNVEIQLVF.EQMT VTVFYRAKFTGEDD IVYYSDLKF.ERAP NAVNLVAIY.ENTT IVVEQHLAF.EAAD AIVVQQAHC.ENDD ISFVLACRF.ANGI TIIMIPCRM.EEQN KVVLINGLF.DGAD ATAVFYCKH.SEKD RVVFIRCQF.ERAA GGLVLVGACAF.ADGR	VNYSLAY LIRDIEINF RTFIITY IS.ALVTM ADIEFTF FK.VFINY LK.ISYVY VP.LLIKL VI.VRAIFREV IR.FMVAF VT.FDIGF LV.ARLSY LV.YSVGI FD.ITVTL TN.IQVSL VV.YRIAF LD.VQIIF IE.FRILF AE.FSVOF	STASTYYKR NDKEEIAGL NKKNQIIAL DREGKVAGL DEEQQMDSL FPDGSLYNY NKDCKLVKL DPSGKIDDF DGEMKVAGF NQERKVNGL NEDLKIIGL NADGTMAGL AEDGRLVGF DKDEKVAGF NEQDQIQGL DTNYEIAGF DTDMVLMGL NIQGQISGL DEEMDVIQF DEOI.IEGF
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$\begin{array}{c} {\tt A7B2S7.1/55-147}\\ {\tt A0R8Q0.1/36-160}\\ {\tt A0RFH7.1/37-125}\\ {\tt A4AWI0.1/19-104}\\ {\tt A5IK81.1/23-112}\\ {\tt A7AYH7.1/40-142}\\ {\tt A7AYH7.1/40-143}\\ {\tt A9VKZ2.1/96-188}\\ {\tt B1I2Q6.1/43-137}\\ {\tt B5CV17.1/28-117}\\ {\tt C8WGP2.1/123-216}\\ {\tt D5NWE6.1/118-208}\\ {\tt D6E742.1/53-143}\\ {\tt E0I2S6.1/43-137}\\ {\tt E6TQB6.1/58-147}\\ {\tt F4LD36.1/46-137}\\ {\tt E6TQB6.1/58-147}\\ {\tt F4LD36.1/46-134}\\ {\tt F6D290.1/13-102}\\ {\tt F77PH9.1/45-140}\\ {\tt G2MPX0.1/64-153}\\ {\tt H0RRF6.1/25-114}\\ {\tt H1PLQ7.1/41-134}\\ {\tt H366F6.1/35-127}\\ \end{array}$. GEFKEFGKCTYLG . DHIRKEIRVPKSK . GTFEKIEKQSIEE . GTIKTMEFYDVNN . SDFREIAGYEKII . GAFKSYGEFETEM . GGLPENTSPDVSC . GELVDAISIKA.T QAGYFIEIGEVTQKE . GDYVSKEYWQNEA . GTLVEKEWKQ.D . GALKSFGNTYATG . GEFEARLKSDAIG . GGFESYGDVSFAH . GEFEEVLNLES.S . GSLIEAEQPYG.Q . GTFEKEEDSMATG . GLIRLEVVRT.A . GAFRKIEKTAVIS . GEFNQFTSIDYQG . GDYKKVISTEKTV	QIK EQEHELYV KDG SAY QAE TTSS TTSS TTG TTG TTG TTG C VSQ C SYQ C SYQ C SYQ C SYQ C EEQ C EEQ C EER C	DNKKY GFLNEAEQAI L Y G EHSDQ EHSDQ EHSDQ EHSDQ VH VH UI GADGVA GM SY Y SY SY SY SY SY SY SY SY SY SY SY 	GGVIIVVKY.EEGN KKLQKLAKE.EDSS YTVILVAKY.SKEQ VYRTSF.EKAI EIYNFTLKF.DRGE IVVSTEAEY.ENKT IRVEFVIPC.DKGN ISVDSLVEY.TENG TNVEIQLVF.EQMT VTVFYRAKFTGEDD IVYYSDLKF.ERAP NAVNLVAIY.ENTT IVVEQHLAF.EADD AIVVQQAHC.ENDD ISFVLACRF.ANGI TIIMIPCRM.EEQN KVVLINGLF.DGAD ATAVFYCKH.SEKD RVVFIRCQF.ERAA GGLVLVGAY.ENGK PMILVYTEF.SKQN YVCNLKCDY.ENGS	VNYSLAY LIRDIEINF RTFIITY IS.ALVTM AD.IEFTF FK.VFINY VP.LLIKL VP.LLIKL VL.FDIGF LV.ARLSY LV.YSVGI FD.ITVTL TN.IQVSL VV.FTVTI VV.FTVTI VV.FTVTI VV.FTVTI VV.FTVTI VV.FTVTI VV.FTVTI VV.FTVTI VV.FTVTI VV.FTVTI IE.FRILF AE.FSVQF AI.FTIIL	STASTYYKR NDKEEIAGL NKKNQIIAL DREGKVAGL DEEQQMDSL FPDGSLYNY NKDCKLVKL DPSGKIDDF DGEMKVAGF NQERKVNGL NADGTMAGL NADGTMAGL DKDEKVAGF DKDEKVAGF DKDEKVAGF DTDMVLMGL DTNYEIAGF DTDMVLMGL DTNYEIAGF DTDMVLMGL DEEMDVIQF DEQI.IEGF SKNNKVLGI DEKMNIVNL
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because of the complete electron density. The Matthews coefficient (V_{M} ;) is 2.3 Å³ Da⁻¹ and the estimated solvent content is 46.46%. The Ramachandran plot produced by MolProbity shows that 97.4% of the residues are in favoured regions, with no outliers.

The crystal structure of a DUF3887 protein, the hypothetical protein Rumgna_01855 [UniProtKB:A7B2S7] from *Ruminococcus gnavus* (strain ATCC 29149), was determined to 2.25 Å resolution by MAD method and was deposited to PDB as [PDB:4HYZ]. The final model includes two molecules (residues 36–149), six chloride ions, six sulfate ions, eight glycerol and 107 water molecules in the asymmetric unit. The structure is mainly composed of four helices, four turns, and five beta strands. Only Gly0 (that remained at the N-terminus after cleavage of the expression/purification tag) was disordered and not modeled. All the side chains were fully modeled because of the complete electron density. The Matthews coefficient (V_M) is 3.00 Å³ Da⁻¹ and the estimated solvent content is 58.98%. The Ramachandran plot produced by MolProbity shows that 99.6% of the residues are in favored regions, with no outliers.

Comparison of these three structures showed that they are significantly similar to each other, especially for [PDB:3K7C] and [PDB:4HYZ]. FATCAT results showed that the structures of [PDB:3KZT] and [PDB:4HYZ] are

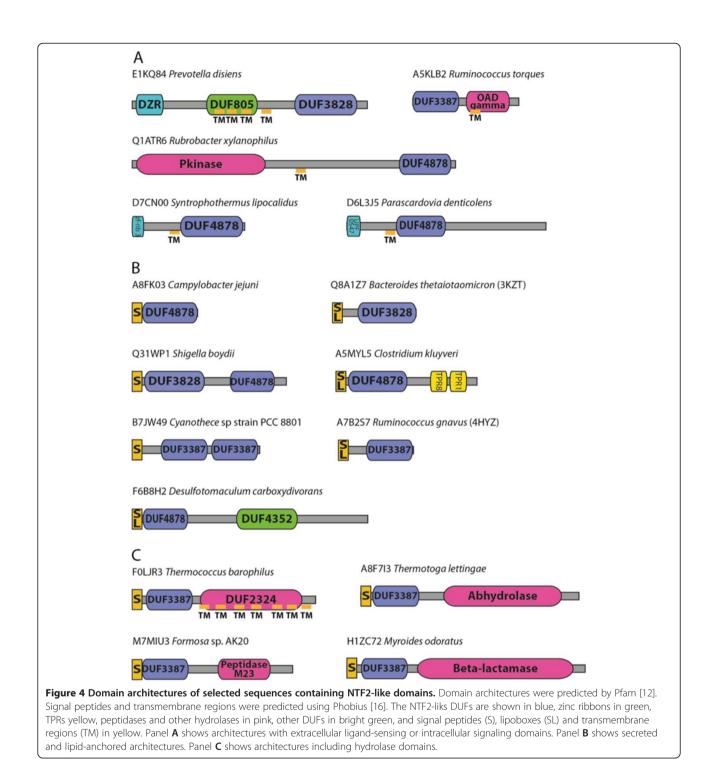
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B7X013.1/26-141	SAC. ATATPEQSQ		AGDFDACIALV	SARN <mark>I</mark> SREQI	LASFEYKL	RRMLAGAKAMI
C2Q545.1/14-115	AAC.GNNRDPEEV.				KIVAFV	
066537.1/19-135	KSCGEPYSGA <mark>K</mark> ET.	VGEFMEEIA	EGEGRDAIKYL	Y P A Y <mark>R</mark> D E L A I	KNFKLPVQFT	EMKPSEVLACV
B1MHS8.1/118-217	PAGGAATA <mark>E</mark> A <mark>A</mark> .				SK	
C7PUV8.1/19-120	GSC.KKSATP <mark>Q</mark> EV.				QLYSFF	
D5USA8.1/49-154	PDSGQI <mark>S</mark> QT.					
B9L7K8.1/17-130	TGC.SKKDSP <mark>E</mark> TA.					
C3XI53.1/20-84	VACSSSDP <mark>K</mark> D <mark>V</mark> .	<mark>A</mark> IS <mark>F</mark> YKA <mark>M</mark> A	NGDEKGAVKLI	HIED <mark>E</mark>		
B2TQV7.1/21-124	CGC.AEKQTP <mark>S</mark> N <mark>M</mark> .				KAEEEKTKFDESE	
D3Q127.1/126-231	VFSGGGP <mark>S</mark> S <mark>A</mark> .				ELEKASGMSE	
B4U8X6.1/35-135	PQT.INNNNPETV.					
B5D1Y3.1/17-129	AACSSNTP <mark>T</mark> N <mark>T</mark> .	VEKAFDAMI	KGDYETYVRSF	YVED <mark>K</mark> SEPEI	KVENDIQDLV	KMIQRNAENHP
Q0PBT7/1-111	$ \begin{array}{c} \beta 1 \\ \hline 70 \\ \star \end{array} $	► <u></u> 80	β2 9 0 TT -	β3		
0000000 /1 111	•	•	•	•		
Q0PBT7/1-111	KRMGGVKDIQIEEK					
D1PEL1.1/17-132	KGMVKVIVLSAKAD'		FLQVVYGDSTK	EQIVVPMVE	. VKDAWKMR	
B7X013.1/26-141 C2Q545.1/14-115	DSKGGLAKVEVVER' KDLKSYKIRKFEEK	LS.EDQQVVKL	RVLVTYGDGNT	. K K E K I N L L D	. EQGVWKVQ	
066537.1/19-135	LSTMGRNIDEVEIK					
B1MHS8.1/118-217	IAOWPVGNIRILNS					
C7PUV8.1/19-120	IKKAGIEVIDTEEN					
D5USA8.1/49-154	LDENGIKNVOVN					
B9L7K8.1/17-130	SNLKSVEVKNVKOI					
C3XI53.1/20-84						
B2TOV7.1/21-124	YKINSENID					
D30127.1/126-231	EKEGLTADYEIVEE'					
B4U8X6.1/35-135	LNTYNVKSITIKDI					
B5D1Y3.1/17-129	EENIKSYEILKE	ESS.KTGKW <mark>V</mark> R <mark>V</mark>	GIKLIIYQNGKE	TTSDFYLTKI	DEDGS <mark>M</mark> KIQ	
	EENIKSYEILKE gnment of DUF4878. Co					is shown above
Figure 3 Sequence ali		nserved residues are				is shown above

significantly similar with P-value of 1.53e-⁰³ and the structure alignment has 85 equivalent positions with an RMSD of 1.72 Å; the structures of [PDB:3KZT] and [PDB:3K7C] are significantly similar with P-value of 2.57e-⁰³ and the structure alignment has 95 equivalent positions with an RMSD of 2.53 Å; the structures of [PDB:4HYZ] and [PDB:3K7C] are significantly similar with P-value of 1.55e-⁰⁶ and the structure alignment has 95 equivalent positions with an RMSD of 2.99 Å [19]. In all cases, FATCAT program detected flexibility in the structure, mostly limited to the relative position of helices with respect to the central beta sheet. There is low sequence similarity between the three structures, and no positions are conserved in all three structures.

The three structures ([PDB:3K7C], [PDB:3KZT] and [PDB:4HYZ]) all possess NTF2-like folds, despite being dissimilar in sequence (Figures 6 and 7, Table 1). A hydrophobic cavity with the potential for ligand-binding has been described in NTF2-like proteins before [20]. We used the MarkUs functional annotation server to locate potential cavities within the three structures [21]. All three structures contain predicted cavities, but the position of these cavities is not conserved between the structures. The structure of [PDB:3K7C] differs from that of [PDB:3KZT] and [PDB:4HYZ] in that it lacks the edge strands in the beta-sheet but has a longer helix on the opposite side. It has a shallow cavity with positive

electrostatic potential that contains a bound PEG molecule in the crystal structure. Notably, in dimers seen in the crystal structure of [PDB:3K7C] the cavities of individual subunits combine in a contiguous groove that can accommodate a larger ligand than a conventional NTFlike fold can. [PDB:4HYZ] has a cavity of a similar size in a similar position with weakly positive electrostatic potential. Sequence conservation in the region of the cavities in [PDB:3K7C] and in [PDB:4HYZ] is poor. In contrast, the cavity found in [PDB:3KZT] has a negative electrostatic potential, this cavity includes two highly conserved aspartic acid residues (D-103 and D-110) which may be of significance.

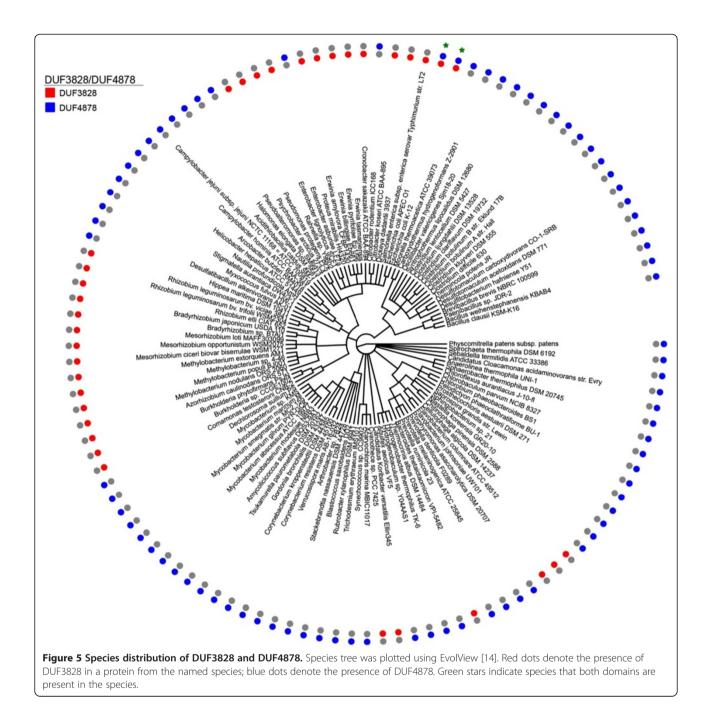
DALI [24] searches revealed that [PDB:3KZC] and [PDB:4HYZ] are more similar to each other than they are to most other members of the NTF2-like superfamily (Z-score 9.8), however [PDB:3KZT] is more distantly related. [PDB:3KZT] is most similar to [PDB:2UX0] (Z-score 8.8) which contains a Calcium/calmodulin dependent protein kinase II association domain [Pfam: PF08332], also a member of the NTF2-like superfamily. This domain functions as an oligomerisation domain [25]. It is also significantly similar to [PDB:2BHM] (Z-score 8.5), a member of the VirB8 family [Pfam: PF04335], a component of the type IV secretion system [10]. It is significantly less similar to [PDB:3K7C] (maximum Z-score of 6.4 when compared to chain A), and



[PDB:4HYZ] (maximum Z-score of 6.8 when compared to chain B). [PDB:4HYZ] and [PDB:3K7C] are most similar to members of the SnoAL_3 family [Pfam: PF13474] including [PDB:3GWR] (Z-score 10.1 when compared to [PDB:3K7C]), and the SnoAL_2 family [Pfam:PF12860] including [PDB:3D9R] (Z-score 9.5 when compared to [PDB:3K7C]).

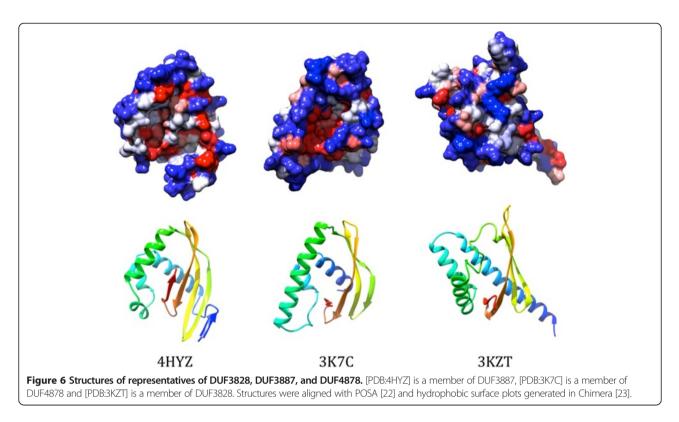
Potential function

NTF2-like domains include both catalytic and noncatalytic versions that tend to bind small molecules using a common substrate-binding pocket. Our analysis of these DUFs did not reveal conserved polar residues suggestive of catalytic activity in DUF3887 or DUF4878. DUF3828 contains a conserved aspartic acid, which

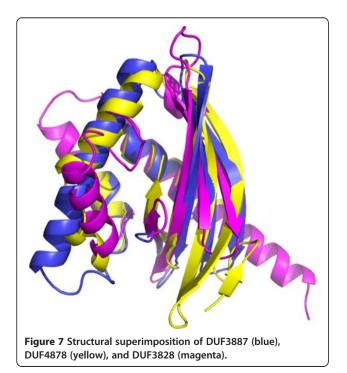


could point to a catalytic function. NTF2-like domains which are enzymatic tend to occur in an intracellular context, however prediction of subcellular localization using Phobius [16] revealed the consistent presence of either N-terminal secretory signals or lipoboxes with a conserved cysteine which helps anchor the protein to the membrane. Those proteins that lack either of these features have transmembrane regions with predicted membrane topologies suggestive of an extracellular location for the DUF (Figure 4). Together these observations suggested that these three DUFs are novel NTF2like domains that are likely to be extracellular domains that recognize a small molecule ligand via their binding pocket.

Further evidence for such a function is offered by the domain architectures of these proteins (Figure 4). Where the DUF is found at the N-terminus of OAD γ chain domain the sensing of a ligand could help allosterically



regulate sodium flux [26]. Where the DUF is found at the N-terminus of a protein containing a C-terminal peptidase or other hydrolase domain, it is conceivable that the sensing of a ligand by the N-terminal DUF regulates the catalytic domain. Similar domain architecture associations were also observed for DUF4352,



which occurs fused to DUF4878 in certain contexts: DUF4352 is also linked to metallopeptidase (M56), protein kinase and TPR repeats and is also associated with lipid attachment signal or signal peptides or transmembrane regions. Hence it is possible that the two domains perform comparable functions and cooperate in recognition of extracellular ligands on occasions. The versions combined in operons with the NlpC/P60 like peptidases/amidases might potentially regulate the export and/or the activity of these peptidoglycan hydrolyzing proteins that could have a potentially suicidal effect on the cell. Thus, they could play a role in regulating peptidoglycan remodeling.

Conclusions

Here we present a comparison of first crystal structures of three DUFs belonging to the NTF2-like superfamily. This work expands our structural knowledge of the

Table 1 Percentage identity of the three proteins forwhich structure has been determined, calculated usingDALI [24]

3KZT	3K7C	4HYZ
	11%	14%
11%		10%
14%	10%	
	11%	11%

sequence diverse NTF2 superfamily. Analysis of the three-dimensional structure, sequence and associated domains can provide clues about the likely function of a protein domain. We present a detailed analysis of these three domains, which suggests that they may play a role in binding to small molecule ligands.

Methods

Sequence and gene context analysis

Data for families DUF3828 and DUF4878 are taken from Pfam release 27.0 [12]. The definition of DUF3887 has been improved during the course of this work and the updated version will form a part of Pfam release 28.0. Signal peptides and transmembrane domains were predicted using Phobius [16]. A phylogenetic tree was constructed from proteomes in representative proteomes RP75 [15] using the NCBI taxonomy common tree [27]. This was annotated and displayed using EvolView [14].

With the DUF genes as anchors, the gene neighbourhood was also comprehensively analyzed using a custom Perl script. This script uses either the PTT file (downloadable from the NCBI ftp site) or the Genbank file in the case of whole genome shot gun sequences to extract the neighbors of a given query gene. The protein sequences of all neighbors were clustered using the BLASTCLUST program (ftp://ftp.ncbi.nih.gov/blast/documents/blastclust.html) to identify related sequences in gene neighbourhoods. Each cluster of homologous proteins were then assigned an annotation based on the domain architecture or conserved shared domain which were detected using Pfam models and in-house profiles run using RPS-BLAST [28]. This allowed an initial annotation of gene neighbourhoods and their grouping based on conservation of neighborhood associations. In further analysis care was taken to ensure that genes are unidirectional on the same strand of DNA and shared a putative common promoter to be counted as a single operon. If they were head to head on opposite strands they were examined for potential bidirection promoter sharing patterns.

Structure determination

Protein purification and crystallization was performed by the JCSG crystallomics core [29-31]. All X-ray diffraction data were collected at the Stanford Synchrotron Radiation Lightsource (SSRL) on beamline 11–1. Data sets were collected at 100 K using a Rayonix MX-325 CCD detector. X-ray diffraction data were collected from a single crystal at wavelengths corresponding to the inflection (λ_1), high energy remote (λ_2), and peak (λ_3) [PDB:3K7C]; the peak(λ_1), inflection (λ_2), and high energy remote (λ_3) [PDB: 4HYZ]; or the inflection (λ_1) and high energy remote (λ_2) [PDB:3KZT], of a multi-wavelength or a two-wavelength selenium multiwavelength anomalous diffraction (MAD). The data were integrated and scaled using the XDS and XSCALE programs respectively [32,33] [PDB:3K7C] or the MOSFLM [34] and SCALA [35] programs [PDB:3KZT][PDB:4HYZ]. Data statistics are summarized in Additional file 1: Tables S1-S3. The selenium substructures for the three proteins were solved with SHELXD [36] and the MAD phases were refined with autoSHARP [37]. Iterative automated model building was performed with RESOLVE [38] at a resolution of 2.00 Å [PDB:3K7C] or Arp/Warp [39] at a resolution of 2.15 Å [PDB:3KZT] or with Buccaneer [40,41] at a resolution of 2.25 Å [PDB:4HYZ] from densitymodified electron density. Model completion was performed using the interactive computer-graphics program COOT [42] and MAD-phase-restrained refinement was accomplished using the program REFMAC ver 5.5.0102 [PDB:3K7C], ver 5.5.0053 [PDB:3KZT] [43] or BUSTER ver 2.10.0 [44] [PDB:4HYZ].

Structure validation and deposition

The quality of the crystal structure was analyzed using the JCSG Quality Control Server [45]. This server verifies: the stereochemical quality of the model using AutoDepInputTool, MolProbity and WHATIF 5.0 [18,46,47]; agreement between the atomic model and the data using SFcheck 4.0 and RESOLVE [38,48]; the protein sequence using CLUSTALW [49]; atom occupancies using MOLEMAN2.0 [50]; and consistency of NCS pairs. It also evaluates differences in Rcryst/ Rfree, expected Rfree/Rcryst, and maximum/minimum B-values by parsing the refinement log-file and PDB header. Protein quaternary structure analysis used the EBI PISA server [51]. Atomic coordinates and experimental structure factors have been deposited in the PDB and are accessible under the codes [PDB:3KZT], [PDB:3K7C] and [PDB:4HYZ]. Electrostatic potential and cavity prediction was performed using the MarkUs functional annotation server [21].

Availabilty of supporting data

The data sets supporting the results of this article are included within the article (and its Additional file 1: Tables S1-S3).

Additional file

Additional file 1: Table S1. Data collection and refinement statistics (PDB 3kzt). Table S2. Data collection and refinement statistics (PDB 3k7c). Table S3. Data collection and refinement statistics (PDB 4hyz).

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

RYE wrote the majority of the manuscript and produced Figures 1, 2, 3, 4 and 5. YC wrote a section of the manuscript and produced Figure 7. AB contributed to the study ideas and organization of the manuscript. AGM contributed to structure descriptions. HLA wrote structure determination and validation methods. WCH provided Figure 6. LA provided potential function discussion. All authors read and approved the final manuscript.

Acknowledgements

We are grateful to the Sanford Burnham Medical Research Institute for hosting the DUF annotation jamboree in June 2013, which allowed the authors to collaborate on this work. We would like to thank all the participants of this workshop for their intellectual contributions to this work, who, in addition to the authors, were Penny Coggill, Debanu Das, Robert D. Finn, Adam Godzik, Lucasz Jaroszewski, Padmaja Natarajan, Marco Punta, Neil Rawlings, Daniel Rigden, Mayya Sedova, Anna Sheydina and John Wooley. We thank the members of the JCSG high-throughput structural biology pipeline for their contribution to this work.

Funding

Wellcome Trust (grant numbers WT077044/Z/05/Z); Howard Hughes Medical Institute; Work by LA is supported by the intramural funds of the National Library of Medicine, USA.; NIH (R01GM101457); Work by AGM was supported by the UK Medical Research Council [MC_U105192716]; This work was supported in part by National Institutes of Health Grant U54 GM094586 from the NIGMS Protein Structure Initiative to the Joint Center for Structural Genomics. The DUF annotation jamboree was supported by National Science Foundation (IIS-0646708 and IIS-1153617); Portions of this research were carried out at the Stanford Synchrotron Radiation Lightsource, a Directorate of SLAC National Accelerator Laboratory and an Office of Science User Facility operated for the U.S. Department of Energy Office of Science by Stanford University. The SSRL Structural Molecular Biology Program is supported by the DOE Office of Biological and Environmental Research, and by the National Institutes of Health, National Institute of General Medical Sciences (including P41GM103393) . The contents of this publication are solely the responsibility of the authors and do not necessarily represent the official views of NIGMS, NCRR or NIH.

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Received: 11 July 2013 Accepted: 15 November 2013 Published: 19 November 2013

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doi:10.1186/1471-2105-14-327

Cite this article as: Eberhardt *et al.*: **Filling out the structural map of the NTF2-like superfamily.** *BMC Bioinformatics* 2013 14:327.

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