#### **Supporting Information:**

# Divergence of Structure and Function in the Haloacid Dehalogenase Enzyme Superfamily: *Bacteroides Thetaiotaomicron* BT2127 is an Inorganic Pyrophosphatase<sup>+</sup>

Hua Huang<sup>1</sup>, Yury Patskovsky<sup>2</sup>, Rafael Toro<sup>2</sup>, Jeremiah D. Farelli<sup>3</sup>, Chetanya Pandya<sup>4</sup>, Steve Almo<sup>2\*</sup>, Karen N. Allen<sup>3\*</sup>, and Debra Dunaway-Mariano<sup>1\*</sup>

<sup>1</sup>Department of Chemistry and Chemical Biology, University of New Mexico, Albuquerque, New Mexico 87131; <sup>2</sup> Department of Biochemistry, Albert Einstein College of Medicine, Jack and Pearl Resnick Campus, 1300 Morris Park Avenue, Bronx, NY 10461; <sup>3</sup>Department of Chemistry, Boston University 590 Commonwealth Avenue, Boston, MA 02215-2521, <sup>4</sup>Bioinformatics Graduate Program, Boston University, 24 Cummington Street Boston, MA 02215-2521

\*To whom correspondence should be addressed regarding X-ray structure determination (S.A. or K.N.A.) or kinetic analyses (D.D.-M.)

Contents: 20 pages total, which contain Tables S1-S8 and Figures S1-S9.

BT2127	PDB	Ligand	Crystallization conditions
	code		
WT	3QU2	citrate, Cl <sup>-</sup> ,	0.1 M sodium citrate, pH 5.6, 30% PEG4000, 0.2 M ammonium acetate, 5 mM, MgCl <sub>2</sub> , 294 K
		glycerol, Mg <sup>2+</sup>	
WT	3QXG	acetate, Ca <sup>2+</sup> ,	0.1 M sodium acetate, 0.2 M calcium acetate, 30% PEG400, 5 mM MgCl <sub>2</sub> , 294 K
		$Mg^{2+}, PO_4^{2-},$	
		tartrate	
WT	3QUQ	Cl <sup>-</sup> , formate, Mg <sup>2+</sup> ,	0.1 M Bis-Tris, pH 6.5, 25% PEG3350, 0.2 M MgCl <sub>2</sub> , 294 K
		unknown	
WT	3QX7	$Mg^{2+}, PO_4^{2-}$	0.056 M sodium phosphate monobasic, pH 8.2, 1.34 M potassium phosphate dibasic,
			5 mM MgCl <sub>2</sub> , 294 K
D11N	3QU5	Cl	0.1 M Bis-Tris, pH 6.5, 25% PEG3350, 0.2 M MgCl <sub>2</sub> , 294 K
D13A	30U4	Acetate, Cl <sup>-</sup> ,	0.1 M MES, pH 6.0, 20% PEG8000, 0.2 M calcium acetate, 5 mM MgCl <sub>2</sub> ,
		$Mg^{2+}$	291 K
D13N	3QU9	Cl <sup>-</sup> , glycerol, Mg <sup>2+</sup> ,	0.1 M potassium sodium tartrate, pH 8.0, 0.1 M imidazole, 0.2 M NaCl,
		tartrate	5 mM MgCl2, 294 K
D13N	3QU7	Acetate, Ca <sup>2+</sup> ,	0.1 M sodium acetate, pH 4.5, 30% PEG400, 0.2 M calcium acetate,
		PO <sub>4</sub> <sup>2-</sup>	5 mM MgCl <sub>2</sub> , 294 K
D13N	3QUT	$Cl^{-}$ , $Mg^{2+}$ , malate	0.15 M Malic acid, pH 7, 20% PEG3350, 5 mM MgCl <sub>2</sub> , 294 K
E47D	3R9K	$SO_4^{2-}$	0.1 M Tris-HCl, pH 8.5, 30% PEG4000, 0.2 M LiSO <sub>4</sub> , 5 mM MgCl <sub>2</sub> , 294 K
E47N	30YP	Ca <sup>2+</sup> Cl <sup>-</sup> glycerol	0.1 M MES pH 6.0 20% PEG8000 0.2 M calcium acetate 5 mM MgCl <sub>2</sub>
,		$PO_4^{2^-}$ , unknown	294 K
E47N	3QUC	SO <sub>4</sub> <sup>2-</sup>	0.1 M Tris-HCl, pH 8.5, 30% PEG4000, 0.2 M LiSO <sub>4</sub> , 5 mM MgCl <sub>2</sub> , 294 K
E47A	3QUB	SO <sub>4</sub> <sup>2-</sup>	0.1 M Tris-HCl, pH 8.5, 30% PEG4000, 0.2 M LiSO <sub>4</sub> , 5 mM MgCl <sub>2</sub> , 294 K

 Table S1. Crystallization conditions used for wild-type and mutant BT2127.

Table S2. Data collection and refinement statistics for wild-type BT2127. Numbers in parenthesis are those for the high resolution shell.

PDB ID	3QUQ	3QU2	3QX7	3QXG
Cap orientation	Opened	Closed	Closed	Closed
Space group	P212121	C2	P3121	C2
Unit cell dimensions (Å)	-	-	-	-
-a	45.20	137.60	84.58	114.07
-b	65.34	71.76	84.58	70.59
-C	75.62	114.53	79.27	76.32
Cell angles (degrees)	-	-	-	-
-alpha	90.00	90.00	90.00	90.00
-beta	90.00	105.80	90.00	119.77
-gamma	90.00	90.00	120.00	90.00
Molecules per asymmetric unit	1	4	1	2
Solvent content	38.42	51.25	61.05	50.18
Matthew's Coefficient	2.00	2.52	3.16	2.47
Ligands	Cl <sup>-</sup> , formate, Mg <sup>2+</sup> , unknown	Citrate, Cl <sup>-</sup> , glycerol, Mg <sup>2+</sup>	Mg <sup>2+</sup> , PO <sub>4</sub> <sup>2-</sup>	Acetate, Ca <sup>2+</sup> , Mg <sup>2+</sup> , PO4 <sup>2-</sup> , tartrate
X-ray source	NSLS X29A	NSLS X29A	NSLS X29A	NSLS X29A
Wavelength	1.0750	1.0809	0.9791	0.9791
Resolution	49.45-1.65	40.00-1.94	20.00-2.00	50.00-1.24
Reflections	28,023	79,445	22,599	147,352
Completeness (%)	99.2 (92.1)	99.3 (93.1)	95.00	99.0 (86.0)
I/sigma (I)	6.10 (3.00)	3.40 (1.20)	7.40 (1.00)	7.40 (0.90)
R <sub>sym</sub>	0.092 (0.530)	0.124 (0.800)	0.078 (0.900)	0.056 (0.920)
R <sub>work</sub> (R <sub>free</sub> )	16.4 (17.8)	23.4 (27.5)	19.1 (24.3)	15.2 (18.2)
R <sub>free</sub> reflections (%)	683 (3.2%)	2349 (3.0%)	683 (3.2%)	4418 (3.0%)
Average B factor (overall)	23.69	20.31	58.11	22.23
-amino acid residues	22.54	19.78	58.15	20.26
-waters	33.12	25.21	56.95	35.98
-ligands	26.74, 13.70, 47.62, 13.19	43.90, 32.70, 32.49, 13.95	51.78, 58.89	19.22, 18.43, 24.61, 21.26, 21.78
Root-mean square deviation	-	-	-	-
-bond lengths	0.011	0.010	0.011	0.012
-bond angles	1.293	1.273	1.293	1.411
Ramachandran favored/allowed (%)	99.1 (0.9)	99.1 (0.9)	98.7 (1.3)	98.8 (1.2)
Number of solvent molecules	98	649	98	525

**Table S3**. Data collection and refinement statistics for BT2127 D11N. Numbers in parenthesis are those for the high resolution shell

PDB ID	3QU5
Mutation	D11N
Cap orientation	Closed
Space group	P21
Unit cell dimensions (Å)	-
-a	42.80
-b	77.21
-c	70.76
Cell angles (degrees)	-
-alpha	90.00
-beta	90.41
-gamma	90.00
Molecules per asymmetric unit	2
Solvent content	45.44
Matthew's Coefficient	2.25
Ligands	Cl
X-ray source	NSLS X29A
Wavelength	0.9786
Resolution	40.00-1.24
Reflections	129,987
Completeness (%)	96.3 (68.4)
I/sigma (I)	8.00 (1.40)
R <sub>sym</sub>	0.043 (0.550)
R <sub>work</sub> (R <sub>free</sub> )	13.0 (16.0)
R <sub>free</sub> reflections (%)	3775 (3.0%)
Average B factor (overall)	22.35
-amino acid residues	19.62
-waters	35.36
-ligands	23.42
Root-mean square deviation	-
-bond lengths	0.011
-bond angles	1.407
Ramachandran favored/allowed (%)	99.4 (0.6)
Number of solvent molecules	764

PDB ID	3QU4	3QUT	3QU7	3QU9
Mutation	D13A	D13N	D13N	D13N
Cap orientation	Closed	Opened	Closed	Closed
Space group	P1	P212121	C2221	P3121
Unit cell dimensions (Å)	-	-	-	-
-a	69.94	45.47	72.55	84.17
-b	76.22	65.40	136.87	84.17
-c	95.59	76.17	114.83	79.36
Cell angles (degrees)	-	-	-	-
-alpha	89.97	90.00	90.00	90.00
-beta	89.97	90.00	90.00	90.00
-gamma	90.00	90.00	90.00	120.00
Molecules per asymmetric unit	8	1	2	1
Solvent content	47.95	38.42	53.48	59.60
Matthew's Coefficient Ligands	2.36 Acetate, Cl <sup>-</sup> , Mg <sup>2+</sup> Rotating	2.00 Cl <sup>-</sup> , Mg <sup>2+</sup> , malate	$\begin{array}{c} 2.64\\ \text{Acetate, Ca}^{2+},\\ \text{PO}_4^{2-}\end{array}$	3.04 Cl <sup>-</sup> , glycerol, Mg <sup>2+</sup> , tartrate
X-ray source	Anode/Rigaku	NSLS X29A	NSLS X29A	NSLS X29A
Wavelength	1.5418	0.9791	0.9792	1.0750
Resolution	50.00-2.00	50.00-1.50	50.00-1.90	40.00-1.87
Reflections	133,986	37,187	45,325	27,292
Completeness (%)	93.2 (83.9)	100.0 (100.0)	99.8 (99.5)	99.1 (92.8)
I/sigma (I)	4.50 (0.60)	7.40 (3.00)	7.70 (2.00)	8.10 (1.00)
R <sub>sym</sub>	0.101 (0.730)	0.067 (0.600)	0.053 (0.680)	0.069 (0.820)
R <sub>work</sub> (R <sub>free</sub> )	21.8 (28.6)	14.5 (17.2)	19.0 (22.6)	20.9 (25.2)
R <sub>free</sub> reflections (%)	3211 (3.0%)	1152 (3.1%)	1408 (3.1%)	826 (3.2%)
Average B factor (overall)	36.17	25.13	47.74	51.00
-amino acid residues	36.24	23.78	47.63	50.92
-waters	35.32	35.55	49.74	52.02
-ligands	42.94, 32.50, 9.15	27.87, 14.21, 16.22	38.21, 37.62, 37.76	52.69, 80.66, 39.26, 40.96
Root-mean square deviation	-	-	-	-
-bond lengths	0.009	0.011	0.009	0.011
-bond angles	1.177	1.387	1.202	1.352
Ramachandran favored/allowed (%)	98.3 (1.7)	98.7 (1.3)	98.7 (1.3)	97.0 (3.0)
Number of solvent molecules	982	243	275	110

**Table S4.** Data collection and refinement statistics for BT2127 D13. Numbers in parenthesis are those for the high resolution shell

#### Table S5. Data collection and refinement statistics for BT2127 E47.

PDB ID	3QUB	3R9K	3QUC	3QYP
Mutation	E47A	E47D	E47N	E47N
Cap orientation	Closed	Closed	Closed	Closed
Space group	P3121	P3121	P3121	P21
Unit cell dimensions (Å)	-	-	-	-
-a	85.38	84.60	84.72	42.94
-b	85.38	84.60	84.72	77.18
-c	78.92	79.24	79.21	70.80
Cell angles (degrees)	-	-	-	-
-alpha	90.00	90.00	90.00	90.00
-beta	90.00	90.00	90.00	90.21
-gamma	120.00	120.00	120.00	90.00
Molecules per asymmetric unit	1	1	1	2
Solvent content	59.60	59.60	59.60	43.50
Matthew's Coefficient	3.04	3.04	3.04	2.17
Ligands	SO4 <sup>2-</sup>	SO4 <sup>2-</sup>	$\mathrm{SO_4}^{2-}$	Ca <sup>2+</sup> , Cl <sup>-</sup> , glycerol, PO <sub>4</sub> <sup>2-</sup> , unknown
X-ray source	NSLS X29A	NSLS X29A	NSLS X29A	NSLS X29A
Wavelength	1.0750	1.0750	1.0750	0.9792
Resolution	40.00-1.90	50.00-1.80	50.00-1.87	50.00-1.60
Reflections	27,369	30,588	27,575	61,148
Completeness (%)	99.1 (99.6)	99.7 (100.0)	97.2 (95.3)	95.3 (69.0)
I/sigma (I)	4.60 (1.00)	8.50 (1.20)	4.30 (1.20)	9.50 (1.00)
R <sub>sym</sub>	0.137 (0.770)	0.071 (0.800)	0.076 (.760)	0.065 (0.800)
R <sub>work</sub> (R <sub>free</sub> )	19.8 (24.3)	19.0 (22.7)	21.6 (28.3)	18.5 (21.7)
R <sub>free</sub> reflections (%)	846 (3.2%)	966 (3.2%)	703 (3.2%)	1776 (3.1%)
Average B factor (overall)	43.06	44.14	57.09	29.12
-amino acid residues	42.58	43.57	57.04	28.16
-waters -ligands	47.80 32.25	49.74 38.55	58.06 58.69	36.31 23.05, 48.68, 56.89, 23.89, 41 27
Root-mean square deviation	-	-	-	-
-bond lengths	0.010	0.011	0.010	0.012
-bond angles	1.253	1.225	1.256	1.343
Ramachandran favored/allowed (%)	99.1 (0.9)	98.3 (1.7)	98.7 (1.3)	99.6 (0.4)
Number of solvent molecules	191	192	127	467

**Table S6**. The apparent first order rate constants for BT2127 catalyzed hydrolysis of phosphate esters and anhydrides at pH 7.5 and 25 °C. Reaction solutions initially contained 0.3 mM substrate, 8.4  $\mu$ M BT2127, 1 mM MgCl<sub>2</sub>, 1.0 unit/mL purine nucleoside phosphorylase and 0.2 mM MESG in 50 mM Tris (pH 7.5). The k<sub>obs</sub> value was calculated by dividing the initial velocity of the reaction by the enzyme concentration.

Substrate	k <sub>obs</sub> (min <sup>-1</sup> )	Substrate	$k_{obs}$ (min <sup>-1</sup> )
Pyrophosphate	19	β-fucose-1-phosphate	0.10
Imidodiphosphate	0.06	GMP	0.38
Glyceraldehyde 3-phosphate	0.17	UDP	0.17
Glycerate-3-phosphate	0.31	ATP	0.20
D-erythrose-4-phosphate	0.20	dATP	0.18
Dihydroxyacetone phosphate	0.30	Farnesylpyrophosphate	0.059
Glycerol-2-phosphate	0.49	PLP	NA <sup>a</sup>
Glucose-1-phosphate	0.12	СТР	NA <sup>a</sup>
Glucose-6-phosphate	0.19	Serine-3-phosphate	NA <sup>a</sup>
Fructose-6-phosphate	0.32	Threonine phosphate	NA <sup>a</sup>
$\alpha$ -fucose-6-phosphate	0.21		

<sup>a</sup> NA represents no detectable activity.

**Table S7**. The apparent first order rate  $(k_{obs} (min^{-1}))$  constants for BT2127 catalyzed hydrolysis of phosphate esters and anhydrides at pH 7.5 and 25 °C. Reaction solutions initially contained 300  $\mu$ M substrate, 8.4  $\mu$ M mutant BT2127, 1 mM MgCl<sub>2</sub>, 1.0 unit/mL purine nucleoside phosphorylase and 0.2 mM MESG in 50 mM Tris (pH 7.5). The  $k_{obs}$  value was calculated by dividing the initial velocity of the reaction by the enzyme concentration.

Substrate	wild-type	E47A	E47N	M20A	M20L	M20K
pyrophosphate	1.9 x 10 <sup>1</sup>	4.7 x 10 <sup>-4</sup>	5.5 x 10 <sup>-4</sup>	8.4 x 10 <sup>-4</sup>	3.1 x 10 <sup>-3</sup>	6.5 x 10 <sup>-3</sup>
D-ribose-5-P	2.0 x10 <sup>-1</sup>	2.5 x 10 <sup>-4</sup>	7.3 x 10 <sup>-4</sup>	1.3 x10 <sup>-3</sup>	2.1 x 10 <sup>-3</sup>	2.3 x 10 <sup>-4</sup>
glycerol-1-P	3.5 x 10 <sup>-1</sup>	4.4 x 10 <sup>-4</sup>	4.6 x 10 <sup>-4</sup>	4.8 x 10 <sup>-3</sup>	4.2 x 10 <sup>-3</sup>	4.0 x 10 <sup>-3</sup>
P-nitrophenylphosphate	5.8 x 10 <sup>-3</sup>	4.2 x 10 <sup>-4</sup>	3.8 x 10 <sup>-4</sup>	2.1 x 10 <sup>-5</sup>	2.6 x 10 <sup>-3</sup>	4.6 x 10 <sup>-3</sup>
fructose-6-P	5.3 x 10 <sup>-3</sup>	2.5 x 10 <sup>-4</sup>	9.5 x 10 <sup>-5</sup>	4.4 x 10 <sup>-4</sup>	1.6 x 10 <sup>-3</sup>	3.6 x 10 <sup>-4</sup>
UMP	1.5 x 10 <sup>-1</sup>	2.16 x 10 <sup>-4</sup>	2.6 x10 <sup>-4</sup>	3.16x10 <sup>-4</sup>	1.6 x 10 <sup>-3</sup>	3.7 x 10 <sup>-3</sup>
imidodiphosphate	1.03 x 10 <sup>-3</sup>	6.2 x 10 <sup>-5</sup>	2.2 x 10 <sup>-4</sup>	6.0 x 10 <sup>-3</sup>	3.1 x 10 <sup>-3</sup>	4.4 x 10 <sup>-3</sup>
glucose-1-P	2.0 x 10 <sup>-3</sup>	1.1 x 10 <sup>-4</sup>	9.5 x 10 <sup>-5</sup>	8.4 x 10 <sup>-4</sup>	1.3 x 10 <sup>-3</sup>	2.9 x 10 <sup>-3</sup>
glucose-6-P	3.2 x10 <sup>-3</sup>	1.9 x 10 <sup>-4</sup>	2.9 x 10 <sup>-4</sup>	2.8 x 10 <sup>-4</sup>	6.2 x 10 <sup>-4</sup>	3.7 x 10 <sup>-3</sup>
β-glucose-1,6-P	4.1 x 10 <sup>-3</sup>	3.0 x 10 <sup>-5</sup>	2.8 x 10 <sup>-5</sup>	6.3 x 10 <sup>-4</sup>	6.7 x 10 <sup>-4</sup>	1.5 x 10 <sup>-4</sup>
α-fucose 1-P	3.5 x 10 <sup>-3</sup>	2.3 x 10 <sup>-4</sup>	9.2 x 10 <sup>-4</sup>	$2.5 \times 10^{-4}$	2.1 x 10 <sup>-3</sup>	1.6 x 10 <sup>-3</sup>
β-fucose 1-P	1.7 x10 <sup>-3</sup>	5.5 x 10 <sup>-4</sup>	3.2 x 10 <sup>-4</sup>	2.3 x 10 <sup>-4</sup>	1.9 x 10 <sup>-3</sup>	9.1 x 10 <sup>-4</sup>
glycerol-2-P	8.16 x 10 <sup>-3</sup>	2.1 x 10 <sup>-4</sup>	2.7 x 10 <sup>-4</sup>	1.6 x 10 <sup>-4</sup>	1.6 x 10 <sup>-3</sup>	3.7 x 10 <sup>-3</sup>
serine-3-P	3.3 x 10 <sup>-6</sup>	1.4 x 10 <sup>-4</sup>	4.1 x 10 <sup>-4</sup>	3.5 x 10 <sup>-4</sup>	1.0 x 10 <sup>-3</sup>	3.5 x 10 <sup>-3</sup>

PDB	Z-score	<u>Organism</u>	Name
3DV9	14.7	Bacteriodes vulgatis	putative BPGM
3NAS	10.6	Bacillus subtilis	putative BPGM
1LVH	10.2	Lactoccocus lactis	BPGM
3D6J	10.2	Bacteriodes fragilis	putative HAD member
2HSZ	9.5	Haemophilus somnus	predicted phosphatase
2HDO	9.2	Lactobacillus plantarum	putative phosphoglycolate phosphatase
3MC1	8.8	Clostridium acetobutylicum	predicted phosphatase
2AH5	8.7	Streptococcus pneumoniae	putative HAD member
2G07	8.3	Streptococcus pneumoniae	putative HAD member
1RDF	7.8	Bacillus cereus	phosphonoacetaldehyde hydrolase
3KBB	7.4	Thermotoga maritima	putative BPGM
2FI1	7.4	Streptococcus pneumoniae	putative hydrolase
2HI0	7.4	Lactobacillus delbrueckii	putative phosphoglycolate phosphatase
1TE2	7.3	Escherichia coli K12	putative phosphatase Ynic
2HCF	7.3	Chlorobium tepidum	putative HAD member
3L5K	6.8	Homo sapiens	putative HAD member
2NYV	6.2	Aquifex aeolicus	putative phosphoglycolate phosphatase
2HOQ	5.1	Pyrococcus Horikoshii	putative HAD member
3E58-	5	Streptococcus thermophilus	putative BPGM
2FDR	4.5	Agrobacterium tumefaciens	putative HAD member
3ED5	4.5	Bacillus subtilis	putative HAD member
3IRU	4	Oleispira antarctica	putative phosphonoacetaldehyde hydrolase

## **Table S8**. Structures of HADSF proteins that have cap domains similar to that of BT2127.



**Figure S2.** The pH-rate profiles measured for BT2127 catalyzed hydrolysis of pyrophosphate. (See Materials and Methods for details).



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**Figure S3**. Double reciprocal plot of the initial velocities BT2127 catalyzed hydrolysis of inorganic pyrophosphate at varying concentration (3, 5, 8, 10, 15, 20  $\mu$ M) measured as a function of imidodiphosphate concentration (0  $\mu$ M, 10  $\mu$ M, 35  $\mu$ M, 50  $\mu$ M). Reaction solutions contained 1 mM MgCl<sub>2</sub>, 0.2 mM MESG and 1.0 unit/mL purine nucleoside phosphorylase in 50 mM Tris (pH 7.5; 25 °C). Data were fitted to equation 2.



Figure S4. (Top) Superposition of BT2127 (gray ribbon) bound to phosphate and  $Mg^{2+}$  (magenta sphere) (PDB ID 3QX7) and  $\beta$ -PGM (cyan ribbon) bound to  $Mg^{2+}$  and  $\beta$ -glucose 1,6-(bis)phosphate (PDB ID 1008). (Bottom) The active site of the overlayed structures.



## Figure S5. Multiple alignment of the amino acid sequences of BT2127 orthologues.

lc1 12539			1
			÷
1c1 12539			MRKK
g1   2934/53/			MRKK
g1 20001			MDK K
g1 2 5 3 5 3 7 6 6			MKK K
gi   260174129			MKK
gil237720029			MKKK
gi 160885231			MKKK
gi 294644124			MKKK
gi 53715098			MFQEAIAQYLKQNH
gi 255011243			MFQEAITQYLQQNH
gi 60683056			
gi 167764833	MCNIKR	LFLDSQLSVLYSPISNFLFSI	YQVFKEAISRYLREHG
gi 329957690			MFKESITRYLKKHG
g1 189463942			MFQEAIARYLQSSG
g1   224536081			MFQEAISRYLQSSG
g1   160889281	MRIERWLHNKCEENR	SPILNSLFI.IPAFLNSQSPI	MEE VATEDVIKHNG
g1 329960268			MEE ESITDVIEKHC
gi   218128650	MTIFLEE	SKFEYRFCVILCPIOOOT	. MFE VAISBYLKHHG
gi 319903121			. MFE ESIARYLEKHG
gi 212691210			MFKEAINNYLHAHG
gi 150006590			MFKEAINNYLHTHG
gi 198275658			MFQQEINQYLTTHH
gi 333031526			MYKQQIINYLTQHK
gi 189459664			MFQQAIENYLTTHH
gi 154493629			MIQEAIAQYLQKQR
gi 218262603			MIQEAIARYLQKQQ
gi 150006815			MIQEAIIRYLRKHR
g1 313205499			MFTAEIEKFIRSKN
g1   260885482			MMNDYIQAIQNYLKDHG
g1 2 90 5 7 2 10 1			MNG
91/2540/4401			
1-1-60530	β1	α1	α2 α.
lc1 12539		αl <u>0000000000000</u> 20 30	α2 α΄. <u>000000</u> <u>0000000</u> 40 <u>50</u>
1c1 12539		αι 20000000000000 2000000000000000000000	α2 α. <u>0000000</u> <b>40</b> <b>50</b> <b>1</b> <b>1</b> <b>1</b> <b>1</b> <b>1</b> <b>1</b> <b>1</b> <b>1</b>
lcl 12539 lcl 12539	βI 10 LKAV LFDMDGVLF	α Ι 20000000000000000 2000000000000000000	α2 α. 000000 000000 40 50 SREEAYMHEGRTGASTINI
<i>lcl 12539</i> lcl 12539 gi 29347537 gi 253570881	βΙ 10 LKAVLFDMDGVLF LKAVLFDMDGVLF IKAVLFDMDGVL	α Ι 200000000000000 20 ΝSMPYHSEAWHQVMKTHGIDI NSMPYHSEAWHQVMKTHGIDI NSMPYHSEAWHQVMKTHGIDI	α2 000000 40 50 SREEAYMHEGRTGASTINI SREEAYMHEGRTGASTINI SREEAYMHEGRTGASTINI SREEAYMHEGRTGASTINI
<i>lcl</i>   <i>12539</i> lcl 12539 gi 29347537 gi 253570881 gi 258383766	βl 10 LKAV LPDMDGVLF LKAV LPDMDGVLF LKAV LPDMDGVLF LKAV LPDMDGVLF	αl 200000000000000 2039 NSMPYHSEAWHQVMKTHGLDI NSMPYHSEAWHQVMKTHGLDI NSMPYHSEAWHQVMKTHGLDI NSMPYHSEAWHQVMKTHGLDI	α2 α΄ 000000 40 50 SREEAYMHEGRTGASTINI SREEAYMHEGRTGASTINI SREEAYMHEGRTGASTINI SREEAYMHEGRTGASTINI
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<pre>lcl 12539 lcl 12539 gi 29347537 gi 253570881 gi 298383766 gi 153808810 gi 260174129</pre>	βI 10 . LKAV LFDMD GVL F . LKAV LFDMD GVL F . LKAV LFDMD GVL F . LKAV LFDMD GVL F . LKAV LFDMD GVL F	α1 2000000000000 20 NSMPYHSEAWHQVMKTHGLDI NSMPYHSEAWHQVMKTHGLDI NSMPYHSEAWHQVKKTHGLDI NSMPYHSEAWHKVKKSHGLTI SMPYHSEAWHKVKKSHGLTI	a2 c) a c) a c) c) c) c) c) c) c) c) c) c)
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lcl 12539 gi]29347537 gi]253570881 gi]298383766 gi]153808810 gi]260174129 gi]20174029 gi]160885231	β 10 LKAV LFDMDGVLF LKAV LFDMDGVLF LKAV LFDMDGVLF LKAV LFDMDGVLF LKAV LFDMDGVLF LKAV LFDMDGVLF LKAV LFDMDGVLF	α1 20000000000000 20 30 NSMPYHSEAWHQVMKTHGLDI NSMPYHSEAWHQVMKTHGLDI NSMPYHSEAWHQVMKTHGLDI NSMPYHSEAWHQVMKTHGLDI DSMPYHSEAWHKVMKSHGLTI DSMPYHSEAWHKVMKSHGLTI DSMPYHSEAWHTVMKSHGLTI	α2 α΄ 000000 40 50 S R E E A Y M H E G R T G A S T I N I S R E E A Y M H E G R T G A S T I N I S R E E A Y M H E G R T G A S T I N I S R E E A Y M H E G R T G A S T I N I S R E E A Y M H E G R T G A S T I N I S R E E A Y M H E G R T G A S T I N I S C E E A Y M H E G R T G A S T I N I S R E E A Y M H E G R T G A S T I N I S R E E A Y M H E G R T G A S T I N I S R E E A Y M H E G R T G A S T I N I
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lcl 12539 gi 29347537 gi 253570881 gi 298383766 gi 153808810 gi 260174129 gi 237720029 gi 160885231 gi 294644124 gi 53715098 gi 255011243	β ι LKAV LPDMDGVLF LKAV LPDMDGVLF LKAV LPDMDGVLF LKAV LPDMDGVLF LKAV LPDMDGVLF LKAV LPDMDGVLF LKAV LPDMDGVLF LKAV LPDMDGVLF LKAV LPDMDGVLF QLKSV LFDMDGVLF QLKSV LFDMDGVLF	α1 2000000000000000 20 30 NSMPYHSEAWHQVMKTHGLDI NSMPYHSEAWHQVMKTHGLDI NSMPYHSEAWHQVMKTHGLDI NSMPYHSEAWHKVMKSHGLTI DSMPYHSEAWHKVMKSHGLTI DSMPYHSEAWHKVMKSHGLTI DSMPYHSEAWHTVMKSHGLTI DSMPYHSEAWHTVMKSHGLTI DSMPYHSEAWHTVMKSHGLTI NSMPYHAEAWHKTMKAHGLNI NSMPYHAEAWHKTMEAHGLNI	α2         α2           40         50           S         REEAYMHEGRTGASTINI           S         REEAYHEGRTGASTINI           S         REEAYHEGRTGASTINI
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<pre>Lcl 12539 gi 29347537 gi 253570881 gi 298383766 gi 153808810 gi 260174129 gi 237720029 gi 160885231 gi 294644124 gi,53715098 gi 255011243 gi 60683056 gi 167764833 gi 329957690 gi 189463942 gi 224536081 gi 160889281 gi 317475556</pre>	βI . L KAV LFDMD GVL F . LKAV LF F . L	α1 200000000000000 20 30 NSMPYHSEAWHQVMKTHGLDI NSMPYHSEAWHQVMKTHGLDI NSMPYHSEAWHQVMKTHGLDI NSMPYHSEAWHQVMKTHGLDI DSMPYHSEAWHVMKSHGLTI DSMPYHSEAWHVMKSHGLTI DSMPYHSEAWHTVMKSHGLTI DSMPYHSEAWHTVMKSHGLTI DSMPYHAEAWHTVMKSHGLTI DSMPYHAEAWHTVMKSHGLTI DSMPYHAEAWHTVMKSHGLTI NSMPYHAADAWHKVMERHGLHI NSMPYHADAWHKVMERHGLHI NSMPYHADAWHKVMERHGLHI NSMPYHADAWHKVMERHGLHI	a2         a           000000         50           40         50           50         50           SREEAYMESGRTGASTINI         SREEAYMESGRTGASTINI           SREEAYMESGRTGASTINI         SREEAYMESGRTGASTINI           SREEAYMESGRTGASTINI         SREEAYMESGRTGASTINI           SREEAYMESGRTGASTINI         SREEAYMESGRTGASTINI           SREEAYMESGRTGASTINI         SREEAYMESGRTGASTINI           SREEAYMESGRTGASTINI         SREEAYMESGRTGASTINI           SREEAYMESGRTGASTINI         SREEAYMESGRTGAGTINI           SREEAYMESGRTGAGTINI         SREEAYMESGRTGAGTINI           SREEAYMESGRTGAGTINI         SREEAYMESGRTGAATINI           SREEAYMESGRTGAATINI         SREEAYNESGRTGAATINI           SREEAYMESGRTGAATINI         SREEAYNESGRTGAATINI           SREEAYMESGRTGAATINI         SREEAYNESGRTGAATINI
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<pre>Lcl 12539 gi 29347537 gi 253570881 gi 298383766 gi 153808810 gi 260174129 gi 237720029 gi 260174129 gi 237720029 gi 160885231 gi 255011243 gi 53715098 gi 255011243 gi 60683056 gi 167764833 gi 329957690 gi 28463942 gi 224536081 gi 160889281 gi 329960268 gi 28128550 gi 319903121</pre>	βI . L KAV LFDMD GVL F . LKAV LF . LKAV	α1 20 20 30 NSM PYH SEAWHQVMKTHGLDI NSM PYH SEAWHQVMKTHGLDI NSM PYH SEAWHQVMKTHGLDI NSM PYH SEAWHQVMKTHGLDI DSM PYH SEAWHVWKSHGLTI DSM PYH SEAWHVWKSHGLTI DSM PYH SEAWHVWKSHGLTI DSM PYH SEAWHVWKSHGLTI DSM PYH SEAWHVWKSHGLTI DSM PYH SEAWHVWKSHGLTI DSM PYH AEAWHKTMKAHGLNI NSM PYH AEAWHKTMKAHGLNI NSM PYH ADAWHVMERHGLHI NSM PYH ADAWHVMERHGLHI NSM PYH ADAWHVMERHGLHI NSM PYH ADAWHKVMERHGLHI NSM PYH ADAWHVMERHGLHI NSM PYH ADAWHVMERGLHI NSM PYH ADAWHVM	a2         a:           000000         50           50
<pre>lcl 12539 gi 29347537 gi 253570881 gi 298383766 gi 153808810 gi 260174129 gi 237720029 gi 160885231 gi 265011243 gi 53715098 gi 255011243 gi 606830261 gi 167764833 gi 329957690 gi 189463942 gi 214536081 gi 2160889281 gi 216128650 gi 218128650 gi 218128650 gi 218128650 gi 150006590</pre>	βI 10 . LKAVLFDMDGVLF . LKAVLFDMDGVLF 	α1 <u>2000000000000000000000000000000000000</u>	a2         a:           000000         0000000           40         50           50         50           SREEAYMEEGRTGASTINI         NI           SREEAYMEEGRTGASTINI         NI           SREEAYMEEGRTGASTINI         SREEAYMEEGRTGASTINI           SREEAYMEEGRTGASTINI         SREEAYMEEGRTGAATINI           SREEAYMEEGRTGASTINI         SREEAYMEEGRTGAATINI           SREEAYMEEGRTGASTINI         SREEAYMEEGRTGAATINI           SREEAYMEEGRTGAATINI         SREEAYMEEGRTGAATINI           SREEAYMEEGRTGAATINI         SREEAYMEEGRTGAATINI           SREEAYMEEGRTGAATINI         SREEAYMEEGRTGAATINI           SREEAYMEEGRTGAATINI         SREEAYMEEGRTGAATINI           SREEAYMEEGRTGAATINI         SREEAYMEEGRTGAATINI           SREEAYMEEGRTGATINI         SREEAYMEEGRTGAATINI           SREEAYMEEGRTGAATINI         SREEAYMEEGRTGAATINI           SREEAYMEEGRTGAATINI         SREEAYMEE
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<pre>Lcl   12539 gi   29347537 gi   253570881 gi   298383766 gi   153808810 gi   260174129 gi   237720029 gi   160885231 gi   16088526 gi   255011243 gi   255011243 gi   224536081 gi   167764833 gi   329957690 gi   224536081 gi   160889281 gi   224536081 gi   160889281 gi   218128650 gi   329960268 gi   218128650 gi   319903121 gi   150006590 gi   189459664 gi   2845664</pre>	β . L LKAV LFDMD GVL F . LKAV LFDMD GVL F	α1 2000000000000000000 20 30 NSMPYHSEAWHQVMKTHGLDI NSMPYHSEAWHQVMKTHGLDI NSMPYHSEAWHQVMKTHGLDI NSMPYHSEAWHVVMKSHGLTI DSMPYHSEAWHVVMKSHGLTI DSMPYHSEAWHVVMKSHGLTI DSMPYHSEAWHVVMKSHGLTI DSMPYHSEAWHVVMKSHGLTI DSMPYHSEAWHVVMKSHGLTI DSMPYHAEAWHKVMKSHGLTI DSMPYHAEAWHKTMKAHGLNI NSMPYHAADAWHVMERHGLHI NSMPYHADAWHVMERHGLHI NSMPYHADAWHVMERHGLHI NSMPYHADAWHVMERHGLHI NSMPYHADAWHVMERHGLHI NSMPYHADAWHVMERHGLHI NSMPYHADAWHKVMERHGLHI NSMPYHADAWHKVMERHGLHI NSMPYHADAWHKVMERHGLHI NSMPYHADAWHKVMERGIHI NSMPYHADAWHKVMERGIHI NSMPYHADAWHKVMERGIHI NSMPYHADAWHKVMERGIHI NSMPYHADAWHKVMERGIHI NSMPYHADAWHKVMERGIHI NSMPYHADAWHKVMERGIHI NSMPYHADAWHKVMERGIHI NSMPYHADAWHKVMERGIHI NSMPYHADAWHKVMERGIHI NSMPYHADAWHKVMERGIHI NSMPYHADAWHKIMKRFGFGI SMPNHAESWHKIMKRFGFGI SMPNHAEAWNKVMKRHNLDA SMPNHAEAWNKVMKRHNLDA	a2         a2           cooco         cooco           40         50           50
<pre>lcl 12539 gi 29347537 gi 253570881 gi 293883766 gi 153808810 gi 260174129 gi 237720029 gi 160885231 gi 260174129 gi 23775098 gi 255011243 gi 606830281 gi 1606830281 gi 167764833 gi 329957690 gi 189463942 gi 218128650 gi 218128650 gi 218128650 gi 218128650 gi 19803121 gi 150006590 gi 198275658 gi 333031526 gi 159459664 gi 154493662</pre>	βI 10 . LKAV LFDMD GVL F . NLKAV LF . NLKAV LFDMD GVL F . NLKAV LFDMD GVL F . NLKAV LFDMD GVL F . NLKAV LF . N	α1 <u>2000000000000000000000000000000000000</u>	a2         a           000000         0000000           40         50           50         50           SREEAYMESGRTGASTINI         SREEAYMESGRTGASTINI           SREEAYMESGRT
<pre>lcl 12539 gi 29347537 gi 253570881 gi 298383766 gi 153808810 gi 237720029 gi 160885231 gi 294644124 gi 53715098 gi 255011243 gi 60683056 gi 167764833 gi 329957690 gi 189463942 gi 224536081 gi 160889281 gi 317475556 gi 329960268 gi 218128650 gi 319903121 gi 218128550 gi 319903121 gi 212691210 gi 198275658 gi 33031526 gi 198275658 gi 33031526 gi 184493629 gi 154493629 gi 128462603 gi 154493629 gi 218262603</pre>	β . LKAVLFDMDGVLF . NLKAVLFDMDGVLF . NLKAVLF . NLKAVF . NLKAVLF . NLK	al 2000000000000000000000000000000000000	a2         a           50         50           S         S
<pre>Lcl   12539 gi   29347537 gi   253570881 gi   298383766 gi   153808810 gi   260174129 gi   237720029 gi   160885231 gi   255011243 gi   53715098 gi   255011243 gi   6683056 gi   167764833 gi   329957690 gi   189463942 gi   224536081 gi   160889281 gi   160889281 gi   212691210 gi   129903121 gi   212691210 gi   150006530 gi   333031526 gi   333031526 gi   15443622</pre>	β . L LKAV LFDMD GVL F . LKAV LF DMD GV	α1 20 20 30 NSM PYH SEAWHQVMKTHGLDI NSM PYH SEAWHQVMKTHGLDI NSM PYH SEAWHQVMKTHGLDI NSM PYH SEAWHQVMKTHGLDI DSM PYH SEAWHVWKTHGLDI DSM PYH SEAWHVWKSHGLTI DSM PYH SEAWHVWKSHGLTI DSM PYH SEAWHVWKSHGLTI DSM PYH SEAWHVWKSHGLTI DSM PYH SEAWHVWKSHGLTI DSM PYH SEAWHVWKSHGLTI DSM PYH SEAWHVWKSHGLTI NSM PYH AEAWHKVMKGHGLNI NSM PYH AEAWHKTMKAHGLNI NSM PYH ADAWHVWERHGLHI NSM PYH ADAWHVWERHGLHI NSM PYH ADAWHVWERHGLHI NSM PYH ADAWHVWERHGLHI NSM PYH ADAWHKVMERGLHI NSM PYH ADAWHKVMERGLHI NSM PYH ADAWHKVMERGLHI NSM PYH ADAWHKVMERGLHI NSM PYH ADAWHKVMERGLHI NSM PYH ADAWHKVMERGLHI DSM PYH ADAWHKVMERGLHI DSM PNH ADAWHKVMERGLHI DSM PNH ADAWHKVMERGLHI DSM PNH ADAWHKVMERGLHI DSM PNH AEAWHKIMKRFGFGI DSM PNH AEAWHKIMKRFGFGI DSM PNH AEAWHKIMKRFGFGI DSM PNH AEAWHKIMKRFGFGI DSM PNH AEAWNKVM KRHNLD DSM KNH AAAWHEAMKQYGMHI DSM KNH AAAWHEAMKQYGMHI DSM FHA RAWYETATHHQLIS DSM FHA RAWYETATHHQLIS DSM FHA RAWHEVATLHQUT	$a^{2}$ $b^{2}$ $b^{2$
<pre>Lcl   12539 gi   29347537 gi   253570881 gi   298383766 gi   153808810 gi   260174129 gi   237720029 gi   160885231 gi   260174124 gi   53715098 gi   255011243 gi   6088056 gi   167764833 gi   329957690 gi   189463942 gi   224536081 gi   16088281 gi   218128650 gi   319903121 gi   189459624 gi   21826508 gi   15409031526 gi   38045964 gi   154493629 gi   15409645 gi   15409645 gi   15409645 gi   15409645 gi   15409645 gi   150006815 gi   313205499 gi   26885489</pre>	βI IC LKAVLFDMDGVLF LKAVLFDMDGVLF LKAVLFDMDGVLF LKAVLFDMDGVLF LKAVLFDMDGVLF LKAVLFDMDGVLF LKAVLFDMDGVLF LKAVLFDMDGVLF QLKSVLFDMDGVLF RLKAVLFDMDGVLF QLKSVLFDMDGVLF RLKAVLFDMDGVLF RLKAVLFDMDGVLF RLKAVLFDMDGVLF RLKAVLFDMDGVLF RLKAVLFDMDGVLF RLKAVLFDMDGVLF RLKAVLFDMDGVLF NLKAVLF NLKAVLFDMDGVLF NLKAVF NLKAVF NLKAVF NLKAVF NKF NKF NKF NKF NKF NKF NKF NK	α1 20 20 30 NSM PYHSEAWHQVMKTHGLDI NSM PYHSEAWHQVMKTHGLDI NSM PYHSEAWHQVMKTHGLDI NSM PYHSEAWHQVMKTHGLDI NSM PYHSEAWHVMKSHGLTI DSM PYHSEAWHVMKSHGLTI DSM PYHSEAWHVMKSHGLTI DSM PYHSEAWHVMKSHGLTI DSM PYHSEAWHVMKSHGLTI DSM PYHSEAWHVMKSHGLTI DSM PYHSEAWHVMKSHGLTI DSM PYHSEAWHVMKSHGLTI NSM PYHAEAWHKVMKSHGLTI NSM PYHAEAWHKTMKAHGLNI NSM PYHAADAWHVMERHGLHI NSM PYHADAWHKVMERHGLHI NSM PYHADAWHKVMERHGLHI NSM PYHADAWHKVMERHGLHI NSM PYHADAWHKVMERHGLHI NSM PYHADAWHKVMERHGLHI NSM PYHADAWHKVMERHGLHI NSM PYHADAWHKVMERGI SM PYHADAWHTVMR SM PYHADAWHTVMR SM PYHADAWHTVMR SM PYHADAWHTVMER SM PYHADAWHTVMERGI SM PYHADAWHTVMER SM PYHADAWHTVMER SM PYHADAWHTYMER SM PYHADAWHTYME	a2         a           y         50           s         50
<pre>lcl 12539 gi 29347537 gi 253570881 gi 29347537 gi 253570881 gi 293883766 gi 153808810 gi 260174129 gi 237720029 gi 160885231 gi 26048124 gi 53715098 gi 255011243 gi 6068302 gi 16764833 gi 329957690 gi 189463942 gi 224536081 gi 160889281 gi 218128650 gi 319903121 gi 218128650 gi 319903121 gi 218128650 gi 319903121 gi 21826508 gi 33031526 gi 33031526 gi 33031526 gi 319459664 gi 154493629 gi 218262603 gi 154493629 gi 218262603 gi 313205499 gi 260885482</pre>	βI 10 . LKAV LFDMD GVL F . NLKAV F	α1 <u>2000000000000000000000000000000000000</u>	a2         a           000000         0000000           40         50           50         50           SREEAYMESGRTGASTINI         SREEAYMESGRTGASTINI           SREEAYMESGRTGASTINI         SREAYMESGRTGASTINI           SREEAYMESGRTGASTINI         SREAYMESGRTGASTINI           SREEAYMESGRTGASTINI         SREAYMESGRTGASTINI           SREEAYMESGRTGAS
<pre>lcl 12539 gi 29347537 gi 253570881 gi 298383766 gi 153808810 gi 296174129 gi 237720029 gi 160885231 gi 294644124 gi 53715098 gi 255011243 gi 60683056 gi 167764833 gi 329957690 gi 1894639281 gi 317475556 gi 329960268 gi 218128650 gi 319903121 gi 212691210 gi 198275658 gi 319903121 gi 212691210 gi 198275658 gi 319903121 gi 212691210 gi 198275658 gi 319903121 gi 2126085482 gi 31205499 gi 2180685482 gi 313205499 gi 260885482 gi 31205499 gi 260885482 gi 31205499 gi 298372101</pre>	βΙ           10           .	x1202030NSMPYHSEAWHQVMKTHGLDINSMPYHSEAWHQVMKTHGLDINSMPYHSEAWHQVMKTHGLDINSMPYHSEAWHQVMKTHGLDIDSMPYHSEAWHQVMKTHGLDIDSMPYHSEAWHQVMKTHGLDIDSMPYHSEAWHQVMKTHGLDIDSMPYHSEAWHKVMKSHGLTIDSMPYHSEAWHKVMKSHGLTIDSMPYHSEAWHKVMKSHGLTIDSMPYHSEAWHKVMKSHGLTIDSMPYHSEAWHKVMKSHGLTIDSMPYHSEAWHKVMKSHGLTIDSMPYHAEAWHKTMKAHGLNINSMPYHAEAWHKTMKAHGLNINSMPYHAADAWHKVMERHGLHINSMPYHAADAWHKVMERHQLIISMRFHARAWYETATHHQLISSMRFHARAWYETATHHQLISSMRFHARAWYETATHHQLISSMRFHARAWYEANLEYNLEPSMRFHARAWYEANLEYNLEPSMRFHARAWYEANLEYNLEPSMRFHARAWYEANLEYNLEPSMRFHARAWYEANLEYNLEPSMRFHARAWYEANLEYNLEPSMRFHARAWYEANLEYNLEPSMRFHARAWYEANLEYNLEPSMRFHARAWYEANLEYNLEPSMRFHARAWYEANLEYNLEPSMRFHARAWYEANLEYNLEP<	a2         a           40         50           50         50           SREEAYMESGRTGASTINI         50           SREEAYMESGRTGASTINI         10           SREEAYMESGRTGAATINI

# Figure S5 Continued

	α4		α5	β2	α6	α7	η1β3 η2
lc1 12539	± 80	90	<u>00000000000</u> *100 * *	110	0000 120	<u>2222</u> 130	202 <b>-&gt;</b> 202 140
lcl  12253 gi  23347537 gi  253570881 gi  253570881 gi  253570881 gi  253570881 gi  253570881 gi  253570881 gi  26074823 gi  26085231 gi  277029 gi  277029 gi  25011243 gi  60885356 gi  257012433 gi  6088356 gi  2774833 gi  28453424 gi  28453424 gi  28453424 gi  28453424 gi  21826500 gi  31903121 gi  226912100 gi  150006590 gi  158275658 gi  319227658 gi  319227658 gi  319459664 gi  154493629 gi  1520499 gi  218262003 gi  1500485482 gi  208372101 gi  294674461	* B ESIY HEKSILENS ESIY HEKSILENS ESIY HEKSILENS ESIY HEKSILENS ESIY QEKSVLENS ESIY QEKSVLENS ESIY QEKSVLENS ESIY QEKSVLENS ESIY QEKSVLENS ESIY QEKSVLENS ESIY QEKSVLENS ESIY QEKSVLENS ESIY QEKSVLENS ESIY ALEKSIEPNK ESIY ALEKSIEPNK ESIY ALEKSIEPNK ESIY ALEKSIEPNK ESIY ALEKSEEPNK KSIY ALEKSAEPNS ESIY ALEKSAEPNS ESIY ALEKSAEPNS ESIY ALEKSAEPNS ESIY ALEKSAEPNS ESIY ALEKSAEPNS ESIY ALEKSAEPNS ESIY ALEKSAEPNS KSIY EEKSALENS KAIY QAKTEEPNK KAIY QAKTEEPNK KAIY QAKTEEPNK KAIY QAKTEEPNK KAIY QAKTEEPNK KSIY EEKALLENQ KSIY EEKALLENQ QTIY KEKADLENT KSIY EEKALLENQ CISIY CISIY EEKALLENQ CISIY EEKALLENQ CISIY EEKALLENQ CISIY EEKALLENQ CISIY EEKALLENQ CISIY EEKALLENQ CISIY EEKALLENQ CISIY EEKALLENG CISIY EEKALLENG C	Y PEA & R M F Y PEA & R M F H PQA & R M F C P K A & R M F H PE P R M F H SE P R M F S M S M S M S M S M S M S M S M S M	************************************	110 3LTP MVVTGS 3LTP MVVTGS 5LTP MVVTGS 5LTP MVVTGS 5LTP MVVTGS 5LTP MVVTGS 5LTP MVVTGS 5LTP MVVTGS 5LTP MVVTGS 5LIP MVVTGS 5LIP MVVTGS 5LIP MVVTGS 5LIP VLVTGS 5LVP MVVTGS 5LVP MVVTGS 5LVP MVVTGS 5LTP VLVTGS 5LTP VLVTGS 5LTP VLVTGS 5LTP MVVTGS 5LTP MVVTGS 5LQ TLVVTGS 5LQ TLVVTGS		T 3 0 R LE H NF P GM F R LE H NY P GM F R LE H NY P GM F R LE H NY P GM F R LE H NF P GM F R LE H NF P GM F R LE H NF P GM F R LA H NF P G M F R LA H NF P M T F M T F M T F M T F M T F M T F M T F M T F M T F M T F M T F M T F M T F M T F M T F M T F M T F M T	1         1           7         HKE LMVTAFD           7         RELMVTAFD           7         RELMVTAFD <t< th=""></t<>
lc1 12539	α8 ΤΤ <u>00000</u> 150	3 00000 160	η <sup>3</sup> β4	α9 20202020 180	β5 *19#	α10 20200 200	
<i>lcl 12539</i> lcl 12539	۵۵ ۲۳ <u>۵۵۵۵۵</u> ۱۶ <u>۰</u> ۷۸۲ <mark>۲<u>6۲ Β</u>Ν<u>Ρ</u>ΕΡΥΙΜ</mark>	3 00000 160 A <mark>lkkgg.</mark> 1	η3 β4 202 ±7φ ΚΑ DE A VV IE NAP	α9 20000000 180 .GVEAGHKAG	β5 ★19★ IFTIAVN	α10 <u>00000</u> <b>200</b> TGPIDGQVLI	$\frac{\beta 6}{210}$
<i>lcl</i>   <i>12539</i> lcl 12539 gi 29347537 gi25570881	48 TT <u>00000</u> 150 VKYGKPNPEPYLM VKYGKPNPEPYLM	3 00000 160 ALKKGG.I ALKKGG.I	$\eta 3 \qquad \beta 4$ $200 \qquad 170$ KADEAVVIENAP	α9 20000000 180 GVEAGHKAG GVEAGHKAG	β5 ★19★ IFTIAVN IFTIAVN	α10 <u>2000</u> 200 TGP1DGQVLI TGP1DGQVLI TGP1DGQVLI	β6 210 LDAGADLLFPS LDAGADLLFPS
<i>lcl</i>   <i>12539</i> lcl 12539 gi 29347537 gi 253570881 gi 298383766	0000 TT 0000 150 VKYGKENEEPYIM VKYGKENEEPYIM VKYGKENEEPYIM VKYGKENEEPYIM	3 0 0 0 0 0 1 6 0 A L K K G G . I A L K K G G . I A L K K G G . I A L K K G G . F	$\begin{array}{c c} \eta 3 & \beta 4 \\ \hline 0 & 1 \\ \hline 1 &$	α9 180 LOVEAGHKAG GVEAGHKAG GVEAGHKAG GVEAGHKAG	β5 ★199 IFTIAVN IFTIAVN IFTIAVN IFTIAVN	α10 2000 200 10 μ μ σ σ ν μ 10 μ μ σ σ ν μ 10 μ μ σ σ ν μ 10 σ μ μ σ σ ν μ 10 σ μ μ σ σ ν μ	bagaDLLFPS LDAGADLLFPS LDAGADLLFPS LDAGADLLFPS
lcl 12539 gi 29347537 gi 25570881 gi 298383766 gi 153808810 gi 26174129	TT         QOOD           150           VKYGKENEEPYIM	ALKKGG.I ALKKGG.I ALKKGG.I ALKKGG.I ALKKGG.I ALKKGG.I ALKKGG.I	$\eta^3  \beta^4$ $2 \circ 2 \circ 2$ $\pm 7 \circ 2 \circ 2$ KA DE A VVIE NAP $KA DE A VVIE NAPKA DE A IVIE NAPKA DE A VVE NAPKA DE A VVE NAP$	α9 180 180 GVEAGHKAG GVEAGHKAG GVEAGHKAG GVEAGHKAG GVEAGHKAG	β5 *19 IFTIAVN IFTIAVN IFTIAVN IFTIAVN IFTIAVN IFTIAVN IFTIAVN	αl0 2000 200 TGP LD GQVLI TGP LD GQVLI TGP LD GQVLI TGP LD GQVLI TGP LD GQVLI TGP LD GQVLI	β6 210 LDAGADLLFPS LDAGADLLFPS LDAGADLLFPS LDAGADLLFPS LDAGADLLFPS LDAGADLLFPS
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<pre>lcl 12539 lcl 12539 gi 29347537 gi 29347537 gi 298383766 gi 153808810 gi 260174129 gi 237720029 gi 160885231 gi 294644124 gi 53715098</pre>	VKYGKENEEPYIM           VKYGKENEPYIM           VKYGKENEPYIM           VKYGKENEPYIM           VKYGKENEPYIM           VKYGKENEPYIM           VKYGKENEPYIM           VKYGKENEPYIM	3 00000 160 ALKKGG.I ALKKGG.I ALKKGG.I ALKKGG.I ALKKGG.I ALKKGG.I ALKKGG.I ALKKGG.I ALKKGG.I ALKKGG.I	$\eta 3$ $\beta 4$ 0 0 0 $k 7 \phi$ k a DE A VV IE NAP $k a DE A VV IE NAPk a DE A VV IE NAPk A DE A VV E NAPk A DE A VVE NAPk A DE A VVE NAPk A DE A IV E NAPk A DE A IV IE NAP$	a9 180 180 GVEAGHKAG GVEAGHKAG GVEAGHKAG GVEAGHNAG GVEAGHNAG GVEAGHNAG GVEAGHNAG GVEAGHNAG	β5 <b>*19</b> IFTIAVN IFTIAVN IFTIAVN IFTIAVN IFTIAVN IFTIAVN IFTIAVN IFTIAVN IFTIAVN IFTIAVN	α10 <u>2000</u> 2000 TGP LD GQVLI TGP LD GQVLI	β6 21 21 21 21 21 21 21 21 21 21
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gi 160885231	Μ	Q	A	L	S	D	Н	W	D	т	L	F	Е	Κ	Ν	Т											
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gi 255011243	Μ	Q	A	L	С	Е	S	M	Е	Α	L	A	R	F	L	Н	Q	Ρ	Ρ	L	K	Т	Т	Ι	A	D	Ν
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gi 167764833	Μ	Q	A	F	С	D	N	W	Е	A	V	R	D	A	L	A	·	·	S	E	E	•	·	·	·	·	·
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gi 1108275658		5	7	5	14	L. L.	14	Tel I	5	т Т	С Ц	P	0	- -	7	0	ž	υ υ	÷	÷	•	•	•	1		•	•
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Figure S6. Interactions at the BT2127 cap domain (yellow)-catalytic domain (gray) interface.



Figure S7. Alignment of the BT2127 sequence with the sequences of more distantly related homologues that do not conserve the marker residue Asn172.

33849/1-224		αl 000000000000000000000000000000000000	α2 2020202	α3
33849/1-224 313635524/1-220 16802022/1-220 47097361/1-220 2289436073/1-220 224498331/1-220 254851866/1-220 46990920/1-220 163788164/1-220 254827399/1-220 254827399/1-220 254827399/1-220		FISM PY BSEAN HOVNKTHO TDTAHYBYLAMKKTAESIC TDTAHYBYLAMKKTAESIC TDTAHYBYLAMKKTAESIC TDTAHYBYLAMKKTAESIC TDTAHYBYLAMKKTAESIC TDTAHYBYLAMKKTAESIC TDTAHYBYLAMKKTAESIC TDTAHYBYLAMKKTAESIC TDTAHYBYLAMKKTAESIC TDTAHYBYLAMKKTAESIC TDTAHYBYLAMKKTAESIC TDTAHYBYLAMKKTAESIC TDTAHYBYLAMKKTAESIC TDTAEYBYQAMKATATEC VDTPLEKKAYYKMFEDS TDTAEYBYQAMKATATEC	$ \begin{array}{c} \textbf{S} \textbf{L} \textbf{D} \textbf{L} \textbf{S} \textbf{R} \\ \textbf{S} \textbf{T} \textbf{E} \in \textbf{F} \textbf{D} \textbf{C}  \textbf{Y} \textbf{N} \textbf{.} \textbf{.} \textbf{E} \textbf{N} \\ \textbf{S} \textbf{T} \textbf{E} \in \textbf{F} \textbf{D} \textbf{C}  \textbf{F} \textbf{N} \textbf{.} \textbf{.} \textbf{E} \textbf{N} \\ \textbf{S} \textbf{T} \textbf{E} \in \textbf{F} \textbf{D} \textbf{C}  \textbf{A} = \textbf{N} \textbf{.} \textbf{.} \textbf{E} \textbf{N} \\ \textbf{S} \textbf{T} \textbf{E} = \textbf{T} \textbf{D} \textbf{C}  \textbf{A} = \textbf{N} \textbf{.} \textbf{.} \textbf{E} \textbf{N} \\ \textbf{S} \textbf{T} \textbf{E} = \textbf{T} \textbf{D} \textbf{C}  \textbf{A} = \textbf{N} \textbf{.} \textbf{.} \textbf{E} \textbf{N} \\ \textbf{S} \textbf{T} \textbf{E} = \textbf{T} \textbf{D} \textbf{D} \textbf{A} = \textbf{F} \textbf{N} \textbf{.} \textbf{.} \textbf{E} \textbf{N} \\ \textbf{S} \textbf{T} \textbf{E} = \textbf{T} \textbf{D} \textbf{D} \textbf{A} = \textbf{F} \textbf{N} \textbf{.} \textbf{E} \textbf{N} \\ \textbf{S} \textbf{T} \textbf{E} = \textbf{T} \textbf{D} \textbf{D} \textbf{A} = \textbf{F} \textbf{N} \textbf{.} \textbf{E} \textbf{N} \\ \textbf{S} \textbf{T} \textbf{E} = \textbf{T} \textbf{D} \textbf{D} \textbf{A} = \textbf{F} \textbf{N} \textbf{.} \textbf{E} \textbf{N} \\ \textbf{S} \textbf{T} \textbf{E} = \textbf{T} \textbf{D} \textbf{D} \textbf{A} = \textbf{F} \textbf{N} \textbf{.} \textbf{E} \textbf{N} \\ \textbf{S} \textbf{T} \textbf{E} = \textbf{T} \textbf{D} \textbf{D} \textbf{A} = \textbf{F} \textbf{N} \textbf{.} \textbf{E} \textbf{N} \\ \textbf{S} \textbf{T} \textbf{E} = \textbf{T} \textbf{D} \textbf{D} \textbf{A} = \textbf{F} \textbf{N} \textbf{.} \textbf{E} \textbf{N} \\ \textbf{S} \textbf{T} \textbf{I} = \textbf{F} \textbf{D} \textbf{D} \textbf{A} = \textbf{F} \textbf{N} \textbf{.} \textbf{S} \textbf{N} \\ \textbf{S} \textbf{T} \textbf{I} = \textbf{F} \textbf{P} \textbf{S} \textbf{R} \textbf{N} \\ \textbf{S} \textbf{S} \textbf{S} \textbf{E} \textbf{S} \textbf{S} \textbf{S} \textbf{S} \textbf{S} \textbf{S} \textbf{S} S$	TGAS TIN IVFQ KGVSRIDSLLILKKORRE KGVSRIDSLLIKKORRE KGVSRIDSLLIKKORRE KGVSRIDSL
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#### Figure S9. Multiple sequence alignment of the amino acid sequences of TON0002 orthologues.

