

Comparative genomics of defense systems in archaea and bacteria

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Supplementary tables

Table S1. Poorly characterized genes in the genomic neighborhoods of the Dnd defense system^a

Gene and Family	Comment and References
Gene in the modification cluster	
DndB pfam14072	ParB family nuclease, also known as DGQHR domain, associated with many defense systems (1), often contains additional HEPN superfamily domain, predicted endoribonuclease (2)
DndD	ABC type ATPase of Mre11/Rad50 subfamily
DndE pfam8870	The structure has been solved and DNA-binding demonstrated (3); HHPred identifies significant similarity of N-terminal region with RelE family of RHH fold, an antitoxin associated with many TA systems; this domain is also fused to FtsK and HerA-like ATPases, usually associated with <i>dnd</i> genes
Associated gene families	
DndF	The N-terminal domain belongs to the HEPN endoribonuclease superfamily (2), C-terminal domain is a predicted NTPase likely specifically GTPase
DndG pfam08747	C-terminal HTH domain
DndH	The C-terminal domain is a HerA-like helicase/ATPase, the domain next to it belongs to the PD-(D/E)xK endonuclease superfamily. This protein is the predicted main REase subunit of the system.
PSHAb0092-like	Loosely associate gene, belongs to the MutL-related paraMORC family; proteins of this family are encoded in the vicinity of many R-M systems (4)

^aIdentification of protein domains and functional prediction for experimentally uncharacterized proteins was based on the results of protein sequence and structure database searches using the PSI-BLAST and HHPred methods (5,6).

Table S2. Genes in the genomic neighborhoods of the Pgl defense system^a

Family	Comment and references
Core genes	
pfam08665	PglZ, alkaline phosphatase family enzyme
COG1002	Methylase subunit associated with R-M systems; often encoded in a separate locus
COG4930	ATP-dependent Lon-type protease
Associated gene families	
pfam08747	Uncharacterized protein
COG0553	Superfamily II DNA helicase; often fused to a methylase domain
pfam08849	Similar to an uncharacterized family DUF3387 which is often fused to R-M. Structure is solved - pdb: 3bhw; DALI reveals structural similarity with recognition domains of R-M systems
COG1201	Lhr-like helicase
pfam10923	ATPase domain-containing protein
COG0863	DNA modification methylase
COG1479/ COG3472	RloF-like component of potential R-M system found in predicted operon for type I R-M system (7); contains N-terminal DGQHR (ParB family nuclease) domain and C-terminal HNH-type nuclease domain
COG1061	Superfamily II DNA helicase
COG2865	Transcriptional regulator containing an HTH domain and diverged ATP-binding domain (Schlafen-like)
COG0515	Duplicated serine/threonine protein kinase domains; some contain nuclease-related NERD domain

^aIdentification of protein domains and functional prediction for experimentally uncharacterized proteins was based on the results of protein sequence and structure database searches using the PSI-BLAST and HHPred methods (5,6).

Table S3. Poorly characterized and recently predicted TA systems^a

TOXINS Family and genes	Predicted or solved (PDB) structure and activity	ANTITOXIN Family and genes	Predicted or solved (PDB) structure	Comments and references
Target is unknown				
HEPN COG2250/ COG2445/ COG2361	Ribonuclease (1jog)	MNT, COG1708/ COG1669	Nucleotidyl- transferase (1no5)	HEPN of the COG2250 family is one of the most prominent genomic determinants of the thermophilic life style
COG2856	Zn-dependent protease (3dtk)	Xre	HTH fold	Often fused to antitoxin domain. Frequently associated with RelE and PIN toxins
COG3832	Cyclase/dehydratase family protein, START domain superfamily (1xuv)	ArsR-like	HTH fold	
GNAT	GNAT acetyltransferase	Xre and RHH	HTH fold and RHH fold	(8)
COG2929/ DUF497	No prediction or structure	COG5304 and COG3514	RHH fold	Toxin sequences are compatible with RelE secondary structure
RES COG5654	RES domain superfamily	Xre COG5642	HTH fold	(8)
DUF397	No prediction or structure	Xre	HTH fold	Potential pleiotropic regulator that affects morphogenesis, antibiotic production, and catabolite control in Streptomyces (9)
AbiG, AbiE DUF1814/ COG2253/ COG4849/ COG4914	Nucleotidyltransferase	COG5340/ COG4861	Contains HTH domain	See also ABI systems
MAE_32580 COG4634/ DUF82	Compatible with PIN structure and motifs	COG2442	winged HTH – HTH fold	(1)
GinC COG4476 DUF1071	Unique BH2638- like fold (2oy9)	COG1393, ArsC, Arsenate reductase	Thioredoxin – fold	Thioredoxin-like proteins involved in transcriptional regulation, (10) shown to be antitoxins (11)
DUF4160, MAE_01690	Metal-dependent enzyme, possibly a nuclease	DUF3532/ DUF2442	NE0471 N- terminal domain-like fold (2auw) and (in some) xre family HTH fold	(1)
Mechanism of antitoxin is unknown				
RnlA/IsoA	RNase LS (N-terminal TBP- like substrate- binding, C-terminal HEPN domain)	RnlB/IsoB	No prediction	TA system that cleaves bacteriophage T4 mRNAs (12) and contributes to mRNA turnover in <i>E. coli</i> (13), often associated with RNase H

	ribonuclease)			
HicA COG1724	Translation-independent mRNA interferase; RBD-like fold (1whz)	HicB	RNAse H-like domain. Often fused to a DNA-binding domain, either RHH or HTH	HicA has a bacteriostatic rather than a bactericidal effect (14)
Unknown structure and/or mechanism of the toxin				
YafO	No prediction or structure, ribosome dependent mRNA interferase	YafN	PHD/YefM	(15); (16)
YeeV DUF1219 CbtA/Ykfl/Y pjF toxin family	Inhibits cell division by targeting FtsZ and MreB	YeeU	Antitoxin homologous to toxins YoeB and RelE (2inw)	(17) Structure of YeeU has been solved (18), Proposed TA system type IV: antitoxin protects target but does not bind the toxin (19)
COG4396 GinA Gam	Antiparallel coiled-coil fold (2p2u)	COG4712/ DUF1071 Sak-like	Rad52/22 family; dsRNA-binding domain-like fold	Toxic effect demonstrated (11). GinA is a close homolog of phage Mu host-nuclease inhibitor protein Gam which inhibits RecBCD binding to dsDNA ends (20); Sak is single-strand annealing protein (21); present predominantly in Firmicutes
DUF3169, GinD	Membrane protein	COG1476	Xre family – HTH fold	Experimentally validated using genetic approach (11) Also often encoded in one operon with membrane associated metal-dependent protease of DUF3267 (peptidase M50) (22)
GhoT/YjdO, DUF2566	Membrane protein	GhoS/YjdK, DUF2622 endo- ribonuclease	Ferredoxin fold (2llz)	Proposed type V toxin-antitoxin system, antitoxin cleaves toxin mRNA (23), Specific for Gamma-proteobacteria

^aIdentification of protein domains and functional prediction for experimentally uncharacterized proteins was based on the results of protein sequence and structure database searches using the PSI-BLAST and HHPred methods (5,6).

Table S4. Abortive infection and phage exclusion systems^a

Name	Source	Reference	Phyletic spread	Comments and additional references
AbiA/ abi829	<i>Lactococcus lactis</i> plasmid pCI829	(24,25)	Several diverse Firmicutes	RT domain fused to C-terminal HEPN domain (2); also pTR2030;affects phage DNA replication (26)
AbiB/ abi416	<i>L. lactis subsp.</i> <i>lactis</i> IL416 genome	(27,28)	<i>Lactococcus</i> only	AbiB prevents phage growth by promoting degradation of phage transcripts by endonucleolytic cleavage. Putative PD-(D/E)xK family nuclease (motif and secondary structure prediction)
AbiC	<i>L.lactis</i> pTN20	(29)		See AbiP; interferes with capsid production
AbiD1 AbiD (abi_2)	<i>L.lactis</i> plasmids pBF61 pIL105	(30-33)	Abundant in bacteria	HEPN domain, predicted ribonuclease (2) Over-production of AbiD1 shown to possess bacteriostatic effect; expression of the <i>abiD1</i> gene is specifically translationally activated by phage and is temperature-dependent; affects expression of <i>Lactococcus</i> phage bIL66 orf3, RuvC resolvase, necessary for phage replication
AbiE	<i>L.lactis subsp. lactis</i> biovar <i>diacetylactis</i> DRC3 plasmid pNP40	(34)		See AbiG; interferes with DNA packaging
AbiF	<i>L.lactis subsp. lactis</i> biovar <i>diacetylactis</i> DRC3 plasmid pNP40	(34)		See AbiD
AbiG (AbiGi and AbiGii)	<i>L. lactis subsp.</i> <i>cremoris</i> UC653 pCI750	(35)	Abundant in bacteria and archaea	Predicted toxin-antitoxin system: toxin is a predicted nucleotidyltransferase (COG2253/COG4849/COG4914 families) and antitoxin is an HTH domain-containing protein (COG5340/COG4861 families); constitutively expressed; inhibits synthesis of both early and late phage c2 transcripts
AbiH	<i>L.lactis ssp. lactis</i> biovar. <i>diacetylactis</i> S94 chromosome	(36)	Abundant in bacteria	Predicted nuclease of the Sir2 family
AbiI	<i>L.lactis subsp. lactis</i> M138 plasmid pND852	(37)	Abundant in bacteri, also present in several archaea and phages (Gp21 protein [<i>Listeria</i> phage 2389])	Ribonuclease H superfamily, related to DUF3800 family; interferes with DNA packaging
AbiJ	<i>L.lactis</i> biovar. <i>diacetylactis</i> UK12922	(38)	Abundant in bacteria	C-terminal HEPN domain, predicted ribonuclease, also known as Abi-859 (2)

	plasmid pND859			
AbiK	pSRQ800 10708383	(39)		see AbiA; RT domain; interferes with phage DNA replication
AbiLi AbiLii	<i>L. lactis</i> <i>diacetylactis</i> pND861	(7,40)	Abundant in bacteria, also present in several archaea	AbiLi: ATPase (COG4637 or COG1106 family); AbiLii: Toprim domain, homolog of <i>rloB</i> , the gene found within Type I R-M system locus in <i>Campylobacter jejuni</i> (7)
AbiN	<i>L.lactis subsp. cremoris</i> S114 prophage	(41)	Diverse bacteria, several archaea and phages	Membrane-associated coiled-coil protein homologous to N-terminal domain present in RNase Y family (42)
AbiO	<i>L.lactis ssp. lactis</i> MG1363 plasmid pPF144	(43)	Mostly diverse Firmicutes, Mollicutes and several phages	PD-(D/E)xK-family nuclease domain fused to a helicase (COG3410)
AbiP	<i>L. lactis sp. lactis</i> IL1403 plasmid pIL2614	(44)	Patchy distribution in diverse bacterial lineages	See AbiC; membrane anchored protein, shown to bind nucleic acids with an approximately 10-fold preference for RNA relative to ssDNA; interferes with phage DNA replication
AbiQ	<i>L. lactis</i> LM0230 plasmid pSRQ900	(45,46)	Patchy distribution in diverse bacterial lineages	Type III TA system with a ToxN toxin related to MazF superfamily type II toxins (47) and a RNA antitoxin interacting with the ToxN protein; interferes with DNA packaging
AbiR	<i>L. lactis subsp. lactis</i> <i>bv.diacetylactis</i> KR2 plasmid pKR223	(48)	Abundant in bacteria and in archaea (COG0553)	ORF1,2,3 (COG0553),4 are involved; inhibits phage DNA replication; always associated with R-M systems
AbiS	<i>L. lactis subsp. cremoris</i> W56 plasmid pAW601	(49,50)	Unique	Not associated with any protein coding region, mostly functional against lactococcal 936-phages probably because of repeated DNA sequences are similar to cos regions of these phage; repeated DNA sequences may titer factors necessary for phage development
AbiT	<i>L. lactis</i> W51 plasmid pED1	(51)	Patchy distribution in bacteria	AbiT _i and AbiT _{ii} are fused in many cases; hydrophobic region in AbiT _i protein is important for antiphage defense; interferes with phage DNA replication; AbiT _{ii} domain could fused to HEPN domain and DNA-binding HHH domain
AbiU1/ AbiU2 RloA	<i>L.lactis subsp. lactis</i> UK21371 Plasmid pND001	(52)	Abundant in bacteria (AbiU1); patchy distribution in bacteria (AbiU2)	AbiU1/AIPR N-terminal domain PD-(D/E)xK-family nuclease; C-terminal domain, ParB-like nuclease fold (DGQHR/AIPR domain); AbiU2: HEPN domain (2)
AbiV	<i>L.lactis subsp. cremoris</i> MG136	(53,54)	Patchy distribution in	AbiV belongs to the HEPN superfamily (2); <i>Sav</i> is a phage gene, that is affected by AbiV mechanism

	chromosomally-encoded		bacteria	
AbiZ	<i>L.lactis</i> DPC3147 plasmid pTR2030	(55)	<i>Lactococcus</i> and <i>Enterococcus</i> only	Small, mostly helical protein. AbiZ possibly interacts with holin to cause premature cell lysis
RexA/ RexB	bacteriophage lambda	(56)	RexA shows a patchy distribution in bacteria; only a few homologs of RexB identified	RexA senses infection and activates RexB, a membrane protein that reduces membrane potential and causes cell death; RIIA and RIIB proteins of phage T4 abrogate this effect
PrrC/ RloC	<i>Escherichia coli</i> K-12	(57,58)	Patchy distribution in bacteria	ATP-dependent anticodon tRNase associated with type Ic R-M systems; N-terminal domain: AAA superfamily ATPase (COG4694); C-terminal tRNase domain is a diverged member of the HEPN superfamily (2); PrrC is activated by Stp, the T4-encoded PrrI restriction nuclease inhibitor
Lit	<i>Escherichia coli</i> K-12	(59)	Mostly in Proteobacteria and several Bacteroidetes	Metallopeptidase U49 homologous to DUF955 associated with toxin-antitoxin systems; activated by the major head protein of T4 phage; cleaves host translation factor EF-Tu leading to cell death
PifA	<i>Escherichia coli</i> K-12 F-plasmid	(60)	Abundant in bacteria	Membrane-associated P-loop NTPase (COG4928), involved in phage T7 exclusion through membrane damage; <i>E.coli</i> membrane protein FxsA sequesters PifA and prevents phage exclusion (61)

^aIdentification of protein domains and functional prediction for experimentally uncharacterized proteins was based on the results of protein sequence and structure database searches using the PSI-BLAST and HHPred methods (5,6).

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