Research

Open Access

Comprehensive comparative-genomic analysis of Type 2 toxin-antitoxin systems and related mobile stress response systems in prokaryotes

Kira S Makarova, Yuri I Wolf and Eugene V Koonin*

Address: National Center for Biotechnology Information, NLM, National Institutes of Health, Bethesda, Maryland 20894, USA

Email: Kira S Makarova - makarova@ncbi.nlm.nih.gov; Yuri I Wolf - wolf@ncbi.nlm.nih.gov; Eugene V Koonin* - koonin@ncbi.nlm.nih.gov * Corresponding author

Received: 26 May 2009 Accepted: 3 June 2009

Published: 3 June 2009

Biology Direct 2009, 4:19 doi:10.1186/1745-6150-4-19

This article is available from: http://www.biology-direct.com/content/4/1/19

© 2009 Makarova et al; licensee BioMed Central Ltd.

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<u>http://creativecommons.org/licenses/by/2.0</u>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Abstract

Background: The prokaryotic toxin-antitoxin systems (TAS, also referred to as TA loci) are widespread, mobile two-gene modules that can be viewed as selfish genetic elements because they evolved mechanisms to become addictive for replicons and cells in which they reside, but also possess "normal" cellular functions in various forms of stress response and management of prokaryotic population. Several distinct TAS of type I, where the toxin is a protein and the antitoxin is an antisense RNA, and numerous, unrelated TAS of type 2, in which both the toxin and the antitoxin are proteins, have been experimentally characterized, and it is suspected that many more remain to be identified.

Results: We report a comprehensive comparative-genomic analysis of Type 2 toxin-antitoxin systems in prokaryotes. Using sensitive methods for distant sequence similarity search, genome context analysis and a new approach for the identification of mobile two-component systems, we identified numerous, previously unnoticed protein families that are homologous to toxins and antitoxins of known type 2 TAS. In addition, we predict 12 new families of toxins and 13 families of antitoxins, and also, predict a TAS or TAS-like activity for several gene modules that were not previously suspected to function in that capacity. In particular, we present indications that the two-gene module that encodes a minimal nucleotidyl transferase and the accompanying HEPN protein, and is extremely abundant in many archaea and bacteria, especially, thermophiles might comprise a novel TAS. We present a survey of previously known and newly predicted TAS in 750 complete genomes of archaea and bacteria, quantitatively demonstrate the exceptional mobility of the TAS, and explore the network of toxin-antitoxin pairings that combines plasticity with selectivity.

Conclusion: The defining properties of the TAS, namely, the typically small size of the toxin and antitoxin genes, fast evolution, and extensive horizontal mobility, make the task of comprehensive identification of these systems particularly challenging. However, these same properties can be exploited to develop context-based computational approaches which, combined with exhaustive analysis of subtle sequence similarities were employed in this work to substantially expand the current collection of TAS by predicting both previously unnoticed, derived versions of known toxins and antitoxins, and putative novel TAS-like systems. In a broader context, the TAS belong to the resistome domain of the prokaryotic mobilome which includes partially selfish, addictive gene cassettes involved in various aspects of stress response and organized under the same general principles as the TAS. The "selfish altruism", or "responsible selfishness", of TAS-like systems appears to be a defining feature of the resistome and an important characteristic of the entire prokaryotic pan-genome given that in the prokaryotic world the mobilome and the "stable" chromosomes form a dynamic continuum.

Reviewers: This paper was reviewed by Kenn Gerdes (nominated by Arcady Mushegian), Daniel Haft, Arcady Mushegian, and Andrei Osterman. For full reviews, go to the Reviewers' Reports section.

Background

Bacterial toxin-antitoxin systems (TAS, also referred to as TA loci) originally have been characterized in the 1980s as molecular systems encoded in plasmids and ensuring the persistence of a plasmid in a host lineage during replication by making the cells "addicted" to the plasmid so that only plasmid-containing daughter bacteria survived after a cell division [1,2]. As implied by their name, the overwhelming majority of TAS consist of two components encoded in an operon [3]. The toxin component of all TAS is a protein that kills cells if expressed above a certain level, whereas the antitoxin component regulates the expression of the toxin and/or inactivates the toxin, thereby preventing cell killing. The mechanism of postsegregational killing of plasmid-less cells, which is also the mechanism of plasmid maintenance, is simple and elegant. The antitoxin is metabolically unstable unless in a complex with the toxin, whereas the toxin is considerably more stable. Therefore, unless the antitoxin is continuously replenished through gene expression, the free toxin accumulates in amounts sufficient to kill a cell, which is what occurs after cell division if a daughter cell does not receive the TAS-encoding plasmid [3-5]

The TAS are currently classified into two major types on the basis of the nature of the antitoxin [3,6]. Type I TAS encompass an antisense RNA antitoxin that is complementary to the toxin mRNA and prevents its translation; the toxin of type I TAS is, typically, a small hydrophobic protein with a holin-like mechanism of action that kills cells by impairing the membrane [6,7].

Type II TAS employ a protein antitoxin to keep the toxin inactivated via protein-protein interaction. These systems show considerable structural and functional diversity among both the toxins and the antitoxins. The most common activity of Type II toxins seems to be that of an mRNA-specific endonuclease, termed interferases [8,9]. In particular, the interferase activity was demonstrated for the widespread toxins of the RelE and MazF. In addition, there are at least two other mechanisms of action of Type II toxins. The well-explored CcdB and ParE toxins are inhibitors of DNA gyrase that abrogate cell reproduction by blocking DNA replication. The recently characterized HipA toxin is a protein kinase [10] that abrogates bacterial reproduction and renders bacterial cells dormant by inhibiting translation through phosphorylation of the elongation factor EF-Tu [11]. All type II antitoxins are dual-function, two-domain proteins that consist of a protein-protein interaction domain and a DNA-binding domain. When not complexed with other proteins, antitoxins have largely disordered structures and are highly susceptible to proteolysis, and hence unstable. Upon interaction with the respective toxins via their proteinprotein interaction domains, the antitoxins assume compact structures and are accordingly stabilized. The antitoxin binding inhibits the activity of the toxin, and the stable TA complex binds to the operator of the corresponding TAS operon via the DNA-binding domain of the antitoxin and (auto)represses its transcription. Thus, the antitoxin exerts control over the activity of the TAS at two levels, by directly inhibiting the toxin and by repressing the expression of both TAS components.

The TAS were originally discovered on plasmids and appeared to be devices employed by the plasmid replicons to "manipulate" the host bacteria to maintain the plasmids. However, when multiple bacterial and archaeal genomes were sequenced, it became obvious that many of them contained multiple, diverse TA loci [3-5,12,13]. Concomitantly, functions of TAS in bacterial physiology were discovered that seem to have nothing to do with plasmid maintenance, namely, a central role in stress response. The best characterized model is the involvement of the RelBE TAS in bacterial stringent response to amino acid starvation. During starvation, the RelE toxin is activated as a result of the proteolysis of the RelB antitoxin which also leads to the activation of transcription of the relBE operon. The end result is the extensive cleavage of ribosome-associated mRNA, a major shutdown of translation, and concomitant increase of the pool of charged tRNAs [14]. It is thought that this modulation of the state of the translation system results in the adjustment of nutrient consumption and to increased translation fidelity, two critical adaptations that apparently allow bacteria to survive starvation. In other words, the RelBE TAS seems to exert quality control of protein synthesis. Similar observations were reported for the MazEF TAS where MazF is a ribosome-independent mRNA interferase [15].

The study of MazEF led to a major reappraisal of the biological effects of TAS. Originally, it was proposed that the unleash of MazF under stress induced programmed cell death (PCD) in E. coli [16]. Although TAS-mediated PCD might indeed occur under a variety of stress conditions [17,18], the more common mechanism of TAS seems to be the induction of reversible bacteriostasis (dormancy or persistence) [19]. The induction of persistence is also the mechanism of action of the HipAB TAS that was recently reported to be mediated by translation inhibition via phosphorylation of EF-Tu [11]. On the other hand, a recent study on the developmentally complex bacterium Myxococcus xanthus showed that the solitary MazF toxin (mRNA interferase) triggered PCD which in this case is a regular developmental stage [20]. Thus, in addition to their well-characterized role in stress response, some of the TAS components can be prokaryotic development regulators. Generally, it appears that, depending on the specific conditions, TAS can affect the fates of prokaryotic cells in different manners. In particular, TAS-mediated

persistence and PCD are likely to be a common mechanism of resistance to various environmental assaults including diverse antibiotics and other drugs [21,22].

The results briefly summarized above suggest that TAS are essential components of prokaryotic cell biology rather than simply plasmid addiction modules. It might be premature to consider this concept firmly established, and the proposed cellular functions of TAS remain a matter of debate [23,24]. Indeed, deletion of all 5 TA loci in E. coli did not result in a significant decrease of the fitness of the bacteria [23]. Thus, the possibility is still considered that the TA operons are completely selfish and are maintained in the population owing to the segregational (recombinational) bias for addictive modules [5,24]. A potential compromise between a purely selfish life style of TAS and integral cellular functions could be a role of chromosomally encoded TAS in the protection of prokaryotic cells against post-segregational killing induced by plasmidencoded homologous TAS whereby the antitoxin encoded by a chromosomal gene sequesters a plasmid-encoded toxin. Experimental evidence of such protection was reported, and elimination of the chromosomal TAS in the presence of the respective plasmid did adversely affect the fitness of the host bacterium [25].

Despite the uncertainty about "normal" functions of TAS or, perhaps, fueled by the multiplicity of possibilities in this area, the increasing interest in TAS resulted in both experimental [3,4,6] and computational [13,26] identification and prediction of scores of new TA modules in most of the sequenced prokaryotic genomes, with the exception of small genomes of parasitic bacteria, especially, intracellular parasites. Comparative-genomic studies also demonstrated a remarkable horizontal mobility of TA operons [13,26]. Identification and annotation of genes for toxins and antitoxins are problematic due to the small size of most of these genes and likely atypical (because of frequent lateral transfers) GC content and codon usage. Recently, these problems prompted the development of specialized software for the identification of TA gene pairs [27,28]. These tools utilize the information on already characterized families of toxins and antitoxins and are helpful, primarily, for finding missing ORFs in two-gene TA operons.

The steadily increasing diversity of TAS paralleled by the exponential growth of number of sequenced genomes suggests that numerous new TAS await discovery in genomic sequences that are already present in current databases. Here we attempt to identify new TAS (and highly derived versions of the known ones) by using comparative-genomic approaches guided by the "guilt by association" principle [29-31] and specific properties of TAS. We also present a comprehensive survey of TAS in the

sequenced archaeal and bacterial genomes, in an attempt to reveal general trends in their distribution and evolution.

Results and discussion

Two complementary approaches for the prediction of new TAS

The TAS are prone to frequent horizontal gene transfer (HGT) and intragenomic recombination, so they are commonly described as mobile genetic elements [26,27,32]. Apparently, as a result of this mobility, TAS show a patchy distribution among prokaryotic genomes, with some genomes encoding tens of TAS and others encoding only a few or none. Keeping in mind this characteristic distribution of TAS across the prokaryotic world, we utilized phyletic patterns of COGs (Clusters of Orthologous Genes [33]) to develop a search strategy for pairs of genes that are significantly non-uniformly distributed among prokaryotic genomes and, in addition, form recurrent two-gene (predicted) operons (Figure 1).

For each COG from 110 bacterial and archaeal genomes (see Methods for details), the variability of the abundance of the member genes was estimated. To this end, the coefficient of variation (CV) was computed as the ratio of the standard deviation of the number of paralogs to the mean number of paralogs, excluding species that had no genes from the given COG. The representatives of 2000 COGs with the highest CV values (ranging from 2.98 to 0.47) were mapped to the genome DNA, and pairs of COGs that were adjacent at least three times in at least one genome were selected for further analysis. This filter yielded 315 pairs of COGs (Additional File 1) which were examined case by case using the STRING program [34] to exclude those that belonged to longer (three or more genes) conserved operons.

The 23 pairs of COGs that passed the final filter are listed in Table 1. As expected, the majority of the identified COGs were components of already characterized TAS. Notably, this group included the hicA-hicB gene pair that has been predicted to comprise a new TAS pair on the basis protein sequence and comparative-genomic analysis [32], a prediction that was supported by a recent experimental study [35] (see below). Several of these gene pairs were not so far associated with any known TAS, and deserve further attention as potential candidates for new TAS. Three of these candidate TAS consist of distinct subfamilies of minimal nucleotidyltransferases (MNT) and the accompanying subfamilies of the HEPN (Higher Eukaryotes and Prokaryotes Nucleotide-binding) proteins. Both these protein families have been described previously [36-38] but their biological functions remain elusive.



Two computational strategies for the identification of TAS.

In addition, we employed a more straightforward and widely used approach to detect potential new TAS components (Figure 1). It was observed previously that a particular toxin can combine in (predicted) TAS operons with different, often structurally unrelated antitoxins, and conversely, homologous antitoxins combine with different toxins [3,4,12]. Therefore, a detailed analysis of the gene neighbors of known or predicted TAS-related genes has the potential to uncover previously unnoticed TAS components (see Methods for details). To this end, we first used representatives of all known TA protein families and the new candidates identified with the first approach as queries for exhaustive PSI-BLAST [39] searches. To characterize the diversity of each family as completely as possible, the most divergent sequences detected in these searches were also used as queries for a second round of PSI-BLAST searches. Altogether, for 18 superfamilies of (predicted) toxins and antitoxins, approximately 30,470

hits were collected for further analysis. All these genes were mapped onto the respective chromosome or plasmid sequences, and co-directed neighbors separated by less than 100 base pairs. The protein sequences thus obtained were classified into families using the CDD database [40] and/or BLASTCLUST (see Methods for details), and all the clusters for which at least 20 instantiations were detected (78 distinct pairs) were examined case by case (Table 2).

As with the first approach, most of the pairs belonged to already known TAS, and several pairs were found to belong to larger operons and were, accordingly, discarded (Table 2). Also, we excluded three conserved gene pairs where a membrane protein was associated with a Xre family repressor (antitoxins in several known TAS) because no type II TAS with a membrane component were detected so far, whereas Xre family repressors are known to perform a variety of regulatory functions unrelated to TAS [41-44].

COG number	Toxin family	с۷	COG number	Antitoxin family	с۷
COG1848	PIN	1.1	COG8614	RHH	1.0
COG3832	Ahal family	1.2	COG0640	ArsR family HTH	0.8
COG1708	MNT	0.9	COG2250	HEPN	1.0
COG4679	RelE	0.8	COG5606	НТН	0.6
COG2026	RelE	0.7	COG7997	MJI 172-like	0.7
COG3668	RelE	0.9	COG2161	StbD/axe	0.5
COG1708	MNT	0.4	COG2445	HEPN	0.9
COG3657	RelE	0.7	COG3636	нтн	0.6
COG1848	PIN	0.4	COG2002	AbrB/MazE/PemI	0.9
COG3668	RelE	0.9	COG3609	RHH	0.4
COG1669	MNT	0.7	COG2361	HEPN	0.6
COG9434	MazF	0.6	COG5302	CcdA	0.7
COG1598	hicB	0.7	COG1724	hicA	0.6
COG3549	RelE	0.7	COG3093	нтн	0.6
COG2026	RelE	0.4	COG2161	StbD_axe	0.9
COG3668	RelE	0.7	COG9004	RHH	0.5
COG6187	RelE	0.6	COG2944	НТН	0.6
COG1487	PIN	0.7	COG4710	RHH	0.4
COG1487	PIN	0.6	COG4456	AbrB/MazE/PemI	0.4
COG3742	PIN	0.5	COG4423	RHH	0.4
COG1487	PIN	n/a	COG5450	RHH	0.5

Table I: Previously characterized and new candidate TAS detected with the the first approach

COG numbers below 5600 correspond to the COGs that are available on the NCBI site: <u>http://www.ncbi.nlm.nih.gov/COG/grace/uni.html</u> COGs that were predicted to include novel toxins and antitoxins in this work are shown by bold type.

CV – coefficient of variation.

The potential new TAS detected by these complementary approaches are listed in Table 3 and discussed below.

The HicAB system as a paradigm for the prediction of new TAS

The HicAB system was described in depth previously [32]. Briefly, the evidence in support of the hypothesis that HicAB is a novel TAS is the following: 1) The *hicA* and *hicB* genes form a predicted two-gene operon that is found in

many bacterial genomes; 2) both genes encode relatively small proteins; 3) the putative operon shows a strongly non-uniform distribution among the genomes and appears to be mobile, presumably, owing to frequent horizontal transfers and recombination; 4) the HicAB system is also present in many phages and plasmids; 5) one of the proteins, HicB, often contains a helix-turn-helix (HTH) DNA-binding domain of the Xre family or a ribbon-helixhelix (RHH) domains; these domains are often found in

Query family	Source	Adjacent gene family	Adjacent gene function; reasons if discarded.	Number of occurrences observed
AbrB/MazE	[3]	PIN	Nuclease	312
		MazF	RNA interferase	97
		Fic/Doc	AMPylation enzyme	48
		RelE	RNA interferase	27
ArsR	Table I	COG3832	Ahal domain	280
		COG0394*	Arsenate reductase arsC; Part of a larger conserved gene associations	98
		COG2217*	Cation transport ATPase; Part of a larger conserved gene associations	83
		COG0798*	Arsenite efflux pump ACR3; Part of a larger conserved gene associations	74
		COG2391*	YeeE/YedE family, DUF395; Part of a larger conserved gene associations	64
		COG1055*	Arsenical pump membrane protein; Part of a larger conserved gene associations	53
RHH	[3]	RelE	RNA interferase	376
		PIN	Nuclease	335
		GNAT	Acetyltransferase	139
		MazF	RNA interferase	62
		COG3505*	TraG/TraD/VirD4 family; Part of a larger conserved gene associations	58
		COG2929	DUF497	55
		ParA*	ParA, plasmid partitioning ATPase; Part of a larger conserved gene associations	54
		HicA	RNA interferase	26
		RHH	DNA-binding domain	23
		COG0716*	Flavodoxin; Part of a larger conserved gene associations	22
		COG4962*	Type II/IV secretion system protein; Part of a larger conserved gene associations	21
Fic_Doc	[3]	AbrB	DNA-binding domain	55
		xre	DNA-binding domain	22
		yhfG	Unknown	11
MazF	[3]	AbrB	DNA-binding domain	107

Table 2: Previously characterized and potential new TAS components detected with the second approach

		5		<u>.</u>
		RHH	DNA-binding domain	81
		MazF/ccd	RNA interferase	43
		XF1863	Unknown	29
RelE	[3]	xre	Transcriptional regulator	730
		RHH	DNA-binding domain	510
		PHD	DNA-binding domain	337
		COG2856	Zn peptidase (fused to HTH)	15
		COG1753	Predicted DNA-binding domain; RHH fold	10
PIN RNA nuclease	[3]	RHH	DNA-binding domain	366
		AbrB	DNA-binding domain	348
		PHD	DNA-binding domain	285
		COG2442	Protein of unknown function DUF433	97
		COG2886	Uncharacterized protein family (UPF0175)	46
		COG2856	Zn peptidase (fused to HTH)	42
		MazF/ccd	COG5302	41
		COGI2II*	4-diphosphocytidyl-2-methyl-D-erithritol synthase; Part of a larger conserved gene associations	39
		MerR	Transcriptional regulator	33
		COG1066*	Sms; Part of a large conserved gene associations	26
		COG1092*	SAM-dependent methyltransferase; Part of a larger conserved gene associations	26
		COG2880	Predicted DNA-binding protein; AbrB superfamily	24
		pfam00155*	Aminotransferase; Part of a larger conserved gene associations	24
		COG5257*	Translation initiation factor 2; Part of a larger conserved gene associations	20
		COG1753	Predicted DNA-binding domain; RHH fold	20
PHD	[3]	PIN	Nuclease	276
		SMa0917	PemK/MazFI	15
MNT	Table I	HEPN	Unknown	445
HEPN	Table I	MNT	Predicted nucleotidyltransferase	482

Table 2: Previously characterized and potential new TAS components detected with the second approach (Continued)

,,,				-FF(
Xre	[3]	RelE	RNA interferase	614
		HipA	EF-Tu kinase	244
		COG2856	Zincin protease	194
		xre	A variety of proteins containing xre-like HTH, many fused with various domain, not a distinct set	97
		PIN	Nuclease	67
		DUF397	Unknown	64
		COG0800*	2-keto-3-deoxy-6-phosphogluconate aldolase; Part of a larger conserved gene associations	46
		COG3842*	PotA is ABC-type transporter; Part of a larger conserved gene associations	40
		PA2784-like*	A membrane protein, likely an exporter	36
		YoaS-like*	A membrane protein, likely permease	32
		antirepressor	BRO family; KilA – letal to host cells	30
		GNAT	Acetyltransferase	30
		COG3063*	Tfp pilus assembly protein PilF; Part of a large conserved gene associations	27
		PA4076-like*	A membrane protein, likely an exporter	27
		COG4974*	Site-specific recombinase XerD; Apparent phage components with another function	25
		COG0483*	Archaeal fructose-1,6-bisphosphatase; Part of a larger conserved gene associations	21
xre COG5642 subfamily		COG5654	Predicted transcriptional regulator	118
НірА	[3]	xre	Transcriptional regulator	333
		COG3550	HipA C-terminal	51
COG2856	[60]	xre	Transcriptional regulator	145
		PIN	Nuclease	60
		RelE	RNA interferase	22
COG2880	[13]	PIN	Nuclease	25
COG3832	Table I	ArsR	Transcriptional regulator	259
COG4636	[13]	COG4636	Predicted endonuclease	114
COG4679 (RelE family)	[13]	COG5606	Predicted RNA interferase	43

Table 2: Previously characterized and potential new TAS components detected with the second approach (Continued)

New TAS discussed in this work are shown in bold type; other associations marked by asterisk in column 3 were disregarded for reasons indicated in column 4.

Table 3: Predicted new TAS

Toxin (T)	Antitoxin (AT)	Comment
MNT	HEPN	MNT – minimal nucleotidyltransferase, possible toxin; HEPN – possible substrate binding domain; Structure solved (MNT: Ino5 and HEPN: Io3u and Ijog). Molecular mechanism unknown.
PIN	COG2442	Structure of AT is solved (PDB:2ga1):DNA/RNA-binding 3-helical bundle.
PIN	COG2880	Structure of AT is solved (PDB: <u>2nwt</u>); related to AbrB superfamily
PIN	COG1753	AT – RHH (RHH); Specific for archaea
PIN	MerR	AT: truncated MerR
COG4679 subfamily	COG5606 HTH	AT – predicted HTH domain; T – predicted RelE superfamily protein
RelE	MJ1172 RHH	Specific for methanogens; AT – predicted RHH superfamily protein
MazF	XF1863	No prediction for AT
Fic/Doc	YhfG	AT – is predicted DNA-binding protein; Specific for enteroproteobacteria
SMa0917 subfamily	PHD	T – predicted MazF superfamily protein; Molecular mechanism is likely the same as for MazF toxin
COG2929	COG5304 and COG3514 Families	AT: predicted RHH family protein; Molecular mechanism unknown.
DUF397	Xre/cro HTH	T – no prediction; molecular mechanism unknown.
COG2856	Xre/cro HTH	T – predicted Zn-dependent protease. Often fused to AT domain. Frequent association with ReIE and PIN toxins
COG5654	COG5642 subfamily	AT – xre family HTH; T – RES domain; Molecular mechanism unknown.
YgiU/MqsR	Xre/cro HTH	T: motility quorum-sensing regulator mqsR [75]
GNAT	Xre/cro HTH	The closest characterized GNAT family acetyltrasferase is involved in antibiotic resistance [88]
GNAT	RHH	T – is GNAT family acetyltrasferase
Bro	Xre/cro HTH	
COG3832	ArsR-like HTH	T – Cyclase/dehydratase family protein. (PDB: <u>Ixuv</u>) START domain superfamily

New toxins and antitoxins predicted in this work are shown in bold type

experimentally characterized antitoxins; 6) HicB contains a derived RNAse H fold, and HicA contains a doublestranded RNA-binding domain (dsRBD) suggesting that, like with many other TAS, the HicAB system targets RNA. Recently, this prediction was validated by an experimental study which demonstrated that HicA indeed is a nuclease that functions as a translation-independent mRNA interferase, that is, most likely, is a bona fide toxin [35]. Given the successful experimental validation of the prediction, the principal features of the HicAB system listed above and the logic exploited in its analysis were chosen as the paradigm for the prediction and analysis of other TAS as detailed below. Those two-gene models that possessed all of these features could be predicted to function as bona fide TAS with considerable confidence whereas the modules that possessed only some of these characteristics, in particular, the cases where there was no support of the TAS prediction from the domain architecture of the component proteins, could represent other types of stressresponse systems

New antitoxins associated with known toxins

Toxins appear to be more specialized than antitoxins. Most of the toxin protein families (PIN), superfamilies (Kid/CcdB/PemK/MazF) and even folds (Fic/Doc, RelE) seem not to play roles in the cell other than the (broadly defined) toxin function. Thus, the presence of any relatively small protein-coding gene in a conserved two-gene operon that includes a gene for any of the known toxins strongly suggests that the small protein in question is an antitoxin. We identified several such putative new antitoxins as discussed below.

The Tad-Ata (RelE-COG5606) system

A new TAS, denoted Tad-Ata, was recently discovered on Paracoccus aminophilus plasmid pAMI2 [45]. The Tad toxins belong to COG4679 (DUF891), a large family of proteins, often referred to as phage-related because they are found in genomes of several bacteriophages and prophages (e.g. gp49 protein in the E. coli phage N15). It has been reported that Ata antitoxins belong to COG5606 and COG1396, and that they contain a typical HTH domain of the Xre/Cro family. In the course of this study, we independently made the same observations (Table 3; Additional File 2). In addition, we detected significant sequence similarity between the Tad toxin and the RelE family of RNAses (Figure 2A). For instance, in a PSI-BLAST search initiated with the sequence (gi 17228529) as a query (inclusion threshold 0.01), proteins of the RelE family (e.g. gi|15668242) were detected in the 4th iteration with an E-value of 0.001,). Thus, we propose that, similarly to RelE, the Tad (COG4679) family toxins are mRNA-cleaving RNAses (interferases).

New antitoxin families associated with PIN family toxins

The PIN family genes that encode a distinct class of (predicted) RNAse H fold nucleases are abundant in prokaryotic genomes, especially, in archaea [46,47]. We attempted to identify potential novel antitoxins in the neighborhood of PIN genes (Table 2). Here we describe several protein families that are likely to function as previously unnoticed antitoxins for some PIN family nucleases.

The COG2442, DUF433 family is among the most abundant new PIN-associated predicted antitoxins (Table 2). Proteins of this family are seen in a variety of bacterial and a few archaeal genomes but are most abundant in cyanobacteria (8 PIN-COG2442 pairs in *Anabaena variabilis* ATCC 29413) and chloroflexi (up to 9 pairs in *Roseiflexus* RS1) (Figure 3). The domain length is about 70–80 aa; the structure of one of the proteins from *A. variabilis* has been solved (PDB:<u>2GA1</u>) by Joint Center for Structural Genomics (JCSG) and classified in SCOP as a DNA/RNA-binding 3-helical bundle <u>http://scop.mrc-lmb.cam.ac.uk/scop/</u> <u>data/scop.b.c.bgi.b.c.html</u> (Figure 4A). Hence a clear analogy with other DNA-binding antitoxin proteins that regulate the transcription of the respective toxin-antitoxin operons. A reverse search for conserved gene neighbors of COG2442 did not reveal associations other than that with PIN family genes. However, there are several fusions of the COG2442 domain with DNA-binding winged HTH domains (eg. Rv2018 of *Mycobacterium tuberculosis* H37Rv) most of which are also associated with PIN family genes (e.g. Rv2019) suggesting that the transcription of this TAS could be regulated by more than one mechanism.

COG2886 is a family of small proteins associated with PIN genes, mostly, in archaea and cyanobacteria (Figure 3). The PSI-BLAST search (with inclusion threshold 0.01 and almost any query from this COG, for example, gi|118430972) reveals a weak but significant similarity with HTH-domains (eg: gi 170768772 with E-value ~ 0.046; 4th-5th iteration), mainly, of the Fis family [48-50]. Multiple alignment and secondary structure prediction support the PSI-BLAST results and reveal a classical HTH motif in the COG2886 family (Figure 4B). There exists a distinct proteins subfamily, paREP6 (Pyrobaculum aerophilum repetitive family 6), only distantly related to bona fide COG2886 family members, that is also often associated with PIN-coding gene; secondary structure predictions for this subfamily also support the presence of an HTH motif (Figure 4B). This family is overrepresented in Pyrobaculum genomes and is also present in other Thermoproteales and in several other archaea, including the recently sequenced Korarchaeum cryptofilum (eg. Kcr_0836, Kcr_0472, Krc_0407 and Krc_0470).

The COG2880 (DUF104) family is notable owing to its remarkable expansion in the archaeon Archaeoglobus fulgidus (12 paralogs). Some of these genes form clusters and are closely related to each other suggesting tandem duplication that is seen also for the adjacent genes encoding PIN-domain proteins. Recently, the NMR structure of one of the COG2880 proteins from A. fulgidus (AF2212) was solved by the Northeast Structural Genomics Consortium (PDB: 2NWT). Searches with the VAST or DALI programs did not detect any structural neighbors with high confidence; however, a PSI-BLAST search (with inclusion threshold 0.1 and AF2212 amino acid sequence as a query) revealed a statistically significant similarity with the AbrB superfamily of DNA-binding proteins (e.g. GI:15920210 with E-value ~ 0.071, 4th iteration). The AbrB proteins have been identified as antitoxins in wellcharacterized TAS such as MazEF, Kis-Kid and PemIK http://scop.mrc-lmb.cam.ac.uk/scop/data/

scop.b.c.bgi.b.c.html[3,4]. The secondary structure of

A	0733396 Psefluo 6 DVVFVGSALRDIRAEPEDARRAAGEODLDQQGEQPYDCRSVKTIG-PGVETRIHEDSGAFRLFYVWRRAAAIYUHAVRKTRKTEARDIELARARYQET 106 14331468 Niteutr 3 PLEFTGSSLDDLANPEEARRAAGEOGK QAGLDPDDWKPEDSIG-PGYPETRIHEDSGAFRLFYVWRRAAAIYUHAORVUTHAPEKKTQKTEGRURLAETRYRAI 106 1781871 Burphyt 6 EIRWLGSSYHDLLAPEARRRAAGEOLSK QAGLDPDDWKPEDSIG-PGTREIRIKEADGY RRWYTWRFVEAUYUHCGOKKTQRLGPHDRKIAETRYRAI 106 18038597 Burphyt 6 EIRWLGSSYHDLLAPEARRRAAGEOLSK QAGLDPDDWKPEDSIG-PGTREIRIKAADGY RRWYTWRVDYUHCGOKKTQRLGPHDRKIAETRYRAI 106 1705763 Salent 12 EIRWGSSLDDLAAFPITVRKAVGYQLHKDYGIGEPDDWKPESTIG-PGVREIRINDAETYRWMYWAFEEAVUHGCOKKTQTGSGDIDLAKRYKYKI 101 17155763 Azovina 3 VEFLADSLDRLREPEPDARREAGEOLDNI QONGIPDHWKPMTUG-QGVREIRINDAEGAFRYITVATLEOKKTQKTSKEDILAAEKYKI 110 17155763 Azovina 10 PIEFRGSALDDLRAFPSYSARRAGEOLDNQ VONGPDHWKPMTUG-PGVREIRINDAEGAFRYITYAKFANTY VLGCOKKTQKTSKEDILAAEKKREI 110 1715167 Psegyri 1 0 IIFMGSALNDLRAFPSISARREAGEOLDNQ VONGPDHWKPMTUG-PGVREIRINDAAGAFRYITYAKFANTY VLGCOKKTQKTSKEDILAAEKKREI 110 1715167 Psegyri 1 0 IIFMGSALDDLRAFPSYSARRAGEOLDQVONGRPDHWKPMTUG-QGVREIRINDAAGAFRYITYAKFANTY VLGCOKKTQKTSKEDILAAEKKREI 110 1715167	
В	31Pred EEEEE	29 28 27 31 29 28 30 30 28 45 33 35 32 12
С	15892747Riccono2TKYRYNHEKNVKLLNERGIGFEEIIQSIADGNLDDIKLHHNQEKYKGQKILYVQMIAQVVAVLYIKGDKDVIFLNTDFPSRKAKKEF-LKN9112527294Tredent1MIFDWNNEKNMMLKRDRNISFERIIVAIEQDNLDDILEHPNKEKYPNQLLLLVEIDRYVVVPCVLENDVCFLKTIFPSRKMTKQY-LGG89163783245Hydsp1MGIDWDEKNFKLKLERGIGFEDVIAINECKILDILEHPNKEKYPNQLLLLVEIDRYVVVPCVLENDVCFLKTIFPSRKMTKQY-LGG891648927767candTM76KYVPUSEKANNKLKERDICFEDVIAINECKILDILEHPNKDKYPQUILITVEIGGYAVVVPEEEENDIFIFLTIFIFSRKMTKQY-LGG9414892767candTM76KYVPUSEKANNKLKERDICFEDVIAIDIGKHPVULRYIAQVLIEIGEGYAVVVPEEETNDEIFIFLTIFPSRKMTKQY-LGG94148262643Geouran2KPINWNSDKNMQLKAERGISFEEVLVAVSQGALDVVEHPNKDKYPQRIIIVRIHGYAFLVSFVETNDEIFIFLTIFPSRKMTKY-LPE901713058777REFAWRPEKNAQLLAERRCFEAVVAIEAGDLDVUEHPNKDKYPLQRIEIVRIHVGHETCYAFLVSFVENUNEITITTAENEEPEEKKY9215358771MEFDWDEA-NVAHIARHOVRPWEAEEALTDPLRVMSVVADCKRYLAGGT-DEGRLUVVYEVENUNEITITTAENEEPEEKKY9215978190Thether1MEFDWDEA-NVAHIARHOVRPWEAEEALTDPLRVMSVVADCKRYLAGGT-NEGRKLEVVYTVERGRVRVITARDATPGEKRY851612474Caucres5DEPOWDEA-NNEQKIGWSIAEEKULGDPLADDURDSTTEERFIAVCMG-MMSLLUVVYTKKDGIRLISARATKQERKY93163760Chlepi8TGEQWDECNLAKNPEKKGWSIBESESIFFNQELVADDVKHSELESKVALGOT-NEGKLEVVYTVKKDGIRVISFRANKREVKKY871594254Neimein1MKEEDSEKWQNIEEKNLPEKSGURMETAUVDDUCTDYPEPRYVAAAYLGOT-NEGKLEVVTVK	

Figure 2

Predicted new families of toxins. A. Multiple alignment of COG4679 family (RelE interferase supefamily). **B.** Multiple alignment of SMa0917 family (PemK/MazF interferase superfamily). **C.** Multiple alignment of COG2929 family (RelE interferase superfamily) representative. The sequences are denoted by Gene Identification (GI) numbers from the GenBank database and abbreviated species names. Species name abbreviations (generally consisting of 3 first letters of genus name and 4 first letters of species) for all alignments are given in Additional file 13. The positions of the first and the last residues of the aligned region in the corresponding protein are indicated for each sequence. The numbers within the alignment represent poorly conserved inserts that are not shown. The coloring is based on the consensus shown underneath the alignment; h indicates hydrophobic residues (ACFILMVWY), p indicates polar residues (STEDKRNQH), s indicates small residues (AGSVC) and a indicates aromatic residues (WYFH). The secondary structure elements are shown according to structural data if the structure is available or predicted using the PSIPRED program [106]; E indicates β -strand and H indicates α -helix.



Figure 3

Distribution of TAS across bacterial and archaeal taxa. Black: TAS absent in the taxon while random expectation is significantly non-zero. Dark gray: TAS absent in the taxon with random expectation not significantly different from zero. Blue: TAS is significantly underrepresented in a taxon with more than twofold difference from random expectation. Cyan: TAS is significantly underrepresented in a taxon with less than twofold difference from random expectation. Light gray: abundance of a TAS in a taxon does not significantly differ from random expectation. Orange: TAS is significantly overrepresented in a taxon with less than twofold difference from random expectation in a taxon with less than twofold difference from random expectation. TAS is significantly overrepresented in a taxon with more than twofold difference from random expectation. Red: TAS is significantly overrepresented in a taxon with more than twofold difference from random expectation. The random expectation estimate is based on the total number of TAS of the given type and the total number of protein-coding genes in the given taxon. The statistical significance was estimated using the χ^2 test (critical χ^2 value of 3.84 for 1 degree of freedom and p-value of 0.05).

Δ	126661464	Cyasp	12	ILIDEN	JIPI	F <mark>I</mark> QGT <mark>S</mark>	TK <mark>I</mark> VE	LVTS	IQAY	GWSPEE <mark>I</mark>	LHFQYPH	SMSQ	IYSA	<mark>L</mark> A <mark>YY</mark> WEHKQE	IDED	75
~	28868150	Psesyri	170	<mark>V</mark> VLDPARNF	ΚP	V <mark>L</mark> TITG	IDTAA	IYHS	YLAE (G <mark>QSAKR</mark>	/ALLY-E	PPAA	/EAA	VN <mark>FE</mark> HRIAA-		230
	15609155	Myctube	183	VVLDPRRGY	QP	V <mark>F</mark> DGSG	<mark>v</mark> r <mark>v</mark> ae	VLGP	LR-A	ATFQA <mark>N</mark>	/ADDY-G <mark>V</mark>	/TPDQ <mark>1</mark>	RDA	LD <mark>AI</mark> AA		239
	110668810	Halwals	7	IVKTPDVLH	KPI	r <mark>i</mark> egtr	ISVFS	IGIT	AREH	ATVEE <mark>I</mark>	LDDYPD	DRAQ	<mark>/</mark> QAA	LD <mark>YY</mark> DEHPEL	MEYI	73
	118431948	Aerpern	10	LEVVPGRRG <mark>C</mark>	RP?	r <mark>v</mark> kgtr	ITVDE	ILEA	LA-N	GWSVEE <mark>N</mark>	/ADNY-R	PIEA	/YEA	<mark>lrya</mark> letlrk	VEVV	74
	94267135	delprot	21	ITLNPKVMA	KP	V <mark>V</mark> KGTR	LT <mark>V</mark> EY	ILNL	LA-H	GATTAE	LREYKG <mark>I</mark>	TPED	IQAC	IL <mark>FA</mark> TKSLES	TTFM	86
	15838624	Xylfast	24	I TQHPGVMG	KA	C <mark>I</mark> RGMR	IT <mark>V</mark> G№	I <mark>V</mark> VGQ	IG-S	HSVDE	LTDFPY	EHDD	e MQ	<mark>lrya</mark> awrade	REIM	89
	86739102	Frasp	9	VVADPTVGH	QAQ	C <mark>I</mark> RGTR	<mark>vpv</mark> sv	VLDC	LA-D	GMS DGE	[IAEYPS]	TVSG	IRAA	<mark>a</mark> a <mark>yg</mark> arlare	DLVP	74
	116625255	Solusit	8	ILVDPNICF	KP	C <mark>I</mark> RGTR	IWVSI	LLDF	LA-SC	VTMEE	LDDYPQ <mark>1</mark>	KRED	ILA <mark>A</mark>	IA <mark>YG</mark> AEMSRQ	RYVD	73
	37521595	Gloviol	9	<mark>I</mark> SVDPNICH <mark>C</mark>	KV	C <mark>I</mark> KGTR	IMVSV	' <mark>I</mark> LDN	LA-A	ESHQA	[MDSY-H	EEAD	e qa	<mark>lfya</mark> adlare	RMVA	73
	83589039	Moother	7	ITIDPSVCH	KA	C <mark>I</mark> KGTR	I P <mark>V</mark> SV	' <mark>I</mark> LDN	LA-E	JISQEE	LKSYPS <mark>I</mark>	SLED	I KAA	<mark>IA<mark>YG</mark>AMLAKE</mark>	RHIA	72
	39935887	Rhopalu	45	<mark>I</mark> DINPEVMG <mark>C</mark>	KP	v <mark>v</mark> rgtr	I P <mark>V</mark> EM	ILRK	LG-A	JLSTAE	IADHPR	TADD	[LA <mark>V</mark>	<mark>q</mark> t <mark>fa</mark> adylae	QDVI	110
	119358407	Chlphae	7	ITIDPDICH	KP	C <mark>I</mark> RGMR	Y P <mark>V</mark> EN	VLEW	LA-G	3MSIDD <mark>I</mark>	[LGDYED]	QKDD	[LAV	<mark>l</mark> a <mark>ya</mark> arlahi	KSIK	72
	119484409	Lynsp	9	ITLNPDICH	KP	C <mark>I</mark> RGLR	Y P <mark>v</mark> ef	'ILEL	LS-SC	MSPEE	LEDYED <mark>I</mark>	ERDD	[LA <mark>A</mark>	L <mark>QFA</mark> TRLTQI	KGIY	74
	146302688	Flajohn	9	<mark>I</mark> SINPDIRF <mark>C</mark>	KP.	r <mark>i</mark> tgtr	ICVSI	ILSW.	LS-IC	3MSFEE <mark>1</mark>	[IEDFPE]	NKEH	I LA <mark>A</mark>	<mark>lafa</mark> anreni	TKII	74
	17231452	Nossp	11	ITQIPGQCG <mark>C</mark>	RP	C <mark>I</mark> RGMR	IRVSI	ILEM.	LG-E	VISVSE <mark>I</mark>	[LEDFPD]	EAKD	IQAC	<mark>llfa</mark> arrtdf	PRLT	76
	16519725	Rhisp	132	VTSSPDILG <mark>(</mark>	TP	v <mark>v</mark> rgtr	<mark>v</mark> p <mark>v</mark> ye	VAAS	VA-A	HSVER	4LEAWPS	DAEK	IRL <mark>A</mark>	<mark>SIYA</mark> EANPLF	GRRR	197
	87309157	Blamari	50	<mark>I</mark> VATPKVCG <mark>C</mark>	SAI	R <mark>l</mark> irtr	I P <mark>V</mark> WI	' <mark>l</mark> erm	RQ-L	FTEAD	[LQSFPT]	QALD	LVQA	<mark>w</mark> a <mark>yv</mark> aqhrqe	IEQE	115
	148654836	Rossp-	12	ITVDPNIVS <mark>C</mark>	ΤP	V <mark>F</mark> RGTR	V P <mark>V</mark> QI	LFDY	LA-D	GYTLEE <mark>I</mark>	TLDNFPT	/KRED <mark>/</mark>	AIQI	<mark>l</mark> eq <mark>a</mark> tqylrv	GAVQ	77
	93279945 2	2GA1	34	IQITPGVCG <mark>(</mark>	QAI	R <mark>I</mark> RNTR	I P <mark>V</mark> WI	' <mark>L</mark> VAY	RQ-Q	GAPDKE <mark>I</mark>	LANYPG <mark>I</mark>	TAED	LSAA	<mark>W</mark> H <mark>YY</mark> EQNPEÇ	IDRE	99
			1	EE	I	EE	HHH	нннн	нн	ННН	ННН		ннн	нннннн-ннн	IHHHH	
	consensus	/90%	1	h	3.s	.hR	h.h	h!	hs	s.opł	nhah	np1	ns	h.hh		

В

57642089	Thekoda	29	RELFME	IVIS	A <mark>Y</mark> -IDGL	ISLGK	AEVL	G <mark>VT</mark> R	EEV	iee <mark>f</mark> k	R 67		
113477683	Trieryt	25	RDMRLA	AAIY	W <mark>Y</mark> -QKGE	ISQEK	A AQ <mark>V</mark> A	G <mark>ln</mark> r	RDF	las <mark>l</mark> a	R 63		
37520184	Gloviol	25	DEMRFA	AAVK	L <mark>Y</mark> -ELER	LSSGA	AAN <mark>L</mark> A	G <mark>V</mark> PR	tv <mark>f</mark>	lsk <mark>l</mark> a	D 63	5764181	0 The
119356482	Chlphae	27	RELRVI	. <mark>AAV</mark> K	L <mark>F</mark> -EMGR	LSSGR	ASE <mark>L</mark> A	g <mark>ms</mark> r	VE <mark>F</mark>	lls <mark>l</mark> n	R 65	1184319	43 Ae
16331968	Synsp-	26	NDWLRE	IAI A	L <mark>F</mark> -EQEH	ISLAR	ASK <mark>I</mark> S:	S <mark>ME</mark> I	ME <mark>F</mark>	QKL <mark>L</mark> S	D 64	12/0275	52 HT
147677030	Pelther	70	MEALKE	LAA T	F <mark>Y</mark> -ADGS	LSLGK	a ae <mark>l</mark> ai	N <mark>V</mark> SK	(RE <mark>F</mark>	ldf <mark>l</mark> G	A 108	1240275	52 II <u>)</u>
88602478	Methung	25	EELLKE	LAI A	L <mark>Y</mark> -TRGI	LSSGQ	SCK <mark>L</mark> A	G <mark>M</mark> KR	eyq <mark>w</mark>	eee <mark>l</mark> g	K 63	1095449	2 Met
11498205	Arcfulg	26	EEAKLI	. <mark>VAI</mark> E	L <mark>Y</mark> -REGI	<mark>V</mark> SLGK	a ae <mark>i</mark> ai	D <mark>LS</mark> I	REF	LYE <mark>L</mark> R	R 64	5764066	8 The
57640148	Thekoda	25	KLVRIY	'LAVE	L <mark>Y</mark> -REGV	<mark>V</mark> SLGK	AAE I A	G <mark>V</mark> TK	(AE <mark>M</mark>	ME I <mark>L</mark> A	S 63	1240284	60 н.
55380145	Halmari	23	QAMKQE	LAVS	L <mark>Y</mark> -ARDV	LSFGK	ARA <mark>L</mark> AI	ELSH	IRE <mark>F</mark>	QTL <mark>L</mark> G	D 61	E2C4010	7
17230297	Nossp-	18	KELILE	LIIL	L <mark>F</mark> -QKKN	ISLGK	ASQ <mark>L</mark> A	Q <mark>V</mark> PI	.LQ <mark>F</mark>	QHE <mark>L</mark> A	K 56	5/64012	/ The
57640852	Thekoda	22	RELRVI	LAVI	L <mark>Y</mark> -QRGI	LPLGK	AAKLA(G <mark>M</mark> TK	(RE <mark>F</mark>	lee <mark>l</mark> a	K 60	1452108	0 Pyı
118430972	Aerpern	26	KRLRIE	LALR	L <mark>Y</mark> -EKGI	ASLGQ	ARKIA	GLSK	WDF	LEL <mark>L</mark> A	R 64	8860316	9 Met
68549395	Pelphae	26	QEIRLM	IAA I T	YF-QEKK	LSLGK	AADLA	GCNR	(LNF)	MDL <mark>L</mark> A	R 64	5764027	0 mb
15789400	Halsp-	14	PELRLS	LAVE	K <mark>Y</mark> -QSGA	VSLNR	AAELA	G <mark>V</mark> SV	EAF	KDELA	D 52	5764027	0 1116
11497720	Arctulg	32	KELFEE		AY-VEGL	ISLSK	ASELL.	ETIR	(DEM	AEILR	K 70	5764084	4 The
118431250	Aerpern	21	REVKLA	YAVD	L <mark>F</mark> -LRGI	VSVER	AAELA	GMSL	'ADE	lve <mark>l</mark> r	R 59	1149930	2 Arc
jpssm		004	HHHHHH	HHHH	HH-HHHH	-HHHH	HHHHH	H	IHHH.	ннннн	Н	11/0703	0 Arc
170768772	Escalbe	284	MQQEKE	LLQL	SL-QQGK	FNQKR	AAEL	GLIY	HQP	RALLK	K 322	1140700	O AIC
6/464081 .	TOTE	266	VDVEKE		AL-EKTG	GNKTE	AARQL	GTIR	(KT <mark>L</mark>	LAK <mark>L</mark> L	5 300	AF2212	2NWT
170200000	CanKora	20	ODDUTE		VETERCE	TVD				DEUDV	п р 76		
126459622	Purcali	31	TDDDOD	AALU	VVIETCD		ACDIA		EFF	NEIDI	R 73 R 68	Consens	us aa
18311011	Pyraero	51	TDDKIK	AAUK	IVIETCO	TPT	AOKIS		FDF		D 88	1500001	~_~~
18313633	Pyraero	29	LPERHE	AALK	FYTETGD	LRL	AOOLS	GLDE	EDF	RELLR	K 66	1592021	0
145591172	Purareo	20	T D D D T D	AAVK	IFIETCO	TPT	AOSTS		DDF	DETTD	K 66	ArbB	1YFB
18312946	Pyraero	51	LPPRLE	TALM	YYTETGD	LYV	ASRTA	GTAA	EFF		R 88		
ipssm	1 / 14010	01	HHHH	нннн	HHH	HHH	нннн-	H	HHH	ннннн	H UU		
consensus	/90%			hhh.	. h	h	s.ph.	.hs.	h	h .	n		
								· · · · ·			-		

641810 Thekoda	1	ME <mark>VV</mark> E <mark>A</mark> IYE	N <mark>GVL</mark> KLKKK <mark>I</mark>	NLPDGTE <mark>V</mark> SVKLI	32
8431943 Aerpern	2	SK <mark>VI</mark> R <mark>V</mark> RYE	K <mark>G</mark> VLKPIGE <mark>V</mark>	VLREGEELEVVV	33
4027552 Hypbuty	2	SK <mark>VI</mark> RVRYE	N <mark>GVL</mark> KPLEP <mark>I</mark>	EFEEGKELVIRII	33
954492 Metjann	5	SE <mark>II</mark> E <mark>V</mark> IYE	D <mark>GVL</mark> KPLKP <mark>I</mark>	KIKGKKRLKIKIV	36
640668 Thekoda	2	ME <mark>II</mark> E <mark>A</mark> VYEI	N <mark>GVL</mark> IPLKK <mark>F</mark>	K <mark>L</mark> KEHSK <mark>VII</mark> KII	33
4028460 Hypbuty	8	SR <mark>VI</mark> R <mark>V</mark> RFE	K <mark>GVF</mark> KPLDR <mark>V</mark>	D <mark>F</mark> REGEE <mark>L</mark> VVFVR	39
640127 Thekoda	5	VE <mark>VV</mark> E <mark>A</mark> VYEI	N <mark>GVL</mark> KPLKP <mark>I</mark>	K <mark>l</mark> kegeh <mark>l</mark> vikly	36
521080 Pyrabys	2	GE <mark>II</mark> E <mark>V</mark> IYE	N <mark>GIL</mark> KPLKK <mark>I</mark>	PFKEGEK <mark>LIVEV</mark> K	33
603169 Methung	2	GE <mark>II</mark> E <mark>A</mark> IYE	D <mark>GVF</mark> KPLKK <mark>F</mark>	DLADKTK <mark>A</mark> TIIQ	33
640270 Thekoda	1	MG <mark>VI</mark> E <mark>A</mark> VYEI	N <mark>GVL</mark> KPLKK <mark>I</mark>	TLPEKKR <mark>V</mark> K <mark>I</mark> IIL	32
640844 Thekoda	2	RL <mark>GI</mark> K <mark>A</mark> VYRI	N <mark>GVF</mark> KPLEK <mark>V</mark>	ELPEGIE <mark>VEV</mark> VIR	33
499302 Arcfulg	2	GE <mark>II</mark> E <mark>A</mark> VYQ	K <mark>GVL</mark> KPLRK <mark>V</mark>	S <mark>L</mark> REGEI <mark>V</mark> K <mark>VEI</mark> R	33
497930 Arcfulg	51	PK <mark>II</mark> E <mark>A</mark> IYEI	N <mark>GVF</mark> KPLQK <mark>V</mark>	N <mark>F</mark> RPGSK <mark>V</mark> RIVIQ	82
2212 2NWT	2	PK <mark>II</mark> E <mark>A</mark> VYEI	N <mark>GVF</mark> KPLQK <mark>V</mark>	D <mark>lkegerv</mark> kikle	33
		EEEEEE	EEEE	EEEEEE	
nsensus_aa:		hhph.ap	.Ghhp .h	.ph.pph.h.h.	
920210	9	GY <mark>IV</mark> TVDER	G <mark>RVI</mark> IPKQIREK <mark>I</mark>	N <mark>l</mark> kegsk <mark>vev</mark> dle	43
bB 1YFB	13	GI <mark>V</mark> RKVDEL	G <mark>RVV</mark> IPIELRRT <mark>I</mark>	.G <mark>I</mark> AEKDA <mark>LEI</mark> Y <mark>V</mark> D	47
		EEEE	EEE HHHHHH	EEEEEE	

Figure 4

Predicted new families of antitoxins. A. Multiple alignment of COG2442 family domain, a predicted DNA-binding antitoxin protein of winged HTH motif superfamily. B. Multiple alignment of COG2886 family of predicted antitoxins containing the HTH domain. C. Multiple alignment of COG2880 family, an AbrB superfamily representative. Designations are the same as in Figure 2.

С

AF2212 and multiple alignment of this family support the PSI-BLAST results and reveal at least three β -strands that are most conserved in other AbrB superfamily members [51] (Figure 4C). The proteins of this family are found mostly in the genomes of thermophiles with only a few exceptions such as *Methanospirillum hungatei* (archaea isolated from bovine rumen) and *Lyngbya sp.* (a cyanobacterium).

COG1753 (DUF217) (20) is an archaea-specific family of proteins that are often encoded within predicted operons with PIN family toxins. Notably, in several methanogens, this antitoxin is associated with RelE-like toxins rather than with PIN family toxins (e.g. MA0375- MA0376 sys-

tem in *Methanosarcina acetivorans*). A PSI-BLAST search started with a query sequence of one from the above proteins (gi|126179419, with inclusion threshold E-value 0.01), detects RHH superfamily proteins after the second iteration (eg. gi|189499687 with E-value 3×10^{-4}), and secondary structure prediction and multiple alignment support the presence of the RHH domain (Figure 5A).

MerR (33) is a well-characterized transcriptional regulator involved in stress response, especially, in heavy metal resistance [52]. We identified a distinct family of proteins that contain a HTH domain related to that of MerR and are associated with PIN-family toxins. These proteins belong to a distinct group of MerR-like DNA-binding A

в

с

120610402 Ad

nsensus/958

21730893 1EA4

RHH domain of COG1753 family

11499279	Arcfulg	2	KNIM	RDEVYEK	LQKM	KKGRESF	SDVI	LRLIEGRK	36
126008684	Feracid	3	KTIT.	KKSVYDK	LIG <mark>F</mark>	KKENESF	SELL	DR <mark>LI</mark> KSQS	37
70606300	Sulacid	3	KVIT.	SDDVYDK	LSKI	KKGRSF	SETI	NELIEFYN	36
15669309	Metjann	5	ATIT	DDDVYKE.	LLKI	KGR <mark>KS</mark> V	SEFI	KELLEERK	38
14590900	Pyrhori	13	KTIT.	ADDVYYE	LVK	KGKRSF	SEVI	RELIGKKK	46
PSIPRED			-EEE	с-нннннн	ннн	Нн	нннн	ннннннн	
55377876	Halmari	3	SSIR	SDETKAK	LEAV	KREDETF	DELI	DRLAITRT	37
15922259	Sultoko	3	KTIT:	ISEEAYRL.	LSE	KREG <mark>ESF</mark>	SDVI	IR <mark>LV</mark> KSSR	37
134102275	Saceryt	6	QIRD	/PEDVYRT	L-KI	RAVEAGQSY	SEFI	RG <mark>LL</mark> TQAA	41
88603943	Methung	14	KR <mark>V</mark> A	TPDTWVA	LSNI	KEPGKTL	GD TV	ADLIAEHQ	48
57641697	Thekoda	2	KTIA	/DENTWKK	IKLI	KDKLDAKSY	DEVI	QRLIETWH	38
21730893	1EA4	5	LTIT	SESVLEN	LEK <mark>M</mark>	ARE-MGL <mark>S</mark> K	S <mark>A</mark> MI	SV <mark>AL</mark> ENYK	40
			EEEEE	сенннннн	нннн	ННН-НН	нннн	ННННННН-	
Consensus	/90%		pph.1	np	hh	poa	sphh	hh	
88603892	Methung	14	KR <mark>I</mark> P.	TPKTWEK	LSIL	KKPGETF	DHLI	TDLIEERE	48
73667773	Metbark	28	TTIQ	SKKNRDE	LKK <mark>I</mark>	GSMGDDY	NT <mark>VI</mark>	EK <mark>LI</mark> REYR	62
126179419	Metmari	5	AT <mark>I</mark> K.	IDTELKRR.	LNTI	KRH-PRETY	SDVI	RR <mark>LT</mark> ETAI	40
21226652	Metmaze	2	STIA	DPDVKES	LKEI	KLA-PEESY	NSVV	KR <mark>LI</mark> GEVK	37
126178613	Metmari	3	TTIQI	QPETKSR	LDTL	KTH-PRESY	DETI	NR <mark>IM</mark> DALI	38
20088947	Metacet	5	TTIQ	KQSTKEA	LER <mark>M</mark>	KIY-KRETY	NDVL	ERLIEDVQ	40

RHH domain in MJ1172 family

150400393	Metvann	1	MVQV	VDLSD	D <mark>S</mark> NF	RITEI	КАОН	ISIP <mark>K</mark>	(SI	IDMF	ISO	FASYGKE	-ALE	NPAF	KE	IEHSKSTEFIDITD	KKSRRKHL	79
45358040	Metmari	1	MVQVQ	VDLSD	D <mark>S</mark> NF	RIIEI	KAQH	ISIP <mark>K</mark>	(SI	IDMF	ISQ	FASYGKE	-ALE	NPAF	VKE.	LEHSKGTEFIDITD	KKSRRKH <mark>L</mark>	79
15669361	Metjann	4	M <mark>V</mark> KA:	VDITD.	E <mark>N</mark> NF	RI <mark>I</mark> NI <mark>N</mark>	KAKY	NLRD	(<mark>s</mark> Q	INKI	IEE	YAEFLL-	-EDE <mark>I</mark>	KPEY	IEK.	RNIMKNEKPIYIGS	IENLKKR <mark>Y</mark>	81
21227970	Metmaze	3	MIQAI	R <mark>V</mark> K <mark>MS</mark> D	R <mark>T</mark> NÇ	2V <mark>L</mark> NI <mark>V</mark>	KAKY	NLKD	(SA	LDLV	VAQ <mark>1</mark>	YEEKIL-	-EPQ <mark>y</mark>	SPEF	I KE	LDSESDEVIGPFKN	ADELKAY <mark>I</mark>	80
21228783	Metmaze	2	IYMV	VD <mark>IS</mark> D	D <mark>T</mark> Nζ	2I <mark>L</mark> GI <mark>N</mark>	KTKF	NLK <mark>D</mark>	SA.	IDFI	VAQ <mark>(</mark>	CEIDML-	-EPE <mark>I</mark>	KPEF	IEE <mark></mark>	QNIIAGKHIGPFKT	VDDLKAY	79
20091001	Metacet	11	M <mark>A</mark> QA:	INID	HTKF	KI <mark>L</mark> DI <mark>I</mark>	KTRY	DLK <mark>DI</mark>	E <mark>S</mark> A	I ELM	ATQ <mark>1</mark>	YEEEIL-	-EPE <mark>I</mark>	RPEF	/EK	QNIMKEEP-IDIGT	IEDLRARY	87
21228652	Metmaze	1	M <mark>V</mark> QA:	INIDE	R <mark>T</mark> NF	RI <mark>L</mark> NI <mark>I</mark>	KAKY	GLKD	(SA	<mark>l</mark> nkm	AEE	YEEEIL-	-EPE <mark>I</mark>	KPEY	IEK <mark>I</mark>	KKIEKQEA-IEVGT	VENLRKRY	77
73671151	Metbark	4	V <mark>V</mark> QA:	INIDE	R <mark>T</mark> NF	RILNI	KAKY	GLKD	(<mark>S</mark> A	I NKI	AEE	YEDVIL-	-GPE <mark>I</mark>	KPEY	IEK]	KKIGKQEA-IEIGT	VEHLRKLY	80
159904821	Metmari	1	M <mark>V</mark> KA:	INISD	N <mark>S</mark> NÇ	2I <mark>L</mark> NI <mark>N</mark>	KAKY	ALKD	(SE	I EKV	IEE!	YSQEML-	-EPN <mark>I</mark>	RPEF	/EK	NKIMEKKT-VKVGS	VQNLRNRY	77
159904839	Metmari	1	MAVKS	FNVDE	E <mark>V</mark> YS	SK <mark>F</mark> SK <mark>F</mark>	<mark>1</mark>	-CKD	R <mark>G</mark> M.	S <mark>M</mark> SKQ	VEF <mark>1</mark>	FMRSIVE.	EEPE <mark>I</mark>	RQEY	IEK.	ERICKGKF-IK	VNNFSEE	71
134046182	Metmari	18	N <mark>V</mark> KR'	YSIDE	T <mark>V</mark> VF	(K <mark>f</mark> se <mark>)</mark>		-CD <mark>E</mark>	2 <mark>G</mark> L	M <mark>M</mark> SRQ	IET	FMKYVVE	-GPE <mark>N</mark>	RPEY	LEK	EKIRKGEF-IP	VKDFAKHY	87
150403111	Metmari	2	N <mark>V</mark> KR!	YS <mark>ID</mark> E	T <mark>V</mark> VF	(K <mark>f</mark> se <mark>)</mark>		-CD <mark>EI</mark>	۲ <mark>G</mark> L	<mark>M</mark> GKQ	IET]	<mark>F</mark> MKYVVE	-GSE <mark>V</mark>	RPKY	LEK	EEIRKGEF-IP	VKDFAKHY	71
150403708	Metmari	19	N <mark>V</mark> KR'	YSIDE	T <mark>V</mark> VF	(K <mark>f</mark> se <mark>)</mark>		-CDEI	RGL	<mark>M</mark> GKQ	IET	FMKYVVE	-GSE <mark>N</mark>	RPKY	LEK	EEIRKGEF-IP	VKDFAKHY	88
			EEH	CEE	-HHF	нннн	нннн	II	HHH	нннн	ннн	ННННН		-HHHI	ннн	ННННН	нннннн	
consensus,	/100%		h	hphsp	ps.p	.hł		pr	s.s	sh	h1	h	ph	npal	nppł	n.pp	.pph	
			{			RHH	mot	if				}						

RHH domain in COG5304/COG3514

120610402	Aciaven	40	MQS	IS	IR	LPKGM	IDA	YKLIGAHH	VG	YOPL	MRD	IL	QRFIPE	80
77163627	Nitocea	34	QTK	vı	IS	LSSES	VAF	FKEEAKKHI	RMO	YOKM	IRO	LL	DEYVAQ	74
42527306	Tredent	40	KEK	IC	VI	<mark>l</mark> akqd	INN	LKAKAFEE	ME	YEIF	AGS	VL	HKYLTG	80
148262644	Geouran	49	DKR	IN	IR	LSSHD	LED	IOMRAAEE	GMP	YOTL	IAS	IL	HKYASG	89
15892400	Riccono	52	DTR	IN	IR	ISSSD	LMR.	IKQKAAYE	GLP	YQTL	ISS	IL	HKYSAG	92
21673649	Chltepi	47	MKT	IS	LR	L PEML	LNR.	IKTLANER	DVP	YQSL	MKM	YL	RERIDS	87
16124743	Caucres	41	EAR	. <mark>V</mark> N	MR	LPEPL	LEA	VKKRASAR	GIP	<mark>Y</mark> QRF	I RE	AL	ETALSE	81
55978189	Thether	54	TRA	IS	LR	LDEDL	LRR.	LKAVARRK	GKG	YQTL	LKE	FV	LERLYE	94
				EE	ΕE	HHH	ннн	ннннннн	-	HH	ннн	НH	НННННН	
53687313	Nospunc	30	PVT	IT	VK	V DPET	FAW	FKEQ	GET.	AEQQ	MAV	AL	KIYAEA	75
16763335	Salente	59	КТÇ	AS	VR	I DADV	MEW	LKRP	GKG	<mark>Y</mark> QTR	LNA	IL	REAMLR	95
126657956	Cyasp-	55	KQQ	V1	L R	LDPEI	IDY	FKSIK	DG	WQTR	LNQ	AI	KSYIDE	92
15964371	Sinmeli	69	KKÇ	VТ	LR	LDEDV	IAK	FRAG	GKG	WQSR	MNE	AL	RKAAGI	105
15794253	Neimeni	62	KQI	V1	IR	LSADV	<mark>v</mark> ek	FRAG	GKG	WQTR	INE	VL	RQYVAQ	98
15838164	Xylfast	71	KVF	TA	IR	LDADL	LEA	FKAT	GKG	WQTR	<mark>V</mark> NA	AL	RQFIAE	107
113867366	Raleutr	56	KEI	vs.	IR	<mark>Y</mark> DADI	LDA	FRAS	GEG	WQTL	MNA	ΤL	NVALQQ	92
22126311	Yerpest	56	KEP	VK	LR	I DHDV	<mark>V</mark> DA	YRAQ	DG	WQTK	MNE	AL	RDYAKT	92
33596570	Borpara	52	KQV	V1	IR	LSPDV	<mark>v</mark> ea	FKAS	GTG	WQTR	<mark>V</mark> DA	AL	RDWLKT	88
15837134	Xylfast	55	KRÇ	IT	LR	I DADV	LDF	FRNT	KR	<mark>Y</mark> QTR	INA	VL	RSYVEA	91
21673297	Chltepi	67	KVV	LN	MR	<mark>V</mark> DYEV	MEF	FRGQ	GKG	<mark>Y</mark> QKK	INA	VL	RSYVEH	103
	(

.hshph...h.hp....s.hp.h.hh. 2 KKRLTITLSESVLENLEKMAREMGLSKSAMISVALENYKKG

-ЕЕЕЕЕЕННИНИНИНИНИНА---ИНИНИНИНИНИ

RHH domain fused to HEPN domain (paREP 1 subfamily)

18313619	Pyraero	1	1	1 D	VE	NS	LL	EE	AKI	R	-REI	DIVI	LL	SKA	L	G	VD	PPSRASAH	37	
159041114	Calmaqu	1	1	ИE	IF	KE	LI	RI	AE F	2	-KGI	NIVE	D <mark>LV</mark>	LSE	II	-SK	SD	PSESMRIR	38	
18312682	Pyraero	1	1	ИE	LF	PΤ	LV	ΕA	LRI	R	-GGL	DVGE	I <mark>VV</mark>	DAL		AKS	LD	PPSLAKAH	38	
119720275	Thepend	3	КТ <mark></mark>	VV	IF	RR	LV	EE	VE F	K	-RGL	SVES	LV	VDA	LSF	ALD	LD	PEVVAEAR	45	
119873418	Pyrisla	1	MA	VV	LF	ER	LV	RE	AE F	R	-RGI	DVGE	:VA	LEA	LAF	RALE	LD	PADVAAAR	43	
119719880	Thepend	3	AP	IТ	IF	ER	LV	KE	AVI	K	-KGL	DIEA	AS <mark>A</mark>	VDF	?	AKT	LN	TDPSAEAR	42	
119720599	Thepend	1	-M	VТ	IS	RG	FA	EE	AE F	R	-RGV	DLEG	AL	PS-		RAL	VD	PVEVAGAR	38	
15920871	Sultoko	6	YS	/ R	LF	PΤ	LV	KE	LMI	R	-MNV	DEAD	IA	EVV	/LN-	SFN	ID	NDLKPKIY	47	
159040880	Calmaqu	1	MS	LV	LS	PQ	LV	NL	LRI	<u></u> L	AGGR	DVEA	FI	IDI	.I	AER	LD	PPHRVKLY	43	
119871616	Pyrisla	1	MA	IТ	LS	PA	VA	EL	LKI	R −−A	AGDR	DVEA	FL	ADI	L	AGR	LD	PPERVELY	43	
18313508	Pyraero	1	MS	LV	IS	SP	VA	EV	LRI	KA	AGGR	DVEE	FL	LEI	V	ASR	LD	PSERIDVY	43	
124027094	Hypbuty	2	ST	GF	LF	SE	LV	EL	LEF	REAE	QRGS	T PEA	LT	VQI	L	LRL	ΑP	EEERPRIL	46	
15921011	Sultoko	3	KE	IV	IF	DK	LY	ΕY	LE1	QGI	TRRL	PSE	IV	VEI	.I	LNN	<mark>M</mark> D	IKERINYM	47	
146303309	Metsedu	2	KΤ	LE	VE	EΤ	LA	ΤK	LFE	SISE	RSRK	RPYE	VI	AEI	L	LDR	ME	EAERLSTL	46	
15921347	Sultoko	1	1	ИE	ΙF	RL	LE	ΕA	LRI	EAF	EKGI	DEEI	LL	IDK	(L	LRD	LD	PSTRFTLY	43	
18312955	Pyraero	2	EI	LS	LF	ΕV	LT	KR	LRI	AAE	SAGI	SLEI	9 <mark>71</mark>	LEV	/S	LAG	<mark>a</mark> d	PPERARAY	46	
126466410	Stamari	3	VV	ΙI	ΙF	RR	VA	EН	<mark>a</mark> ri	REAE	KKGM	LEE	ΥI	IEL	L	SHN	LD	PMDKAIEY	47	
119720319	Thepend	3	VA	<mark>7</mark> S	LF	RV	LV	ER	<mark>a</mark> ri	REAE	RLGV	SLEE	YF	LEV	/I	SGN	LD	PRDKAEAF	47	
124027557	Hypbuty	5	AA	/ R	LF	RS	VV	ER	LEF	REAR	RLGL	SFEE	YV	LEI	V	LRD	LD	PTERAREY	49	
21730893	1EA4	5	LT	IТ	LS	ES	VL	EN	LEF	MAR	EMGL	SKSA	MI	SVA	L	ENY	KK	GQEK	45	
			EEF	ΞE	EF	HH	HН	HHI	HHE	ннн	HH	-HHE	IHH	ннн	IH	HHH				
consensus/	/90%		. ł	h.	hs		hh	c.l	h.d	c		s	hh				hc			

Figure 5

Multiple alignments of distinct predicted antitoxin families containing ribbon-helix-helix (RHH) domains. A. RHH domain of COG1753 family. B. RHH domain in MJ1172 family. C. RHH domain in COG5304/COG3514. D. RHH domain fused to HEPN domain (paREP I subfamily). Designations are as in Figure 2.

43

D

domains known as truncated HTH domains that lack the Wing 2 region composed of two α -helices and the long dimerization helix [52,53]. In addition to the MerR-like domain, proteins of this family also contain a small domain at the N-terminus that might interact with the PIN domain (Additional file 3).

A new antitoxin family associated with RelE family toxins One of the new families that we identified in association with RelE-like toxins is typified by the MJ1172 (COG7997) protein and so far found only in methanogens. The members of this family can be recovered using the sequence gi 159904821 as a query after 5th iteration of PSI-BLAST with inclusion threshold 0.1. In this search,

several proteins of the RHH superfamily appear slightly below the threshold (gi|186903258 with E-value 1.1). Secondary structure prediction for COG7997 proteins reveals a strand-helix-helix motif characteristic of the RHH superfamily (Figure 5B). The proteins of the RHH fold, such as RelB, are well-characterized antitoxins for RelE toxins [3,4]. Thus, it appears most likely that MJ1172-like proteins are a highly diverged family of RHH domain-containing antitoxins.

A new antitoxin family associated with MazF family toxins

We detected a specific family of small proteins associated with MazF toxin family that is predominantly present in proteobacteria and chlorobii/bacteroidetes groups and is typified by XF1863 (Figure 3). No functionally or structurally characterized homologs of these proteins were detected. Secondary structure prediction for this family does not precisely fit any characterized antitoxin families but indicates the presence of a strand-helix-helix motif, resembling the structure of RHH domains (Additional file 4). One of these proteins (gi 152585) is encoded on the Plasmid RSF1010 in a predicted operon with a small "unknown protein E" (gi|152584), and the two proteins have been reported to form a dimer that is involved in the regulation of the plasmid copy number [54]. These findings are compatible with the prediction that MazF-XF1863 proteins comprise a new TAS.

A new antitoxin family associated with Fic/Doc family toxins

A new family of predicted antitoxins associated with Fic/ Doc toxins, typified by the *E. coli* protein **YhfG**, is present only in Enterobacteria. These small proteins are predicted to possess, mostly, α -helical structure and are enriched in positively charged amino acids, which is compatible with a DNA-binding capacity (Additional file 5).

New toxins associated with known antitoxins

The antitoxin families are much less specialized than the known toxin families, that is, include numerous members that perform other functions in prokaryotic cells. In particular, many of these proteins are transcriptional regulators that are involved in the control of a variety of functional systems, mostly, related to stress response. This multifunctionality of antitoxins complicates prediction of new toxins solely on the basis of genomic association with antitoxin genes. Nevertheless, such cases are worth examining in search of putative TAS with novel molecular mechanisms that might merit experimental validation. Here we describe *in silico* evidence supporting the existence of several potential TAS with a novel toxin component.

The SMa091-like family of putative toxins associated with PHD antitoxins

PHD family antitoxins are found in association with three structurally unrelated toxin families, namely, Fic/Doc,

PIN and RelE [13]. Our approach revealed a new α-proteobacteria-specific family of proteins encoded next to PHD antitotin genes; the family is typified by the SMa0917 gene that is located on the *Sinorhizobium meliloti* pSymA megaplasmid [55]. A PSI-BLAST search using this protein as a query with the inclusion threshold 0.1 detected proteins of the PemK/MazF family in the 6th iteration (eg. gi|59801978 with E-value 0.016). The secondary structure prediction for the SMa0917-like proteins is compatible with the structure of PemK/MazF domains (Figure 2B). Thus, it appears that the SMa0917 family belongs to the PemK/MazF superfamily of mRNA interferases and represents the fourth group of toxins associated with PHD antitoxins.

A putative toxin family associated with RHH antitoxins

A predicted two-gene operon comprised of two families of small uncharacterized proteins (COG2929/DUF497 and COG5304/COG3514) is widespread in prokaryotes. We detected over 200 instances of this operon in a variety of bacteria representing most of the major bacterial lineages, and in several archaea. PSI-BLAST searches failed to identify reliable similarity of COG2929 proteins to any characterized proteins; however, the multiple alignment includes several conserved positions occupied by polar residues which is compatible with an enzymatic activity of the COG2929 family proteins (Figure 2C). The predicted secondary structure of these proteins is most similar to that of RegB/RelE nuclease superfamily, suggesting the possibility that COG2929 proteins are highly derived RelE-like interferases [56].

There are no functionally characterized proteins in COG5304 but several of these proteins are annotated as containing the RHH domain. Indeed, database searches identify a RHH domain in these proteins (PSI-BLAST search with gi|148262862 as a query with inclusion threshold 0.1 detects proteins of the RHH family after 5th iteration, e.g. gi|93006664, with E-value 0.035; the RHH domain also can be detected in these proteins with any methods using comparison with profiles, like SMART or CDD). Secondary structure prediction revealed a C-terminal strand-helix-helix motif, in agreement with the PSI-BLAST results (Figure 5C).

Taken together, these observations, suggest that COG2929 proteins are toxin nucleases distantly related to Regb/RelE whereas COG5304 proteins are DNA-binding antitoxins containing the RHH domain. This operon is seen in several bacteriophages (*Burkholderia* phages phi52237 and phiE202) and plasmids (pLB, pNL14, pANL), suggesting horizontal mobility. Taken together, all these observations are compatible with the hypothesis that COG2929 and COG5304 proteins comprise a previously undetected TAS.

The DUF397 family of putative toxins associated with HTH domaincontaining protein

The DUF397-HTH pair of genes encodes proteins that are most abundant in actinobacteria, with a specific expansion in *Salinispora tropica* CNB-440 (20 operon copies). This gene pair is present on several plasmids (plasmid pA387 from *Amycolatopsis benzoatilytica*, plasmid pNO33 of *Streptomyces albulus*; linear plasmid SCP1 of *Streptomyces coelicolor*, pNF1 of *Nocardia farcinica*). One of the genes in this pair (e.g. the SCO6130 gene from *S. coelicolor*) encodes a protein of approximately 300 amino acids that consists of an easily identifiable N-terminal HTH domain of the Xre family and an uncharacterized C-terminal domain.

The protein product of the second gene (DUF397, e.g. SCO6129) has been characterized previously as a potential pleiotropic regulator that affects morphogenesis, antibiotic production, and catabolite control in Streptomyces [57]. It has been reported that the BldB protein of the DUF397 family forms a dimer, is structurally flexible and regulates its own promoter [57,58]. Although it has been suggested that BldB contains an HTH motif [57,58], we were unable to validate this observation (Additional File 6). Considering all features of this gene pair, including non-uniform expansion of the two-gene operons in bacterial genomes, their presence on plasmids, the presence of the Xre domain in one of the encoded proteins and the pleiotropic regulatory effect, we suspect that the proteins containing the Xre domain function as antitoxins whereas DUF397 family proteins are novel toxins.

Zn-dependent proteases associated with HTH domains

Proteins of COG2856 (approximately 160 amino acids long) contain a conserved HEXXH motif that is the sequence signature of numerous families of metzincin Zndependent proteases [59] and show statistically significant sequence similarity to proteins of the Peptidase_MX (CL0150) family. This family of predicted Zn-dependent proteases is one of the most abundant gene families that form putative operons with HTH domain-containing proteins of the Xre family (eg. ydcM, COG2856 and ydcN, xre family HTH in Bacillus subtilis genome). In more than half of the cases, COG2856 domain and the Xre domain are fused within a single two-domain protein (e.g. Mycobacterium tuberculosis Rv2515c). Many of the fused protein genes are located in the same (predicted) operon with other toxins, mostly, of the PIN or RelE families (Table 2). These putative operons are abundant in various phages and prophages (Staphylococcus phage phiETA3, Clostridium phage phiC2, Leptospira biflexa temperate bacteriophage LE1, Mycobacterium phage Che9c, etc.) and several plasmids (Sphingomonas pCAR3, Microscilla sp. pSD15). Lineage-specific expansion of this pair of genes is seen in several bacteria, especially, Firmicutes (Figure 3) including the largest expansion in *Enterococcus faecalis* V583 (8 predicted operons, one fusion) and three copies of the operon encoded in several strains of *Streptococcus pyogenes*, bacteria with relatively small genomes.

These proteins have been previously implicated in the genetic control of bacterial suicide through the demonstration that induction of late genes of prophage PBSX causes cell death and the gene largely responsible for this effect is *xre* (which is encoded in one operon with ORF2 that belongs to COG2856) [60]. The mechanism of killing remains unclear but the connection of the expression of these genes with response to DNA-damaging agents has been established [61]. Furthermore, it is known that the Xre protein regulates not only its own expression but also the expression of other genes including a complex regulatory cascade downstream [60]. Considerable experimental data have been amassed on another protein of this family, the product of the *irrE(pprI*) gene (DR0167) of Deinococcus radiodurans which contains fused COG2856 and Xre domains. It was shown that IrrE/PprI protein is a key regulator of the recA gene induction after irradiation [62,63]. Unlike recA, which is strongly induced following irradiation [64,65], the irrE gene appears to be constitutively expressed, with no post-irradiation induction [64,66]. Also, the IrrE/PprI protein does not appear to bind the promoter region of *recA* or other induced genes [66]. These observations point to a pleiotropic effect of the expression of this gene pair, which is consistent with the data on the action of other TAS. The domain architecture of the COG2856-Xre fusion protein invokes the analogy with the well-characterized SOS response regulator LexA, an autoprotease and a repressor of a complex regulon that includes, among other genes, several TAS operons, [67-69]. In agreement with this hypothesis, it has been recently shown that the COG2856 protein ImmA (YdcM) from B. subtilis is required for the proteolytic inactivation of the Xre family protein ImmR, the repressor of the transposable element ICEBs1 [70]. Considering the strong link between the COG2856-Xre fusion protein and the RelE and PIN toxins, it appears most likely that this protein functions as a protease that cleaves a Xre family repressor which is either the antitoxin for the RelE/PIN toxin or a part of another, more complex regulatory cascade involving other stress-response genes. These findings suggest the existence of a novel, three-component TAS, with a more complex regulatory circuit than those of the currently described TAS. Experimental validation of this prediction and elucidation of the specific regulatory targets of the Xre repressor associated with the COG2856 family protease will be of considerable interest.

The RES domain associated with Xre HTH domains

The RES domain (~160 amino acids long) was named after three amino acids, arginine, glutamate and serine,

which are conserved in the sequences of the respective proteins, suggesting a potential enzymatic activity <u>http://pfam.sanger.ac.uk/family?PF08808</u>. In most cases, genes encoding RES-domain proteins form predicted operons with genes of the uncharacterized COG5642. A PSI-BLAST search shows that the COG5642 proteins contain a Xre family HTH domain (this relationship can be easily demonstrated using any COG5642 query and running 2–3 search iterations).

The operons containing these genes are often present on plasmids including pSymB of *Sinorhizobium meliloti* 1021, pKB1 megaplasmid of *Gordonia westfalica*, pCAR1 of *Pseudomonas resinovorans*, pTi-SAKURA of *Agrobacterium tumefaciens*, plasmids pRL11, pRL9 and pRL12 of *Rhizobium leguminosarum*. Lineage-specific expansions of this gene pair are seen in many genomes including *R. leguminosarum* (4); *S. meliloti* 1021 (4); *Azotobacter vinelandii* (4); *Burkholderia vietnamiensis* G4 (5). Despite the lack of conclusive evidence on the activity of RES-domain proteins, it is tempting to speculate that this domain is an uncharacterized nuclease, and accordingly, COG5654-Xre (COG5642) gene pair encodes a novel TAS that could be a plausible target for further experimental analysis.

Mobile two-gene modules with conflicting lines of evidence

There are several conserved two-gene operons identified by our approaches (Figure 1) that possess some but not all of the characteristic features of TAS or else possess experimentally characterized properties that do not seem to support the TAS prediction. Some of these modules could be TAS with novel mechanisms whereas others are likely to represent other classes of stress-response systems including determinants of antibiotic resistance.

The MNT-HEPN system

The MNT-HEPN pair is by far the most widespread in this class of mobile two-gene modules. MNT and HEPN genes that are predicted to form an operon are among the most abundant genes in many archaeal genomes, but their functions remain enigmatic [36-38,46]. Several combinations of MNT and HEPN domain subfamilies were detected by the procedure for finding "mobile" COGs that form conserved two-gene operons (Table 1). Hence two arguments in support of the hypothesis that the MNT-HEPN pair is a hitherto unrecognized TAS: 1) these genes form a two-component system; 2) the predicted MNT-HEPN operons appear mobile given their non-uniform distribution across genomes. In addition, both MNT and HEPN are small proteins, typically, less than 150 amino acids in length. The two MNT subfamilies (COG1708 and COG1669) are well-conserved [37] whereas HEPN domain families are much more diverged, especially, COG2250 and COG2445/COG2361 groups (Figure 6). Structures of representatives of both HEPN subfamilies have been solved and shown to belong to the nucleotidyltransferase substrate-binding domain superfamily of the four-helical bundle fold http://scop.mrc-lmb.cam.ac.uk/ scop/data/scop.b.b.dg.bi.c.html[71]. Therefore, unlike most previously identified antitoxins, HEPN is, probably, not a DNA-binding domain. The situation is similar to that observed with the HicAB system where HicB domains themselves, most likely, are not DNA-binding, but some are fused either to RHH domains or to Xre family HTH domains. The present comparative-genomic analysis revealed a subfamily of HEPN-domain-containing proteins that contain a fusion of HEPN and RHH domains (Figures 6 and 5D). This particular subfamily of HEPN proteins is expanded in Thermoproteales, especially, in Pyrobaculum (paREP1 family, Pyrobaculum aerophilum repetitive family 1 [72]) although, surprisingly, none of these genes forms an operon with MNT. Nevertheless, the fusion with the RHH domain provides an indirect connection between HEPN and known antitoxins.

The molecular mechanism of action of the putative MNT-HEPN TAS remains unknown but it is tempting to speculate that the HEPN-MNT complex targets nucleic acids analogously to numerous other TAS. More specifically, the predicted toxin, MNT, might nucleotidylates RNA molecules to tag them for degradation whereas the predicted antitoxin, HEPN, could inhibit this reaction, perhaps, via non-productive nucleotide-binding. It seems possible that there is a DNA-binding component encoded in-trans that cooperates with MNT-HEPN, making it a three-component system.

Several HEPN-MNT units are located on plasmids, such as the Rms149_p38-39 pair of genes on Pseudomonas aeruginosa plasmid Rms149 or a HEPN-MNT fusion on Agrobacterium tumefaciens plasmid pAgK84. Furthermore, in some closely related species, it is possible to trace very recent insertions or deletions of the HEPN-MNT module. For instance, in Deinococcus radiodurans, a HEPN-MNT (DR0679-DR0680) gene pair is present within a gene cluster that mostly consists of GNAT-family acetyltransferase-related genes (DR0678-DR0684), whereas D. geothermalis lacks this putative operon in the otherwise syntenic orthologous locus (Dgeo_2060-Dgeo_2065). An analogous case is seen in two strains of Thermus themrophilus where a MNT-HEPN module is inserted within the lysine biosynthesis operon in the HB8 strain but not in the HB27 strain. This apparent recent mobility of the HEPN-MNT modules is compatible with the hypothesis that these genes comprise a novel TAS.

The predicted HEPN-MNT TAS shows an unusual phyletic distribution. We have shown previously that HEPN domains of a particular subfamily (COG2250) is represented, mostly, in thermophiles and can be considered

| | 15897708 Sulsolf
 | 2 | 0 TIE <mark>S</mark> LDE <mark>L</mark> ALGIKLIKEG | FSRNS
 | ank <mark>v</mark> i | FO <mark>SW</mark> | KATTS
 | SA <mark>LT</mark> VINLEKN | IPRNEKEKEWYYKSGE | 23 | LTSV | ALELHE
 | Y−AYNGL | 119 | \
 | |

--
--

Δ
 | 1 | 7 VIESISDILLSLTLWKEG | YTRNS
 | ACKA | | K D T.M
 | SALWUTNEDKI | TATAKDDKEBEMIKKKAH | 23 | LURV |
 | V-OVNGE | 119 | ì
 | |
| 11 | 15920186 Sultoko
 | 1 | 9 VVESIVENDIALEMIKEG | TIKNA
 | CARA | | IKCNVC
 | CALIVERINE | I K-CKDEKEPSWYENUCY | 23 | WWW |
 | F-SYNCE | 120 | I
DO DEE
 | 51 |
| | 18311927 Purporo
 | | 1 VIENIVECDIAVEELEDC | TUDNA
 | ACKA | |
 | ATTOTETORI | MKUNNTDEEDKMI VEDVU | 25 | ATCT |
 | V-OVHCP | 125 | раны
 | - |
| | 10212225 Durporo
 | - 1 | Q ENENAAEANI AFEMI DDE | TVONA
 | | ZMAT |
 | ADDINELDINI | | 2.0 | AUVE |
 | T - AVNCE | 110 | 7
 | |
| | 16909902 Sylcolf
 | - | A STOREUVYPENEERICKC | DIVON
 | CERV | | FEATE
 | T T VASELCNI | TT-NNUKNKCDWKSENIE | 15 | TWE | ADDDDD
 | CE-CEUEI | 07 | /
\
 | |
| | 150000000000000
 | | - UUUUUUUUUUUUUUUU | _uuuuu
 | | JUUUU | IDDUDU
 | | | 15 | LUUUU |
 | | 21 | `
 | |
| | 15020201 0014-00
 | - | | | |
 | CERN | unnn
212 <mark>12</mark> 2 |
 | A DEKENI DI | | 10 | CHCN |
 | IN CRUEN | 1 4 4 |
 | |
| | 10211707 Duncana
 | | 1 AFLAKKIMKECEEILKIS | DAIQAS
 | CDKL | | TEELVE
 | ALAEKENLPE | IIQUAMARGRWIIIILLI | 10 | GWSN | GILLHV
 | W-GEHEA | 121 |
 | |
| | 10311/9/ Pyraero
 | - | ALLALGMIREGLAIVERG | DVAQA
 | | INAV | LEGVE
 | ALAF SRGLPI | AELAASKGRWIVALLD | 12 | AWDA | AIFLHV
 | NGF EVR | 100 | ракьг
 | -0 |
| | 18314224 Pyraero
 | 5 | I LKL <mark>U</mark> EKYLSEAEQLAQRG | DILQA
 | SEKA | NGAA | AQLVr
 | AVAAKRG | VELKSHGDLWRFVTK | 12 | LWHV | ANSLIV
 | N-FTRHG | 136 | ļ
 | |
| | 18313905 Pyraero
 | 4 | 4 LALYEKY <mark>L</mark> REAESLYEKG | NLAQA
 | GERY | NGAV | (TALLA
 | NATAEKRG | MPHYSQRDYAVIIER | 12 | GFRL | AEGLHA
 | AN-F. X HNF. | 129 | (
 | |
| | 1/229931 Nossp
 | 3 | 6 EKVGLLLQEQGEHRHSIY | FLIQAI
 | MERY | /R <mark>AK</mark> | TELEV
 | /DAKNPYFR | KRERTHSIEDALDFL | 23 | GEIK | FNWLHN
 | NLRYPFY | 134 | \
 | |
| | 15643760 Themari
 | 1 | 2 RRRARECLDDAKLLLKNE | RLHSA
 | VNRI | í Y <mark>al</mark> | FYQVS
 | SALLL-AKG | LSFSKHSGVLAAFNR | 14 | FYNR | MFEHRF
 | (TGD Y GEL | 100 | 1
 | |
| | 20091443 Metacet
 | 2 | 6 LSIAERF <mark>L</mark> HSAQKNLEIE | EYEMV
 | QLA <mark>A</mark> | Y N <mark>S</mark> A | AFHS <mark>A</mark> F
 | RA <mark>LL</mark> F-SKG | YTERSHSCLGIALNH | 17 | MRVS | SHNVQY
 | GGT <mark>F</mark> VTF | 117 |
 | |
| | 11497913 Arcfulg
 | | 8 IRKAEKLVQDAKKEFEMG | LYERCO
 | CST <mark>A</mark> | YY <mark>AM</mark> | 1FHAAF
 | KA <mark>ML</mark> L-GYG | RDSKTHRGTIYLIWE | 13 | KLSR | <mark>a</mark> fdlre
 | ESD <mark>y</mark> giy | 95 | COG18
 | 395 |
| | 15668785 Metjann
 | 1 | .7 IEI <mark>A</mark> EEN <mark>L</mark> SAAKILFENK | LYRDA
 | VAR <mark>A</mark> | YY <mark>AI</mark> | FHS <mark>A</mark> F
 | KA <mark>LL</mark> L-TKN | LNPKKHAGVIKMFGL | 14 | IITK | SYNLRW
 | IKAD <mark>y</mark> ttd | 105 | /
 | |
| | 18977737 Pyrfuri
 | 5 | 53 MVE <mark>A</mark> KRT <mark>L</mark> ASAYSDLREG | YYEWA:
 | s f K <mark>a</mark> g | 2Q <mark>AA</mark> | <mark>i</mark> ela <mark>v</mark> k
 | KA <mark>IL</mark> R-GLS | FAPIGHSITKLLREL | 13 | FAMK | LDRNY I
 | ALR <mark>y</mark> pda | 140 | \
 | |
| | 14521103 Pyrabys
 | 1 | .1 IKQ <mark>A</mark> ERN <mark>L</mark> RSALRDLEGG | DYEWAS
 | sfk <mark>a</mark> g | 2Q <mark>AA</mark> | <mark>i</mark> ela <mark>v</mark> k
 | KA <mark>LL</mark> R-GMG | SAPIGHSITRLLRNL | 13 | IAMK | LDRNYM
 | 1ASR <mark>Y</mark> PHV | 98 |
 | |
| | 15921131 Sultoko
 | | 6 KRN <mark>A</mark> LDF <mark>F</mark> AGAEYDIRNG | KHNSAI
 | MSH <mark>V</mark> I | EQ <mark>SL</mark> | <mark>l</mark> qla <mark>l</mark> k
 | KY <mark>VL</mark> FQLKG | SFEKTHDIISLLDEV | 18 | TLEV | IRESYI
 | KSR <mark>y</mark> FHF | 99 | 1
 | |
| | 15920981 Sultoko
 | 1 | .0 KER <mark>S</mark> KYF <mark>Y</mark> KESMNDSKNK | RYDIA
 | lfh <mark>l</mark> i | eq <mark>al</mark> | _QLG <mark>L</mark> k
 | KA <mark>YL</mark> LKNKG | DFPRTHSLRDLI-EL | 15 | IVSL | LTDAYV
 | /GSR <mark>Y</mark> LLR | 99 | 1
 | |
| | 18313583 Pyraero
 | 1 | .4 ITM <mark>A</mark> ERT <mark>L</mark> SSARLDASHG | EYNWA
 | CFK <mark>a</mark> i | hq <mark>aa</mark> | <mark>efal</mark> f
 | KA <mark>LL</mark> Y-GVG | RPARGHSLTHLLGEV | 12 | LCRL | LDKFYV
 | /PTRCVDA | 100 | 1
 | |
| | 18311673 Pyraero
 | 1 | .0 LEE <mark>A</mark> EDD <mark>F</mark> NAAADLARLG | RYAKA
 | CFL <mark>S</mark> Q | 2Q <mark>AA</mark> | <mark>eka</mark> lk
 | KA <mark>LL</mark> IAKAG | RYERTHSVYALLLAA | 13 | AGEE | LDRHYV
 | /LSR <mark>Y</mark> PNA | 98 | 1
 | |
| | 14590309 Pyrhori
 | 1 | .3 IVE <mark>A</mark> KRT <mark>L</mark> SSAYSDLKEG | YYEWAS
 | s f k <mark>a</mark> q | 2Q <mark>AA</mark> | <mark>i</mark> ela <mark>v</mark> k
 | KA <mark>IL</mark> R-GLG | FAPIGHSITRLLKDL | 14 | FAME | LDRNYI
 | APR <mark>y</mark> pda | 101 | 1
 | |
| | 20808362 Theteng
 | 1 | .4 LET <mark>A</mark> EKD <mark>Y</mark> NTMLHLYESK | DYHWSI
 | lfm <mark>g</mark> i | HL <mark>VI</mark> | EKL <mark>L</mark> f
 | KA <mark>LY</mark> VKNIGP- | DVPRTHDLLRIAEKI | 10 | YFDL | LTTFNI
 | TAR <mark>y</mark> pdy | 100 | 1
 | |
| | 14521555 Pyrabys
 | 1 | .0 FHR <mark>S</mark> KDY <mark>M</mark> SLANVAFKEG | KFDVA
 | IFL <mark>A</mark> (| GQ <mark>S</mark> L | QLY <mark>L</mark> F
 | KA <mark>TL</mark> VKYAD | LRLRT <mark>H</mark> SIRELLINI | 19 | LLRE | <mark>l</mark> edayi
 | DAR <mark>y</mark> epr | 104 | COG22
 | 250 |
| | 18311760 Pyraero
 | | 7 LDR <mark>G</mark> IAF <mark>M</mark> KMAYIALSSG | VYNLT
 | CFN <mark>A</mark> I | hq <mark>ai</mark> | EMF <mark>l</mark> f
 | (G <mark>LI</mark> VDATG | SRPFTCSLTELLEFL | 13 | EAEW | MEPHYI
 | LAR <mark>y</mark> par | 95 | 1
 | |
| | 15899495 Sulsolf
 | 1 | .5 ITQ <mark>A</mark> EER <mark>L</mark> DLAKTEYERK | KYNIV
 | VRL <mark>C</mark> | 2E <mark>AV</mark> | /ELS <mark>L</mark> k
 | KA <mark>CL</mark> RLVNI | EPPKFHDVGPILKNN | 17 | YSRS | <mark>l</mark> rkere
 | LSM <mark>y</mark> gde | 107 |
 | |
| | 14600946 Aerpern
 | 1 | .4 LRA <mark>A</mark> RRD <mark>L</mark> GRAEYSLKVG | DRAAA'
 | rfws | 2Q <mark>AA</mark> | EKA <mark>l</mark> f
 | kg <mark>ll</mark> lafkg | DYPKTHSIRRLLEDL | 13 | AFE- | LTQYYY
 | LSR <mark>Y</mark> PDV | 101 | 1
 | |
| | 20094728 Metkand
 | 12 | 1 LER <mark>G</mark> ERF <mark>L</mark> RSAVESEERG | WNDLA
 | ALH <mark>A</mark> H | hq <mark>av</mark> | /ELT <mark>I</mark> ř
 | KA <mark>AL</mark> IALGE | APPGTHFLGKLLGRL | 18 | ELRE | LSHAWS
 | SEVR <mark>Y</mark> GHY | 214 | 1
 | |
| | 16264326 Sinmeli
 | 19 | 96 P-S <mark>A</mark> PSF <mark>L</mark> DTAQYLVRKN | QLRHSA
 | AFE <mark>L</mark> I | HQ <mark>SI</mark> | ETAYS
 | SC <mark>LL</mark> LTLTN | YSPPSHSLKFLRGLA | 20 | WYNI | LNEAYV
 | /KAR <mark>Y</mark> SKH | 290 | 1
 | |
| | 17938549 Agrtume
 | 17 | '0 FEA <mark>G</mark> TEF <mark>F</mark> VLSCHARNSG | FTKRA
 | AFL <mark>L</mark> | 10 <mark>a i</mark> | EQAYS
 | SC <mark>VL</mark> LTLTN | YGPASHNIKFLRSLA | 20 | WFNT | INEAYV
 | /KAR <mark>Y</mark> SKH | 265 | i i
 | |
| | 15669494 Metjann
 | 1 | .5 IKR <mark>A</mark> EED <mark>L</mark> EVAKVLLKTN | HYPDS
 | VYHS | DOCV | /EKAV
 | KA <mark>VLI-LNG</mark> | IIFRRHVVSGVFRNV | 19 | KIES | LEEHWV
 | MPRYPEP | 108 | i
 | |
| | 15921028 Sultoko
 | 1 | 0 KRR <mark>A</mark> LRF <mark>L</mark> EEAKRDLSEG | YYDIG
 | AFHV | EOAL | OLYIK
 | KA <mark>VI</mark> FELFG | KDYEGHGIRELIGYL | 25 | OLVD | IEDAYI
 | DSRYEII | 110 | i
 | |
| | 15899265 Sulsolf
 | 1 | 0 FRO <mark>A</mark> LED <mark>L</mark> ATAKDTITTG | HYYAS
 | AFW <mark>A</mark> I | EÕAA | -
EKALF
 | KALLI-ENG | KIERTHDLNOLLYVI | 13 | ~
EVNK | LTLHY1
 | ISRYPDA | 97 | i
 | |
| | 14601301 Aerpern
 | 1 | 5 LROAKHTLESIRVDYEGG | FYSWAG
 | CEKAI | | EYSTR
 | AVLR-AAG | LESEGHDLMALWRRA | 12 | CTAV | LNKLYI
 | PPRYPDA | 101 | i
 | |
| | 11498201 Arcfulg
 | 1 | 1 BRRAMGEMDAAKERLKVG | DYDLTO
 | FMA | ZOAV |
 | SVILELSG | EVPRTHSTROLLSTL | 13 | OLVE | LEDAYT
 | KARYLGA | 99 | i
 | |
| | 15643379 Themari
 | - | 1 MDAAKDDLEHAKHDLEHG | FYNWAG
 | CESS | | EKAV
 | AVEO-RMG | AOAWGYSVPDFLGEL | 12 | HALE | LDKACT
 | PTRYPDA | 87 | /
 | |
| | 156/3379 103U
 | | |
 | | uua? | 00000
 | | | 12 | μμαΛ | UU
 | | | ,
 | |
| | CORSORCUS/90%
 | | s b p | 11111111
 | h | uh. | 5111111111
b
 | hb | nindo ininin | 12 | 11110.4 | h
 | 2 | |
 | |
| | 15923918 Staauro
 | 17 | OALTDDYHESKHNHY | AFFRI
 | | r F <mark>S</mark> S | SVDTGN
 | JMTTDAFT 24 | | 00 | FINK | TVDTR
 | | DTKVT | MPME
 | 110 \ |
| р | 21397441 Bacantr
 | 22 | TEOEKKIYETEEEEY | ATEDT
 | | | IT DUCK
 | JAMIDORI 2/ | | | CMKE |
 | MUTOVION | NUDEL |
 | 115 1 |
| в | 15615992 Bachalo
 | 22 | UFCSOSEWTSETEDI | ATEDT
 | | | TDVGP
 | ISMIDGET 24 | | 00 | GUILL |
 | | | KOTE
 | 115 |
| | 16000302 Dacharo
 | 22 | HI COQOEWI OBIEKE |
 | <u>ч</u> пп л - | | TDVGD
 | NO <mark>M</mark> IDGEI Z. | | Gζ | | TTTTCK
 | The Addition | | NQ I P
 | TTO 1 |
| |
 | | IFDSOTDWOSFIGEL | ALORT (
 | CHT.T. | ТЕСТ |
 | JOMTOGET 24 | | GF | FLKK | TTAYR
 | TT.VOVI.I.Z | DSGEL | YRT.T
 | 115 |
| | 18311077 Cloporf
 | 22 | LFDSQTDWQSEIGEL | ALQRI
 | GHLL. | | LDTGN
 | NDMIDGFI 24 | | GE | ELKK | LIAYR
 | TLVQYLL | DSGEL | YRLI
 | 115 |
| | 18311077 Cloperf
 | 22 | LFDSQTDWQSEIGEL
RLGEEAFLKDFKNVD | ALQRIC
STKYLI
 | GHLL
LRSS | | LDTGN
/LDLSN
 | ND <mark>MIDGFI 24</mark>
NYAVISNG 24 | | GE
FE | ELKK
EYME | LIAYRA
LVNLKI
MTLLK
 | TLVQYLLA
KLTFYASI
KLISW-FY | DSGEL
EDEFI | YRL <mark>I</mark>
FNEL
 | 115
120
260 |
| | 18311077 Cloperf
15606770 Aquaeol
20808390 Theteng
 | 22
27
170
21 | LFDSQTDWQSEIGEL
RLGEEAFLKDFKNVD
SQGEEEFKKTPMYYD | ALQRI
STKYLI
RVKYF
 | GHLL
LRSS
YQVA | IECI
IEAV
YDSL | LDTGN
/LDLSN
LFDICK
 | NDMIDGFI 24
NYAVISNG 24
KHLAPKFG 23 | | GE
FE
YE | ELKK
EYME
TVLK | LIAYRA
LVNL KI
MTL <mark>LKN</mark>
 | TLVQYLLA
KLTFYASI
KLISW-E <mark>V</mark> | DSGEL
EDEFI
SPEEL | YRL <mark>I</mark>
FNEL
YRSL
 | 115
120
260 |
| | 18311077 Cloperf
15606770 Aquaeol
20808390 Theteng
 | 27
170
21 | LFDSQTDWQSEIGEL
RLGEEAFLKDFKNVD
SQGEEEFKKTPMYYD
KEALAIEVTNEIIID | ALQRIO
STKYLI
RVKYF
GVIQRI
 | GHLL
LRSS
YQVA
FEFTI | IE <mark>C</mark> I
IEAV
YD <mark>S</mark> L
FELA | LDTGN
/LDLSN
JFDICK
AWKIMK
 | NDMIDGFI 24
NYAVISNG 24
KHLAPKFG 23
KDYLAYEG 21 | | GI
FE
YE
GE | ELKK
EYME
TVLK
MWID | LIAYRK
LVNLKI
MTLLKN
MLMDRN
 | TLVQYLLA
KLTFYASI
KLISW-EV
RTTHYNSK | DSGEL
EDEFI
SPEEL
MALEI | YRL <mark>I</mark>
FNEL
YRSL
YENI
 | 115
120
260
111 C |
| | 18311077 Cloperf
15606770 Aquaeol
20808390 Theteng
18311663 Pyraero
18311757 Duraces
 | 22
27
170
21
14 | LFDSQTDWQSEIGEL
RLGEEAFLKDFKNVD
SQGEEEFKKTPMYYD
KEALAIEVTNEIIID
LELLAQRLQTGGDIF | ALQRI
STKYLI
RVKYF
GVIQRI
ALERLI
 | GHLL
LRSS
YQVA
FEFTI
AELV | IECI
IEAV
YDSL
FELA
AQST | LDTGN
/LDLSN
LFDICK
AWKIMK
LDLAA
 | NDMIDGFI 24
NYAVISNG 24
KHLAPKFG 23
KDYLAYEG 21
AMWIAFEK 21 | | GI
FE
YE
GE
EE | ELKK
EYME
TVLK
MWID
FLRG | LIAYRK
LVNLKI
MTLLKN
MLMDRN
LVAFRN
 | TLVQYLLA
KLTFYASI
KLISW-EV
RTTHYNSK
HIIVHYYHI | DSGEL
EDEFI
SPEEL
MALEI
EEKKE | YRLI
FNEL
YRSL
YENI
MEAF
 | 115
120
260
111 C
104 C |
| | 18311077 Cloperf
15606770 Aquaeol
20808390 Theteng
18311663 Pyraero
18312757 Pyraero
 | 22
27
170
21
14
1
20 | LFDSQTDWQSEIGEL
RLGEEAFLKDFKNVD
SQGEEFKKTPMYYD
KEALAIEVTNEIIID
LELLAQRLQTGGDIF
WVSKPYESLSKAEKY | ALQRIC
STKYLI
RVKYF
GVIQR
ALERLI
AIRYSI
 | GHLL
LRSS
YQVA
FEFTI
AELVI
LIIII | IECI
IEAV
YDSL
FELA
AQST
AETV | ILDTGN
/LDLSN
LFDICK
AWKIMK
ILDLAA
/SALAI
 | NDMIDGFI 24
NYAVISNG 24
KHLAPKFG 23
KDYLAYEG 21
AMWIAFEK 21
LHIARRAL 24
LHIARRAL 24 | | GI
FE
YE
GE
EE | ELKK
EYME
TVLK
MWID
FLRG
ELER | LIAYRY
LVNLKI
MTLLKN
MLMDRN
LVAFRN
LVKLRN
 | TLVQYLLA
KLTFYASI
KLISW-EV
RTTHYNSF
IIVHYYHI
LLAHYWAV | DSGEL
EDEFI
SPEEL
MALEI
EEKKE
DDRRV | YRL <mark>I</mark>
FNEL
YRSL
YENI
MEAF
YES <mark>V</mark>
 | 115
120
260
111 C
104 C
94 C |
| | 16000253 BacSub
18311077 Cloperf
15606770 Aquaeol
20808390 Theteng
18311663 Pyraero
18311757 Pyraero
18312935 Pyraero
 | 22
27
170
21
14
1
20
25 | LFDSQTDWQSEIGEL
RLGEEAFLKDFKNVD
KEALAIEVTNEIIID
KEALAIEVTNEIID
KEALAQRLQTGGDIF
NSRPYESLSKAEKY
IRRRGVNWDDVFELY | ALQRIC
STKYLI
RVKYF
GVIQRI
ALERLI
AIRYSI
AVLHAI
 | GHLL
LRSS
YQVA
FEFTI
AELV
LIII
LQIH | IECI
IEAV
YDSL
FELA
AQST
AETV
SQSI | ILDTGN
/LDLSN
LFDICK
AWKIMK
ILDLAF
/SALAI
IDYLI
 | NDMIDGFI 24
NYAVISNG 24
KHLAPKFG 23
KDYLAYEG 21
AMWIAFEK 21
LHIARRAL 24
LHTCAVVG 23 | | GE
FE
GE
EE
CI
RE | ELKK
EYME
TVLK
MWID
FLRG
ELER
ALRR | LIAYRY
LVNLKI
MTLLKN
MLMDRN
LVAFRN
LVKLRN
LVGFRN
 | TLVQYLLA
KLTFYASI
KLISW-EV
RTTHYNSF
IIVHYYHI
LLAHYWAV
IIVHYGEI | DSGEL
EDEFI
SPEEL
MALEI
EEKKE
DDRRV | YRLI
FNEL
YRSL
YENI
MEAF
YES <mark>V</mark>

 | 115
120
260
111 C
94 C
108 2 |
| | 16080263 BacSub 18311077 Cloperf 15606770 Aquaeol 20808390 Theteng 18311633 Pyraero 18312935 Pyraero 18312935 Pyraero 14399752 Arcfulg 19212047 Puraero
 | 22
27
170
21
14
1
20
25
21 | LFDSQTDWQSEIGEL
RLGEEAFLKDFKNVD
KEALAIEVTNEIIID
LELLAQRLQTGGDIF
WSKPYESLSKAEKY
IRRRGVNWDDVFELY
NWI-EEAKVDKKSRL | ALQRIC
STKYLI
RVKYF
GVIQRI
ALERLI
AIRYSI
AVLHAI
AVLHAI
 | GHLL
LRSS
YQVA
FEFTI
AELV
LIIII
LQIH
AQEA | IECI
IEAV
YDSL
FELA
AQST
AETV
SQSI
/EAA | ILDTGN
/LDLSN
LFDICK
AWKIMK
ILDLAP
/SALAI
IIDYLI
ACDLVP
 | NDMIDGFI 24
NYAVISNG 24
KHLAPKFG 23
KDYLAYEG 21
MMIAFEK 21
LHIARRAL 24
LHTCAVVG 23
AMFLRDSG 21 | | GI
FE
GE
EE
CI
RE
SE | ELKK
EYME
TVLK
MWID
FLRG
ELER
ALRR
CLKV | LIAYRY
LVNLKI
MTLLKN
MLMDRN
LVAFRN
LVKLRN
LVGFRN
ANGLRN
 | TLVQYLLA
KLTFYASI
KLISW-EV
RTTHYNSK
IIVHYYHI
ILLAHYWAV
IIVHYGEI
RLVHYNGI | DSGEL
EDEFI
SPEEL
MALEI
EEKKE
DDRRV
NVEKI
DDRIA | YRLI
FNEL
YRSL
YENI
MEAF
YES <mark>V</mark>

LNSI
 | 115
120
260
111 C
94 C
108 2
114 4 |
| | 1606023 BacSub 1831107 Cloperf 15606770 Aquaeol 20808390 Theteng 1831163 Pyraero 1831235 Pyraero 18312035 Pyraero 11499752 Arcfulg 18312047 Pyraero 15921020 Sultop
 | 22
27
170
21
14
1
20
25
21
21 | LFDSQTDWQSEIGEL
RLGEAFLKDFKNVD
SQGEEFKKTPMYYD
KEALAIEVTNEIIID
LELLAQRLQTGGDIF
WSKPYESLSKAEKY
IRRRGVNWDDVFELY
VVKRGYDLSNWDDUM
VVKRGYDLSNWDDUM | ALQRIC
STKYLI
RVKYFT
GVIQRI
ALERLI
AIRYSI
AVLHAI
AVYKAI
RILHAI
 | GHLL
LRSS
YQVA
EEFTI
AELV
LIIII
LQIH
AQEA
LQLQ | IECI
IEAV
YDSL
YELA
AQST
AETV
SQSI
YEAA
AQAL | ILDTGN
/LDLSN
LFDICK
AWKIMK
ILDLAF
/SALAI
IIDYLI
ACDLVF
LIDMAQ
 | NDMIDGFI 24
NYAVISNG 24
KHLAPKFG 23
KDYLAYEG 21
HMWIAFEK 21
HIARRAL 24
HTCAVVG 23
AMFLRDSG 21
PRAASLLG 23 | | GI
FE
GE
EE
CI
RE
SE
LA | ELKK
EYME
TVLK
FLRG
ELER
ALRR
CLKV
LYRA | LIAYRK
LVNLKI
MTLLKN
MLMDRN
LVAFRN
LVKLRN
LVGFRN
ANGLRN
VVGFRN
VVGFRN
 | TLVQYLLA
KLTFYASI
KLISW-EV
RTTHYNSM
IIVHYYHI
LLAHYWAV
IIVHYGEI
RLVHYNGI
VLVHYASI | DSGEL
EDEFI
SPEEL
MALEI
EEKKE
DDRRV
NVEKI
DDRIA
DTDRV | YRLI
FNEL
YRSL
YENI
MEAF
YESV

LNSI
DEIL
 | 115
120
260
111 C
94 C
108 2
114 4
113 4 |
| | 160602/3 BadSub1 18311077 Cloperf 15606770 Aquaeol 20808390 Theteng 18311663 Pyraero 18312935 Pyraero 184312935 Pyraero 184312937 Arcfulg 18312030 Sultako 1499752 Arcfulg 1831000 Sultako
 | 22
27
170
21
14
1
20
25
21
21 | LFDSQTDWQSEIGEL
EGEAFLKDFKNVD
 | ALQRIC
STKYLI
RVKYFT
GVIQRI
ALERLI
AIRYSI
AVLHAI
AVYKAI
RILHAI
AILHGI
 | GHLL
LRSS
YQVAY
FEFTI
AELV7
LIII7
LQIH3
AQEAY
LQLQ2
LQIQ2 | IECI
IEAV
YDSL
FELA
AQST
AETV
SQSI
VEAA
AQAL
AQIV | ILDTGN
/LDLSN
LFDICK
AWKIMK
FLDLAF
/SALAI
IIDYLI
ACDLVF
LIDMAQ
/LDILQ
 | NDMIDGFI 24
VYAVISNG 24
KHLAPKFG 23
KDYLAYEG 21
AMWIAFEK 21
LHIARRAL 24
LHICAVVG 23
AMFIRDSG 21
DRASLLG 23
DRLISNMG 23 | | GI
FE
GE
CI
RE
SE
LA
EK | ELKK
EYME
TVLK
ELRG
ELER
ELER
CLKV
LYRA
FLNA | LIAYRY
LVNLKI
MTLLKN
MLMDRN
LVAFRN
LVKLRN
LVGFRN
ANGLRN
VVGFRN
VVGFTN
 | TLVQYLLA
KLTFYASI
KLISW-EV
RTTHYNSK
IIVHYYHI
ILLAHYWAV
IIVHYGEI
RLVHYNGI
VLVHYASI
IIVHYSEV | DSGEL
EDEFI
MALEI
EEKKE
DDRRV
DDRIA
DDRIA
DTDRV
NLGTV | YRLI
FNEL
YRSL
YENI
MEAF
YESV
LNSI
DEIL
DEIL
 | 115
120
260
111 C
104 C
94 C
108 2
114 4
113 4
113 5 |
| | 16060263 BadSubt 18311077 Cloperf 15606770 Aquaeol 20808390 Theteng 18311663 Pyraero 18312935 Pyraero 18312935 Pyraero 18312937 Pyraero 18312047 Pyraero 15921020 Sultoko 11500009 Arcfulg 20002020 Werburge
 | 22
27
170
21
14
1
20
25
21
21
21
4 | LFDSQTDWQSEIGEL
SQGEEEFKKTPMYD
KEALAIEVTNEIIID
LELLAQRLQTGGDIF
NVSKPYESLSKAEKY
IRRRGVNWDDVFELY
NWI-EEAKVDKKSRL
VVKRGYDLSNWDDLM
VVEKGYDLNWRDQM
LSEIPERVKTPIEVS | ALQRIC
STKYLI
RVKYF
GVIQRI
ALERLI
AIRYSI
AVLHAI
AVLHAI
RILHAI
GVFYNI
GVFYNI
 | GHLL
LRSS
YQVA
FEFTI
AELV/
LIII/
LQIHS
AQEA
LQLQ/
LQIQ
LLTS | IECI
IEAV
PELA
AQST
AETV
SQSI
VEAA
AQAL
AQIV
IESA | ILDTGN
JEDICK
JEDICK
AWKIMK
FLDLAF
JSALAI
IIDYLI
ACDLVF
JIDMAÇ
VLDILÇ
AMDISF
 | NDMIDGFI 24
YYAVISNG 24
KHLAPKFG 23
CNVLAYEG 21
AMWIAFEK 21
LHIARRAL 24
LHICAVVG 21
AMFLRDSG 21
ARFLRDSG 23
ARFLRDSG 23
QRLLSNMG 23
ANLVKDLG 23
ANLVKDLG 24 | | GI
FE
GE
CI
RE
SE
LA
EK
AE | ELKK
EYME
TVLK
MWID
FLRG
ELER
CLKV
CLKV
ILYRA
FLNA
GLKK | LIAYRA
LVNLKI
MTLLKN
MLMDRN
LVAFRN
LVKLRN
LVGFRN
ANGLRN
VVGFRN
VVGFRN
OVGFRN
 | TLVQYLLA
KLTFYASI
KLISW-EV
RTTHYNSK
IITVHYYHI
ILLAHYWAV
IIVHYGEI
RLVHYNGI
VLVHYASI
IIVHYSEV
WLVHYNSV | DSGEL
EDEFI
SPEEL
MALEI
EEKKE
DDRRV
DDRRV
DDRIA
DTDRV
NLGTV
DKELV | YRLI
FNEL
YRSL
YENI
MEAF
YESV

LNSI
DEIL
DEIL
LSS-
 | 115
120
260
111 C
104 C
94 C
108 2
114 4
113 4
113 5
95
117 |
| | 160802/3 BadSub1 18311077 Cloperf 15606770 Aquaeol 20808390 Theteng 18311633 Pyraero 18312935 Pyraero 18312935 Pyraero 11499752 Arcfulg 18313047 Pyraero 15921020 Sultoko 1500009 Arcfulg 20090702 Metmaze
 | 22
27
170
21
14
1
20
25
21
21
21
4
24 | LFDSQTDWQSEIGEL
RLGEEAFLKDFKNVD
KEALAIEVTNEIIID
LELLAQRLQTGGDI
NVSKPYESLSKAEKY
NWI-EEAKVDKKSRL
VVKRGYDLSNWDDLM
VVEKGYDLSNWDDLM
LSEIPERVKTPIEVS
QYSFEEIEQNYVLRG | ALQRIC
STKYL
RVKYF
GVIQR
ALERL
AIRYS
AVLHA
AVLHA
AVYKA
RILHA
GVFYN
AVERY
 | GHLL
LRSS
YQVAX
FEFTI
AELVY
LIIII
LQIHS
AQEAX
LQLQ
LLTS
LQISI | IECI
IEAV
YDSL
YELA
AQST
AETV
SQSI
YEAA
AQA
L
AQIV
IESA | ILDTGN
VLDLSN
LFDICK
AWKIMK
FLDLAF
VSALAI
IIDYLI
ACDLVF
LIDMAÇ
VLDILÇ
AMDISF
MLDIGE
 | NDMIDGFI 24
VYAVISNG 24
KHLAPKFG 23
AMWIAFEK 21
LHIARRAL 24
LHICAVVG 23
AMFLRDSG 21
PRASLLG 22
PRLLSNMG 23
AMLVKDLG 23
SIIISMEK 24 | | GI
FE
GE
EE
CI
RE
SE
LA
EK
AE | ELKK
EYME
TVLK
MWID
ELER
ALRR
CLKV
LYRA
ELNA
GLKK
KIEP | LIAYR
LVNLKI
MTLLKN
MLMDRN
LVAFRN
LVKLRN
LVGFRN
ANGLRN
VVGFRN
VVGFRN
AVGFRN
AVGFRN
AVGFRN
 | TLVQYLLA
KLTFYASI
RTTHYNSY
I IVHYYHI
I LAHYWAV
I IVHYGEI
RLVHYNGI
VLVHYASI
I IVHYSEV
WLVHYNRV
I LVHYARV
I LVHYARV | DSGEL
EDEFI
SPEEL
MALEI
EEKKE
DDRRV
NVEKI
DDRIA
DTRV
NLGTV
VLGTV
ZEVDKL | YRLI
FNEL
YRSL
YENI
MEAF
YESV

LNSI
DEIL
DEIL
LSS-
YEKL
 | 115
120
260
111 C
104 C
94 C
108 2
114 4
113 5
95
117
110 |
| | 16060233 BadSub1 18311077 Cloperf 15606770 Aquaeol 20808390 Theteng 1831163 Pyraero 18312935 Pyraero 18313047 Pyraero 18313047 Pyraero 1590202 Sultoko 1500009 Arcfulg 20090702 Metmaze 14520238 Pyraero
 | 22
27
170
21
14
1
20
25
21
21
21
4
24
27
26 | LFDSQTDWQSEIGEL
EGEAFLKDFKNVD
KEALAIEVTNEIIID
LELLAQRLQTGGIF
NVSKPYESLSKAEKY
IRRRGVNWDDVFELY
VWRGYDLSNWDDLM
VVERGYDLSNWDDLM
VERGYDLNYWRDQM
LSEIPERVKTPIEVS
DLGLEEFLTNSHIRY
DLGLEEFLTNSHIRY | ALQRIC
STKYL
RVKYF
GVIQR
ALERL
AIRYS
AVLHA
AVYKA
RILHA
GVFYN
AVERY
AXEYL
CMYER
 | SHLL
LRSS
YQVA
FEFTI
AELVY
LIII
LQIH
AQEA
LQLQ
LQIQ
LLTS
LQISI
LIMA | IECI
IEAV
YDSL
YELA
AQST
AETV
SQSI
YEAA
AQAL
AQIV
IESA
LECM | ILDTGN
VLDLSN
JFDICK
AWKIMK
FIDLAF
VSALAI
IIDYLI
ACDLVF
JIDMAQ
VLDILQ
AMDISF
MLDIGE
AFSICN
 | NDMIDGFI 24
VYAVISNG 24
VYAVISNG 24
VYAVISNG 24
VHIAPEK 2
LHIARTAL 24
LHIARTAL 24
LHICAVVG 23
VAMFLRDSG 21
VRASLLG 22
VRLISNMG 23
VRLISNMG 23
VRLISNMG 24
VRLVVRKG | | GI
FE
GE
CI
RE
SE
LA
EK
AE
AE | ELKK
EYME
FURG
ELER
ALRR
CLKV
ELYRA
GLKK
KIEP
RLAQ | LIAYR
LVNLKI
MTLLK
MLMDR
LVAFR
LVKLR
LVGFR
ANGLR
VVGFR
VVGFT
CNGLR
AVGFR
MAKFR
MAKFR | TLVQYLLA
KLTFYASI
KLISW-EV
RTTHYNSK
IIVHYYHI
LLAHYWAV
IIVHYGEI
RLVHYNGEI
VLVHYASI
IIVHYSEV
WLVHYNRV
ILVHYARV
MLVHYWRI
 | DSGEL
EDEFI
SPEEL
MALEI
EEKKE
DDRRV
NVEKI
DDRIA
DDRIA
VLGTV
VLGTV
EVDKL
DDEKY | YRLI
FNEL
YRSL
YENI
MEAF
YESV

LNSI
DEIL
DEIL
LSS-
YEKL
FEIL | 115
120
260
111 C
94 C
108 2
114 4
113 5
95
117
119
 |
| | 180302/23 BadSub1 18311077 Cloperf 15606770 Aquaeol 20808390 Theteng 18311663 Pyraero 18312935 Pyraero 18312935 Pyraero 18312935 Pyraero 15921020 Sultoko 1500009 Arcfulg 20090702 Metmaze 14520238 Pyraero 156778322 Metthar
 | 22
27
170
21
14
1
20
25
21
21
21
4
24
27
26 | LFDSQTDWQSEIGEL
RLGEAFLKDFKNVD
KEALAIEVTNEIIID
KEALAIEVTNEIID
NEULAQRLQTGGDIF
NWI-EEAKVDKKSRL
VKRGYDLSNWDDLM
VKRGYDLSNWDDLM
VKRGYDLSNWDDLM
LSEIPERVKTPIEVS
QYSFEEIEQNVULRG
PESFGEFSELGLIRD | ALQRIC
STKYL
RVKYF
GVIQR
ALERL
AIRYS
AVLHA
AVYKA
RILHA
GVFYN
AVERY
AXVERY
GVFYN
GMYKR
 | SHLL
LRSS
YQVA
FEFTI
AELVY
LIIII
LQIH
AQEA
LQLQ
LQIQ
LLTS
LQISI
LIMA
LEFA | IECII
IEAV
YDSL
FELA
AQST
AETV
SQSI
VEAA
AQAL
AQIV
IESA
LECM
IGGA | ILDTGN
VLDLSN
LFDICK
AWKIMK
FLDLAF
VSALAI
IIDYLI
ACDLVF
LIDMAC
VLDILC
AMDISF
MLDIGE
AFSICN
VYDICS
 | NDMIDGFI 2/
VIAVISNG 2/
VIAVISNG 2/
VIAVISNG 2/
VIAVEG 2/
VIA
VIA
VIA
VIA
VIA
VIA
VIA
VIA
VIA
VIA | | GE
YE
GE
CE
CE
CE
CE
CE
CE
C | ELKK
EYME
FLRG
ELER
CLKV
CLKV
CLKV
CLKV
CLKK
EFLNA
CLKK
EFLNA
CLKK
EFLNA | LIAYR
LUNLKI
MTLLK
MLMDR
LVAFR
LVKLR
LVKFR
ANGLR
VVGFR
VVGFR
VVGFR
AVGFR
AVGFR
MAKFR
MRGFR | TLVQYLLA
KLTFYASI
KLISW-EV
RTTHYNSK
IIVHYYHI
LLAHYWAV
IIVHYGEI
RLVHYGEI
VLVHYASI
IIVHYSEV
WLVHYNRV
ILVHYARV
MLVHYNRV
ILVHYARV
 | DSGEL
EDEFI
SPEEL
MALEI
EEKKE
DDRRV
DDRIA
DDRIA
DDRIA
VILGTV
VEVDKL
DDEKV
DDEKV
DDEK | YRLI
FNEL
YRSL
YENI
MEAF
YESV

LNSI
DEIL
DEIL
LSS-
YEKL
FEIL
LEYS | 115
120
260
111 C
94 C
94 C
108 2
114 4
113 4
113 5
95
117
119
119
107 -
 |
| | 16080263 BadSubJ 18311077 Cloperf 15606770 Aquaeol 20808390 Theteng 18311663 Pyraero 18312935 Pyraero 18312935 Pyraero 18312935 Pyraero 19312047 Pyraero 15921020 Sultoko 11500009 Arcfulg 20090702 Metmaze 14520238 Pyraero 15678332 Mether 18133349 Pyraero
 | 22
27
170
21
14
1
20
25
21
21
21
4
24
27
26
14 | LFDSQTDWQSEIGEL
RLGEEAFLKDFKNVD
KEALAIEVTNEIIID
KEALAIEVTNEIID
KEALAIEVTNEIID
WSKPYESLSKAEKY
NWI-EEAKVDKKSRL
VVKRGYDLSNWDDLM
VVERGYDLSNWDDLM
LSEIPERVKTPIEVS
QYSFEEIEQNYVLRG
DLGLEEFLTNSHIRY
 | ALQRIC
STKYLL
RVKYF
GVIQR
ALERL
ALERL
AVKAA
RILHA
AVKAA
GVFYN
AVERY
AAKYLL
GIERL
GUERL
 | SHLL
LRSS
YQVA
FEFTI
AELV7
LIII
LQIH
LQIQ
LQIQ
LLTS
LQIS
LITS
LEFA
EQLI | IECII
IEAV
YDSL
FELA
QST
AETV
SQSI
YEAA
QAL
AQIV
IESA
LECM
IGGA
YENV | ILDTGN
VLDLSN
VLDLSN
VLDLAF
VSALAI
IIDVLI
ACDLVF
JIDMAÇ
VLDILÇ
AMDISF
MLDIGE
AFSICN
VYDICS
VLDLGV
 | NDMIDGFI 22
VYAVISNG 22
KDYLAYEG 21
MAWIAFEK 21
LHIARRAL 22
LHICAVVG 23
MAFLRDSG 21
QRAASLLG 23
PAASLLG 23
MILVKDLG 23
UHISVEKG 24
STILNSEK 24
STILNSEK 24
MALSALG 24
MALSALG 24 | | GI
FE
GE
EE
RE
RE
RE
RE
RE
R | ELKK
EYME
TVLK
MWID
FLRG
ELER
ALRR
CLKV
LYRA
GLKK
SLAQ
KIEP
RLAQ
KIEA | LIAYR
LVNLKI
MTLLKN
MLMDRN
LVAFRN
LVKFRN
ANGLRN
VVGFRN
VVGFRN
AVGFRN
MAKFRN
MRGFRN
LAGLRN
VNGTR
 | TLVQYLLA
KLTFYASI
KLTFYASI
RTTHYNSK
IIVHYYHI
LLAHYWA
IIVHYGEI
RLVHYNGI
VLVHYASI
IIVHYSEV
WLVHYNRV
ILVHYSEV
MLVHYNRI
IVVRYGKI
IIVHYAAV
IIVHYAAV | DSGEL
EDEFI
SPEEL
MALEI
EEKKE
DDRRV
DDRRV
DDRIV
DDRIV
DDRIV
DDRIV
DDRIV
DDRIT
EPEKI | YRLI
FNEL
YRSL
YENI
MEAF
YESV
DEIL
DEIL
LSS-
YEKL
FEIL
FEIL
LEYS
 | 115
120
260
111 C
94 C
94 C
108 2
114 4
113 4
113 5
95
117
119
119
119
107 |
| | 1803023 BadSub1 18311077 Cloperf 15606770 Aquaeol 20808390 Thetang 18311663 Pyraero 18311235 Pyraero 18312935 Pyraero 11499752 Arcfulg 1831009 Arcfulg 20090702 Metmaze 14521420 Pyraero 15502032 Mether 1831334 Pyraero 14321460 Purcabuston | 22
27
170
21
14
20
25
21
21
21
21
24
24
27
26
14
18 | LFDSQTDWQSEIGEL
EGEAFLKDFKNVD
KEALAIEVTNEIIID
KELLAQRLQTGGDIF
VUKRGYDLSKAEKY
NVKRGYDLSNWDDLW
VVKRGYDLSNWDDLM
VVKRGYDLSNWDDLM
VVKRGYDLSNWDDLM
VVKRGYDLSNWDLM
VKRGYDLNYWRDQM
 | ALQRIG
STKYLL
RVKYF
GVIQR
ALERL
AIRYS
AVLHA
AVYKA
GVFYN
AVYKR
GIERL
GVFYN
GIERL
AVLYS
SAVW | SHLL
LRSS
YQVA
FEFTI
AELV7
LIII
LQIH
LQIQ
LQIQ
LLTS
LQISI
LIMA
LEFA
EQLII | IECI
IEAV
YDSL
AQSL
AETV
SQSI
YEAA
AQAL
AQIV
IESA
IEGAA
YENV
IQAL | ILDTGN
VLDLSN
VLDLSN
VLDLCK
WKIMK
FLDLAF
VSALAI
IIDYLI
ACDLVF
VIDULQ
VLDILQ
VLDILQ
VYDICS
LLDLGV
VMDIVF | NDMIDGFI 22
VYAVISNG 24
VYAVISNG 24
VYAVISNG 24
VILAYEG 21
MAWIAFEK 21
LHIARRAL 24
HIARRAL 24
MARANG 23
VILATCAVVG 23
VILATCAVVG 23
VILATCAVVG 23
VILATCAVVG 23
VILATCAVVG 23
VILATCAVVG 23
VILATCAVCG 23
VILATCAVCG 24
VILATCAVCG | | GE
FE
GE
EE
CE
RE
SE
EK
AE
AE
AE
AE
AE
AE
A | ELKK
EYME
TVLK
MWID
FLRG
ELER
CLKV
CLKV
GLKK
GLKK
KIEP
RLAQ
KIKA
FLRA
LLRA | LIAYR
LVNLKI
MTLLKN
MLMDRN
LVAFRN
LVAFRN
ANGLRN
VVGFRN
VVGFTN
CNGLRN
AVGFRN
MAKFRN
MAKFRN
MAGFRN
LAGLRN
YNGLRN | TLVQYLLA
KLTFYASI
KLTFYASI
RTTHYNSY
IIVHYYAI
IIVHYGEI
RLVHYMGI
VLVHYASI
VLVHYASI
WLVHYNRV
IIVHYAKV
IIVHYAKV
IIVHYAKV
IIVHYAKV
ILVHYAAV
ALAHYNHI | DSGEL
EDEFI
SPEEL
MALEI
EEKKE
DDRRV
DDRRV
DDRIV
DDRIV
DDRIV
DDRIV
DELV
DDRIT
EPERI
DDSW | YRLI
FNEL
YRSL
YENI
MEAF
YESV
LNSI
DEIL
LSS-
YEKL
FEIL
FEIL
LEYS
ERAL | 115
120
260
111 C
94 C
108 2
108 2
114 4
113 5
95
117
119
119
119
119
110
114 4
113 4
114 4
115 |
| | 16060263 BadSubt 18311077 Cloperf 15606770 Aquaeol 20808390 Theteng 18311663 Pyraero 18312935 Pyraero 18312935 Pyraero 18312935 Pyraero 15921020 Sultoko 1500009 Arcfulg 20090702 Metmaze 14520238 Pyraero 156778322 Metther 18313394 Pyraero 1498552 Arcfulg 142521460 Pyrabys 20806962 Theteng | 22
27
170
21
14
10
25
21
21
21
21
21
24
24
27
26
14
18
41
30 | LFDSQTDWQSEIGEL
RLGEAFLKDFKNVD
KEALAIEVTNEIIID
KEALAIEVTNEIID
RRRGVNBDVFELY
NWI-EEAKVDKKSRL
VKRGYDLSNWDDLM
VKRGYDLSNWDDLM
VKRGYDLSNWDDLM
VKRGYDLSNWDDLM
VSEGEDNYVLRG
DLGLEEFLTNSHIRY
PEFGEFSELGLIRD
FFGEFSELGLIRD
RATEHAMSDEVRKR
NLDVEEFLKNKHVSS | ALQRIG
STKYLL
RVKYF
GVIQR
ALERLS
AVLHA
AVYKA
AVLHA
AVYKA
GVFYN
AVERY
AVERY
GIERL
GVFYN
AVERY
GIERL
SAKYN
AAFSF | GHLL
LRSS
YQVA
FEFTI
AELVY
LIIII
LQIHS
LQLQ
LQIQ
LQIQ
LLTS
LQISI
LIMA
LEFA
EQLI
IMTA
LLVA | IECII
IEAV
YDSL
FELAAQS
TELAAQS
VEAA
AQAL
VEAA
QAL
IES
AQI
VEA
VEN
VEN
VEN
VEN
VEN
VEN
VEN
VEN
VEN
VEN | ILDTGN
VLDLSN
VLDLSN
VLDLAF
VSALAI
IIDYLI
ACDLVF
VLDILÇ
VLDILÇ
VLDILÇ
VYDICS
LLDLGV
VMDIVF
CIDIAY | NDMIDGFI 22
VYAVISNG 24
VYAVISNG 24
VKILAPKFG 23
VDYLAYEG 21
VAMWIAFEK 21
VAMWIAFEK 21
VAMWIAFEK 21
VAMVIAFEK 22
VALLSNNG 23
VALLSNNG 23
VALVNKG 24
VALVNKG 24
VALVNKG 25
VALVNKG 24
VALVNKG 24
VALVNKG 24
VALVNKG 25
VALVNKG 25
VALVNKG 24
VALVNKG 24
VALVNKG 25
VALVNKG 25
VALVNK | | GC
FE
GE
GE
CC
RE
SE
LA
EK
AE
AE
AE
FF
AE
AE
AE
AE | ELKK
EYME
TVLK
EFLRG
ELER
ELER
CLKV
LYRA
GLKK
KIEP
RLAQ
KIKA
ILRA
CLLRR
RLIL
KLVE | LIAYR
LVNLKI
MTLLKN
MLMDRN
LVAFRN
LVKLRN
LVGFRN
VVGFRN
VVGFRN
VVGFRN
ANGFRN
MAKFRN
MAGFRN
MAGFRN
MAGFRN
MAGFRN | TLVQYLLA
KLTFYASI
KLISW-EQ
RTTHYNSP
I TVHYYH
LLAHYWAY
I IVHYSE
VLVHYASI
I IVHYSE
WLVHYNGI
I LVHYASI
I VYRYGKI
I VYRYGKI
I UVHYAK
A LAHYNHI
RLVHYWDI | DSGEL
EDEFI
SPEEL
MALEI
DDRRV
DDRRV
DDRIA
DDRIA
DDRIA
DEKEV
DDEKV
DDRIT
VEPEKI
DDRV
DDRIT
VEPEKI
DDRV
DNRV | YRLI
FNEL
YRSL
YENF
MEAF
JESF
LNSI
DEIL
DEIL
LSS-
YEKL
FEIL
FRIL
LEYS
ERAL
YKII | 115
120
260
111 C
94 C
108 2
114 4
113 5
95
117
119
119
119
119
119
119
119
114 4
113 4
124
124
124
124
124
124
124
124
124
125
126
12 |
| | 18030263 BadSubt 18311077 Cloperf 15606770 Aquaeol 20808390 Theteng 18311633 Pyraero 18312935 Pyraero 18312935 Pyraero 18312935 Pyraero 18313047 Pyraero 15921020 Sultoko 11500009 Arcfulg 20090702 Metmaze 14520238 Pyraero 15678332 Mether 1813334 Pyraero 11498552 Arcfulg 14521460 Pyrabys 20806962 Theteng
 | 22
27
170
21
14
20
25
21
21
21
4
24
27
26
14
18
41
8
41
30
32 | LFDSQTDWQSEIGEL
RLGEAFLKDFKNVD
KEALAIEVTNEIIID
KEALAIEVTNEIID
KEALAIEVTNEIID
VUSKPYESLSKAEKY
 | ALQRIC
STKYLL
RVKYF
GVIQR
ALERL
ALERL
AVLHA
AVVKA
RILHA
GVFYN
AVERY
AVERY
GVFYN
AKYLL
GWYKR
GIERL
AVLYS
SAKYN
AAESF
MVLYS
 | GHLL
LRSS
YQVAY
FEFTI
AELVY
LIIII
LQIHS
LQIAS
LQIAS
LQIAS
LQISI
LEFAY
EQLI
IMTAY
LEFAY
EQLI
IMTAY | IECII
IEAVV5
FELAAQST
FELAAQST
VEAAQALI
VEAAQALI
IESAAQALI
IESAAQALI
IESAAQALI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI | ILDTGN
VLDLSN
LFDICK
AWKIMK
FLDLAF
VLDLAF
VLDLVF
LIDYLI
ACDLVF
LIDMAQ
VLDISF
MLDIGE
AMDISF
MLDIGE
VYDICS
LLDLGV
VMDIVF
CIDIAY
UFDIGE
 | NDMIDGFI 24
VYAVISNG 24
VYAVISNG 24
KDYLAYEG 21
VAWIAFEK 21
HATARAK 24
LHIARRAK 24
LHIARRAK 24
LHICAVVG 25
RAASILG 25
RAASILG 25
RAASILG 25
RAASILG 25
LINSDLN 24
VHIVVKRG 25
SILNSDLN 24
VMALSALG 24
KHIVSKK 24
KHISKNK 24
KHISKNK 24
KHISKNK 24
RELAKSG 25
LAKEG 26 | | GC
FE
GE
CC
RE
SE
LA
EK
AE
AE
AE
AE
FK
AE
AE
AE
AE
AE | ELKK
EYME
TVLK
EFLRG
ELER
ALRR
CLKV
CLKV
GLKK
KEP
RLAQ
KLRR
CLRR
CLRR
CLRR
CLRR
CLRR
CLLRR
CLLRR | LIAYR
LVAFR
MTLLK
MILDR
LVAFR
LVKLR
LVKLR
VVGFR
ANGLR
VGFT
CNGLR
AVGFR
MAGFR
LAGLR
MAGFR
MAGFR
MAGFR
MAGFR
MAGFR
MAGFR
 | TLVQYLL&
KLTFYASI
KLISW-EV
RTTHYNS
IIVHYHI
IIVHYGEI
ILAHYMAV
IIVHYGEI
IIVHYSE
IIVHYSE
IIVHYSE
IVVYSE
IVVYXC
IVVYXC
IVVYXC
IIVHYAN
RUVHYML
RAHYNLL
WIVWYNL | DSGEL
EDEFI
SPEEL
MALEI
DDRRV
DDRRV
DDRIA
DDRIA
DTDRV
VEVDKL
DEKV
DDRIT
SPEKI
DDSKV
DDSKV
DDSKV
TDEEL | YRLI
FNEL
YRSL
YENI
MEAF
JEST
LNSI
DEIL
DEIL
LSS-
YEKL
FEIL
FEIL
FRIL
LEYS
ERAL
YKII
YCI
 | 115
120
260
111 C
94 C
108 2
114 4
113 4
113 5
95
117
119
119
119
119
119
110
124
125 |
| | 1803023 BadSub1 18311077 Cloperf 15606770 Aquaeol 20808390 Thetang 18311663 Pyraero 18311637 Pyraero 18312935 Pyraero 18312935 Pyraero 11499752 Arcfulg 20090702 Metmaze 14520238 Pyraero 15678332 Mether 18313394 Pyraero 144521460 Pyraby 20806962 Thetang 21227575 Metmaze | 22
27
170
21
14
20
25
21
21
21
4
24
27
26
14
18
41
30
224 | LFDSQTDWQSEIGEL
EGEAFLKDFKNVD
ELLAQRLQTGGDIF
ELLAQRLQTGGDIF
VKRGYDLSNWDDVFELY
VVKRGYDLSNWDDLM
VVKRGYDLSNWDDLM
VVKRGYDLSNWDDLM
VVKRGYDLSNWDDLM
VKRGYDLSNWDDLM
VKRGYDLSNWDDLM
 | ALQRI
STKYL
RVKYF
GVIQR
ALERL
AIRYS
AVLHA
AVYKA
RILHA
AVYKA
GVFYN
AVERY
AAKYL
GWFYN
AKYL
GWFYR
GIERL
AVLYS
SAKYN
AAESF
MVLHAI | GHLL
LRSS
YQVA
FEFTI
AELVZ
LIII
LQIH
AQEA
LQLQ
LQLQ
LQLQ
LQLQ
LQLQ
LQLQ
LQLQ | IECII
IEAVV5
FELA
AQST
FELA
AQST
VEA
AQALIES
AQALIES
AQALIES
AQALIES
VEA
VEA
VEA
VEA
VEA
VEA
VEA
VEA
VEA
VEA | ILDTGN
VLDLSN
LFDICK
AWKIMK
FLDLAP
VLDLAP
VLDLAP
VLDLVP
LIDMAQ
VLDILQ
VLDILQ
VLDILQ
VLDILQ
VLDILQ
VLDICS
LLDLGV
VMDIVP
CIDIAY
IFDIGF
AIDIAT | NDMIDGFI 24
VYAVISNG 24
VYAVISNG 24
VYAVISNG 24
VYAVISNG 24
VILAYPEG 21
VILAYPEG 21
VILAYPEG 21
VILAYPEG 21
VILAYPEG 21
VILAYPEG 22
VILAYPEG 22
VILAYPEG 23
VILAYPEG 24
VILAYPEG 25
VILAYPEG 25
VILAYP | | GE
FE
GE
CE
CE
CE
CE
CE
CE
C | ELKK
EYME
TVLK
MWID
FLRG
ELER
ALRR
CLKK
FLNA
GLKK
FLNA
GLKK
FLNA
GLKK
FLNA
GLKK
FLNA
GLKK
FLNA
GLKK
FLNA
GLKK
FLNA
GLKK
FLNA
GLKK
FLNA
GLKK
FLNA
GLKK
FLNA
GLKK
FLNA
GLKK
FLNA
GLKK
FLNA
GLKK
FLNA
GLKK
FLNA
GLKK
FLNA
GLKK
FLNA
GLKK
FLNA
GLKK
FLNA
GLKK
FLNA
GLKK
FLNA
GLKK
FLNA
GLKK
FLNA
GLKK
FLNA
GLKK
FLNA
GLKK
FLNA
GLKK
FLNA
GLKK
FLNA
GLKK
FLNA
GLKK
FLNA
GLKK
FLNA
GLKK
FLNA
GLKK
FLNA
GLKK
FLNA
GLKK
FLNA
GLKK
FLNA
GLKK
FLNA
GLKK
FLNA
GLKK
FLNA
GLKK
FLNA
GLKK
FLNA
GLKK
FLNA
GLKK
FLNA
GLKK
FLNA
GLKK
FLNA
GLKK
FLNA
GLKK
FLNA
GLKK
FLNA
GLKK
FLNA
GLKK
FLNA
GLKK
FLNA
GLKK
FLNA
GLKK
FLNA
GLKK
FLNA
GLKK
FLNA
GLKK
FLNA
GLKK
FLNA
GLKK
FLNA
GLKK
FLNA
GLKK
FLNA
GLKK
FLNA
GLKK
FLNA
GLKK
FLNA
GLKK
FLNA
FLNA
FLNA
FLNA
FLNA
FLNA
FLNA
FLNA | LIAYR
LVAFR
MTLLK
MILDAFR
LVAFR
LVAFR
LVKLR
LVKFR
ANGLR
VVGFT
CNGLR
AVGFR
MAKFR
MAKFR
MAKFR
MAGFR
MARFR
MAGYR
LAGFR
AACFR | TLVQYLL&
KLTFYAS
RTHINNSK
RTHINNSK
I IVHYYH
LLAHYWA
I IVHYGE
RUVHYGE
VLVHYGE
I IVHYGE
I IVHYGE
I IVHYSE
WLVHYNK
MLVHYWR
I IVHYSK
MLVHYWR
I IVHYAK
A IAHYNHI
RLVHYWD
VLVHYWD
VLVHYWD
VLVHYWD | DSGEL
EDEFI
SPEEL
MALEI
EEKKE
DDRRV
DDRRV
DDRIA
DDRV
MLGTV
VEVEKI
DDRIT
EPEKI
DDRV
DDRIT
TEEL
DDRV
DDRV
DDRV | YRLI
FNEL
YRSI
MEAF
YESV
LNSI
DEIL
DEIL
LSS-
YEKL
FEIL
FEIL
LEYS
ERAL
YKII
YEII
YEII | 115
120
260
111 C
94 C
108 C
108 C
114 4
113 4
113 5
95
117
119
119
119
119
110
124
125
124
125
127
128
129
129
120 |
| | 16060263 BadSubt 18311077 Cloperf 15606770 Aquaeol 20808390 Theteng 18311663 Pyraero 18312935 Pyraero 18312935 Pyraero 18312935 Pyraero 15921020 Sultoko 1500009 Arcfulg 20090702 Metmaze 14520238 Pyraero 15678322 Methare 18313394 Pyraero 1498552 Arcfulg 142521460 Pyrabys 20806662 Theteng 21227575 Metmaze 21227636 Metmaze | 22
277
21
14
1
20
25
21
21
21
21
21
21
21
21
21
21
21
21
21 | LFDSQTDWQSEIGEL
RLGEAFLKDFKNVD
 | ALQRI
GTVL
RVKYF
GVIQR,
ALERL,
ALERL,
ALERL,
AVLHA
AVLHA
AVLHA
GVFYN
AVERY
GEELL
GWYKR
GIERL
GVFYN
AVLYS
SAKYN
ALESF
MVLHA
AIENY | LURAN
LINES
SUPPORT
LINES
LINES
LINES
LUNES
LUNES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINES
LINE | LECILEAUX
YDSLL
YDSLL
YDSLL
YDSL
YDSL
YDSL
YDSL
Y | LLDTGN
/LDLSN
LFDICK
AWKIMK
/LDLAK
/SALAI
IDYLI
ACDLVF
LIDMAC
/LDLK
AMDISF
ALDIGE
AFSICN
/YDICS
LLDLGV
/MDIVF
LIDIAY
IFDIGE
AIDIAT
IDIAT | NDMIDGFI 24
VYAVISNG 24
VYAVISNG 24
VKILAPKFG 23
VDVLAYEG 21
VAMWIAFEK 21
VAMWIAFEK 21
VAMWIAFEK 21
VAMWIAFEK 24
VAMWIAFEK 24
VAMPLANG 23
VAMPLANG 25
VIIISNEK 24
VALSKAG 25
VALSKAG 25
VALSKAG 26
VALSKAG 26
VAL | | GE
FE
GE
CE
CE
CE
CE
CE
CE
C | ELKK
EYME
TVLK
MWIDG
ELER
ALRR
CCLKVV
LYRA
GLKK
KIEP
GLKK
KIEP
KLAQ
KLAR
KLAR
KLAR
KLAR
KLAR
KLAP | LIAYR
LVNLKI
MTLLKN
MTLLKN
LVAFR
LVAFR
LVGFR
VVGFT
VVGFT
VVGFT
VVGFT
VNGFR
MAGFR
MAKFR
MAKFR
MAKFR
MAGFR
MARFR
MARFR
MARFR
MARFR | TLVQYLLE
KLIFYAS
KLISW-EV
RTTHYNS
IIVHYYHI
ILAHYWA
VUHYASE
RLVHYGE
IIVHYSE
WLVHYNG
IIVHYSE
WLVHYNG
IIVHYSE
IIVHYSE
IIVHYSE
RLVHYWD
RLVHYWD
RLVHYWD
VLVHYMC
VLVHYMD
VLVHYMD | SSGEL
EDEFI
SPEEL
MALEI
EEKKE
DDRRV
DDRVKI
DDRDV
DTDRV
VNLGTV
VNLGTV
CVDKL
DDRV
DDRIT
EEEKI
DLSKV
DDRSV
TDEEL
DRDQV
DNRW
ZDORK | YRLI
FNEL
YRSI
MEAF
YESV
LNSI
DEIL
LSS-
YEKL
LSS-
YEKL
LEYS
ERAL
YKII
YEII
YEII
YSIL
YSIL | 115
120
260
111 C
104 C
108 2
114 4
113 4
113 4
113 4
113 4
117
119
117
119
117
119
117
119
124
125
111
125
111
124
125
111
124
125
111
124
125
111
124
125
124
125
124
125
124
125
124
125
125
126
12 |
| | 16060263 BadSub2 18311077 Cloperf 15606770 Aquaeol 20808390 Theteng 1831163 Pyraero 18312935 Pyraero 18312935 Pyraero 18312935 Pyraero 15921020 Sultoko 1500009 Arcfulg 20090702 Metmaze 183133047 Pyraero 15678322 Mettmer 18313344 Pyraero 15678322 Metmaze 18313344 Pyraero 15678432 Metmaze 12297575 Metmaze 21227575 Metmaze 1313569 Pyraero 15678404 Metther
 | 222
277
1700
21
14
120
255
211
21
21
24
24
26
26
21
21
21
21
21
21
21
21
21
21
21
21
21 | LFDSQTDWQSEIGEL
RLGEAFLKDFKNVD
KEALAIEVTNEIIID
KEALAIEVTNEIID
KEALAIEVTNEIID
WSKPYESLSKAEKY
VKRGYDLSNWDDLW
VKRGYDLSNWDDLW
VKRGYDLSNWDDLW
VKRGYDLSNWDDLW
 |
ALQRI
GVIQR
ALERL
ALERL
ALERL
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AVYKA
AV | LRSS
VQVA
YQVA
PFETI
LLSS
UIIII
LUIII
LUIII
LUII
LUII
LUII | LECILEAUX
YDSLL
YDSLL
YDSLL
YDSL
YEAA
QS
YEAA
QS
YEAA
QALL
ECAA
YEAU
LECAA
YEAL
LACAA
YEAL
YEAL
YEAL |
ILDTGN
VLDLSN
VLDLSN
VLDLAF
VSALAI
IIDVLI
ACDLVF
VLDILQ
VLDILQ
VLDILQ
VLDILQ
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS
VTDICS | NDMIDGFI 24
VYAVISNG 24
VYAVISNG 24
VYAVISNG 22
VATANA
MARANERS 21
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATANA
VATAN | | GE
FE
GE
CE
RE
SE
LA
EK
AE
AE
AE
AE
AE
SK
AE
SK
AE
SK
AE
SK
AE
SK
AE | ELKK
EYME
TVLK
MWID
ELER
CLKV
CLKV
CLYRA
ALRR
CLKV
KI
PL
R
LLRR
R
LLRR
R
LLRR
R
LLLR
R
LLLR
K
LVK
L
S
D
D
S
D
S
D
S
D
S
D
S
D
S
D
S
D
S
S
D
S
S
S
S
S
S
S
S
S
S
S
S
S
S
S
S
S
S
S
S | LIAYR
LVNLKI
MTLLKN
MILLKN
LVAFR
LVKFR
LVGFR
VVGFT
CNGLR
ANGFR
MARFR
MAKFR
MAKFR
MAGFR
LAGLR
LAGFR
LAGFR
LAGFR
LAGFR
LAGFR
 | TLVQYLLE
KLIFYASI
KLISW-EV
RTHYNSK
ITVHYHI
ILVHYGEI
ILVHYGEI
ILVHYGEI
ILVHYSE
WLHYNNCI
ILVHYSE
ILVHYSE
ILVHYNCI
RWHYNR
RLVHYMDI
RWHYNL
RWHYNL
VLHYYQI
VLHYYQI
VLHYYQI
LLVHYFQ | SSGEL
EDEFI
SPEEL
MALEI
EEKKE
DDRRV
DDRIN
DDRIN
VIGTV
VIGTV
DDEKV
DDRIT
ZEPEKI
DDRV
DDRIT
ZEPEKI
DDRV
DDRIT
ZEPEKI
DDRV
DDRIT
ZEPEKI
DDRV
DDRU | YRLI
FNEL
YRSI
MEAF
YESV
LNSI
DEIL
LSS-
YEKL
FEIL
FRIL
YEIL
YEII
YEII
YEII
YGIL
YSHL
YNSV
 | 115
120
120
111 C
94 C
94 C
94 C
108 2
114 4
113 5
95
117
109
107
119
107
110
124
125
117
124
125
127
128
127
128
129 |
| | 1803023 BadSub1 18311077 Cloperf 15606770 Aquaeol 20808390 Thetang 18311663 Pyraero 18311637 Pyraero 18312935 Pyraero 18312935 Pyraero 11499752 Arcfulg 20090702 Metmaze 14520238 Pyraero 15502090 Arcfulg 20090702 Metmaze 14521460 Pyraero 14521460 Pyraey 14521460 Pyraey 2122755 Metmaze 2122755 Metmaze 2122763 Metmaze 18313569 Pyraero 15678491 Metther | 222
277
170
21
14
1
20
255
21
21
21
21
24
24
24
27
26
14
14
18
30
322
24
22
26
22
27 | LFDSQTDWQSEIGEL
EGEAFLKDFKNVD
ELLAQRLQTGGDIF
ELLAQRLQTGGDIF
WSKPYESLSKAEKY
NWI-EEAKVKDVKSSL
VWRGYDLSNWDDLM
VVERGYDLSNWDDLM
VVERGYDLSNWDDLM
VVERGYDLNYWRDQM
 | ALQRI
STKYL
RVKYF
GVIQR
ALERL
ALERL
ALERL
ALERL
AVLHA
AVLHA
GVFYN
AVYKA
GVFYN
AXYL
GWFYN
AXYL
GWFYN
AXYL
GVFYN
AXYL
GVFYN
AXYL
GUERL
AVLYS
SAKYN
ALERY
ALRYQ
ALRYQ | LINE
ACCENTION OF THE SECOND | IECIIEAVUS
IEAVUS
IEAVUS
IEAVUS
IESAA
IESAA
IESAA
IEACIIEACIIEA
IEACIIEACIIEA
IEACIIEACI | ILDTGN
VLDLSN
VLDLSN
VLDLSN
VLDLAF
VSALAI
IIDYLI
ACDLVF
VLDLVF
VLDLQ
VLDLQ
VLDLG
VLDLG
VVDLGS
LLDLG
VMDIVF
CIDIAY
IFDIGF
AIDIAT
IIDICE
LASMCM | NDMIDGFI 24
VYAVISNG 24
VYAVISNG 24
VYAVISNG 24
VALAYEG 21
JHIARRAL 22
JHIARRAL 22
JHIARRAL 22
VALAYEG 23
VALAYEG 23
VALAYEG 23
VALAYEG 24
VALASALG 24
VALASALG 24
VALASALG 24
VALASALG 24
VALASALG 25
SLIAKEG 24
VALASALG 25
VALASALG 25
V | | GE
FE
GE
CE
RE
SE
LA
EK
AE
AE
AE
AE
AE
AE
SE
AE
SE
S | ELKK
EYME
TVLKMMWID
ELER
ALRR
CLKV
LYRA
FLNA
GLKK
KLYK
RA
GLKK
KLAP
KLAP
KLAP
KLAP
KLAP
KLAP | LIAYR
LVNLKI
MTLLKN
MTLLKN
LVAFRN
LVAFRN
LVGFRN
ANGLRN
VVGFRN
AVGFRN
AVGFRN
MAKFRN
MAKFRN
MARFRN
MARFRN
MARFRN
MAGFRN
LAGFRN
LISLRN
AAGFRN | TLVQYLLE
KLIFYAS
KLIFYAS
RTHINNSK
IIVHYHL
LLAHYWA
IIVHYGE
RUVHYGE
VLVHYGE
IIVHYGE
IIVHYSE
WLVHYNE
VLVHYSE
IIVHYSE
VLVHYWO
IVVRYGKI
ILVHYAV
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLVHYMO
VLX
VLX
VLX
VLX
VLX
VLX
VLX
VLX
VLX
VLX | DSGEL
EDEFI
SPEEL
MALEI
EEKKE
DDRRV
DDRRV
DDRIK
DDRIK
VDKEV
DDEKV
DDEKV
DDEKV
DDEKV
DDEKV
DDEKV
DDEKV
DDRIT
DDRV
DDRV
DDRV
DDRL
DVRU
DDRV
DDRIT | YRLI
FNEL
YRSL
YESV
YESV
HEAF
LNST
LNST
LLSS-
YEKL
FEIL
LEYS
ERAL
YEII
YEII
YEII
YEII
YSHL
YNSV
AEVL | 115
1200
2600
111 C
94 C
94 C
108 2
114 4
113 5
95
117
119
119
119
119
110
124
125
111
125 |
| | 1803023 BadSub2 18031077 Cloperf 15606770 Aquaeol 20808390 Theteng 1831163 Pyraero 1831163 Pyraero 18312935 Pyraero 18312935 Pyraero 11499752 Arcfulg 18313047 Pyraero 15921020 Sultoko 1500009 Arcfulg 1000702 Metmaze 14520238 Pyraero 15678332 Metther 18313394 Pyraero 1498552 Arcfulg 14521460 Pyrabys 20806962 Theteng 21227575 Metmaze 18213569 Pyraero 15678491 Metther 15678491 Metther 16272048 Haeinf1
 | 222
27
1700
21
14
12
25
21
21
21
21
24
24
24
27
26
14
18
41
30
22
24
22
26
30 | LFDSQTDWQSEIGEL
RLGEAFLKDFKNVD
KEALAIEVTNEIIJD
KEALAIEVTNEIIJD
 | ALQRI
STKYL
RVKYF
GVIQR
ALERL
AIRYS
AVLHA
AVLHA
AVLHA
GVFYN
AVERY
AVERY
AVERY
AVERY
AVERY
AVERY
AVERY
ALFRN
ALERY
AIERN
GALQR
 | LIRSS
LANGE
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLASS
ALLA | IECIIEAV
IECUIEAV
IEAV
SOSII
VEAA
QIVEAA
IECM
VEAA
IECM
VEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEA
IEACIEACIEA
IEACIEACIEA
IEACIEACIEACIEACIEACIEACIE
IEACIEACIEACIEACIEACIEACIEACIEACIEACIEAC | LLDTGN
VLDLSN
VLDLSN
VLDLAA
VSALAI
VSALAI
UIDYLL
ACDLVA
VLDILQ
VLDILQ
VLDILQ
VLDILQ
VVDICS
LLDLG
VVDICS
VDICS
LLDLG
VMDIVA
VMDIVA
IFDIGF
AIDIAT
41DICS
LASMCM
ALDTGE
SLKMMF
 | NDMIDGFI 24
VYAVISNG 24
VYAVISNG 24
VYAVISNG 24
VALAYEG 21
VALAYEG 21
VALAYEG 21
VALAYEG 21
VALAYEG 21
VALAYEG 21
VALAYEG 21
VALAYEG 22
VALAYEG 22
VALAYEG 24
VALAYEG | | GE
FE
CE
RE
SE
SE
SE
SE
SE
SE
S | ELKK
EYME
TVLKM
MWID
FELRG
ELER
ALRR
CLKV
LYRA
GLKK
KIPD
RLAQ
GLKK
KIPP
RLAQ
GLKK
KIPP
RLAQ
CL
KIP
KLAP
VLSS
RFSE
KWVA | LIAYR
LVNLK
MTLLKN
MTLLKN
LVAFRN
LVKIRN
LVKIRN
ANGLRN
VVGFTN
CNGLRN
AVGFRN
MAKFRN
MAKFRN
MAKFRN
MAGFRN
LAGFRN
LAGFRN
LAGFRN
LAGFRN
LAGFRN
LAGFRN
LAGFRN
LAGFRN
LAGFRN
LAGFRN
LAGFRN
LAGFRN
LAGFRN
LAGFRN
LAGFRN
LAGFRN
LAGFRN
LAGFRN
LAGFRN
LAGFRN
LAGFRN
LAGFRN
LAGFRN
LAGFRN
LAGFRN
LAGFRN
LAGFRN
LAGFRN
LAGFRN
LAGFRN
LAGFRN
LAGFRN
LAGFRN
LAGFRN
LAGFRN
LAGFRN
LAGFRN
LAGFRN
LAGFRN
LAGFRN
LAGFRN
LAGFRN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGFNN
LAGF | TLVQYLLE
KLIFYAS
KLISW-EV
RTTHYNS
IIVHYYHI
ILAHYWA
VUHYASE
RLVHYGE
IIVHYSE
WLVHYGE
IIVHYSE
WLVHYNC
IIVHYSE
MLVHYWR
IIVHYSE
AIAHYNHI
RLVHYWD
VLVHYWDI
VLVHYDD
LLVHYDQ
IISHYDQ
ISHYDQ
ISHYDQ
 | DSGEL
EDEFI
SPEEL
(SPEEL
(MALEI
EEKKE
DDRRV
DDRNV
DTRV
DTRV
DTRV
DTRV
DTRV
DTRV
DDEKV
DDEKV
DDEKV
DDRNV
TDEEL
DFRV
DISKV
DISKV
DISKV
DISKV
DISKV
DISKV | YRLI
FNEL
YESU
YESU
YESU
UNSI
DEIL
DEIL
DEIL
LSS-
YEKL
LEYS
ERAL
YEIL
YEIL
YEIL
YSHL
YSHL
YSHL
YAQU | 115
1200
2600
1011 C
94 C
94 C
108 2
114 4
113 4
113 5
95
117
119
119
119
119
119
119
124
124
124
127
117
124
124
125 R
 |
	180302/3 BadSub2 18031107 Cloperf 15606770 Aquaeol 20808390 Theteng 1831163 Pyraero 18312935 Pyraero 18312935 Pyraero 18312935 Pyraero 15921020 Sultoko 1500009 Arcfulg 20090702 Metmaze 14520238 Pyraero 15678332 Mether 18313047 Pyraero 15678322 Metmaze 123052 Arcfulg 14520238 Pyraero 15678322 Methaze 1231334 Pyraero 15678322 Methaze 20806962 Theteng 12227575 Metmaze 21227575 Metmaze 1313569 Pyraero 15678491 Metther 16272048 Haeinf1 16272048 Haeinf1	222 27 170 21 14 1 20 25 21 21 21 4 24 27 26 30 32 22 6 30	LFDSQTDWQSEIGEL RLGEAFLKDFKNVD SQGEEEFKKTPMYYD KEALAIEVTNEIIID KEALAIEVTNEIID WISKPYESLSKAEKY VWKRGYDLSNWDDLM VVKRGYDLSNWDDLM VVKRGYDLSNWDDLM VVKRGYDLSNWDDLM VEKGYDLNYWRDQM LSEIPERVKTPIEVS PSFGEFSELGLIRD IKGYAVELESERSYR NLGLEEFLTNSHIRY PSFGEFSELGLIRD IKGYAVELESERSYR NLDVEEFLKNKHYVS SMCARTLSDKNNS VISLEDLKKDRDKNN USSEPFENT	ALQRI STKYL SVKYF GVIQR ALERL AIRYS AVLHA AVVHA AVVKA AILHA GVFYN AVERY AAKYL GVFYN AAKYL GVFYN AAKYL SAKYN ALERY ALERY ALERY AIERN GAIQK HHHHAA	LRSS LRSS FEFTI LITIN LUIIN LUIIN LQIN LQUQ LQUQ LUIS LUIS LUIS LIMA LEFA MEVS LIVL LRTT LRTT LRTT LLVA LRTT LIVL LQIA LEFA MEVS LIVL LQIA LEFA LEFA LIVL LQIA LEFA LIVL LQIA LEFA LIVL LQIA LVIA LVIA LVIA LVIA LVIA LVIA LVIA LV	IECIIEAVYDSL IEAVYDSL FELAAQSTFELAAQST VEAAQAUVYEA IESAAQIVVEA IEACUVEV IQALLEAII IEACULEAII IEACULEAII IEACULEAII IEACULESA	ILDTGN VLDLSN FDICK VSALAT VSA	NDMIDGFI 24 NYAVISNG 24 KNILPEK 21 KNILPEK 21 KNILPEK 21 KNILPEK 21 KNILPEK 21 KNILPEK 21 KNILPEK 21 KNILPEK 24 KNILPEK 2		GE FE GE CE RE SE SE SE SE SE SE S	ELKK EYME TVLK MWID ELER CLKV LYRA GLKK KLEP GLKK KK ELSO LLRR RLIL RRLI	LIAYR LVNLK MTLLK MTLLK LVAFR LVKLR LVKLR LVGFR VVGFT CNGLR AVGFR MAGFR MAGFR LAGLR LAGLR LAGFR LAGFR LAGFR LAGFR LISLR AAGFR LISLR AAGFR MAGYR	TLVQYLLE KLITYASI KLITYASI KLITYASI ITVHYHI LLAHYWA IIVHYGE RLVHYNGI IIVHYGE IIVHYSE MLVHYNGI ILVHYAK ILVHYNG ILVHYNG ILVHYNG RMHYNL RVHYND VLVHYOI LLVHYFO ILVHYFO ILVHYFO IISHYDO IISHYDO	DSGEL CEDEFI SPEEL MALEI DDRIV DDRIV DDRIV VILGTV VEVDKL DDRIV ZEVDKL DDRIT DDRIV DD	YRLI FNEL YESU YESU YESU YESU YESU LNSI DEIL DEIL LSS- VEEL FRIL VEIL YEIL YEIL YEIL YEIL YEIL YEIL YEIL HHIH	115 120 120 120 101 C 94 C 94 C 94 C 104 C 104 C 94 C 104 C
	1803023 BadSub1 1803107 Cloperf 15606770 Aquaeol 20808390 Thetang 1831163 Pyraero 1831163 Pyraero 1831235 Pyraero 1831235 Pyraero 11499752 Arcfulg 20090702 Metmaze 14521600 Pyraero 1557832 Metther 18313394 Pyraero 14521460 Pyrabys 20806962 Thetang 21227575 Metmaze 21227575 Metmaze 18313569 Pyraero 15678491 Metmaze 16272048 Haeinf1 16272048 LJOG	222 27 170 21 14 10 205 21 21 21 21 21 21 21 21 21 21 21 21 21	LFDSQTDWQSEIGEL EGEAFLKDFKNVD ELLAQRLQTGGDIF ELLAQRLQTGGDIF VKRGYDLSNWDDVFELY VVKRGYDLSNWDDLM VVKRGYDLSNWDDLM VVKRGYDLSNWDDLM VVKRGYDLSNWDDLM VVKRGYDLSNWDDLM VKRGYDLSNWDDLM 	ALQRI STKYL STKYL RVKYF ALERL ALERL ALT SVLHA AVLHA AVLHA AVLHA AVLHA AVLHA AVLYS SAKYN AAKYL SAKYN ALERY ALERN ALERN GALQK HHHGC	Y Y Y Y Y Y Y Y Y Y Y Y Y Y	IECIIEAVYDSL IEAVYDSL FELAAQST FELAAQST VEAAQAL IESAAQIVVEA IGGAAQIVVEA IEACUVEVVI IEACULEAI IEACMVEAL IEACMVEAL IESAAVYEAL	ILDTGN JFDICY JFDICY WKIMWKIM VIDLA VSALAH IDVLI ULDIC CCDLV/ VLDIL LIDMA CCDLV/ VIDIAA VIDIAA SALADIGE FSICO VYDICS LIDLA VIDLAS VYDICS LIDLA VIDLAS	NDMIDGFI 24 VIAVISNG 24 VIAVISNG 24 VIAVISNG 22 VIAVISNG 24 VIAVISNG 24 VIAVISNG 24 VIAVISNG 24 VIAVISNG 25 VIAVISNG 25 VIAVISNG 25 VIAVISNG 25 VIAVISNG 25 VIAVISNG 25 VIAVISNG 25 VIAVISNG 26 VIAVISNG 26 VIAVIS		GE FE GE RE RE RE RE RE RE R	ELKK EYMEK TVLK MWID ELER CLKV LYRA GLKK KLP GLKK GLKK	LIAYR LVNLKI MTLLKN MILDRN LVAFRN LVGFRN ANGERN ANGFRN MRGFRN MAKFRN MAKFRN MARFNN MAR	TLVQYLLA KLTFYAS RTHINNSK RTHINNSK I LVHYNH LLAHYWA I LVHYGE I LVHYGE I LVHYGE I LVHYGE I LVHYGE I LVHYSE WLWHYNE I LVHYSE WLWHWR VLVHYMD VLVHYMD I LVHYFQ I LVHYTQ I LVHYTQ I SHYDQF I LVHYFQ	DSGEL GEDEFI (SPEEL (DDRRV DDRRV DDRVKI DDRV DTDRV DTDRV DTDRV DTRV DDRV DDRV D	YRLI FNEL YESU YESU YESU YESU YESU UEST DEIL DEIL LSS- YEEL LEYS FRIL YEIL YEIL YEIL YSHL YSHL YAQI HHHH	115 120 260 104 C 104 C 104 C 108 C 108 C 104 C 108 C 104 C 108 C 104 C 108 C 104 C 107 107 10
	1803023 BadSub2 1803107 Cloperf 15606770 Aquaeol 20808390 Theteng 18311663 Pyraero 18311663 Pyraero 18311757 Pyraero 18312935 Pyraero 11499752 Arcfulg 120090702 Metmaze 14520238 Pyraero 15678332 Mether 18313394 Pyraero 1498552 Arcfulg 14520238 Pyraero 1498552 Arcfulg 14521460 Pyraeyo 1498552 Metmaze 21227575 Metmaze 18313569 Pyraero 15678491 Metmaze 16272048 Haeinfl 16272048 LajoG 15805707 Piraeira 16329607 Synsp 162320607 Synsp	222 27 170 21 14 1 20 25 21 21 21 21 21 21 21 27 26 14 18 41 30 32 24 22 6 30 32 25 24	LFDSQTDWQSEIGEL EGEAFLKDFKNVD 	ALQRI STKYLJ GVIQRI ALERL AIRYSJ AVLHAL AVLHAL AVLHAL AVLHAL AVLHAL AVLHAL ALERC GVFYN AAESFI MVLHAL ALERVI	YQVAN YQVAN YQVAN AELVI LIIII LIIII LUIII LUIII LUIII LUII LU	IECIIEAU IEAU YDSL FELAA AQST AETV SQSI VEAA AQAL VEAQ IEAC VEAL VEAU IECAUU IECAU IECAU IECAU IECAU IECAUU IECAU IECAU IECAU IECAU IECAU	ILDTGN ILDLSN FFDICK IDVLN VSALAI IDVLL ACDLVA VSALAI IDVL IDVL IDVL IDVL IDVL IDVL IDVL IDV	NDMIDGFI 24 VYAVISNG 24 VYAVISNG 24 VKILAPKFG 23 VAVIAVEG 21 AMWIAFEK 21 AMWIAFEK 21 AMWIAFEK 21 AMIVATOR 22 AMIVATOR 22 PRASLLG 22 PRASLLG 22 PRASLLG 22 PRASLLG 22 VKILNNG 23 VMIVATOR 23 VMIVATOR 23 VMIVATOR 24 VMIVATOR 2		GE FF GE EF EF EF EF EF	ELKK EYME FIRGGU ELERR CLYRA FFLNA KT	LIAYR LVNLK MUMDRN LVAFR LVAFR LVKLRN NGFR ANGLR VVGFT CNGLR AVGFT MAKFR MAGFR LAGFR AAGFR LAGFR AAGFR AAGFR AAGLR YRDMR Q4HHH LRGLR YRDMR	TLVQYLLR KLIFYAS KLISW-EV RTHINDSK IIVHYNHI IIVHYNH RUVHYNGI VUVHYASE IIVHYSE WLVHYNGI IIVHYSE WLVHYNG IIVHYSE VUVHYSE IIVHYSE VLVHYWDI VLVHYWDI ILVHYAV VLVHYWDI IIVHYDQ IIVHYDQ IIVHYDQ VLVHYDQ	DSGEL EDEFI SPEEL DRW DDRW NUEKI DDRW DDRIT DDRW DDRU DDRU DDRU DDRU DDRU TDEEL DDRW TDEEL DDRW TDEEL DDRW TDEEL DDRW TDEEL DDRW SSPEIL DDRW DCKI DDRI DCKI DDRW TDEEL	YRLI FNEL YYSL YESU YESU YESU DEIL LNSI DEIL LSS- YEKL FEIL LSS- YEKL ERAL LYSI YEIL YSI YEII YSI YSI YNSU AEVL YAQI HHHH HHHH	1115 120 120 1211 C 94 C 94 C 108 2 114 4 113 4 113 4 113 1 117 117 119 127 127 128 2 127 129 2 127 2 128 2 129 2 1
	1803023 BadSub2 18031077 Cloperf 15606770 Aquaeol 20808390 Theteng 1831163 Pyraero 18311663 Pyraero 18312935 Pyraero 18312935 Pyraero 15921020 Sultoko 11500009 Arcfulg 20090702 Metmaze 14520238 Pyraero 15678332 Mether 18313394 Pyraero 154521460 Pyrabys 20806962 Theteng 21227575 Metmaze 1313569 Pyraero 15678491 Metther 16272048 Haeinf1 16329607 Synsp 16330629 Synsp 1620060 Synsp	222 27 1700 21 14 20 25 21 21 21 21 24 24 24 27 266 30 32 24 22 26 30 25 24 29 20 25 24	LFDSQTDWQSEIGEL RLGEAFLKDFKNVD 	ALQRI STKYLL SVKYLF GVIQR ALERL ALENS AVLHA AIRYS AVLHA AILHG GVFYNI AVERY AKYLL GMYKR GIERLI AKYL ALERYI ALERYI GAIQK ALERYI ALERYI ALERYI ALERYI ALERYI ALERYI ALERYI ALERYI ALERYI ALERYI ALERYI ALENYI ALENYI ALIYQ ATLINX	V V V V V V V V V V V V V V V V V V V	IECIIEAV IEAV YDSL FELAA AQST AQST AQST AQIV EAA AQIV IEAA VEAU IESA VEAU IEAC IEAC IEAC IEAC IESA IESA HHHH EEAV IEAC	LLDTGN LIDLSN FPDICY FPDICY SALAT USA	NDMIDGFI 24 NYAVISNG 24 NYAVISNG 24 KILAPKRG 23 KDYLAYEG 22 KDYLAYEG 22 KDYLAYEG 22 KDYLAYEG 22 KILSNNG 23 KMIVKDLG 23 KILSNNG 24 KILSNNG 24 KI		GE FE GE EE EE RE EE RE EE E	ELKK EYME KARA MWID FFLRG ELER ALRR CCLKVV LYRA ALRR CCLKV KI EV RLA GLKK KI KA KI KKI KKI KKI KKI KKI KKI KKI	LIAYR LIAYR WTLLK MMLDR UVAFR UVGFR VVGFR VVGFR VVGFR VVGFR VVGFR VVGFR NAG R MAFR LAGFR AAG R AA AAG R AAG R AAG R AAG R AAG R AAG R AAG R AAG R AAG R AAG R AAG	TLVQYLLE KLITYASI KLISW-EX RTHYNSK IIVHYNG ILLAHYWA RLVHYNGI IIVHYGE IIVHYGE IIVHYSE MLVHYNGI IIVHYSE MLVHYNG IIVHYNG IIVHYNG IIVHYNG RWHYNL VLVHYNC VLVHYNC ILLHYFO IISHYDOF HH VVHYFO ITSHYDOF HH VVHYFC RLHHYG RLHHLG RLHHLG	DSCEL EDEFI SPEEL MALEI EEKKE DDRRW NVEKI DDRRW NLGTV WLGTV WLGTV EVCKI DDRV DDRV VEVVKI DDRV DDRV DDRV DDRV DDRV DDRV DDRV DDR	YRLI FNEL YYESL YESU YESU YESU YESU TESE TESE TESE YESU YESU YESU YESU YESU YESU YESU Y	1115 120 120 120 120 120 120 111 C 104 C 104 C 108 2 114 4 113 5 117 113 5 117 119 119 124 125 111 124 125 124 125 127 128 129 1
	1803023 BadSub2 1803107 Cloperf 15606770 Aquaeol 20808390 Theteng 1831163 Pyraero 1831163 Pyraero 1831235 Pyraero 1831235 Pyraero 11499752 Arcfulg 20090702 Metmaze 14521600 Pyraero 1550232 Mether 18313344 Pyraero 1557832 Mether 18313344 Pyraero 14521460 Pyrabys 20806962 Theteng 21227575 Metmaze 21227563 Metmaze 18313569 Pyraero 15678491 Metmaze 16272048 LJOG 16330629 Synsp 16330629 Synsp 16330629 Synsp 16300680 Deiradi	222 27 1700 21 14 1 20 255 21 21 21 24 24 26 26 300 255 24 226 26 300 255 24 29 266 25 26 26 26 26 26 26 26 26 26 26 26 26 26	LFDSQTDWQSEIGEL EGEAFLKDFKNVD ELLAQRLQTGGDIF ELLAQRLQTGGDIF VKRGYDLSNWDDVFELY VVKRGYDLSNWDDLM VVKRGYDLSNWDDLM VVKRGYDLSNWDDLM VVKRGYDLSNWDDLM VKRGYDLSNWDDLM 	ALQRI STKYLL KVKYF GVIQRI ALERL ALERSI AVLHA AVKAL AVKAL GVFYNI AVERSI GVFYNI AVERSI GVFYNI AVERSI SAKYN ALERYI ALEYI ALIYI ALIYI ALIYI ALIYI ALIYI ALIYI ALIYI ALIYI ALIYI ALIYI ALIYI ALIYI ALIYI ALIYI ALIYI ALIYI ALIYI ALIYI ALIYI ALIYA ALI	VYVVA VYVVA VYVVA VYVVA VYVVA VVVA VVVA	IECIIEAUV IEAUV SQSIIESAAQST IESAAQSUVEAAAQAUV IESAAQAUV IESAAQIUV IEACCUVEV VEV VEAULACM VEA	ILDTGN ILDLSN FFDICK WKIMM ILDLAN VSALAII IDVLL IDVLL IDVLL IDVLL IDVLL IDVL IDV	NDMIDGFI 24 VIAVISNG 24 VIAVISNG 24 VIAVISNG 22 VIAVISNG 24 VIAVISNG 24 VIAVISNG 24 VIAVISNG 24 VIAVISNG 25 VIAVISNG 26 VIAVISNG 25 VIAVISNG 26 VIAVISNG 26 VIAVIS			ELKK FURE NUT ALL PLAN PLAN PLAN PLAN PLAN PLAN PLAN P	LIAYR LIAYR WTLLK WMIDR UVAFR ANGLR ANGLR ANG RAG RAG RAG RAG RAG RAG RAG RAG RAG RA	TLVQYLLA KLTFYAS KLISW-EV RTTHYNSK KLISW-EV RTTHYNSK KLISW-EV LIVHYGE I LVHYGE I LVHYGE I LVHYGE I LVHYGE I LVHYSK MLVHYNK I LVHYSK VLVHYMC I LVHYF I LVHYFO I LVHYFQ I LVHYFQ VLVHYDQ I LVHYFQ VLVHYDQ I LVHYFQ VLVHYDQ I LVHYFQ VLVHYDQ I LVHYFQ VLVHYDQ I LVHYFQ VLVHYDQ I LVHYFQ VLVHYDQ I LLHYFG VLLHYCG VLLHYCG VLLHYCG VLLHYCG VLLHYCG VLLHYCG VLLHYCG VLLHYCG VLLHYCG	DSGEL EDEFI SPEEL MALEI EEKKE DDRRW NVEKI DDRRW NVEKI DDRRW NVEKI DDRW VDKL DDRW VDKL DDRW DDEKV DDRW DDEKV DDRW DDEKV DDRW DDEKV DDRW DDEKV DDRW DDEKV DDRW DDRW DDRW DDEKV DDRW DDEKV DDRW DDEKV DDE	YRLI FNEL YRSL YESV YESV YESV TESV TEST UNSI DEIL LINSI DEIL LSS- YEKL LEYS ERAL YEII YGIL YSHL YSHL YAQU HHHH HHHHQUV WDVI WDVI WDVI	115 120 120 111 C 260 111 C 104 C 108 2 1114 4 113 4 113 5 95 117 113 5 95 117 119 119 119 119 111 2 113 5 95 117 111 2 113 4 113 5 113 4 113
	1803023 BadSub2 1803107 Cloperf 15606770 Aquaeol 20808390 Theteng 18311663 Pyraero 18311663 Pyraero 1831163 Pyraero 18312935 Pyraero 11499752 Arcfulg 120090702 Metmaze 14520238 Pyraero 15678332 Mether 18313394 Pyraero 1498552 Arcfulg 14521460 Pyraero 1498552 Metmaze 21227575 Metmaze 18313569 Pyraero 15678491 Metmaze 16272048 Haeinfl 16272048 Haeinfl 16272048 HJOG 15806808 Piraeira 15806808 Piraeira 15806808 Deiradi 15806808 Deiradi 2089652 Metacet	222 27 1700 211 44 20 255 211 211 21 4 424 27 26 26 44 22 26 30 25 24 225 24 225 24 225 24 225 24 226 25 227 26 25 26 26 26 26 26 26 26 26 26 27 27 20 20 20 20 20 20 20 20 20 20 20 20 20	LFDSQTDWQSEIGEL RLGEAFLKDFKNVD KEALAIEVTNEIIID KEALAIEVTNEIIID WSKPYESLSKAEKY 	ALQRI GVIQRL ALRNS ALRNS AVHAA AIRNS AVHAA AIRNS AVHAA AIRNG AVERY AVERY AVERY AVERY AVERY AVERY AVERY AVERY ALRNG GIERL AIERN GAIERN GAIEN ALRNG AIERN GAIEN AIERN GAIEN AIERN GAIEN AIERN GUIRL AIERN GAIEN	SHLLRSS VQOAA FEFT AELVV UIIIA AQEA LQIH LQIH LQIH LQIH LQIH LQIH LQIH LLTS CQIS LIMA LIMA LIMA LIMA LIMA 2 HHH LLVLC 2 HH LLVLC 2 HHH LLVLC 2 HHH LLVLC 2 HHH LLVLC 2 HH LLVLC 2 HHH LLVLC 2 HHH LLVLC 2 HHH LLVLC 2 HHH H LLVLC 2 HH H H H H H H H H H H H H H H H H H	IECIIEAVL IEAVL YDSLAAQST YELAAQST AAETVVEAA AQST VEAA AQST IESAAQAL IESAAQAL VEAVVEAL IESAAQI VEAVVEAL IEACIA VEAVVEAL IEACIA YELS HHHH YELS HHHHHV SEAAT SEAT	LLDTGN LLDTGN VLDLSN VSALAT LLDLAN VLDLA VLDLL CDLVW LLDLA VLDLL CDLVW LLDLG WDLVP HDLC WDLVP WD	NDMIDGFI 24 VYAVISNG 24 VYAVISNG 24 VYAVISNG 25 VDYLAYEG 21 VAMUAFEK 21 VAMUAFEK 21 VAMUAFEK 21 VAMUAFEK 24 VAMUAFEK 24 VAMUAFEK 24 VAMUAFEK 24 VAMUAFEK 24 VALVARG 25 VALVARG 25 VALVARG 24 VALVARG 25 VALVARG 24 VALVARG 25 VALVARG 24 VALVARG 25 VALVARG 25 VALVARG 26 VALVARG 2		GE FE GE EE EE EE EE EE	ELKK EYME KIVLK MWIDDFFLRGR ALRR CLKVVLLYRA CLKVLLYRA CLKVLLYRA KIEPP KILA KLAP KLAP KLAP KLAP VVLSS KRFSE ELSD KLAP PWREG SWKD	LIAYR LIAYR WTLLK MIMDR UVAFR UVAFR UVAFR NGFR ANGFR ANGFR HAGER LIAGIR LIAGIR LIAGIR LIAGIR AAGFR AAGFR AAGFR MAGKR MAGKR MAGKR MAGKR MAGKR	TLVQYLLE KLTFYAS KLISW-EV RTTHYNSK IIVHYYHI ILAHYWA RLVHYNGI VUHYASE RLVHYNGI IIVHYSE WLVHYNGI IIVHYSE WLVHYNGI IIVHYSE IIVHYSE IIVHYSE VIVHYSE VLVHYNO VLVHYNO ILVHYAD IITSHYDO RLIHYG RLIHYG RLIHYG RUHYSE	DSCEL EDEFI SPEEL SPEEL EEKKE EEKKE DDRRW NVEKI DDRRW NUEKI DDRRW NUEKI DDRW DDRW DDRW DDRW DDRW DDRW DDRW DDR	YRLI FNEL YRSL YRSL YESV INST FNEL LNST LNST LNST LSS- LSS- LSS- TSS- TSS- TSS- TSS- TS	115 120 120 120 120 120 94 G 94 G 94 G 94 G 94 G 94 G 111 4 113 4 113 5 95 [117 119 117 119 117 119 117 119 117 119 119 111 4 113 4 113 5 114 4 113 4 113 4 113 4 113 4 113 4 113 4 113 4 113 4 113 4 114 4 113 4 114 4 115 5 117 117 117 117 117 117 117 118 / 117 118 / 118 / 119 119 119 118 / 119 119 119 119 118 / 119 119 118 / 125 118 / 125 125 126 12
	1600023 BadSub2 1631107 Cloperf 15606770 Aquaeol 20808390 Theteng 1831163 Pyraero 1831163 Pyraero 18312935 Pyraero 18312935 Pyraero 15921020 Sultoko 11500009 Arcfulg 20090702 Metmaze 14520238 Pyraero 15678332 Mether 18313394 Pyraero 1498552 Arcfulg 14521460 Pyrabys 20806962 Theteng 21227575 Metmaze 1313569 Pyraero 15678491 Metther 16272048 LJOG 1563206707 Puraeria 153062907 Synsp 15306290 Synsp 15306290 Synsp 15306292 Metacet 15005283 Deiradi	222 27 170 21 14 1 20 255 21 21 4 24 25 26 30 32 26 30 25 24 29 26 30 25 24 29 26 30	LFDSQTDWQSEIGEL RLGEAFLKDFKNVD SQGEEEFKKTPMYYD KEALAIEVTNEIIID KEALAIEVTNEIID WISKPYESLSKAEKY NWI-EEAKVDKKSRL VKRGYDLSNWDDLM VKRGYDLSNWDDLM VKRGYDLSNWDDLM 	ALQRI STKYLI SVLVF GVLQR ALERCL ALENCL ALINS AVLHA ALINS SVLHA AURYS AVLHA ALING GVFYNI AVERYI AKYLI GYLRL ALING ALING ALING ALING ALING ALING ALING CTIRQ ALING CTIRQ ALING	Very of the second seco	IECIIEASU IEASU AQST AETVEAAQST AETVEAAQST AETVEAAQS IESAAQAL IESAAQAL IESAAQAL IESAAQI IESAAL IESAU I	LLDTGN LLDTGN VLDLSN VSALAITIOVLI LLDVL LLDVL LLDVL LLDVL LLDVL LLDVL LLDLGV VYDLC LLDLGV LLDLGV VYDLC LLDLGV LLDLGV VZ VZ LLDLGV LLDLGV VZ VZ LLDLGV VZ VZ VZ VZ VZ VZ VZ VZ VZ VZ VZ VZ VZ	NDMIDGFI 24 VIAVISNG 24 VIAVISNG 24 VIAVISNG 24 VIAVISNG 24 VIAVISNG 24 VIAVISNG 24 VIAVISNG 24 VIAVISNG 25 VIAVISNG 25 VIAVIS		GE FE GE GE GE GE SE CC RE SE AE AE AE AE AE AE A	ELKK EYME KANNE KA	LIAYR LIAYR WTLLX MMLDX MILOR RUVGFR UVGFR VVGFR VVGFR VVGFR VVGFR NAGFR MAFR MAFR AGGR AGGR AGGR AGGR AGGR AGGR MAFR MAGR IIITR MAGR IIITR MAGR IIITR MAGR IIITR MAGR IIITR	TLVQYLLE KLITYASI KLISW-EX RTHYNSK IIVHYNSI IIVHYSE RLVHYNGI RLVHYNGI IIVHYSE IIVHYSE IIVHYSE MLVHYNG IIVHYSE IIVHYNG IVVYNG IIVHYNG RUHYND VLVHYNL VLHYND IISHYDOF HH VUHYNO IISHYDOF RLHYFG VLHYSO VLHYDG RLHYFG VLHYSG LLHYFG VLHYDG RLHYFG VLHYSG LLHYFG VLHYSG VLHYDG RLHYFG VLHYSG LLHYFG VLHYSG VLHYSG LLHYFG VLHYSG V	DSGEL EDEFI SPEL MALEI EEKKE DDRRW NVEKI DDRRW NLGTV VLCTV VLCTV EVCKI DDRTV EVCKI DDRV DDRV DDRV DDRV DDRV DDRV DDRV DDR	YRLI FYRSL YYENI WEAF YESV ULNSU ULNSU ULNSU ULNSU ULSS- ULS	115 120 120 120 120 120 94 G 94 G 94 G 95 117 113 <u>4</u> 113 <u>4</u> 113 <u>4</u> 113 <u>4</u> 113 <u>4</u> 114 <u>4</u> 125 117 125 127 128 128 129 1
	1803023 BadSub2 1803107 Cloperf 15606770 Aquaeol 20808390 Thetang 1831163 Pyraero 1831163 Pyraero 1831235 Pyraero 1831235 Pyraero 11499752 Arcfulg 20090702 Metmaze 14521238 Pyraero 15500090 Arcfulg 20090702 Metmaze 14521460 Pyraero 14521460 Pyraero 14521460 Pyraero 14521460 Pyraero 1227575 Metmaze 21227263 Metmaze 18313569 Pyraero 15678491 Metmaze 16272048 Haeinf1 16272048 Hacinf1 16320607 Synsp 15806808 Deiradi 2089652 Metacet 1580528 Deiradi 20808622 Synsp 15806808 Deiradi 163206	222 27 170 21 14 1 20 25 21 21 21 21 21 21 24 26 30 30 25 24 26 30 25 25 24 29 26 25 21 12 21 21 21 21 21 21 21 21 21 21 21	LFDSQTDWQSEIGEL EGEAFLKDFKNVD ELLAQRLQTGGDIF ELLAQRLQTGGDIF WSKPYESLSKAEKY NWI-EEAKVDKKSRL VWRGYDLSNWDDLM VWRGYDLSNWDDLM 	ALQRI RUKYLF RUKYFF GUIQER ALRYS AUHAN AVYKAA RUHAN AVYKAA RUHAN AVYKAA GUFYN AVERY AVERY AVERY ALRYG ALR	SHLL LRSS VyQvA FEFTI AELVV VQVA AQEA AQEA AQEA AQEA AQEA AQEA AQ	IECIIEAVY HEALESAAAA STELAAAAST VEAAAAST VEAAAAAUVEAAAAAUVEAAAAAUVEAAAAAUVEAAA VEAAAAUVEAUVEAUVEAUVEAUVEAUVEAUVEAUVEAUV	ILDTGN ILDTGN ILDLSN VSALAII USALAII UDUL UDUL UDUL UDUL UDUL UDUL UDUL UD	NDMIDGFI 2 VYAVISNG 24 VYAVISNG 24 VYAVISNG 22 VAVIAVEG 21 VAVIAVEG 21 VAVIAVE		GE FE GE GE SE LA EK AE AE AE AE AE AE A	ELKK EYME KWIDD FFLRG CLKVV CLKVV CLKV CLKV CL KK FFLNA GCKK KK FFLNA KK IL RR LL LL RR RLILL KK KVV KS SK KWVA HHHH HHHH PWSQQ SWKD PWR SQ SWKD PWR SQ SWKD	LIAYR LIAYR WTLLK MMIDR UVAFR UVAFR ANGLR ANGR ANGFR ANGFR MAKFR MACFR LAGER MAKFR MACFR LAGER MACFR MACFR LAGER MACFR LAGER MACFR LAGER MACFR LAGER MACFR LAGER MACFR LAGER MACFR LAGER MACFR LAGER MACFR LAGER MACFR LAGER MACFR LAGER MACFR LAGER MACFR LAGER MACFR LAGER MACFR LAGER MACFR	TLVQYLLE KLTFYAS KLTSW-EV RTTHYNSK KLTSW-EV RTTHYNSK KLTYAS LLAHYWA ULHYNGE VLVHYGE VLVHYGE ULHYSK MUVHYRR UVHYSK MUVHYRR UVHYRR ULHYSC ULHYFC ULHYFC VTHYPO ITSHYDOF HTSHYDOF KLTYFC VLHYDOI RLIHYLC VLHYSC ULHYFC LLAHYFS LLAHYFS LVAHYPE UVAHYPE UVAHYPE	DSGEL EDEFI SPEEL SPEEL EEKKE EEKKE DDRRŪ DDRRŪ DDRVŪ DDRU DDRU DDRU DDRU DDRU DDRU DDRU DDR	YRLI FNEL YESU YESU USS USS USS USS USS USS USS USS USS	115 120 120 120 120 120 120 120 120 121 121 121 123 123 124 125 125 127 128 127 129 12
	1803023 BadSub2 1803107 Cloperf 15606770 Aquaeol 20808390 Theteng 18311663 Pyraero 18311663 Pyraero 1831163 Pyraero 18312935 Pyraero 11499752 Arcfulg 1200009 Arcfulg 20090702 Metmaze 14520238 Pyraero 15678332 Mether 18313344 Pyraero 1498552 Arcfulg 14520238 Pyraero 1498552 Arcfulg 14521460 Pyrabro 15678491 Metmaze 18313569 Pyraero 15678491 Metmaze 16272048 Haoinfl 16272048 Haoinfl 16272048 Hoinfl 16329607 Synsp 15806808 Deiradi 20089652 Metacet 15805283 Deiradi 20140709 Caucres 158	222 27 170 21 14 1 20 25 21 21 4 4 24 27 26 21 21 4 4 130 32 24 22 26 30 30 25 24 4 22 25 24 22 26 30 25 24 22 27 26 26 25 20 26 26 26 26 26 26 27 20 20 20 20 20 20 20 20 20 20 20 20 20	LFDSQTDWQSEIGEL 	ALQRI GVIQR ALREL ALREL ALRES AVLHA AVYAA AIRYS AVVHAA AIRYS AVVRA AVVRY AVVRY ALRYQ ALRYQ ALRYQ ALRYQ ALRYQ ALRYQ ALRYQ ALRYQ ALRYQ ALRYQ CTIRQ ALYE AVVRN GTIRQ AVVRN GVIRC	SHLL LIRSS VQVA FEFT LLIL LLIL LQIH LQIH LQIH LQIH LQIH LQIH	IECIIEAU IEAU YOSLEAU SOSIIEAU SOSIIEAU VEAAAQIVVEAU VEAAAQIVVEAU IESAAQIVVEAU VEAU VEAU VEAU VEAU VEAU VEAU VEAU	LLDTGN LLDTGN VLDLSN VSALAT LLDLAN VLDLAN VLDLL CDLVW LLDLG VLDLL CDLVW LLDLG VLDLL LLDLG VLDLL LLDLG VLDLL VSALAT LLDLG VLDLAN VSALAT VLDLAN VLDN VLDN VLDN VLDN VLDN VLDN VLDN VLD	NDMIDGFI 24 VIAVISNG 24 VIAVISNG 24 VIAVISNG 25 VIAVISNG 24 VIAVISNG 22 VIAVISNG 24 VIAVISNG 25 VIAVISNG 25 VIAVISNG 25 VIAVISNG 25 VIAVISNG 25 VIAVISNG 25 VIAVISNG 25 VIAVISNG 25 VIAVISNG 25 VIAVISNG 26 VIAVISNG 26 VIAVIS		GE FE GE GE CC RE LA EK AE AE AE AE AE AE A	ELKK EYME FYLRK MWIDG ELER CLKV KILV RAALRR CLKV KILV KILV KILV KILV KILV KILV KILV K	LIAYR LIAYR WTLLK MIMDR UVAFR UVAFR UVAFR NGFR ANGFR ANGFR MAKFR MAKFR MACK MACK MACK MACK MACK MACK MACK MACK	TLVQYLLE KLTFYAS KLISW-EV RTTHYNSK IIVHYNFI IIVHYYHI IIVHYSE RLVHYNGI VUHYASE IIVHYSE WLVHYNGI IIVHYSE WLVHYNGI IIVHYSE VIVHYSE IIVHYSE VIVHYRGI ILVHYAV VLVHYMOI VLVHYMOI VLVHYDO IITSHYDOE RLIHYFG RLIHYFG RLIHYFG K	DSGEL EDEFI SPEEL SPEEL ESKE SPEEL DDRRW EEKKE EDRW DDRW DDRW DDRW DDRW DDRW DDRW DDR	YRLI FNEL FNEL YENG YENG YENG LNSI DEIL LSS- LUSI FEIL LEYS FEIL LEYS FEIL LEYS VEIL YGIL YSHL YYAQI HHHH HHHH HHHHHHHQV WMDVI HHHH HHHHHHWSII HHHH HHHHHHWSI	115 120 120 120 120 94 G 94 G 95 G 95 G 98 G 99 G 90 G 9
	1803023 BadSub2 18031077 Cloperf 15606770 Aquaeol 20808390 Theteng 1831163 Pyraero 18311663 Pyraero 18312935 Pyraero 18312935 Pyraero 18312935 Pyraero 15921020 Sultoko 1500009 Arcfulg 20090702 Metmaze 14520238 Pyraero 14520238 Pyraero 14520238 Pyraero 1498552 Arcfulg 14521460 Pyrabys 20806962 Theteng 21227575 Metmaze 18313394 Pyraero 15678491 Metther 16272048 Haeinfl 16329607 Synsp 15306283 Metacet 15805283 Deiradi1 16329607 Synsp 15806808 Deiradi1 16329607 Synsp 15806829 Metacet 1	222 27 170 21 14 20 25 21 21 21 21 21 21 21 21 21 21 21 21 21	LFDSQTDWQSEIGEL RLGEAFLKDFKNVD 	ALQRI STKYLI, SVLVP, GVLQR, ALERL, AVLPA, ALEN, AVLPA, AVYKA, AVYKC, GVEYU, AVEYU, AVEYU, AKYLI GVLVF, GVLVF, ALENYU,	SHLL LRSS V(VAA FEFTI AELVVV (QAA EFFTI LIIII LIIII LIIII LIIII LIIII LQIS LQIS	IECIIEAU IECUIEAU IECUIEAU AQST FELAAQST VEAAAQIV VEAAQALIV EAQALIECUIEAU IECUIEAU VEAU VEAU VEAU VEAU VEAU VEAU VEAU V	ILDTGN ILDTGN VLDLSN VSALAT IIDVLI VLDLAV VL	NDMIDGFI 24 VIAVISNG 24 VIAVIS		GE FE GE GE SE SE LA EK AE AE AE AE AE AE A	ELKK EVME FIRG FLRG CLKV LVRA ALRR CLKV LVRA ALRR CLKV RA CL RA RE RE RE RE RE RE RE RE RE RE RE RE RE	LIAYR LIAYR WTLLX MMIDR UVAFR UVGFR VVGFR VVGFR VVGFR VVGFR VVGFR AGGR AGGR AGGR AGGR AGGR AGGR AGGR A	TLVQYLLE KLIFYASI KLISW-EV RTHYNSK IIVHYNG RUHYNGE RLVHYNGI IIVHYSE IIVHYSE IIVHYSE IIVHYSE MUVHYNG IIVHYNG IIVHYNG RUHYNG RUHYNG RUHYNG RUHYNG IIVHYNG IIVHYNG IIVHYNG IIVHYNG IIVHYNG IIVHYNG IIVHYNG IIVHYNG IIVHYNG RUH	DSGEL EDEFI SPEEL MALEI EEKKE SPEEL DDRRW NVEKI DDRRW NUEKI NUEKI DDRRW NLGTV UNEKU DDRW TDEEL DDRW TDEW TDEEL DDRW TDEW TDEW TDEW TDEW TDEW TDEW TDEW TDE	YRLI FREL YRSL YENU MEAF FULNSI LNSI LSS- LSS- LSS- LSS- VYSL LEYS FEIL LEYS FEIL LEYS FEIL LEYS FEIL LEYS FEIL LYSL VYSL YSL YSL YSL YSL YSL YSL YSL YSL YSL	115 120 120 120 120 120 120 120 121 121 123 123 124 125 127 125 127 125 127 125 127 125 127 128 128 129 12
	1803023 BadSub2 1803107 Cloperf 15606770 Aquaeol 20808390 Theteng 1831163 Pyraero 1831163 Pyraero 1831235 Pyraero 1831235 Pyraero 11499752 Arcfulg 20090702 Metmaze 14521620 Sultoko 15500090 Arcfulg 20090702 Metmaze 14521460 Pyraero 1567832 Metther 16272048 Haeinf1 16272048 Haeinf1 16272048 Haoinf1 16320627 Synsp 15806808 Deiradi 16320627 Synsp 15806808 Deiradi 16320627 Synsp 15806808 Deiradi 16127309 Caucres 15668296 Metjann 22299774 Theelon	222 27 170 21 14 20 25 21 21 21 21 21 21 21 21 21 21 21 21 21	LFDSQTDWQSEIGEL EGEAFLKDFKNVD ELLAQRLQTGGDIF ELLAQRLQTGGDIF WSKPYESLSKAEKY NWI-EEAKVDKKSRL VWRGYDLSNWDDLM VVERGYDLSNWDDLM VVERGYDLNYWRDQM 	ALQRI STKYLI STKYLI STKYLI STKYLI ALRYSI ALRYSI AVLHAA AVYKAA AVYKAA AVYKAA ALRYC	SHLL RSS VQVA FFEFTJ LLRSS FFEFTJ LIII LUII LUII LUII LUII LUII LUII LUI	IECII IEAVY FELAAQST FELAAQST FELAAQST VEAAQAL UEAQIV VEAAQAL IEAQIV VEAQUV IEAQIV VEAU IEACIV IEACIV IEACIA IEACIA VEAU IEACIA	ILDTGN ILDTGN ILDLSN VSALAII UTDVLL VSALAII UTDVL ULDLC ULDC ULD	NDMIDGFI 2 VIVAVISNG 24 VIVAVISNG 24 VIVAVISNG 22 VIVAVISNG 22 VIVAVIS		GE FE GE GE CE RE SE LA EK AE AE AE AE AE AE A	ELKK EVME KEVME KEVME KEVME KEVE KEVE KEVE	LIAYR LIAYR WTLLK MMIDER WMTLK MMIDER LIVER ANGER ANGER MARGER LAGER MARGER LAGER MARGER LAGER MARGER LAGER MARGER LAGER MAGY MAGYR MAGYR LAGER MAGYR LAGER MAGYR LAGER MAGYR LAGER LAGER MAGYR LAGER LAGER LAGER LAGER LAGER LAGER LAGER LAGER LAGER LAGER LAGER LAGER LAGER LAGER LAGER LAGER LAGER LAGER LAGER	TLVQYLLE KLTFYAS KLTSW-EV RTTHYNSK RTTHYNSK KLTYAS LLAHYWA LLAHYWA LLAHYWA ULVHYGE RUVHYGE I IVHYSE WLVHYNR I IUHYSA MLVHYNR I IUHYSA MLVHYWD I IUHYSA ULVHYRO ULVHYDO I TSHYDOF HTSHYDOF KLTHYFC KLTHYFC LLAHYFS LLAHYFC KLTHYFC KLTHYFC KLTHYFC I VVHYFL I IVYFC I IV F I IVYFC I IV F I	DSGEL EDEFI SPELL SPELL DRRW DDRRW DDRV DDRV DDRV DDRV DDRV DDR	YRLI FINEL YRSI YENI MEAF MEAF JDEIL DEIL LUSI LUSI LUSI LUSI VEL YRI YEIL YNI YYGIL YNG YAQI HHHH HQVV WDYI VPVL WYTV WYTV WDIA WETA WETA	115 120 120 120 120 120 94 G 94 G 94 G 95 111 4 113 4 95 117 119 125 98 C 99 C 90 C 99 C 90 C 90 C 90 C 99 C 90 C
	18031077 Cloperf 18311077 Cloperf 15606770 Aquaeol 20808390 Theteng 18311663 Pyraero 18311663 Pyraero 18311663 Pyraero 18311757 Pyraero 18312935 Pyraero 11499752 Arcfulg 1200009 Arcfulg 1500009 Arcfulg 100000702 Metmaze 14520238 Pyraero 15678332 Mether 18313344 Pyraero 1498552 Arcfulg 14521460 Pyraero 15678491 Metmaze 18313569 Pyraero 15678491 Metmaze 16272048 Haoinfl 16272048 Haoinfl 16272048 Hoinfl 16329607 Synsp 15806808 Deiradi 20089652 Metacet 15805283 Deiradi 20089652 Metacet <td< th=""><th>222 27 1700 21 1 20 25 21 21 21 21 21 24 24 24 24 27 26 30 32 24 22 26 30 32 25 24 25 24 25 25 24 25 25 24 25 25 24 25 25 24 25 25 24 25 25 25 27 26 25 26 26 26 26 26 26 26 26 26 26 26 26 26</th><th>LFDSQTDWQSEIGEL </th><th>ALQRI GVIQR ALRAL ALRYS AVHAA AIRYS AVHAA AIRYS AVHAA AIRYS AVERY AVERY AVERY AVERY AVERY ALRYQ ALRYQ ALRYQ ALRYQ AIERN GIERL AIERN GAIEN GIERL AIERN GAIEN GIERL AIERN GAIEN GVIRC AVERY AVERY AVERY AVERY</th><th>SHLL RSS VQVAA FEFTI AELVV UIIII UIII UIII UIII UIII UIII UIII</th><th>IECII IEAVY VOSLIS FELAAQST FELAAQST FELAAQST VELAAQIV VEAAQAL LECMI IEACIVEAL LECMI IEACIVEAL LECMI IEACI LECAILESA VENVVEAL LECAILESA SEAAA SEAAA SEAA SEAAT SEAT SEAVEN</th><th>LLDTGN LLDTGN VLDLSN VSALAT LLDLAN VLDLAN VLDLLQ LLDLG VLDLLQ LLDLG VLDLLQ LLDLG VLDLQ LLDLG VLDLQ LLDLG VLDLQ LLDLG VLDLQ LLDLG VLDLQ LLDLG VLDLQ LLDLG VLDLQ LLDLG VLDLQ VLDLQ LLDLG VLDLQ VLDLQ LLDLG VLDLQ VLDLQ LLDLG VLDLQ VLD VLD VLD VLD VLD VLD VLD VLD VLD VLD</th><th>NDMIDGFI 24 VIAVISNG 24 VIAVISNG 24 VIAVISNG 25 VIAVISNG 24 VIAVISNG 22 VIAVISNG 24 VIAVISNG 25 VIAVISNG 25 VIAVIS</th><th></th><th>GE FF GE GE SE SE SE AE AE AE AE A</th><th>ELKK EVMWID FIERGELERR CCLKVLLYRAA FFLNA GCLKVLLYRAA FFLNA FFLNA GCLKE FFLNA FFLNA FFLNA FFLNA FFLNA FFLA FFLA</th><th>LIAYR LIAYR WTLLX MIMDR UVAFR UVAFR UVAFR NGFR ANGFR ANGFR MAKFR MAKFR MACKR AAGFR AAGFR AAGFR HAGLR H</th><th>TLVQYLLE KLTFYAS KLISW-EV RTTHYNSK IIVHYNFI ILAHYMA RUVHYNGI VUVHYASE RLVHYNGI IIVHYK WLVHYNG IIVHYK MLVHYNG IIVHYK VIVHYSE IIVHYK VIVHYR VIVHYR IIVHYN VLVHYWOI VLVHYWOI VLVHYDO IITSHYDOG RLIHYFG RLIHYFG RLIHYFG KLIHYFG KLIHYFG KLIHYFG KLIHYFG KLIHYFG KLIHYFG KLIHYFG KLIHYFG</th><th>DSGEL EDEFI SPEEL SPEEL ESKES SPEEL DDRRW EEKKE EDRW DDRW DDRW DDRW DDRW DDRW DDRW DDR</th><th>YRLI FNEL FNEL YESU YENI LNSI DEIL LSS- DEIL LSS- TEL FEIL LEYS ERAL YEII YGIL YSHL YSHL YAQU HHHH HHHH HHHH HHHH HHHH HHHH HHHH H</th><th>115 120 120 120 121 C 94 G 94 G 95 G 95 G 98 G 98 G 98 C 98 C 99 C 90 C 9</th></td<>	222 27 1700 21 1 20 25 21 21 21 21 21 24 24 24 24 27 26 30 32 24 22 26 30 32 25 24 25 24 25 25 24 25 25 24 25 25 24 25 25 24 25 25 24 25 25 25 27 26 25 26 26 26 26 26 26 26 26 26 26 26 26 26	LFDSQTDWQSEIGEL 	ALQRI GVIQR ALRAL ALRYS AVHAA AIRYS AVHAA AIRYS AVHAA AIRYS AVERY AVERY AVERY AVERY AVERY ALRYQ ALRYQ ALRYQ ALRYQ AIERN GIERL AIERN GAIEN GIERL AIERN GAIEN GIERL AIERN GAIEN GVIRC AVERY AVERY AVERY AVERY	SHLL RSS VQVAA FEFTI AELVV UIIII UIII UIII UIII UIII UIII UIII	IECII IEAVY VOSLIS FELAAQST FELAAQST FELAAQST VELAAQIV VEAAQAL LECMI IEACIVEAL LECMI IEACIVEAL LECMI IEACI LECAILESA VENVVEAL LECAILESA SEAAA SEAAA SEAA SEAAT SEAT SEAVEN	LLDTGN LLDTGN VLDLSN VSALAT LLDLAN VLDLAN VLDLLQ LLDLG VLDLLQ LLDLG VLDLLQ LLDLG VLDLQ LLDLG VLDLQ LLDLG VLDLQ LLDLG VLDLQ LLDLG VLDLQ LLDLG VLDLQ LLDLG VLDLQ LLDLG VLDLQ VLDLQ LLDLG VLDLQ VLDLQ LLDLG VLDLQ VLDLQ LLDLG VLDLQ VLD VLD VLD VLD VLD VLD VLD VLD VLD VLD	NDMIDGFI 24 VIAVISNG 24 VIAVISNG 24 VIAVISNG 25 VIAVISNG 24 VIAVISNG 22 VIAVISNG 24 VIAVISNG 25 VIAVISNG 25 VIAVIS		GE FF GE GE SE SE SE AE AE AE AE A	ELKK EVMWID FIERGELERR CCLKVLLYRAA FFLNA GCLKVLLYRAA FFLNA FFLNA GCLKE FFLNA FFLNA FFLNA FFLNA FFLNA FFLA FFLA	LIAYR LIAYR WTLLX MIMDR UVAFR UVAFR UVAFR NGFR ANGFR ANGFR MAKFR MAKFR MACKR AAGFR AAGFR AAGFR HAGLR H	TLVQYLLE KLTFYAS KLISW-EV RTTHYNSK IIVHYNFI ILAHYMA RUVHYNGI VUVHYASE RLVHYNGI IIVHYK WLVHYNG IIVHYK MLVHYNG IIVHYK VIVHYSE IIVHYK VIVHYR VIVHYR IIVHYN VLVHYWOI VLVHYWOI VLVHYDO IITSHYDOG RLIHYFG RLIHYFG RLIHYFG KLIHYFG KLIHYFG KLIHYFG KLIHYFG KLIHYFG KLIHYFG KLIHYFG KLIHYFG	DSGEL EDEFI SPEEL SPEEL ESKES SPEEL DDRRW EEKKE EDRW DDRW DDRW DDRW DDRW DDRW DDRW DDR	YRLI FNEL FNEL YESU YENI LNSI DEIL LSS- DEIL LSS- TEL FEIL LEYS ERAL YEII YGIL YSHL YSHL YAQU HHHH HHHH HHHH HHHH HHHH HHHH HHHH H	115 120 120 120 121 C 94 G 94 G 95 G 95 G 98 G 98 G 98 C 98 C 99 C 90 C 9
	18031037 Cloperf 18031077 Cloperf 18031077 Cloperf 18000233 Theteng 18311653 Pyraero 18311653 Pyraero 18311653 Pyraero 18312935 Pyraero 1312935 Pyraero 1313047 Pyraero 15921020 Sultoko 1500009 Arcfulg 20090702 Metmaze 14521460 Pyraero 14521460 Pyrabys 20806962 Theteng 21227253 Metmaze 18313569 Pyraero 15678491 Metther 16272048 1JOG 15805707 Deiradi 16320629 Synsp 15806808 Deiradi 16320629 Synsp 15806808 Deiradi 15805283 Deiradi 15805283 Deiradi 15805283 Deiradi 16127309 Caucres 156	222 27 170 21 14 20 25 21 21 21 21 21 21 21 21 21 21 21 21 21	LFDSQTDWQSEIGEL RLGEAFLKDFKNVD 	ALQRI STKYLI, KVKYFF GVIQR ALERL, AVYKA, AIRYSJ AVHAA AIRYSJ AVYKA AVYKA AAKYLI GVFYNI, AVERYJ AAKYLI GMYKR AAKYL GMYKR ALYSG AILYQ AILRYJ ALRYQJ ALRYQJ ALRYQ AILRYL ALRYQ AILRYL ALRYL ALRYL ALRYQ AILYN CAIQKA AILYQ ATLRN AVYRC, SVYRC AVYRC AVVRC AVVRC AVVRC AVVRC	SHLL LRSS (QVA AELV) AELV) (QIA AELV) LIIII LQIH AQEAA QA AELV) LQIA CQII LLTS CQII LLTS CQII LLTS CQII LLTS CQII LLTTII LLVI CQIA LIVI CQIA LIVI CQIA LIVI CQIA LIVI CQII LLVI CQII LLVI CQII LLVI CQII LLVI CQIA CQII LLVI CQIA CQII LLVI CQIA CQII	IECILEAU IEAU PELAAQST PELAAQAQ PELAAQA PELAAQA PELAAQAT PELAAQAT PELAAQAT PELAACT PELAC	ILDTGN ILDTGN VLDLSN VSALAT IIDVLI VLDLAV VL	NDMIDGFI 2 VIAVISNG 24 VIAVISNG 24 VIAVISN		GE FF GE RE RE RE RE RE RE RE	ELKK EYME FIRGGELER ALRR FIRGGELER FIRGGELK FFLNA KILAQ KILAQ KILAQ KILAQ FFLNA KILAQ KILAQ FFLNA KILAQ FFLNA KILAQ FFLAQ FIRG FIRG FIRG FIRG FIRG FIRG FIRG FIRG	LIAYR LIAYR WTLLK MMIDER UVGER UVGER VVGFR VVGFR VVGFR VVGFR VVGFR VVGFR VVGFR VVGFR VVGFR VVGFR VVGFR AGGR MACFR AGGR AGGR AGGR AGGR AGGR AGGR AGGR AG	TLVQYLLE KLITYASI KLISW-EV RTTHYNS IIVHYHI ILAHYWA RIVHYGEI RLVHYGEI IIVHYSE IIVHYSE IIVHYSE IIVHYSE MLVHYNG IIVHYSE IIVHYNC MLVHYNC IIVHYNC IIVHYNC RUHYNC IIVHYNC IIVHYNC ILWHYNC ILWHYNC IISHYDQF RLHYFC LLAHYFS LLHYFC KLIHYFC K K K K K K K K K K K K K K K K K K K	DSGEL EDEFI EDEFI ESPEL ESKES DDRRW NVEKI DDRRW NLCTV VNLCTV DDRLV DDRLV DDRLV DDRLV DDRLV DDRV DDR	YRLI FNEL YRSL YENU MEAF FUSY DEIL LNSI LSS- LSS- USY TSEL ERAL LSY FEIL LEYS ERAL LEYS ERAL LEYS FRIL LEYS VSHL LYST VSHL VSHL VSHL VSHL VSHL VSHL VSHL VSHL	115 120 120 120 120 120 94 94 94 95 117 113 95 117 113 117 119 125 110 125 111 125 111 125 125 111 125 125 127 127 125 127 125 127 125 127 125 127 127 125 127
	18031027 Cloperf 1831107 Cloperf 15606770 Aquaeol 20808390 Theteng 1831163 Pyraero 1831163 Pyraero 18311757 Pyraero 18312935 Pyraero 11499752 Arcfulg 20090702 Metmaze 14521600 Pyraero 1550232 Mether 18313344 Pyraero 1557832 Mether 18313569 Pyraero 14521460 Pyrabys 20806962 Theteng 21227575 Metmaze 21227563 Metmaze 18313569 Pyraero 15678491 Metmaze 16272048 1JOG 15805707 Deiradi 16320607 Synsp 15806808 Deiradi 16320620 Synsp 15805830 Caucres 15805230 Caucres 15805230 Metaet 15805230															
 | 222
27
1700
211
1
200
221
21
21
21
21
21
21
21
21
21
21
21
21 | LFDSQTDWQSEIGEL
EGEAFLKDFKNVD
ELLAQRLQTGGDIF
ELLAQRLQTGGDIF
VKRGYDLSKAEKY
NWI-EEAKVDKKSRL
VWRGYDLSNWDDLM
VVERGYDLSNWDDLM
VVERGYDLSNWDDLM
 |
ALQRI
STKYLJ
STKYLJ
STKYLJ
ALERLJ
ALRYS
AULHA
AVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SAKYN
AVERY
AVERY
AVERY
AVERY
ALERYI
ALEYY
ALEYY
ALEYY
ALEYY
ALEYY
ALEYY
SVKAJ
SVKN
VYRAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ
SVYKAJ | SHLLRSS
(VQVA
FEFTY
AELV)
(UTIN
LQTH
LQTH
LQTH
LQTH
LQTS
LDTS
LDTS
LQTS
LQTS
LQTS
LQTS
LQTS
LTA
LEFA
MEVS
2 HHH
LLVL
LETT
LTTTI
LETT
LTTTI
LETT
LTTTI
LETT
LTTTI
LETT
LTTTI
LETT
LTTTI
LETT
LTTTI
LETT
LTTTI
LTTTI
LETT
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTI
LTTTTI
LTTTTI
LTTTTI
LTTTTI
LTTTTTTTT | IECIIEAU
IEAU
YDSLLEAAOST
AACTYVEAAOSY
VEAAOSY
VEAAOAU
VEAAOAU
IESAAOIU
IESAAOIU
IESAAOIU
IESAAOIU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEACU
IEA |
LLDTGN
LLDTGN
LLDLSN
VSALAII
UDVLL
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
LLDLA
L | NDMIDGFI 2
VIVAVISNG 24
VIVAVISNG 24
VIVAVISNG 24
VILAPER 21
VIVAVISNG 24
VILAPER 21
VIVAVIS 21
VIVAVIS 21
VIVAVIS 22
VIVAVIS 22
VIVAT 22
VIVAVIS 22
VIVAT 22 | | GE
FF
GE
CE
RE
RE
RE
RE
RE
RE
R | ELKK
ELKK
KWWID
FFLRG
CCLKVV
LIYRA
ALR
CCLKV
LIYRA
CCLKV
CLY
FFLNA
CCLKV
KIPP
KIA
CCLKV
KIPP
KIA
CCLKV
KIPP
KIA
CCLKV
KIPP
KIA
CCLKV
KIPP
KIA
CCLKV
KIPP
KIA
CCLKV
KIPP
KIA
CCLKV
KIPP
KIA
CCLKV
KIPP
KIA
CCLKV
KIPP
KIA
CCLKV
KIPP
KIA
CCLKV
KIPP
KIA
CCLKV
KIPP
KIA
CCLKV
KIPP
KIA
CCLKV
KIPP
KIA
CCLKV
KIPP
KIA
CCLKV
KIPP
KIA
CCLKV
KIPP
KIA
CCLKV
KIPP
KIA
CCLKV
KIPP
KIA
CCLKV
KIPP
KIA
CCLKV
KIPP
KIA
CCLKV
KIPP
KIA
CCLKV
KIPP
KIA
CCLKV
KIPP
KIA
CCLKV
KIPP
KIA
CCLKV
KIPP
KIA
CCLKV
KIPP
KIA
CCLKV
KIPP
KIA
CCLKV
KIPP
KIA
CCLKV
KIPP
KIA
CCLKV
KIPP
KIA
CCLKV
KIPP
KIA
CCLKV
KIPP
KIA
CCLKV
KIPP
KIA
CCLKV
KIPP
KIA
CCLKV
KIPP
KIA
CCLKV
KIPP
KIA
CCLKV
KIPP
KIA
CCLKV
KIPP
KIA
CCLKV
KIPP
KIA
CCLKV
KIPP
KIA
CCLKV
KIXA
KIPP
KIA
CCLKV
KIXA
KIPP
KIA
CCLKV
KIXA
KIPP
KIA
CCLKV
KIXA
KIPP
KIA
CCLKV
KIXA
FINA
KIPP
KIA
CCLKV
KIXA
FINA
KIPP
KIA
CCLKV
KIXA
FINA
KIPP
KIA
CCLKV
KIXA
FINA
KIPP
KIA
CCLKV
KIV
KIPP
KIA
CCLKV
KIPP
KIA
CCLKV
KIPP
KIA
CCLKV
KIPP
KIA
CCLKV
KIPP
KIA
CCLKV
KIPP
KIA
CCLKV
KIPP
KIA
CCLKV
KIPP
KIA
CCLKV
KIPP
KIA
CCLKV
KIPP
KIA
CCLKV
KIPP
KIA
CCLKV
KIP
KIP
KIA
CCLKV
KIPP
KIA
CCLKV
KIPP
KIA
CCLKV
KIPP
KIA
CCLKV
KIP
KIA
CCLKV
KIN
KIP
KIA
CCLKV
KIN
KIP
KIA
CCLKV
KIN
KIN
KIN
KIN
KIN
KIN
KIN
KIN
KIN
KIN | LIAYR
LIAYR
LVNLKI
WILLK
MILDKR
ANGLR
ANGLR
ANGRA
ANGRA
ANGRA
MAKER
MAGRA
LAGER
MAGRA
LAGER
MAGRA
LAGER
MAGRA
LAGER
MAGRA
LAGER
MAGRA
LAGER
IISL
RAGRA
LAGER
MAGRA
LAGER
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
LAGRA
 | TLVQYLLE
KLTFYAS
KLTSW-EV
RTTHYNSK
KLTSW-EV
RTTHYNSK
KLTSW-EV
RTTHYNSK
KLVHYNGE
I LVHYNG
VLVHYRS
I IVHYGE
I LVHYSK
MLVHYNG
I IVHYSK
MLVHYNG
I LVHYSK
VLVHYND
I LVHYSK
VLVHYDO
I TSHYDOF
HTSHYDOF
KLIHYFG
KLIHYFG
KLIHYFG
KLIHYFG
KLIHYFG
KLIHYFG
KLIHYFG
KLIHYFG
KLIHYFG
KLIHYFG
KLIHYFG | DSGEL
EDEFI
SPELL
SPELL
DDRW
DDRW
DDRW
DDRW
DDRW
DDRW
DDRW
DD | YRLI
FINEL
YRSI
YENI
MEAF
MEAF
JDEIL
DEIL
LUSI
LUSI
LUSI
LUSI
LUSI
VEL
YRI
YRI
YRI
YRI
YRI
YRI
YRI
YRI
YRI
YRI
 | $\begin{array}{c c c c c c c c c c c c c c c c c c c $ |
| | 180300263 18031077 Cloperf 15606770 Aquaeol 20808390 Theteng 18311663 Pyraero 18311663 Pyraero 18311637 Pyraero 18312935 Pyraero 11499752 Arcfulg 1200009 Arcfulg 120090702 Metmaze 14520238 Pyraero 15678332 Methre 18313344 Pyraero 1498552 Arcfulg 14520238 Pyraero 15678332 Methre 18313344 Pyraero 1498552 Arcfulg 14527238 Metmaze 21227575 Metmaze 18313569 Pyraero 15678491 Methaze 16272048 Haoinfl 16272048 Haoinfl 16329607 Synsp 15806808 Deiradi 16329627 Synsp 15806808 Deiradi 16127309 <td< th=""><th>222
27
1700
21
1
20
25
21
21
21
21
21
21
21
24
24
27
26
30
32
25
24
22
26
30
25
24
25
24
25
26
25
21
21
21
21
21
21
21
21
21
21
21
21
21</th><th>LFDSQTDWQSEIGEL
</th><th>ALQRI
GVIQR
ALREL
ALRES
AVHAA
AIRYS
AVHAA
AIRYS
AVHAA
AIRYS
AVERY
AVERY
AVERY
AVERY
AVERY
ALRYQ
ALRYQ
ALRYQ
AIERN
GIERL
AIERN
GAIERN
GAIERN
GIERL
AIERN
GAIERN
GAIERN
GIERL
ALRYQ
ALRYQ
ALRYQ
ALRYQ
ALRYQ
ALRYQ
AVERY
AVERY
AVERY
AVERY
AVERY
AVERY
AVERY
AVERY</th><th>SHLLRSS
(VQVA
AELVX
VQVA
AELVX
LIRSS
VQVA
AELVX
LQSA
LQA
LQA
LQA
LQA
LQA
LQA
LQA
LQ</th><th>I EC II EAVY
YDS LLAAQSY
PELAAQSY
PELAAQSY
VEAAQSY
VEAAQAQI
VEAAQAQI
VEAAQAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI</th><th>LLDTGN
LLDTGN
VLDLSN
VSALAT
LLDLAN
VLDLAN
VLDLL
CDLVW
LLDLA
LLDLG
VLDLL
CDLVW
LLDLG
VLDLL
CDLVW
LLDLG
VLDLL
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLD
VLD
VLD
VLD
VLD
VLD
VLD
VLD
VLD
VLD</th><th>NDMIDGFI 24
VIAVISNG 24
VIAVIS</th><th></th><th>GE
YE
YE
YE
RE
RE
RE
RE
R</th><th>ELKK
EVME
FLRGGELER
CCLKVLLYRAA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLA
FFL</th><th>LIAYR
LIAYR
UVNIKI
WILLK
MILDR
UVKIR
ANGIR
UVGFR
UVGFR
ANGFR
ANGFR
ANGFR
HAGIR
LIAGIR
LIAGIR
LIAGIR
LIAGIR
LIAGIR
LIAGIR
LIAGIR
LIAGIR
LIAGIR
LIAGIR
LIAGIR
LIAGIR
LIAGIR
LIAGIR
LIAGIR
LIAGIR
LIAGIR
LIAGIR
LIAGIR
LIAGIR
LIAGIR
LIAGIR
LIAGIR
LIAGIR
LIAGIR
LIAGIR
LIAGIR
LIAGIR
LIAGIR
LIAGIR
LIAGIR
LIAGIR
LIAGIR
LIAGIR
LIAGIR
LIAGIR</th><th>TLVQYLLE
KLTFYAS
KLISW-EV
RTTHYNSK
IIVHYNGI
ULHAYWA
RIVHYGE
RLVHYNGI
UVHYSE
WLVHYNGI
IIVHYK
WLVHYNG
IIVHYSE
WLVHYNG
IIVHYSE
WLVHYNG
VLVHYGKI
IIVHYA
VLVHYMOI
VLVHYMOI
VLVHYMOI
VLVHYMOI
VLVHYMOI
VLVHYDOI
ILVHYFU
VLVHYDO
RLIHYFG
RLIHYFG
KLIHYFG
KLIHYFG
KLIHYFG
KLIHYFG
KLIHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IINFFG
IIVFFG
IINFFG
IIVHYFG
IIVHYFG
IINFFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG</th><th>DSCEL
EDEFI
SPEEL
SPEEL
SPEEL
DDRRW
DDRRW
NVEKI
DDRRW
NUEKI
DDRRW
DDRU
DDRW
DDRW
DDRW
DDRW
DDRW
DDR</th><th>YRLI
FNEL
FNEL
YENG
YENG
VENT
FNEL
FNEL
FNEL
FNEL
VENT
YENE
FNEL
VENT
YENE
YENE
YENE
YENE
YENE
YENE
YENE
Y</th><th>115
120
120
120
120
94 G
94 G
95 [
111 4
113 4</th></td<> | 222
27
1700
21
1
20
25
21
21
21
21
21
21
21
24
24
27
26
30
32
25
24
22
26
30
25
24
25
24
25
26
25
21
21
21
21
21
21
21
21
21
21
21
21
21 | LFDSQTDWQSEIGEL
 | ALQRI
GVIQR
ALREL
ALRES
AVHAA
AIRYS
AVHAA
AIRYS
AVHAA
AIRYS
AVERY
AVERY
AVERY
AVERY
AVERY
ALRYQ
ALRYQ
ALRYQ
AIERN
GIERL
AIERN
GAIERN
GAIERN
GIERL
AIERN
GAIERN
GAIERN
GIERL
ALRYQ
ALRYQ
ALRYQ
ALRYQ
ALRYQ
ALRYQ
AVERY
AVERY
AVERY
AVERY
AVERY
AVERY
AVERY
AVERY | SHLLRSS
(VQVA
AELVX
VQVA
AELVX
LIRSS
VQVA
AELVX
LQSA
LQA
LQA
LQA
LQA
LQA
LQA
LQA
LQ | I EC II EAVY
YDS LLAAQSY
PELAAQSY
PELAAQSY
VEAAQSY
VEAAQAQI
VEAAQAQI
VEAAQAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAQI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI
VEAVI | LLDTGN
LLDTGN
VLDLSN
VSALAT
LLDLAN
VLDLAN
VLDLL
CDLVW
LLDLA
LLDLG
VLDLL
CDLVW
LLDLG
VLDLL
CDLVW
LLDLG
VLDLL
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLDLG
VLD
VLD
VLD
VLD
VLD
VLD
VLD
VLD
VLD
VLD | NDMIDGFI 24
VIAVISNG 24
VIAVIS | | GE
YE
YE
YE
RE
RE
RE
RE
R | ELKK
EVME
FLRGGELER
CCLKVLLYRAA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLA
FFL | LIAYR
LIAYR
UVNIKI
WILLK
MILDR
UVKIR
ANGIR
UVGFR
UVGFR
ANGFR
ANGFR
ANGFR
HAGIR
LIAGIR
LIAGIR
LIAGIR
LIAGIR
LIAGIR
LIAGIR
LIAGIR
LIAGIR
LIAGIR
LIAGIR
LIAGIR
LIAGIR
LIAGIR
LIAGIR
LIAGIR
LIAGIR
LIAGIR
LIAGIR
LIAGIR
LIAGIR
LIAGIR
LIAGIR
LIAGIR
LIAGIR
LIAGIR
LIAGIR
LIAGIR
LIAGIR
LIAGIR
LIAGIR
LIAGIR
LIAGIR
LIAGIR
LIAGIR
LIAGIR
LIAGIR | TLVQYLLE
KLTFYAS
KLISW-EV
RTTHYNSK
IIVHYNGI
ULHAYWA
RIVHYGE
RLVHYNGI
UVHYSE
WLVHYNGI
IIVHYK
WLVHYNG
IIVHYSE
WLVHYNG
IIVHYSE
WLVHYNG
VLVHYGKI
IIVHYA
VLVHYMOI
VLVHYMOI
VLVHYMOI
VLVHYMOI
VLVHYMOI
VLVHYDOI
ILVHYFU
VLVHYDO
RLIHYFG
RLIHYFG
KLIHYFG
KLIHYFG
KLIHYFG
KLIHYFG
KLIHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IINFFG
IIVFFG
IINFFG
IIVHYFG
IIVHYFG
IINFFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG
IIVHYFG | DSCEL
EDEFI
SPEEL
SPEEL
SPEEL
DDRRW
DDRRW
NVEKI
DDRRW
NUEKI
DDRRW
DDRU
DDRW
DDRW
DDRW
DDRW
DDRW
DDR | YRLI
FNEL
FNEL
YENG
YENG
VENT
FNEL
FNEL
FNEL
FNEL
VENT
YENE
FNEL
VENT
YENE
YENE
YENE
YENE
YENE
YENE
YENE
Y | 115
120
120
120
120
94 G
94 G
95 [
111 4
113 4 |
| | Ibox 2023 BadSub1 18311077 Cloperf 15606770 Aquaeol 20808390 Theteng 1831163 Pyraero 1831163 Pyraero 18312935 Pyraero 18312935 Pyraero 11499752 Arcfulg 18313047 Pyraero 15921020 Sultoko 1500009 Arcfulg 1000702 Metmaze 14320238 Pyraero 1498552 Arcfulg 14520238 Pyraero 1498552 Arcfulg 14520238 Pyraero 1498552 Arcfulg 14521460 Pyrabyo 16272038 Metmaze 1831359 Pyraero 15678491 Mether 16272048 HaoInfl 16329607 Synsp 15806808 Peiradi 16329607 Synsp 15806808 Deiradi 16127309 Caucres 15668 | 222
27
170
21
14
20
25
21
21
21
21
21
21
21
24
24
27
26
14
18
41
30
22
5
24
22
6
25
141
25
5
24
22
5
25
25
25
25 | LFDSQTDWQSEIGEL
 | ALQRI
STKYLI,
STKYLI,
RVKYFF
GVIQR,
ALERL,
ALINS,
AVIHA
AIRYS,
AVVRA
AVVRA,
AVVRA,
AVVRA,
AVVRA,
AIRNY,
ALRYQ
AIRYN,
AIRNY,
AIRYN,
AIRNY,
AIRYN,
AIRYN,
AIRNY,
AIRYN,
AIRNY,
AIRYN,
AIRNY,
AIRNY,
AIRNY,
AIRNY,
AIRNY,
AIRNY,
AIRNY,
AIRNY,
AIRNY,
AIRNY,
AIRNY,
AIRNY,
AVVRA,
AVVRA,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVRC,
AVVR | ZHLL
LRSS
(QVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VQVAA
VVVVI
VQVAA
VQVAA
VVVVI
VQVAA
VVVVI
VQVAA
VVVVI
VQVAA
VQVAA
VVVVI
VQVAA
VVVVI
VQVAA
VQVAA
VVVVI
VQVAA
VVVVI
VQVI
VQVAA
VVVVI
VQVI
VQVI
VQVAA
VQVAA
VVVVI
VQVAA
VQVAA
VVVVI
VQVAA
VVVVI
VQVI
VQVI
VQVAA
VQVAA
VVVVI
VQVAA
VQVAA
VVVVI
VQVAA
VVVVI
VQVAA
VVVVI
VVVVI
VQVI
VQVI
VQVI
VQVI
VVVVI
VVVVI
VVVVI
VVVVVVI
VVVVI
VVVVI
VVVVI
VVVVI
VVVVI
VVVVI
VVVVI
VVVVI
VVVVI
VVVVI
VVVVI
VVVVI
VVVVI
VVVVI
VVVVI
VVVVI
VVVVI
VVVVI
VVVVI
VVVVI
VVVVI
VVVVI
VVVVI
VVVVI
VVVVI
VVVVI
VVVVI
VVVVI
VVVVI
VVVVI
VVVVI
VVVVI
VVVVI
VVVVI
VVVVI
VVVVI
VVVVI
VVVVI
VVVVI
VVVVI
VVVVI
VVVVI
VVVVI
VVVVI
VVVVVI
VVVVI
VVVVI
VVVVVI
VVVVVI
VVVVVI
VVVVVI
VVVVVI
VVVVVI
VVVVVVI
VVVVVI
VVVVVI
VVVVVVI
VVVVVVVV | IECILEAVAOS
IEAVAOS
IEAVAOS
IEAVAOS
IEAVAOS
IESAAOS
IESAAOS
IESAAOS
IESAAOS
IESAAOS
IESAAOS
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAVA
IEAV | ILDTGN
ILDTGN
VLDLSN
VSALAI
VLDLSN
VSALAI
VLDLA
VLDV
VLDLA
VLDV
VLDLA
VLDV
VLDLA
VLDV
VLDLA
VSALAI
VLDV
VLDV
VSALAI
VLDV
VSALAI
VLDV
VSALAI
VLDV
VSALAI
VLDV
VSALAI
VLDV
VSALAI
VLDV
VSALAI
VLDV
VSALAI
VLDV
VSALAI
VLDV
VSALAI
VLDV
VSALAI
VLDV
VSALAI
VLDV
VSALAI
VLDV
VSALAI
VLDV
VSALAI
VLDV
VSALAI
VLDV
VSALAI
VLDV
VSALAI
VLDV
VSALAI
VLDV
VSALAI
VLDV
VSALAI
VLDV
VSALAI
VLDV
VSALAI
VLDV
VSALAI
VLDV
VSALAI
VLDV
VSALAI
VLDV
VSALAI
VLDV
VSALAI
VLDV
VSALAI
VLDV
VSALAI
VLDV
VSALAI
VLDV
VSALAI
VLDV
VSALAI
VLDV
VSALAI
VLDV
VSALAI
VLDV
VSALAI
VLDV
VSALAI
VLDV
VSALAI
VLDV
VSALAI
VLDV
VSALAI
VLDV
VSALAI
VLDV
VSALAI
VLDV
VSALAI
VLDV
VSALAI
VLDV
VSALAI
VLDV
VSALAI
VLDV
VSALAI
VLDV
VSALAI
VLDV
VSALAI
VLDV
VSALAI
VLDV
VSALAI
VLDV
VSALAI
VLDV
VSALAI
VLDV
VSALAI
VLDV
VSALAI
VLDV
VSALAI
VLDV
VSALAI
VLDV
VSALAI
VLDV
VSALAI
VLDV
VSALAI
VLDV
VSALAI
VLDV
VSALAI
VLDV
VSALAI
VLDV
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALAI
VSALA | NDMIDGFI 2
VIAVISNG 24
VIAVISNG 24
VIAVISNG 25
VIAVISNG 24
VIAVISNG 24
VIAVISNG 24
VIAVISNG 24
VIAVISNG 25
VIAVISNG 25
VIAVISN | | | ELKK
EYME
FIRGGELER
ALRRV
FFLRGCLKY
FFLRGCLY
FFLNA
GCLKY
FFLNA
CLY
RALAQA
CLY
RALAQA
CLY
RALAQA
FFLNA
CLY
RALAQA
FFLNA
CLY
RALAQA
FFLNA
CLY
RALAQA
FFLNA
CLY
RALAQA
FFLNA
CLY
RALAQA
FFLNA
CLY
RALAQA
FFLNA
CLY
RALAQA
FFLNA
CLY
RALAQA
FFLNA
CLY
RALAQA
FFLNA
CLY
RALAQA
FFLNA
CLY
RALAQA
FFLNA
CLY
RALAQA
FFLNA
CLY
RALAQA
FFLNA
CLY
RALAQA
FFLNA
CLY
RALAQA
FFLNA
CLY
RALAQA
FFLNA
CLY
RALAQA
FFLNA
CLY
RALAQA
FFLNA
CLY
RALAQA
FFLNA
CLY
RALAQA
FFLNA
CLY
RALAQA
FFLNA
CLY
RALAQA
FFLNA
CLY
RALAQA
FFLNA
CLY
RALAQA
FFLNA
CLY
RALAQA
FFLNA
CLY
RALAQA
FFLNA
CLY
RALAQA
FFLNA
CLY
RALAQA
FFLNA
CLY
RALAQA
FFLNA
CLY
RALAQA
FFLNA
CLY
RALAQA
FFLNA
CLY
RALAQA
FFLNA
CLY
RALAQA
FFLNA
CLY
RALAQA
CLY
RALAQA
CLY
RALAQA
CLY
RALAQA
CLY
RALAQA
FFLNA
CLY
RALAQA
FFLNA
CLY
RALAQA
FFLNA
CLY
RALAQA
FFLNA
CLY
RALAQA
FFLNA
CLY
RALAQA
FFLNA
CLY
RALAQA
FFLNA
CLY
RALAQA
FFLNA
CLY
RALAQA
FFLNA
CLY
RALAQA
FFLNA
FFLNA
CLY
RALAQA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA
FFLNA | LIAYR,
LIAYR,
WTLLK
MMILK
MILWAR,
UVAR,
UVGR,
ANGER,
ANGER,
ANGER,
ANGER,
ANGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGER,
AGE | TLVQYLLE
KLITYASI
KLISW-EV
RTTHYNSK
IIVHYHI
ILAHYWA
RIVHYGEI
RLVHYGEI
IIVHYSE
UIVHYSE
IIVHYSE
IIVHYSE
IIVHYSE
IIVHYSE
IIVHYSE
IIVHYND
IIVHYNDI
LLVHYND
ITSHYDOE
IILHYFC
VIVHYDOI
RLIHYSE
LLAHYFS
LLAHYFS
KLIHYFG
KLIHYFG
KLIHYFG
KLIHYFG
KLIHYFG
KLIHYFG
KLIHYFG
KLIHYFG | DSGEL
EDEFI
EDEFI
EDEKI
SPEEL
EDEKI
DDRRW
NVEKI
DDRRW
NVEKI
DDRRW
NLGTV
DDRLW
DDRLW
DDRW
DDRW
DDRW
DDRW
DDRW
TDEEL
DDFW
DDRW
DDFW
DDFW
DDFW
DDFW
DDFW
DDFW | YRLI
FNEL
FNEL
YESY
YENY
YESY
YESY
YESY
TUSY
DEIL
LUSY
TUSY
FEIL
LUSY
FEIL
LUSY
FEIL
LUSY
FEIL
LUSY
FRIL
LEYS
ERAE
YKII
YEYI
YEYI
YAQI
HHHH
HHQVY
WSII
YAQI
HHHHQVY
WSII
YAQI
WSIY
WUSY
WUSY
WUSY
WETA
WETA
WETA
WETA | 115
120
120
120
121
94 G
94 G
94 G
94 G
94 G
94 G
94 G
94 G
94 G
95 [
117
113 <u>1</u>
117
113 <u>1</u>
117
119
125
110
125
111
125
125
111
125
125
127
127
125
127
125
127
125
127
125
127
1 |

Figure 6

Multiple alignment of the conserved cores of two distinct families of HEPN domains. The distinct subfamilies of HEPN domains are indicated by brackets on the right. Designations are as in Figure 2.

one of the most prominent genomic correlates of the thermophilic life style [73]. The distribution of the two HEPN subfamilies across the available genomes of thermophilic and mesophilic prokaryotes (Figure 7A) is highly nonuniform (χ^2 p-value of 5 × 10⁻¹⁷). Considering the lineagespecific expansion in Thermoproteales of the "thermophilic" form (paREP subfamily, Figure 6) of the HEPN that it not associated with MNT, the possible correlation with thermophilic phenotype might be even stronger than previously noticed (Figure 7B). These intriguing observations suggest that there might be systematic differences between related TAS in thermophiles compared to mesophiles.

As shown above, the MNT-HEPN modules possess the major characteristics of TAS, most notably, the persistence of a two-gene module encoding small proteins, the strongly non-uniform distribution among genomes and high horizontal mobility. However, this module also shows some features that are not seen in experimentally characterized TAS: the putative toxin is not a nuclease (although it could be a nucleic-acid-modifying enzyme) whereas the putative antitoxin is unlikely to be a transcription regulator. Therefore the possibility remains that MNT-HEPN is not a bona fide TAS but rather belongs to a broader class of mobile stress response systems. For instance, MNT-HEPN potentially could function as an antibiotic inactivation system, via nucleotidylation of antibiotic molecules.

Other TAS-like gene pairs

Another mobile two-gene module consists of genes for a Xre-family HTH domain-containing protein and a protein of an uncharacterized family typified by E. coli YgiU. Two YgiU-like subfamilies (Additional File 7) are linked to two distinct families of HTH proteins. The proteins of the first subfamily, represented by YgiT, contain an additional Nterminal Zn finger domain, whereas the second subfamily (typified by Lactococcus phage bIL311 protein Orf21) is characterized by the fusion of an N-terminal HTH domain and a domain of the GepA (genetic element protein A) family. The latter family together with its YgiU-like counterpart is present mostly in phages and prophages of Firmicutes, whereas the gepA gene was detected next to a genomic region enriched in TA genes in Dichelobacter nodosus [74]. We detected no large expansions of this gene pair but several genomes contain two or more copies (two in Thermoanaerobacter pseudethanolicus, and three Beggiatoa sp. and Geobacter uraniireducens). The B3022(YgiY) protein is involved in the regulation of cell motility and biofilm formation in *E. coli* and accordingly was renamed motility quorum-sensing regulator, MqsR [75]. Furthermore, it was shown that MqsR overexpression has a toxic effect on E. coli growth, which is partially reduced by the YgiT/ B3023 mutation, and that YgiT/B3023 is a regulator that induces expression of another GntR family gene which in turn controls production of colanic acid, a specific exopolysaccharide that is an important factor of biofilm formation [76]. However, many bacteria (and, of course, phages) that encode this pair of genes are not motile and do not form biofilms, so this module might also coordinate expression of genes with other functions, perhaps, via a TAS-like mechanism such as interference with mRNA translation.

Similar reasoning seems to apply to another pair of genes detected in our search for putative TAS, namely, the repressor and antirepressor that are present in the genomes of many bacteriophages, but not in bacterial genomes. The antirepressor protein contains two domains: an N-terminal Bro-N and a C-terminal Ant or KilA-C family domains [77]. Experimentally characterized antirepressor genes are continuously expressed, interact with the corresponding repressor genes, and together determine the state of the phage (that normally exists as a plasmid in the bacterial cell) by regulating the lytic genes expression [78]. It was also shown that some of the proteins containing Ant domains are toxic to bacteria [79]. These characteristics are reminiscent of TAS. However, given that the antirepressor proteins do not contain domains typical of toxins, it seems likely that this system functions analogously to the COG2856-Xre system, that is, that the formation of the Bro-Xre complex regulates the expression of a still unknown third component.

The only stable two-gene combination that includes HTH DNA-binding domains other than those of the Xre family is the combination of ArsR-like proteins with COG3832 (Table 2). This predicted operon shows a non-uniform distribution typical of TAS, with several prominent expansions (Table 1) including 10 in Rhodococcus RHA1, 9 in Solibacter usitatus, 7 in Mesorhizobium loti and Janibacter sp., and numerous genomes with two to six copies, but so far was not detected in plasmid or phage genomes. The ArsR family repressors are well-characterized regulators of cellular response to stress induced by heavy metals [80]. These repressors usually are associated with proteins responsible for detoxification, often forming two-gene operons ([80] and Table 2). Most of the characterized repressors of this family contain conserved metal-binding motifs [80] that, however, are missing in the ArsR subfamily associated with COG3832 (Additional File 8). Eukaryotic proteins of the COG3832 family play an important role in stress response through the activation of the ATPase activity of HSP90 [81], hence the name AHA1 (activator of Hsp90 ATPase). The N-terminal domain is responsible for binding to HSP90 [82] whereas the function of the C-terminal domain remains unknown. Another protein of this family, CalC, is involved in bacterial resistance to the DNA-damaging agent calicheamicin,



Figure 7

Relative abundance of HEPN_T, HEPN_M and MNT domains in thermophiles and mesophiles. A. The total number of HEPN-MNT pairs in hyperthermophiles and thermophiles ("Thermo"), mesophiles and psychrophiles ("Meso") and all ("Both") genomes. **B.** The number of HEPN_T, HEPN_M and MNT genes in selected genomes. Font color indicates the temperature preference: red – hyperthermophiles; gold – thermophiles; green – mesophiles; blue – psychrophiles. Asterisks indicate Archaea.

via the disruption of the reactive bonds of the calicheamicin molecule accompanied by inactivation of CalC [83]. The structure of CalC has been solved, and it was shown to belong to the TBP (TATA-binding protein) fold [84] and, specifically, to the START superfamily [85] which unites various lipid-binding proteins, bacterial polyketide cyclases/aromatases and plant stress/pathogen response proteins, some of which possess RNAse activity [86]. Thus, although the role of this module in antibiotic resistance appears to be its most plausible function, the potential of this system as a novel TAS also deserves investigation.

Another unexpected observation is the strong link between both Xre family HTH and RHH domain-containing protein and N-acetyltransferases of the GCN5-related (GNAT) superfamily (Table 2). Enzymes of this superfamily catalyze the transfer of the acetyl group of acetyl coenzyme A to a variety of substrates, including diverse small molecules and proteins. In prokaryotes, GNAT acetyltransferases are involved in a variety of cellular functions including regulation of translation by acetylation of ribosomal proteins, arginine and UDP-N-acetylmuramyl pentapeptide biosynthesis, and antibiotic resistance (for review, see [87]). We identified several GNAT-RHH operons located on plasmids (Azoarcus sp. EbN1 plasmid; Shigella flexneri large virulence plasmid) and also observed many lineage-specific expansions of these operons 6 copies in Photorhabdus luminescens, and 4 in Salmonella enterica and Rhodopseudomonas palustris. None of the predicted GNATs associated with DNA-binding proteins has been experimentally characterized. The most similar experimentally studied GNATs are involved in resistance to tabtoxinine-\beta-lactam, the \beta-lactam phytotoxin, and antibiotic of *Pseudomonas syringae* ([88] and Additional file 9). Thus, as in the case of COG3832-ArsR association, it seems most likely that GNAT-RHH and GNAT-Xre operons are involved in antibiotic resistance rather than being a bona fide TAS.

The similarity of the genomic characteristics of these modules to those of bona fide TAS suggests that mobile, regulated two-gene modules could be broadly involved in diverse forms of stress response in prokaryotes.

The distribution of TAS-like systems in prokaryotic genomes

Previous surveys of the occurrence of TAS in prokaryotes revealed that they are typically absent in organisms with small genomes most of which are parasites or symbionts [26,27]. The addition of the new predicted TAS identified in this study has not changed this conclusion (Additional File 10). In particular, we still do not detect any TAS in *Borrelia*, endosymbionts of the gamma- and alpha- proteobacterial lineages, and the majority of Mollicutes (mycoplasmas). Among archaea, no TAS were identified in Thermoplasmatales, several methanotrophs with small genomes, and the only known symbiotic archaeon, *Nanoarchaeum equitans*.

It has been proposed that the absence of TAS in prokaryotes with small genomes could be due to their relatively simple life style in stable environmental conditions [26]. An alternative explanation, however, could be that the observed distribution is a simple consequence of the general "laws" of scaling of differential functional categories of genes with genome size [89-92]. We plotted the number of detected TA gene pairs against the genome size of prokaryotes (Figure 8) and detected a strong positive correlation (Spearman rank correlation 0.61, $p \ll 10^{-10}$). A maximum likelihood estimate (see Additional file 11) indicates the scaling exponent value of 1.64. This value is higher than the exponents of most of the other functional classes but significantly lower than the (near) quadratic scaling that is characteristic for transcriptional regulators and components of signal transduction systems [90,91]. Given the high variance of the abundance of TAS genes, the total absence of TAS in some of the genomes with up to ~3100 genes is expected within the 95% confidence interval (Figure 8). Given that the largest genome with no TAS detected, Prochlorococcus marinus MIT 9303, contains 2997 genes, it is possible that the absence of TAS in certain prokaryotes is a simple consequence of the allometric scaling with genome size and does not require special biological explanations.

The other significant factors (see Additional File 10) that appear to affect the distribution of TAS among genomes independently of the genome size (Table 4) are the host taxonomy (Archaea generally possess more TAS than Bacteria relative to the genome size, *t*-test p-value of 1×10^{-4}), optimal growth temperature (thermophiles tend to be enriched with TA genes compared to mesophiles and psychrophiles, t-test p-value of 5×10^{-4}) and environment (terrestrial and multi-environmental microorganisms typically possess significantly fewer TAS than predicted from the genome size whereas prokaryotes living in aquatic, host-associated and specialized environments often contain a greater number of TAS than predicted, t-test p-value of 2×10^{-3}). The three factors seem to be statistically independent (that is, each retains its significance after adjusting for the others, see Table 4), although the independence between the taxonomic affiliation and temperature preference is difficult to prove conclusively because of the abundance of thermophiles among Archaea.

With respect to the representation in major bacterial and archaeal lineages, the TAS (Additional file 12) ranged from nearly ubiquitous (e.g. HEPN-MNT, AbrB-PIN, PIN-



The relationship between the number of detected TA pairs and genome size.

RHH) to clade-specific (COG2886-RelE in Cyanobacteria, DUF397-Xre in Actinobacteria, MazF-PHD in Alphaproteobacteria and Fic-YhfG in Gammaproteobacteria). The distribution of TAS across phyla is distinctly non-uniform, with many systems significantly over- and underrepresented in various taxa (Figure 3). We identified no archaea-specific TAS but many bacteria-specific ones; this observation seemed somewhat unexpected considering the greater abundance of TAS in archaea although it could simply reflect the greater diversity of available bacterial genomes. The repertoires of TAS (and TAS-like systems) in the hyperthermophilic bacterial phyla, Aquificae and Thermotogacae, resembles that in the Archaea, primarily due to the high abundance of the "thermophilic" version of the HEPN-MNT system and the near-absence of typical bacterial systems. Among bacteria, Bacteroidetes-Chlorobi, Alpha- and Gammaproteobacteria and Cyanobacteria possess the greatest variety of TAS (10-13 statistically overrepresented gene pairs). Among taxa with numerous sequenced genomes, Firmicutes (especially Bacilli) are characterized by a particularly low TAS diversity (3 statistically overrepresented pairs). The most uniformly distributed systems are AbrB-RelE, GNAT-Xre and AbrB-MazF. On the opposite end of the spectrum, several widespread systems, such as HEPN-MNT, PIN-RHH, COG2886-PIN and PHD-PIN, have sharply contrasting distributions (i.e. either significantly over-represented or underrepresented in different host taxa).

Co-occurrence of toxins and antitoxins in TAS operons

The relationships between toxins and antitoxins can be represented by a graph with edges connecting genes that form TA pairs (Figure 9). In a striking demonstration of the versatility and modularity of the TAS, most of the known and predicted TA genes belong to a connected network that covers 87% of the detected TAS. Three (putative) TAS (HEPN-MNT, HicA-HicB and ArsR-COG3832) occur strictly as unique pairs and are never involved in other TA combinations (except for several protein domain fusions discussed above). The principal hubs of the TAS network are two toxins (PIN and RelE) and two antitoxins (Xre and RHH) that, taken together, participate in 76% of all TAS. Accordingly, these four superfamilies have the greatest diversity of antitoxin (toxin) partners (7, 6, 13 and 6, respectively). The three most common TAS (RelE-Xre, PIN-RHH and RHH-RelE; 29% of the total number of systems) are composed entirely of these four genes.

Table 4: Association of TAS with ecological features of prokaryotes

Group 1/Group 2	Group I median	Group 2 median	T-test p-value
Residuals after scaling by genome size			
Archaea/Bacteria	0.39	0.00	0.0001
(hyper)thermophiles/meso- & psychrophiles	0.34	0.05	0.0005
Terrestrial & multi-environmental/other	-0.01	0.05	0.0022
Residuals after scaling by genome size and adjustment by taxonomy			
(hyper)thermophiles/meso- & psychrophiles	0.16	-0.01	0.0592
Terrestrial & multi-environmental/other	-0.05	0.00	0.0157
Residuals after scaling by genome size and adjustment by temperature			
Archaea/Bacteria	0.22	-0.01	0.0133
Terrestrial & multi-environmental/other	-0.05	0.00	0.0180
Residuals after scaling by genome size and adjustment by environment			
Archaea/Bacteria	0.30	-0.01	0.0003
(hyper)thermophiles/meso- & psychrophiles	0.25	-0.01	0.0016

Bold type highlights p-values significant at the 0.05 level.

The versatility and the modular character of the TAS notwithstanding, the combination of toxins and antitoxins is highly selective, even when only the connected component of the network is considered. Compared to random expectations based on overall abundance of genes, some TA pairs are either underrepresented (e.g. PIN-Xre or AbrB-RelE) or conspicuously absent (for instance, pairs involving exclusive toxin partners of Xre or exclusive antitoxin partners of PIN) whereas other pairs are overrepresented (AbrB-Fic is over three times more frequent than expected).

Variability of TAS in closely related genomes

We examined the distribution of TAS in the 41 sets of closely related prokaryotic genomes (Alignable Tight Genomic Clusters, ATGC [93,94]). In 33 of the ATGC at least one of the 37 TAS was detected in at least one of the members. For all identified TAS, the standard deviation of the number of occurrences was computed within each ATGC and the average of this value was calculated across all TA pairs in this ATGC (excluding pairs completely absent from this ATGC) to obtain a single, ATGC-specific measure of variability. As a control, all proteins of the 163 ATGC members were assigned to COGs [33], a random sample of 37 COGs with the mean protein length less or equal to 150 amino acids was selected, and the variability of "regular" COG members was estimated for these 33 ATGCs in the same manner (see Additional file 11). In 32 of the 33 ATGCs, the variability of TAS significantly exceeded that of other COGs (the equal variability hypothesis is rejected with *p*-value of 4×10^{-9}). Thus, the genomic occurrence of TAS shows exceptional variability even at close evolutionary ranges.

Distribution of TAS operons on bacterial and archaeal chromosomes

Random, independent positioning of TAS pairs on prokaryotic chromosomes would produce an approximately exponential distribution of inter-TAS distances. Both the individual TA systems and aggregated data do not statistically differ from the random expectation (χ^2 test of observed vs. expected distributions of inter-TAS distances was performed for distance thresholds approximately corresponding to 25-th, 33-th and 50-th percentiles of the respective observed distributions). However, in many genomes a statistically significant excess of closely spaced TAS pairs (TAS "islands") was detected (Table 5). As in the majority of these cases the closely-spaced TA gene pairs belong to different classes of TAS systems, tandem duplication cannot explain the observed pattern. Possible explanations that are not mutually exclusive include preferential incorporation of TAS in a particular chromosome region and/or HGT of TAS "cassettes" consisting of multiple TA pairs. Conceivably, many prokaryotic genomes contain stress-response islands comparable to pathogenicity of symbiogenesis islands. Examples of essentially random and highly clustered TAS distribution are shown in Figure 10.



Figure 9

Graph of relationships between different families of toxins and antitoxins. Known (black) and predicted (magenta) toxins (red circles) and antitoxins (blue circles) and their operon organizations. Lines connect genes with 5 or more two-component operons found; thickness of a line is proportional to the frequency of the respective operon.

Discussion

"Classic" TAS were defined as two-component systems with a stable toxin and an unstable antitoxin encoded in the same operon and acting as an "addiction" mechanism, that is, requiring constant (over)production of antitoxin for microbial cell survival. The findings reported here reinforce the power of these organizational and functional principles through the discovery of numerous potential new TAS. However, the accumulating data also increasingly indicate that many TAS-like systems do not fit this paradigm. In particular, toxin expression could be extrinsically regulated ([3,6,68]) when the antitoxin is encoded *in trans*. First experimental evidence of this possibility was reported recently when the inhibitory effect of a chromosomally encoded antitoxin on a plasmidencoded toxin was demonstrated [25]. This type of regulation might explain the unexpected high abundance of solo toxins and antitoxins – over 50% of the genes in the largest families – a finding that cannot be explained solely by mis-annotation of small ORFs (Figure 11). An alternative or, more realistically, additional explanation of this finding is that solo homologs of toxins and antitoxins perform functions distinct from those of TAS such as transcriptional regulation of diverse operons by antitoxin homologs. In addition, the antitoxin function can be performed by a small RNA as in Type I TAS ([68]).

In principle, some TAS might function as one-component or three-component systems. One example of a likely solo toxin is the cyanobacteria-specific Uma2 family





(COG4636), that was previously described in connection with TAS [13] and predicted to be an endonuclease of the PD-(D/E)XK superfamily [95,96]. The members of this family are highly abundant in cyanobacteria but are only rarely associated with known antitoxins and instead mostly form cassettes of paralogous genes (Table 2). "Normal" gene regulation systems can also use the combination of stable and unstable components (as probably is the case of Xre-Bro system [78]) whereas TAS with more stable antitoxins might also function as generic regulators (as might be the case for the Xre-COG2856 and/or ArsR-COG3832 associations).

Conceivably, as demonstrated by the case of acetyltransferases associated with HTH and RHH domains, the class of mobile operons resembling TAS could be quite broad, including in particular antibiotic resistance systems. The MNT-HEPN, arguably, the most remarkable two-component system identified here, considering its dramatic overrepresentations in thermophilic archaea, is a case in point: the currently available data hardly allow one to determine whether this is a bona fide TAS or an antibiotic resistance system. The MNT-HEPN system emerges as the prime target for experimental study that will distinguish between the two possibilities. It should be noted that, although potentially mechanistically distinct, the TAS activity and antibiotic resistance can be biologically linked considering that many TAS confer resistance to antibiotics to bacterial cells, primarily, by driving them into persistence [97,98].

On a more general note, the TAS obviously belong to the prokaryotic mobilome [89,99,100] as they are extensively, if not preferentially, spread via plasmid-mediated HGT. Like many if not most of the mobilome members, the TAS are not simply mobile but appear to behave like selfish elements: although they do not carry genes or signals required for autonomous replication, their entire life style is best conceptualized as a strategy ensuring their own maintenance and propagation. There are strong analogies between the TAS and other components of the mobilome, in particular, the restriction-modification systems (RMS) [101]. The RMS are well known to protect prokaryotic cells from heterologous DNA through the destruction of unmodified DNA molecules by the restriction component whereas the host DNA is modified by the modification component of the RMS. This principle of action is strikingly similar to that of bona fide TAS with the exception that, in the case of the RMS, damage to the host cell is prevented not by inactivation of the "toxin" but rather by protection of the target (DNA) via a specific modification. However, this mechanistic distinction should not overshadow the deep biological commonality between the TAS and the RMS that is manifested in the shared "poison-antidote" principle, and in the apparent selfishness of both classes of systems that involves exten-

ACC no.	Genome	TAS pair	NO. of pairs	distance threshold	No. observed	No. expected	Chi2
<u>NC 005070</u>	Synechococcus sp. WH 8102	all	11	3	6	0.3	82.79
<u>NC 011138</u>	Alteromonas macleodii 'Deep ecotype'	all	19	3	6	0.5	48.27
<u>NC_010842</u>	Leptospira biflexa serovar Patoc strain 'Patoc I (Ames)'	all	22	3	7	0.7	47.09
<u>NC_009565</u>	Mycobacterium tuberculosis FI I	all	46	2	12	2.1	43.43
<u>NC 004757</u>	Nitrosomonas europaea ATCC 19718	all	48	3	18	4.5	40.8
<u>NC 009525</u>	Mycobacterium tuberculosis H37Ra	all	57	3	16	3.9	36.41
<u>NC_002755</u>	Mycobacterium tuberculosis CDC1551	all	52	3	14	3.2	35.89
<u>NC 008639</u>	Chlorobium phaeobacteroides DSM 266	all	28	2	8	1.2	35.71
<u>NC 008740</u>	Marinobacter aquaeolei VT8	all	15	7	5	0.5	31.72
<u>NC_002945</u>	Mycobacterium bovis AF2122/97	all	53	3	14	3.5	30.44
<u>NC 007484</u>	Nitrosococcus oceani ATCC 19707	all	32	3	9	1.7	28.88
<u>NC 008769</u>	Mycobacterium bovis BCG str. Pasteur 1173P2	all	58	3	15	4.2	27.66
NC 000962	Mycobacterium tuberculosis H37Rv	all	53	4	14	4.1	23.22
<u>NC_010803</u>	Chlorobium limicola DSM 245	all	26	5	10	2.4	23.02
<u>NC 010602</u>	Leptospira biflexa serovar Patoc strain 'Patoc I (Paris)'	all	20	8	7	1.4	20.53
<u>NC 010831</u>	Chlorobium phaeobacteroides BSI	all	42	3	12	3.5	20.14
<u>NC 007677</u>	Salinibacter ruber DSM 13855	all	13	8	5	0.8	19.39
NC_008212	Haloquadratum walsbyi DSM 16790	all	10	5	3	0.3	19.31
NC 000917	Archaeoglobus fulgidus DSM 4304	all	30	3	8	1.8	18.79
NC 010161	Bartonella tribocorum CIP 105476	all	22	14	12	3.9	18.33
NC_011060	Pelodictyon phaeoclathratiforme BU-I	all	65	5	23	10.3	17.24
<u>NC 008698</u>	Thermofilum pendens Hrk 5	HEPN-MNT	14	3	4	0.7	10.92
<u>NC 000917</u>	Archaeoglobus fulgidus DSM 4304	AbrB-PIN	12	3	4	1.3	4.18

Table 5. TAS Islands in prokaryouc genomes	Table 5	: TAS	"islands"	in	prokary	otic	genomes
--	---------	-------	-----------	----	---------	------	---------

sive horizontal mobility and addiction properties. Indeed, although the RMS are not often considered as a type of TAS, this seems to be due more to tradition than to a true, fundamental difference between the two classes of systems [3].

The biological common denominator between TAS, RMS, phage abortive infection systems [102] and some other molecular systems, such as those involved in antibiotic inactivation, is that they contribute to various forms of stress response. The connection is reinforced by the recent demonstration that one of the phage abortive infection systems, ToxIN, functions as a protein-RNA TA pair [103]. These systems comprise a distinct domain of the mobilome that can be denoted the resistome (this term is currently used to denote the set of microbial genes that confer antibiotic resistance [104] but it seems to make sense to apply it more inclusively). For such systems, the boundary between selfishness and "normal" cellular function seems to be fuzzy and more a matter of convention than a real distinction. Indeed, TAS-like systems tend to make any replicon in which they reside addicted to themselves. In the case of plasmids, this is achieved by dramatically increasing the chances of transmission of TAScarrying molecules during cell division. In the case of chromosomal TAS, the basis for addiction could be resistance to the plasmid versions of the same TAS that allows

the TAS carrying cells to exclude the respective plasmids (antiaddiction [25]). In this case, it might be beneficial for the cell to stay addicted to the domesticated, relatively harmless chromosomal TAS rather than tolerate the TAScarrying plasmids. A similar logic applies more generally: TAS-like systems promulgate their own survival by making cells that carry them resistant to antibiotics or other forms of stress. Furthermore, the addictive character of these systems increases the probability of their fixation after HGT, hence the extensive horizontal mobility that is simultaneously a telltale sign and the dissemination mechanism of all selfish genetic elements. Integration of TAS into "normal" cellular regulatory circuits also can be viewed as continuation of their selfish strategy [5]; however, as they are integrated deeper, the horizontal mobility tends to be restricted and traded for more stable vertical inheritance, gradually pushing these selfish elements towards the status of "regular" chromosomal genes. This "selfish altruism" or "responsible selfishness" of TAS-like systems seems to be paradigmatic of the mobilome and a key feature of the prokaryotic biome in general because in the prokaryotic world the mobilome and the "stable" chromosomes form a dynamic continuum [89].

Conclusion

We report here the most detailed and comprehensive comparative-genomic analysis of type II TAS so far availa-



Figure II

Fractions of solo and two-gene operon occurrences for each family of toxins and antitoxins. Red, fraction of solo genes; blue, fraction of genes in (predicted) operons.

ble (to our knowledge) by using two computational approaches that were specifically developed for TAS prediction and analysis on the basis of the signature features of TAS that typically comprise two-gene operons encoding two relatively small proteins one of which contains a DNA-binding domain. This analysis resulted in the prediction of 12 novel families of toxins and 13 novel families of antitoxins including families that are specific for distinct groups of archaea or bacteria, in particular, thermophiles. In addition, we discovered numerous solo genes for both toxins and antitoxins, a finding that suggest novel principles of TAS functioning, such as in trans regulation, or recruitment of toxins and antitoxins for other functions, or most likely, both of these phenomena. Some of the newly predicted two-operon modules might not function as bona fide TAS but rather as other types of stress-response systems that could be, for instance, involved in antibiotic inactivation. The prime case in point is the MNT-HEPN module which is among the most abundant genes in hyperthermophilic archaea. Experimental study of this and other novel TAS-like systems is expected to reveal the exact functions and to shed new light on the life style of these widespread prokaryotic genetic elements. The TAS-like systems are prominent and typical components of the prokaryotic mobilome, and the interplay between their selfish behavior, addictiveness, and integration into "regular" regulatory circuits of archaea and bacteria seems to be the epitome of the dynamic equilibrium between mobile and more stable parts of the prokaryotic pangenome.

Methods

Identification (prediction) of TAS: approach I

For each COG from the in-house COG database containing 110 bacterial and archaeal genomes (available from the authors by request) the coefficient of variation (CV) for the number of the paralogs (to the exclusion of species with no genes in the given COG) was estimated in order to find the COGs with unevenly distributed "mobile" genes. The top 2000 COGs with the highest CV values (between 2.98 and 0.47) were mapped to the corresponding chromosomes and further checked if they are adjacent to the same COG at least 3 times in at least one genome. This resulted in further reduction of the number of candidates for further analysis to 315 COGs. All these COGs were analyzed one by one using the STRING program [34] to discard those that are parts of larger (>2 genes) (predicted) operons and those where one or both members of a pair were often associated with genes from other families.

TAS identification: approach 2

Exhaustive PSI-BLAST [39] searches were performed for each protein family of known toxins and antitoxins, using a variety sequences from each family as queries (the iterative searches performed for protein larger that 100 amino acids with inclusion threshold 0.01 or for protein smaller that 100 amino acids with inclusion threshold 0.1 until the convergence or until the last iteration before the first known false positives appear). All genes identified by this procedure were mapped to the corresponding genomes; closely located (intergenic regions shorter than 100 bp) co-directed neighbors were collected. Neighbors were then clustered using BLASTCLUST (-L 0.5 -S 1.75) and further classified using CD-Search [40]; results obtained by overlapping CDD profiles were combined. Clusters larger than 20 were further checked on the case-by-case basis to determine whether they form a stable two-gene operon or a larger conserved cluster, and those that belong to larger predicted operons were discarded.

TAS in completely sequenced genomes

All identified TAS genes were grouped by family and clustered using BLASTCLUST (-L 0.75 -S 1.0). Representatives of each cluster were used as queries in a BLAST search (evalue threshold of 0.01) against 750 completely sequenced bacterial and archaeal genomes available on the NCBI Microbial Genomes website at the time of this analysis (September 2008). Significant hits among proteins encoded in these genomes were classified as toxins or antitoxins; in case of multiple matches to different TA families, the protein was assigned according to the highest-scoring match to a TA query. Co-directed genes with adjacent chromosome locations belonging to different toxin/antitoxin families were recorded as a TA pair.

Protein sequence analysis

Multiple alignments of all toxin and antitoxin were constructed using the Muscle program [105] followed by manual correction on the basis of the predicted secondary structure (PSIPRED program [106]) and PSI-BLAST-based local alignments. For the species abbreviations used in all the alignments, see Additional File 13.

Estimation of the scaling parameters

Normally, the allometric scaling coefficient for two variables is easy to estimate as the slope of the straight line on the log-log plot of these variables. Even when both variables are natural numbers (e.g. number of genes belonging to a particular category vs. the genome size expressed as a total number of genes), this direct approach is applicable if the numbers themselves are sufficiently large to minimize the discretization effect [91]. In the specific case of TAS genes, however, this approach cannot be applied because of the overall low abundance of TAS pairs (111 of the analyzed genomes have only 1 or 2 TAS pairs and 119 have none). Obviously, zero values cannot be plotted on a log-scale or used to compute the coefficients of the regression curve; however, omitting the zero points would mean the loss of over one-sixth of the data. To escape this conundrum, we designed a model where the expected number of TAS genes is allometrically scaled with the number of genes in a genome and the observed numbers reflect discretization of log-normally distributed deviation from the expectation. Parameters of this model were obtained by maximization of the likelihood of the observed data (see Additional file 11).

Tests for effects of taxonomic affiliation, temperature and environment

The expected number of TAS pairs for each genome was estimated using the allometric scaling formula with the parameters estimated as described above $(t' = 1.64\log(l))$ -5.08, where l is the total number of genes in the genome (see Additional file 11). At the first round of comparison, log-scale residuals (r = t-t', where t is the logarithm of the observed number of TAS pairs) were compared between different groups of genomes using the two-tailed *t*-test with unequal variances. For genomes with no TAS pairs, the detected t was assigned the value of $\log(0.5)$; however, positive residuals were reduced to 0 (i.e. a genome with zero observed TAS pairs can have less, but cannot have more TAS than expected). The following partitions of genomes were explored: by taxonomy (Archaea and Bacteria); by temperature preference (hyperthermophiles, thermophiles, mesophiles and psychrophiles); by environment (aquatic, terrestrial, host-associated, specialized and multi-environmental). At the second round of comparison, group averages of the first-round residuals were further subtracted from the first-round residuals (that is, the mean of the residuals across Archaea was subtracted from all residuals for archaeal genomes); the secondround residuals were compared between groups using the two-tailed T-test with unequal variances.

TAS	Number detected on plasmids	Number detected on chromosomes	Enrichment (p < 0.01)
MazF-PHD	12	7	Plasmid
COG5654-Xre	55	195	Plasmid
MerR-PIN	9	34	Plasmid
GNAT-RHH	28	154	Plasmid
RelE-RHH	92	511	Plasmid
ArsR-COG3832	13	310	Chromosome
DUF397-Xre	3	129	Chromosome
HEPN-MNT	11	572	Chromosome
GNAT-Xre	0	67	Chromosome

Table 6: Over-representation of TAS on plasmids and chromosome

The enrichment was estimated compared to the random expectation given the analyzed amount of chromosomal and plasmid sequences. The distributions of the rest of the TAS were statistically indistinguishable from the random expectation.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

KSM and EVK initiated the study; KSM performed data analysis; YIW wrote the custom scripts and performed statistical analysis; KSM and YIW wrote the initial draft of the manuscript; EVK wrote the final version of the manuscript that was read and approved by all the authors.

Reviewers' reports Reviewer 1

Kenn Gerdes, Newcastle University Medical School (Nominated by Arcady Mushegian).

General comments: Makarova et al. suggest two straightforward ways to identify potential novel TAS in prokaryotic genomes and identify potential new TAS in 750 completely sequenced genomes and the work appears as a valuable bioinformatics study of TAS and TAS related genes. The manuscript represents a huge amount of work that may serve as one basis for the more detailed and meticulous characterization of TAS. It may also serve as a starting point for the experimental tests of the proposed biological functions and properties of the new TAS.

In general, the manuscript is difficult to follow for nonspecialists. Moreover, it is difficult to reproduce important findings. For example, in the huge (and very useful Table in AF10, how was the number of TAS pairs reached? And how was the number All Toxins reached in AF10? To solve the problem with the Table AF10, the Authors could provide one or two examples describing in detail how they reached these numbers. Alternatively, they could simply provide the identifiers of the genes that they suggest are TAS (GIs or similar) although this would represent some work. In this connection we were surprised to see that the three sequenced *E. coli* K-12 strains W3110, MG1655 and DH10B have 9, 15 and 16 predicted TA loci, respectively.

Authors' response: This is a regular (and, yes, very detailed) research paper and as such most of it is not addressed to non-specialists (that is, non-microbiologists). We do not believe, however, that the paper qualifies as being "esoteric". This being said, we agree that better documentation is desirable, so we prepared Additional File 14which contains the information on all individual toxin and antitoxin families, and toxin-antitoxin pairs.

Most articles use TA loci, not TAS, to abbreviate toxin – antitoxin genes/systems. We think the former appears less esoteric and already accepted by different journals.

Authors' response: We preferred to keep the succinct, threeletter acronym, rather than referring to loci each time. On the two occasions when the acronym is introduced, in the Abstract and in the Background section of the main manuscript, we added "(TAS, also referred to as TA loci)".

Finally, we find the manuscript in several places too speculative (see below) and that it appears hastily written.

Specific points:

1. Abstract:present evidence that HEPN/MNT "is likely to be TAS" is a serious overstatement – please rephrase to "raises the possibility" or something like that.

Authors' response: We do not really agree that this was a "serious" overstatement but the language was changed to: "we present indications that the two-gene module that encodes a minimal nucleotidyl transferase and the accompanying HEPN protein, and is extremely abundant in many archaea and bacteria, especially, thermophiles might comprise a novel TAS."

2. It is not clear to us why TA loci should be included in the "bacterial resistome". The experimental evidence that TAS function in persister cell formation is weak.

Authors' response: The resistome here is broadly defined as the compendium of genes involved in various forms of stress response, so we think that in this context the inclusion of TAS is appropriate. Further, our own perusal of the work on the involvement of TAS in bacterial persistence, in some of which we were involved directly, does not suggest that the evidence is weak, even as we are prepared to defer to Dr. Gerdes on this account.

3. To our view, it is a general misunderstanding that *mazEF* functions in PCD as claimed by one group working with *E. coli* as the model system. We and others have never been able to reproduce PCD by mazEF in *E. coli*. This confusion has been inflated by the recent finding that *mazF* of *Myxococcus xanthus* functions in PCD during the formation of myxospores. In Myxo, *mazF* is not part of a bona fide TA locus. Rather mazF-Mx interacts with the transcription factor MrpC encoded elsewhere on the chromosome suggesting that MazF-Mx was recruited to become a component of the developmental pathway that leads to Myxo spore formation. Thus, MazF-mediated PCD in Myxo is probably not a typical TA locus phenomenon.

Authors' response: The reference to the PCD by mazEF in E. coli is quite cautious. With regard to Myxococcus xanthus, the original text was indeed less than precise. We modified it to indicate that it was a solo mazF that mediated PCD in the Myxococcus Xanthus development.

4. The description of Selection criterium #1 was partly unclear to us because the CVs in Table 1 are low (between 1.1 and 0.5) whereas we would expect a high CV for TA loci. Please comment and explain better on this point. Authors' response: We added some details in Methods section and in Figure 1in order to clarify this. Specifically, we first selected 2000 of ~15000 COGs (with CV range from 2.98 to 0.47) and ran an automatic procedure to select only those that have a relatively conserved neighbor regardless of the CV. This step returned 315 pairs of COGs, and all these pairs were examined one by one. The CV values for all these 315 gene pairs are given in Additional File 1. The known TAS, as can be seen in Table 1 and Additional File 1, do not have extremely high CV values but many of them are within the analyzed CV range. Both comparative-genomic approaches employed here aimed at the detection of new "major" TAS, but not at the comprehensive identification of all representative of known TAS. The latter task was mostly performed by the PSI-BLAST analysis of the protein sequences encoded in 750 complete prokaryotic genomes (Additional File 10and new Additional File 14) once we have delineated all families of interest, with the caveat that we did not attempt to search for missed ORFs.

5. Table 2: It is not entirely correct to call PIN domain proteins for "RNA interferases" – the evidence in the literature is derived from in vitro experiments only, and we have not found nuclease activity with two enteric VapCs, neither in vivo nor in vitro (Winther & Gerdes, in press).

Authors' response: PIN domain proteins are not described as "RNA interferases" but rather as nucleases. In order to be even more cautious, in the revision, PINs are denoted "(predicted)" nucleases" at first mention.

6. We identified two TA loci in *N. equitans* (VapBC loci; [35]) and so far we have not yet identified any archaeal genome without at least one TA locus.

Authors' response: We also identified two PINs (VapC) in N. equitans (see Additional File 14) but not the corresponding antitoxins that apparently have not been annotated in this genome as indeed follows from the Supplementary Material in [35]. As mentioned above, no attempt was made to annotate missing ORFs. That apart, we did not detect any TAS in any of the available Thermoplasma genomes, so there seem to be archaea devoid of TAS.

7. We strongly favor the idea that the lack of TA loci in almost all obligate intracellular organisms have a biological background and is not just a "statistical coincidence". Most strikingly, *Mycobacterium tuberculosis* has more than 60 TA loci, whereas *M. leprae* has none! Since the genome of *M. leprae* was derived from that of *Mtb* by massive genome reduction, this must mean that the selection pressure to retain TA loci in *M. leprae* was lost. In turn, this observation correlates with the obligate intracellular life-style of contrasted by that of *Mtb* that exists both intra- and extracellularly.

Authors' response: We did not claim that the lack of TAS in intracellular parasites and symbionts is a "statistical coincidence". Indeed, the genomes of these bacteria are usually highly reduced and thus are expected to contain fewer TA loci. We show that given the scaling of the number of TAS with genome size, the hypothesis that TAS are missing from genomes of the currently known intracellular organisms for purely stochastic reasons cannot be statistically rejected. Hence there is no evidence of the existence of a selective pressure to lose TAS in these organisms. Such pressure might become apparent when more genomes are available but at present the neutral null hypothesis cannot be rejected. Moreover, we are a little suspicious of the selective hypothesis because, if anything, host-associated bacteria have slightly more TAS than terrestrial and multi-environmental organisms relative to the number expected from the size of their genomes (Table 4). So there seems to be no trend in parasites and symbionts in general, an observation that suggests extra caution with regard to the selective hypothesis of TAS loss in intracellular microbes. Again, this hypothesis remains legitimate but so far no statistical evidence.

8. We are not convinced of the biological meaning of the concept of "anti-addiction" by TA loci as described in Ref 25. Rather, we see the results therein as a mere consequence of how the experiments were set-up and any genuine biological meaning of anti-addiction remains to verified – that is – at its present experimental stage, it's simply too speculative as to incorporate into the already very long list of possible functions for TA loci. Rather, we should make an attempt to pinpoint the facts known about TA loci thus to reduce the confusion in the field.

Authors' response: We find the concept of anti-addiction very sensible and appealing. However, we do not attempt to carefully assess the validity and implications of the experiments described in ref. [25], so the presentation of this idea in the text is very cautious and framed with "could" and "might", and some more such qualifiers were added in the revision.

Reviewer 2

Daniel Haft, J. Craig Venter Institute

This work by Makarova, Wolf, and Koonin reports results from a comprehensive study of prokaryotic toxin-antitoxin system (TAS) protein pairs. These systems once were viewed simply as addiction modules that enforce plasmid maintenance by post-segragational killing upon plasmid loss. However, TAS gene pairs frequently contain a bacteriostatic rather than bacteriocidal toxin, occur chromosomally rather than on plasmids, and perform important regulatory functions in cellular responses to stress. Their detection, however, is tricky because of their small protein sizes, high diversity, and sparse experimental work. They are far more common than once thought, an average ten pairs per prokaryotic genome but sometimes much higher, and therefore are important to detect.

This work serves two functions. First, it is a broad, thorough, well-informed, hundred-plus reference review of the state of the art in predicting and interpreting TAS systems. The survey is essential to the bioinformatic analysis it enables. Second, it is a report of comprehensive predictive analysis of TAS systems in a collection of 750 prokaryotic reference genomes that features a number of new discoveries.

Distinct TAS systems that share no protein-level homology often show similarity in various other attributes: small protein size, arrangement in two-gene operons, sporadic distribution, absence of transmembrane domains from both, presence of a DNA-binding domain in one, and frequent association with plasmid and prophage regions. Several of these filtering criteria were combined in a computational pipeline complemented by human close review, the article's "method 1", which efficiently rediscovered a considerable number of known TAS systems and suggested a few others. The rediscovery helps validate the method, as do repeated demonstrations of appropriate remote sequence relationships in the new systems. The suggested new systems provide a rather large collection of bioinformatics-generated specific functional hypotheses for testing. The scope of this work is a reminder that comparative genomics still is underutilized as a discovery method for the preliminary characterization of largely novel biological systems.

A second computational approach used sensitive iterated searches to push the identification of known and hypothesized TAS pairs close to the limits of detection. This phase explored the notion that TAS modules do not always pair the same toxin family with the same antitoxin family, but rather can exchange families somewhat promiscuously. Again, filtering criteria and well-informed human review followed the computation, so the resulting proposed TAS pairs serve as excellent sets of hypotheses, suitable for greatly improving genomic annotation systems and spurring downsrteam studies. A number of follow-up questions spring to mind.

Type 2 TAS systems act as regulators of their own expression, but *are there other sites to which antitoxins or TA complexes would bind to regulate expression of other genes?*

Authors' response: To our knowledge, no. We are unaware of any experimental evidence or computational study that would identify or predict potential "antitoxin regulons". Search for such regulons indeed would be interesting to pursue considering the fact that some of the antitoxin-binding sites are known, but this is definitely a separate analysis that is beyond the scope of this work. Do chromosomal TAS modules appear to act as carriers or guardians of neighboring "fitness factor" genes that ultimately benefit their host cells? What classes of cellular genes most commonly have TAS cassettes nearby?

Authors' response: Very interesting questions indeed, we are currently investigating these issues.

The limitations of this article for many scientists will lie not in the analyses themselves, but in achieving easy downstream use of the findings. The reported findings are extensive: an implicit biological database of curated TAS gene pairs with curated gene contexts, named protein families, well-researched sequence relationships, and putative functions. An important point is that the protein family definitions alone do not sufficiently represent all the work reported here - many proteins that belong to the families are unpaired orphans or otherwise out of context (see figure 11), and having the final sets of approved pairs itself is important. Therefore I would like to suggest that this paper be paired with supplemental or post-publication materials that explicitly provide the proteins themselves. A tab-delimited file might be sufficient, listing protein unique identifier, species, toxin/antitoxin protein family, COG family id (which I expect not to be exactly synonymous), and partner protein id. Such a resource would be immediately useful for genomic and metagenomic annotation pipelines and in spurring further studies as of DNA binding sites. Currently, varied nomenclatures in the TAS literature and other layers of indirection between publications and protein identifiers are hindering efficient community use of the synthesized knowledge reflected in this paper.

Either supplementary material as part of the publication, or a file deposited post-publication to the Readers' Comments section, of a database-like dump of the collected curated gene pairs would be invaluable.

Authors' response: We agree and accordingly prepared the file with this information for individual toxin and antitoxin families, and for the TA pairs (see Additional File 14).

Method 1 finds a number of different previously known TAS systems, part of the proof of the validity of the method. But I did not find a statement about what fraction of previously known TAS systems was found and what known types were not found. I would expect the rather stringent requirement that at least one genome have at least three pairs of given type in order to nominate the type to cause some known types to be missed. In fact, I imagine there are some known TAS pairs where one or both lack a matching COG family. What TAS systems known to you before you started Method 1 were missed by its stringent filtering criteria? Authors' response: The questions about false positives and false negatives would be fully relevant if we proposed the two approaches used here to predict TAS (method 1 and method 2) as general methods for TAS prediction/identification. However, this is not the case. Rather, these approaches comprise data mining or "fishing expeditions" the goal of which is to predict widespread novel TAS that so far have not been discovered by experimental approaches. Therefore we used extensive manual curation in the course of all work and considered various additional lines of evidence.

To me, one of the most intriguing partitions is that between chromosomal and plasmid positioning, broken down by family. Which of the TAS systems are usually plasmid, and which are usually chromosomal. Did you do this study?

Authors' response: This is undoubtedly an interesting question. There are some problems with plasmid sequences and their identification that call for caution: it can be difficult to distinguish plasmid-derived regions on the chromosomes without much additional work; furthermore, the current plasmid databases are heavily biased toward plasmids of gamma proteobacteria and firmicutes, especially, industrially important ones, so it is not quite clear how to interpret the data. None of the known TAS occur exclusively on plasmids but there are a few that so far were found only on chromosomes. The cases when a particular TAS was often present on plasmids or phages are mentioned in the text. The new Table 6shows the results of an additional statistical analysis that we undertook to address this question. Clearly, there are some TAS that prefer plasmids and others that prefer chromosomes.

The model of chromosomal TAS as a means to prevent addiction to plasmid-mediated post-segragational killing is attractive. This kind of TAS cross-talk, and abundant TAS lateral transfer, suggests there should be a considerable number of dead TAS systems: silenced, truncated, point mutations, etc. Did you find evidence of these?

Authors' response: A genuinely interesting question that is difficult to answer. The majority of the TA families are small, rapidly evolving proteins. Even toxin protein sequences (mostly enzymes) often do not have a single position that would be conserved throughout the entire family, suggesting the possibility that some of the toxins are inactivated (PINs are a good example). It is quite an intriguing possibility that some of these proteins might be functional toxins even in the absence of the enzymatic activity but this of course remains a speculation. Pseudogenes and truncations are harder to detect especially given the typical small size of the TA genes. What we know for a fact is that there are many solo toxins and antitoxins, and these can be reasonably viewed as derivatives of TAS that were exapted for other functions (Figure 11). **Authors' response**: This information is available in Table 2, in the column "Adjacent gene function; reasons if discarded". There are some systems that potentially could be novel TAS, for instance, those that encode a membrane protein as a putative toxin. However, a detailed investigation of such cases is beyond the scope of the paper.

I have read that TAS often flank pathogenicity islands (e.g. [107]), and have wondered about chromosomal TAS modules performing guard functions for neighboring genes. Have you explored these connections yet?

Authors' response: This is a very interesting and potentially important issue that is the subject of our active, ongoing investigation.

I saw a recent paper, January 2009, on connecting TAS to phage abortive infection proteins. And clearly, TAS mediated suicide as a means to protect clonally identical sister cells is a sensible mechanism for viral resistance. A small adjustment to the discussion, and one more reference, seems warranted.

Authors' response: We are aware of this link and mention the parallel between the Abi and TA systems [102]. We also added a sentence on the direct mechanistic parallel demonstrated in the recent interesting paper from the Salmond lab [103]. Again, this connection is one of the central subjects of our ongoing, large-scale efforts on the characterization of the prokaryotic mobilome.

Reviewer 3

Arcady R. Mushegian, Stowers Institute for Medical Research and Kansas University Medical Center

This is a thorough computational study of toxin-antitoxin systems in prokaryotes. I have no qualms about sequence similarities and structure prediction, and only a few technical concerns, but I also feel that the broader biological context requires elaboration. More specifically:

1. Background: the explanation of the post-segregational killing mechanism (italics mine)

"The antitoxin is *metabolically unstable* whereas the toxin is stable. Therefore, unless the antitoxin is continuously replenished through gene expression, the free toxin accumulates in amounts sufficient to kill a cell, which is what occurs after cell division if a daughter cell does not receive the TAS-encoding plasmid"

seems to be at odds with the statement two paragraphs later:

"The antitoxin binding inhibits the activity of the toxin, and the *stable* TA complex binds to the operator of the corresponding TAS operon via the DNA-binding domain of the antitoxin and (auto)represses its transcription."

-- is antitoxin only unstable when not in complex with toxin, whereas the toxin-antitoxin complex is stable? Or is antitoxin also unstable when in complex (or perhaps the complex itself is unstable)? The kinetic aspect seems to be missing! Also, what is the molecular connection between toxin release from the pair and postsegregation?

Authors' response: The first of the quoted statements was indeed incomplete in the original text. It is replaced with: "The antitoxin is metabolically unstable unless in a complex with the toxin, whereas the toxin is considerably more stable." We believe that this amendment should take care for any potential confusion. As for the "molecular connection between toxin release from the pair and post-segregation", the obvious connection is between the toxin release and post-segregational killing (not post-segregation per se): if one of the daughter cells has no means to produce the antitoxin, it is killed by the remaining toxin.

2. Results and Discussion (pp 8-10) and correspond part of the Methods section: The approach that involves the analysis of the coefficient of variation of genes in COGs appears to have identified lots of TAS, but it is not quite clear why this approach should work with such specificity. At least 70% of all COGs have patchy phyletic distribution. Moreover, many COGs may be inherited in short operons, and, more specifically, such tandems as ATPase+permease subunits of transporters, or restriction+modification enzymes, or two-component signal transduction systems, are likely to belong to COGs with widely different paralog membership in different species. Have they been discovered by this approach? If not, why not? Perhaps the authors can discuss in more detail the properties of the whole distribution of COGs by CV values, in addition to its extreme, to mention the range of the CV values of the candidates discarded because they belonged to longer operons, etc.

Authors' response: We expanded the Methods section, addressing some of these issues. The approach using the coefficient of variation is not extremely specific, so applied filtering that is described both in Figure 1 and in the Methods section. We also include Additional File 1 which is an annotated list of the 315 gene pairs that were obtained after automatic analysis of initial top 2000 COGs and were analyzed one by one using the STRING program (for all cases where the necessary information was present in the STRING system) or by manual neighborhood analysis in the few remaining cases. In this file, one can see which gene pairs other than TAS were analyzed. Among these were, of course, many transporter subunits, twocomponent signal transduction systems, transposons, and other usual suspects. However, it is easy to see that the majority of these genes do not form stable two-gene operons, with a few exceptions such as transposons that again can be readily distinguished from TAS.

"For such systems [i.e., "resistome" as defined by the authors], the boundary between selfishness and "normal" cellular function seems to be fuzzy and more a matter of convention than a real distinction."

If this is so, what is a reason to distinguish resistome from the rest of the mobilome? After all, any biosynthetic operon that is mobile may be "selfish" in the sense of J. Lawrence (i.e., it best provides for its own survival when transferred as a complete group of genes coding for a coherent module), but it also has "normal" cellular function. Moreover, the function of a considerable portion of TAS is not (or not only) resistance.

Authors' response: Of course, these boundaries are intrinsically fuzzy. Nevertheless, we believe that the components of the resistome do show a characteristic balance between selfishness and "normal" functioning that distinguishes them, on one end of the mobility range, from transposons and other "genuine" mobile elements, and on the other end, from regular biosynthetic operons. The latter, probably, should not be considered bona fide members of the mobilome although any operon indeed shows a degree of selfishness sensu Lawrence, so that there is not sharp boundary between the mobilome and the rest of the prokaryotic gene pool as noted here and elsewhere (e.g. [89]). Objective delineation of the mobilome is a challenging task, a major problem we are currently working on.

Two general questions:

A. Per the "compromise" proposal and other observations: does it follow that antitoxin genes may be distributed broader than the toxin genes (also because antitoxins may have multiple functions and perhaps multiple stabilizing partners)? Is this actually observed, or is there perhaps a wash with some antitoxins represented by small RNAs?

"A potential compromise between a purely selfish life style of TAS and integral cellular functions could be a role of chromosomally encoded TAS in the protection of prokaryotic cells against post-segregational killing induced by plasmid-encoded homologous TAS whereby the antitoxin encoded by a chromosomal gene sequesters a plasmid-encoded toxin. Experimental evidence of such protection was reported, and elimination of the chromosomal TAS in the presence of the respective plasmid did adversely affect the fitness of the host bacterium [25]."

Authors' response: We do find many more antitoxins than toxins (see Figure 11) but the contribution of other functions of the antitoxins is hard to assess specifically. It seems unlikely that the small RNA antitoxin substantially contribute to this bias. So far this class of antitoxins seems to be associated primarily with type I toxins that are not considered in this work.

B. Toxins appear to be similar to bacteriophages in many regards (highly mobile; potentially toxic; in love-hate relationship with cells), an indeed some TAS are encoded by phage genomes.

What is the connection of TAS to CRISPR loci? Are there any short toxin-derived sequences in CRISPRs?

Authors' response: There is no particularly strong link. Some TAS occur in the vicinity of CRISPR loci but so do many other genes that might belong to the broadly defined mobilome.

Is there any correlation between the number of both types of loci in different genomes?

Authors' response: No correlation beyond what is expected from the scaling of genes in a particular category with the genome size.

Minor comments:

"Resistome domain of the prokaryotic mobilome": do we really speak like this?

Authors' response: *yes, we (the authors) see nothing wrong about it and so do speak like this. The reader is informed by this comment that others do not.*

"The "selfish altruism", or "responsible selfishness", of TAS-like systems..." Is this Chernyshevsky-Randian property of TAS-like systems a defining feature of the whole mobilome, or of its subset resistome?

Authors' response: We appreciate this point and the fully appropriate references to Chernyshevsky (more or less, intended when coining the terms) and Ayn Rand. Upon consideration, we indeed replaced "mobilome" with "resistome" as some other members of the mobilome might show less restrain and responsibility.

The first sentence of Conclusions. Replace "We report here the most detailed and comprehensive comparativegenomic analysis of type II TAS so far available (to our knowledge)" by "We report here a comparative-genomic analysis of type II TAS"?

Authors' response: We understand that this could read like honking our horn. However, the phrase carries a message. We kept it.

Reviewer 4

Andrei Osterman, The Burnham Institute

The excellent article by Makarova, Wolf and Koonin could be indeed termed Genomic Encyclopedia of Prokaryotic TAS-2 for the breadth and depth of coverage of this fascinating system over 750 prokaryotic genomes. However, the accurate cross-genomic projection of the presently known TAS components, no matter how challenging and important, is only one of the remarkable accomplishments of this study. By pushing the boundaries of predictive comparative genomics to a completely new level, the authors also substantially expanded a repertoire of known toxins and antitoxins. They developed a sophisticated workflow elegantly capturing the elusive and mysterious nature of TAS operons, which allowed them to predict dozens of previously unknown players and combinations thereof. This workflow (computational techniques and filters included therein) is yet another remarkable deliverable of this study, which will be inspirational and instructive for those who are chasing after other challenging protein families. The detailed analysis of the resulting monumental picture, a genomic distribution of thousands of TAS elements, provided new insights into their evolution, intra- and interspecies mobility and functional associations. No doubt, this single study provided a great starting point for dozens of experimental biologists to follow upon.

Additional material

Additional file 1

The list of 315 adjacent pairs of COGs. This file contains the list of 315 adjacent pairs of COGs that were further analyzed on a case by case basis for prediction of TAS (approach 1) as described in the Methods section. Click here for file

[http://www.biomedcentral.com/content/supplementary/1745-6150-4-19-S1.xls]

Additional file 2

Multiple alignment of representative sequences of COG5606. The alignment supports the analysis and description of the predicted RelE-COG5606 TAS Click here for file [http://www.biomedcentral.com/content/supplementary/1745-6150-4-19-S2.zip]

Additional file 3

Multiple alignment of truncated members of the MerR-like family. The alignment supports the analysis and description of the predicted PIN-MerR TAS Click here for file [http://www.biomedcentral.com/content/supplementary/1745-6150-4-19-S3.zip]

Additional file 4

Multiple alignment of representative sequences of the XF1663 family. The alignment supports the analysis and description of the predicted MazF-XF1663 TAS Click here for file [http://www.biomedcentral.com/content/supplementary/1745-6150-4-19-S4.doc]

Additional file 5

Multiple alignment of representative sequences of the YhfG family. The alignment supports the analysis and description of the predicted YhfG-Fic/Doc TAS Click here for file [http://www.biomedcentral.com/content/supplementary/1745-6150-4-19-S5.zip]

Additional file 6

Multiple alignment of representative sequences of the DUF397 family. The alignment supports the analysis and description of the predicted DUF397-HTH TAS Click here for file [http://www.biomedcentral.com/content/supplementary/1745-6150-4-19-S6.doc]

Additional file 7

Multiple alignment of representative sequences of the YgiU family. The alignment supports the analysis and description of the predicted YgiUxre TAS Click here for file [http://www.biomedcentral.com/content/supplementary/1745-6150-4-19-S7.txt]

Additional file 8

Multiple alignment of representative sequences of COG3832. The alignment supports the analysis and description of the predicted COG3832-ArsR TAS Click here for file [http://www.biomedcentral.com/content/supplementary/1745-6150-4-19-S8.zip]

Additional file 9

Multiple alignment of a representative set of GNAT family acetyltransferases. The alignment supports the analysis and description of the GNAT-xre and GNAT-RHH systems Click here for file [http://www.biomedcentral.com/content/supplementary/1745-6150-4-19-S9.zip]

Additional file 10

The representation of toxins, antitoxins and toxin-antitoxin pairs in 750 complete genomes of prokaryotes. This file contains the counts of solo toxin and antitoxin genes as well as TA-pairs for all 750 prokaryotic genomes analyzed in this work. Phenotypic characteristics and the total number of protein coding genes are given for each genome. Click here for file

[http://www.biomedcentral.com/content/supplementary/1745-6150-4-19-S10.xls]

Additional file 11

Statistical Appendix for the Methods. The appendix contains additional details concerning the following procedures: i) the likelihood model used to estimate the scaling parameters for the number of TAS pairs relative to the genome size and ii) variability of abundance of different TAS pairs within ATGCs.

Click here for file

[http://www.biomedcentral.com/content/supplementary/1745-6150-4-19-S11.doc]

Additional file 12

 Table S1. Distribution of TAS among prokaryotic taxa

 Click here for file

 [http://www.biomedcentral.com/content/supplementary/1745-6150-4-19-S12.doc]

Additional file 13

Species abbreviations used in the alignments in Figures 2, 4, 5, **and** 6. The provided table spells out the species abbreviations used in the alignments in Figures 2,4,5 and 6

Click here for file

[http://www.biomedcentral.com/content/supplementary/1745-6150-4-19-S13.xls]

Additional file 14

Complete list of GenBank identifiers for all predicted and known toxins and antitoxins. The table contains the GenBank identifiers (GI numbers) for all predicted and known toxins and antitoxins identified in this work in 750 complete prokaryotic genomes Click here for file

[http://www.biomedcentral.com/content/supplementary/1745-6150-4-19-S14.xls]

Acknowledgements

The authors' research is supported by intramural funds of the DHHS (NIH, National Library of Medicine)

References

- Gerdes K, Bech FW, Jorgensen ST, Lobner-Olesen A, Rasmussen PB, Atlung T, Boe L, Karlstrom O, Molin S, von Meyenburg K: Mechanism of postsegregational killing by the hok gene product of the parB system of plasmid RI and its homology with the relF gene product of the E. coli relB operon. Embo J 1986, 5(8):2023-2029.
- Ogura T, Hiraga S: Mini-F plasmid genes that couple host cell division to plasmid proliferation. Proc Natl Acad Sci USA 1983, 80(15):4784-4788.
- 3. Gerdes K, Christensen SK, Lobner-Olesen A: Prokaryotic toxinantitoxin stress response loci. Nat Rev Microbiol 2005, 3(5):371-382.

- Buts L, Lah J, Dao-Thi MH, Wyns L, Loris R: Toxin-antitoxin modules as bacterial metabolic stress managers. Trends Biochem Sci 2005, 30(12):672-679.
- Van Melderen L, Saavedra De Bast M: Bacterial toxin-antitoxin systems: more than selfish entities? PLoS Genet 2009, 5(3):e1000437.
- 6. Gerdes K, Wagner EG: **RNA antitoxins.** *Curr Opin Microbiol* 2007, **10(2):**117-124.
- Fozo EM, Hemm MR, Storz G: Small toxic proteins and the antisense RNAs that repress them. Microbiol Mol Biol Rev 2008, 72(4):579-589. Table of contents.
- Christensen-Dalsgaard M, Overgaard M, Winther KS, Gerdes K: RNA decay by messenger RNA interferases. Methods Enzymol 2008, 447:521-535.
- 9. Yamaguchi Y, Inouye M: mRNA interferases, sequence-specific endoribonucleases from the toxin-antitoxin systems. *Prog Mol Biol Transl Sci* 2009, **85:**467-500.
- Correia FF, D'Onofrio A, Rejtar T, Li L, Karger BL, Makarova K, Koonin EV, Lewis K: Kinase activity of overexpressed HipA is required for growth arrest and multidrug tolerance in Escherichia coli. J Bacteriol 2006, 188(24):8360-8367.
- Schumacher MA, Piro KM, Xu W, Hansen S, Lewis K, Brennan RG: Molecular mechanisms of HipA-mediated multidrug tolerance and its neutralization by HipB. Science 2009, 323(5912):396-401.
- 12. Hayes F: Toxins-antitoxins: plasmid maintenance, programmed cell death, and cell cycle arrest. Science 2003, 301(5639):1496-1499.
- Anantharaman V, Aravind L: New connections in the prokaryotic toxin-antitoxin network: relationship with the eukaryotic nonsense-mediated RNA decay system. Genome Biol 2003, 4(12):R81.
- Christensen SK, Gerdes K: Delayed-relaxed response explained by hyperactivation of RelE. Mol Microbiol 2004, 53(2):587-597.
 Zhang Y, Zhang J, Hoeflich KP, Ikura M, Qing G, Inouye M: MazF
- Zhang Y, Zhang J, Hoeflich KP, Ikura M, Qing G, Inouye M: MazF cleaves cellular mRNAs specifically at ACA to block protein synthesis in Escherichia coli. *Mol Cell* 2003, 12(4):913-923.
- Aizenman E, Engelberg-Kulka H, Glaser G: An Escherichia coli chromosomal "addiction module" regulated by guanosine [corrected] 3',5'-bispyrophosphate: a model for programmed bacterial cell death. Proc Natl Acad Sci USA 1996, 93(12):6059-6063.
- Hazan R, Sat B, Engelberg-Kulka H: Escherichia coli mazEF-mediated cell death is triggered by various stressful conditions. J Bacteriol 2004, 186(11):3663-3669.
- Kolodkin-Gal I, Sat B, Keshet A, Engelberg-Kulka H: The communication factor EDF and the toxin-antitoxin module mazEF determine the mode of action of antibiotics. *PLoS Biol* 2008, 6(12):e319.
- Pedersen K, Christensen SK, Gerdes K: Rapid induction and reversal of a bacteriostatic condition by controlled expression of toxins and antitoxins. *Mol Microbiol* 2002, 45(2):501-510.
- 20. Nariya H, Inouye M: MazF, an mRNA interferase, mediates programmed cell death during multicellular Myxococcus development. *Cell* 2008, **132(1)**:55-66.
- 21. Lewis K: Programmed death in bacteria. Microbiol Mol Biol Rev 2000, 64(3):503-514.
- 22. Jayaraman Ř: Bacterial persistence: some new insights into an old phenomenon. J Biosci 2008, 33(5):795-805.
- Tsilibaris V, Maenhaut-Michel G, Mine N, Van Melderen L: What is the benefit to Escherichia coli of having multiple toxin-antitoxin systems in its genome? J Bacteriol 2007, 189(17):6101-6108.
- Magnuson RD: Hypothetical functions of toxin-antitoxin systems. | Bacteriol 2007, 189(17):6089-6092.
- Saavedra De Bast M, Mine N, Van Melderen L: Chromosomal toxin-antitoxin systems may act as antiaddiction modules. J Bacteriol 2008, 190(13):4603-4609.
- 26. Pandey DP, Gerdes K: Toxin-antitoxin loci are highly abundant in free-living but lost from host-associated prokaryotes. Nucleic Acids Res 2005, 33(3):966-976.
- Sevin EW, Barloy-Hubler F: RASTA-Bacteria: a web-based tool for identifying toxin-antitoxin loci in prokaryotes. *Genome Biol* 2007, 8(8):R155.

- Guglielmini J, Szpirer C, Milinkovitch MC: Automated discovery and phylogenetic analysis of new toxin-antitoxin systems. BMC Microbiol 2008, 8:104.
- 29. Aravind L: Guilt by association: contextual information in genome analysis. Genome Res 2000, 10(8):1074-1077.
- Galperin MY, Koonin EV: Who's your neighbor? New computational approaches for functional genomics. Nat Biotechnol 2000, 18(6):609-613.
- Gabaldon T, Huynen MA: Prediction of protein function and pathways in the genome era. Cell Mol Life Sci 2004, 61(7-8):930-944.
- Makarova KS, Grishin NV, Koonin EV: The HicAB cassette, a putative novel, RNA-targeting toxin-antitoxin system in archaea and bacteria. Bioinformatics 2006, 22(21):2581-2584.
- Tatusov RL, Fedorova ND, Jackson JD, Jacobs AR, Kiryutin B, Koonin EV, Krylov DM, Mazumder R, Mekhedov SL, Nikolskaya AN, et al.: The COG database: an updated version includes eukaryotes. BMC Bioinformatics 2003, 4:41.
- 34. Snel B, Lehmann G, Bork P, Huynen MA: **STRING:** a web-server to retrieve and display the repeatedly occurring neighbourhood of a gene. *Nucleic Acids Res* 2000, **28(18):**3442-3444.
- Jorgensen MG, Pandey DP, Jaskolska M, Gérdes K: HicA of Escherichia coli defines a novel family of translation-independent mRNA interferases in bacteria and archaea. J Bacteriol 2009, 191(4):1191-1199.
- Koonin EV, Mushegian AR, Galperin MY, Walker DR: Comparison of archaeal and bacterial genomes: computer analysis of protein sequences predicts novel functions and suggests a chimeric origin for the archaea. *Mol Microbiol* 1997, 25(4):619-637.
- Aravind L, Koonin EV: DNA polymerase beta-like nucleotidyltransferase superfamily: identification of three new families, classification and evolutionary history. Nucleic Acids Res 1999, 27(7):1609-1618.
- Grynberg M, Erlandsen H, Godzik A: HEPN: a common domain in bacterial drug resistance and human neurodegenerative proteins. Trends Biochem Sci 2003, 28(5):224-226.
- Schaffer AA, Aravind L, Madden TL, Shavirin S, Spouge JL, Wolf YI, Koonin EV, Altschul SF: Improving the accuracy of PSI-BLAST protein database searches with composition-based statistics and other refinements. Nucleic Acids Res 2001, 29(14):2994-3005.
- Marchler-Bauer A, Panchenko AR, Shoemaker BA, Thiessen PA, Geer LY, Bryant SH: CDD: a database of conserved domain alignments with links to domain three-dimensional structure. Nucleic Acids Res 2002, 30(1):281-283.
- 41. Sun D, Setlow P: Cloning and nucleotide sequence of the Bacillus subtilis ansR gene, which encodes a repressor of the ans operon coding for L-asparaginase and L-aspartase. J Bacteriol 1993, 175(9):2501-2506.
- Grose JH, Bergthorsson U, Roth JR: Regulation of NAD synthesis by the trifunctional NadR protein of Salmonella enterica. J Bacteriol 2005, 187(8):2774-2782.
- Barragan MJ, Blazquez B, Zamarro MT, Mancheno JM, Garcia JL, Diaz E, Carmona M: BzdR, a repressor that controls the anaerobic catabolism of benzoate in Azoarcus sp. CIB, is the first member of a new subfamily of transcriptional regulators. *J Biol Chem* 2005, 280(11):10683-10694.
- Cameron S, McLuskey K, Chamberlayne R, Hallyburton I, Hunter WN: Initiating a crystallographic analysis of recombinant (S)-2-hydroxypropylphosphonic acid epoxidase from Streptomyces wedmorensis. Acta Crystallogr Sect F Struct Biol Cryst Commun 2005, 61 (Pt 5):534-536.
- 45. Dziewit L, Jazurek M, Drewniak L, Baj J, Bartosik D: The SXT conjugative element and linear prophage NI5 encode toxinantitoxin-stabilizing systems homologous to the tad-ata module of the Paracoccus aminophilus plasmid pAMI2. J Bacteriol 2007, 189(5):1983-1997.
- 46. Makarova KS, Aravind L, Galperin MY, Grishin NV, Tatusov RL, Wolf YI, Koonin EV: Comparative genomics of the Archaea (Euryarchaeota): evolution of conserved protein families, the stable core, and the variable shell. *Genome Res* 1999, 9(7):608-628.
- Clissold PM, Ponting CP: PIN domains in nonsense-mediated mRNA decay and RNAi. Curr Biol 2000, 10(24):R888-890.
- Yuan HS, Finkel SE, Feng JA, Kaczor-Grzeskowiak M, Johnson RC, Dickerson RE: The molecular structure of wild-type and a mutant Fis protein: relationship between mutational

changes and recombinational enhancer function or DNA binding. Proc Natl Acad Sci USA 1991, 88(21):9558-9562.

- Kelly A, Goldberg MD, Carroll RK, Danino V, Hinton JC, Dorman CJ: A global role for Fis in the transcriptional control of metabolism and type III secretion in Salmonella enterica serovar Typhimurium. *Microbiology* 2004, 150(Pt 7):2037-2053.
 Sallai L, Tucker PA: Crystal structure of the central and C-ter-
- Sallai L, Tucker PA: Crystal structure of the central and C-terminal domain of the sigma(54)-activator ZraR. J Struct Biol 2005, 151(2):160-170.
- Bobay BG, Andreeva A, Mueller GA, Cavanagh J, Murzin AG: Revised structure of the AbrB N-terminal domain unifies a diverse superfamily of putative DNA-binding proteins. FEBS Lett 2005, 579(25):5669-5674.
- Brown NL, Stoyanov JV, Kidd SP, Hobman JL: The MerR family of transcriptional regulators. FEMS Microbiol Rev 2003, 27(2-3):145-163.
- Godsey MH, Baranova NN, Neyfakh AA, Brennan RG: Crystal structure of MtaN, a global multidrug transporter gene activator. J Biol Chem 2001, 276(50):47178-47184.
- Scholz P, Haring V, Wittmann-Liebold B, Ashman K, Bagdasarian M, Scherzinger E: Complete nucleotide sequence and gene organization of the broad-host-range plasmid RSF1010. Gene 1989, 75(2):271-288.
- Barnett MJ, Fisher RF, Jones T, Komp C, Abola AP, Barloy-Hubler F, Bowser L, Capela D, Galibert F, Gouzy J, et al.: Nucleotide sequence and predicted functions of the entire Sinorhizobium meliloti pSymA megaplasmid. Proc Natl Acad Sci USA 2001, 98(17):9883-9888.
- Odaert B, Saida F, Aliprandi P, Durand S, Crechet JB, Guerois R, Laalami S, Uzan M, Bontems F: Structural and functional studies of RegB, a new member of a family of sequence-specific ribonucleases involved in mRNA inactivation on the ribosome. *J Biol Chem* 2007, 282(3):2019-2028.
- Pope MK, Green B, Westpheling J: The bldB gene encodes a small protein required for morphogenesis, antibiotic production, and catabolite control in Streptomyces coelicolor. J Bacteriol 1998, 180(6):1556-1562.
- Mishig-Ochiriin T, Won HS, Lee CJ, Kang SO, Lee BJ: Biophysical and structural property of the putative DNA-binding protein, BldB, from Streptomyces lividans. *Biopolymers* 2003, 69(3):343-350.
- Stocker W, Bode W: Structural features of a superfamily of zinc-endopeptidases: the metzincins. Curr Opin Struct Biol 1995, 5(3):383-390.
- McDonnell GE, Wood H, Devine KM, McConnell DJ: Genetic control of bacterial suicide: regulation of the induction of PBSX in Bacillus subtilis. J Bacteriol 1994, 176(18):5820-5830.
- Okamoto K, Mudd JA, Mangan J, Huang WN, Subbaiah TV, Marmur J: Properties of the defective phage of Bacillus subtilis. J Mol Biol 1968, 34(3):413-428.
- Earl AM, Mohundro MM, Mian IS, Battista JR: The IrrE protein of Deinococcus radiodurans RI is a novel regulator of recA expression. J Bacteriol 2002, 184(22):6216-6224.
- Hua Y, Narumi I, Gao G, Tian B, Satoh K, Kitayama S, Shen B: Pprl: a general switch responsible for extreme radioresistance of Deinococcus radiodurans. Biochem Biophys Res Commun 2003, 306(2):354-360.
- 64. Liu Y, Źhou J, Omelchenko MV, Beliaev AS, Venkateswaran A, Stair J, Wu L, Thompson DK, Xu D, Rogozin IB, et al.: Transcriptome dynamics of Deinococcus radiodurans recovering from ionizing radiation. Proc Natl Acad Sci USA 2003, 100(7):4191-4196.
- 65. Tanaka M, Earl AM, Howell HA, Park MJ, Eisen JA, Peterson SN, Battista JR: Analysis of Deinococcus radiodurans's transcriptional response to ionizing radiation and desiccation reveals novel proteins that contribute to extreme radioresistance. Genetics 2004, 168(1):21-33.
- Ohba H, Satoh K, Yanagisawa T, Narumi I: The radiation responsive promoter of the Deinococcus radiodurans pprA gene. Gene 2005, 363:133-141.
- Fernandez De Henestrosa AR, Ogi T, Aoyagi S, Chafin D, Hayes JJ, Ohmori H, Woodgate R: Identification of additional genes belonging to the LexA regulon in Escherichia coli. Mol Microbiol 2000, 35(6):1560-1572.
- Kawano M, Aravind L, Storz G: An antisense RNA controls synthesis of an SOS-induced toxin evolved from an antitoxin. *Mol Microbiol* 2007, 64(3):738-754.

- Weel-Sneve R, Bjoras M, Kristiansen KI: Overexpression of the LexA-regulated tisAB RNA in E. coli inhibits SOS functions; implications for regulation of the SOS response. Nucleic Acids Res 2008, 36(19):6249-6259.
- Bose B, Auchtung JM, Lee CA, Grossman AD: A conserved antirepressor controls horizontal gene transfer by proteolysis. *Mol Microbiol* 2008, **70(3):**570-582.
- Lehmann C, Lim K, Chalamasetty VR, Krajewski W, Melamud E, Galkin A, Howard A, Kelman Z, Reddy PT, Murzin AG, et al.: The HI0073/HI0074 protein pair from Haemophilus influenzae is a member of a new nucleotidyltransferase family: Structure, sequence analyses, and solution studies. Proteins 2003, 50(2):249-260.
- Fitz-Gibbon ST, Ladner H, Kim UJ, Stetter KO, Simon MI, Miller JH: Genome sequence of the hyperthermophilic crenarchaeon Pyrobaculum aerophilum. Proc Natl Acad Sci USA 2002, 99(2):984-989.
- Makarova KS, Wolf YI, Koonin EV: Potential genomic determinants of hyperthermophily. *Trends Genet* 2003, 19(4):172-176.
 Bloomfield GA, Whittle G, McDonagh MB, Katz ME, Cheetham BF:
- Bloomfield GA, Whittle G, McDonagh MB, Katz ME, Cheetham BF: Analysis of sequences flanking the vap regions of Dichelobacter nodosus: evidence for multiple integration events, a killer system, and a new genetic element. *Microbiology* 1997, 143(Pt 2):553-562.
- Gonzalez Barrios AF, Zuo R, Hashimoto Y, Yang L, Bentley WE, Wood TK: Autoinducer 2 controls biofilm formation in Escherichia coli through a novel motility quorum-sensing regulator (MqsR, B3022). J Bacteriol 2006, 188(1):305-316.
- 76. Zhang XS, Garcia-Contreras R, Wood TK: Escherichia coli transcription factor YncC (McbR) regulates colanic acid and biofilm formation by repressing expression of periplasmic protein YbiM (McbA). *Isme* | 2008, 2(6):615-631.
- 77. lyer LM, Koonin EV, Aravind L: Extensive domain shuffling in transcription regulators of DNA viruses and implications for the origin of fungal APSES transcription factors. Genome Biol 2002, 3(3):RESEARCH0012.
- Heinrich J, Velleman M, Schuster H: The tripartite immunity system of phages PI and P7. FEMS Microbiol Rev 1995, 17(1-2):121-126.
- Hansen EB: Structure and regulation of the lytic replicon of phage P1. J Mol Biol 1989, 207(1):135-149.
- Busenlehner LS, Pennella MA, Giedroc DP: The SmtB/ArsR family of metalloregulatory transcriptional repressors: Structural insights into prokaryotic metal resistance. FEMS Microbiol Rev 2003, 27(2–3):131-143.
- Panaretou B, Siligardi G, Meyer P, Maloney A, Sullivan JK, Singh S, Millson SH, Clarke PA, Naaby-Hansen S, Stein R, et al.: Activation of the ATPase activity of hsp90 by the stress-regulated cochaperone aha1. Mol Cell 2002, 10(6):1307-1318.
- 82. Lotz GP, Lin H, Harst A, Obermann WM: Ahal binds to the middle domain of Hsp90, contributes to client protein activation, and stimulates the ATPase activity of the molecular chaperone. J Biol Chem 2003, 278(19):17228-17235.
- Biggins JB, Onwueme KC, Thorson JS: Resistance to enediyne antitumor antibiotics by CalC self-sacrifice. Science 2003, 301(5639):1537-1541.
- Singh S, Hager MH, Zhang C, Griffith BR, Lee MS, Hallenga K, Markley JL, Thorson JS: Structural insight into the self-sacrifice mechanism of enediyne resistance. ACS Chem Biol 2006, 1(7):451-460.
- Iyer LM, Koonin EV, Aravind L: Adaptations of the helix-grip fold for ligand binding and catalysis in the START domain superfamily. Proteins 2001, 43(2):134-144.
- Bufe A, Spangfort MD, Kahlert H, Schlaak M, Becker WM: The major birch pollen allergen, Bet v I, shows ribonuclease activity. Planta 1996, 199(3):413-415.
- Vetting MW, S de Carvalho LP, Yu M, Hegde SS, Magnet S, Roderick SL, Blanchard JS: Structure and functions of the GNAT superfamily of acetyltransferases. Arch Biochem Biophys 2005, 433(1):212-226.
- He H, Ding Y, Bartlam M, Sun F, Le Y, Qin X, Tang H, Zhang R, Joachimiak A, Liu J, et al.: Crystal structure of tabtoxin resistance protein complexed with acetyl coenzyme A reveals the mechanism for beta-lactam acetylation. J Mol Biol 2003, 325(5):1019-1030.

- Koonin EV, Wolf YI: Genomics of bacteria and archaea: the emerging dynamic view of the prokaryotic world. Nucleic Acids Res 2008, 36(21):6688-6719.
- Ulrich LE, Koonin EV, Zhulin IB: One-component systems dominate signal transduction in prokaryotes. Trends Microbiol 2005, 13(2):52-56.
- 91. van Nimwegen E: Scaling laws in the functional content of genomes. Trends Genet 2003, 19(9):479-484.
- van Nimwegen E: Scaling Laws in the Functional Content of Genomes: Fundumental Constrains of Evolution. In Power Laws, Scale-Free Networks and Genome Biology Edited by: Koonin EV, Wolf YI, Karev GP. Georgetown, Texas: Landes Bioscience/ Eurekah.com; 2006:236-253.
- Novichkov PS, Ratnere I, Wolf YI, Koonin EV, Dubchak I: ATGC: a database of orthologous genes from closely related prokaryotic genomes and a research platform for microevolution of prokaryotes. Nucleic Acids Res 2009:D448-54.
- 94. Novichkov PS, Wolf YI, Dubchak I, Koonin EV: Trends in prokaryotic evolution revealed by comparison of closely related bacterial and archaeal genomes. J Bacteriol 2009, 191(1):65-73.
- Feder M, Bujnicki JM: Identification of a new family of putative PD-(D/E)XK nucleases with unusual phylogenomic distribution and a new type of the active site. BMC Genomics 2005, 6(1):21.
- Kinch LN, Ginalski K, Rychlewski L, Grishin NV: Identification of novel restriction endonuclease-like fold families among hypothetical proteins. Nucleic Acids Res 2005, 33(11):3598-3605.
- 97. Lewis K: Multidrug tolerance of biofilms and persister cells. Curr Top Microbiol Immunol 2008, **322**:107-131.
- Moritz EM, Hergenrother PJ: Toxin-antitoxin systems are ubiquitous and plasmid-encoded in vancomycin-resistant enterococci. Proc Natl Acad Sci USA 2007, 104(1):311-316.
- Frost LS, Leplae R, Summers AO, Toussaint A: Mobile genetic elements: the agents of open source evolution. Nat Rev Microbiol 2005, 3(9):722-732.
- 100. Siefert JL: Defining the mobilome. Methods Mol Biol 2009, 532:13-27.
- 101. Kobayashi I: Behavior of restriction-modification systems as selfish mobile elements and their impact on genome evolution. Nucleic Acids Res 2001, 29(18):3742-3756.
- 102. Chopin MC, Chopin A, Bidnenko E: Phage abortive infection in lactococci: variations on a theme. Curr Opin Microbiol 2005, 8(4):473-479.
- 103. Fineran PC, Blower TR, Foulds IJ, Humphreys DP, Lilley KS, Salmond GP: The phage abortive infection system, ToxIN, functions as a protein-RNA toxin-antitoxin pair. Proc Natl Acad Sci USA 2009, 106(3):894-899.
- 104. Wright GD: The antibiotic resistome: the nexus of chemical and genetic diversity. Nat Rev Microbiol 2007, 5(3):175-186.
- 105. Edgar RC: MUSCLE: multiple sequence alignment with high accuracy and high throughput. Nucleic Acids Res 2004, 32(5):1792-1797.
- 106. McGuffin LJ, Bryson K, Jones DT: The PSIPRED protein structure prediction server. Bioinformatics 2000, 16(4):404-405.
- Arcus VL, Rainey PB, Turner SJ: The PIN-domain toxin-antitoxin array in mycobacteria. Trends Microbiol 2005, 13(8):360-365.

