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1 Protein tunnels: the case of urease accessory proteins

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10

11 **ABSTRACT**

12 Transition metals are both essential micronutrients and limited in environmental availability. The
13 Ni(II)-dependent urease protein, the most efficient enzyme known to date, is a paradigm for
14 studying the strategies that cells use to handle an essential, yet toxic, metal ion. Urease is a
15 virulence factor of several human pathogens, in addition to decreasing the efficiency of soil
16 organic nitrogen fertilization. Ni(II) insertion in the urease active site is performed through the
17 action of three essential accessory proteins: UreD, UreF, and UreG. The crystal structure of the
18 UreD-UreF-UreG complex from the human pathogen *Helicobacter pylori* (*HpUreDFG*) revealed
19 the presence of tunnels that cross the entire length of both UreF and UreD, potentially able to

1 deliver Ni(II) ions from UreG to apo-urease. Atomistic molecular dynamics simulations
2 performed on the *HpUreDFG* complex in explicit solvent and at physiological ionic conditions
3 demonstrate the stability of these protein tunnels in solution and provide insights on the
4 trafficking of water molecules inside the tunnels. The presence of different alternative routes
5 across the identified tunnels for Ni(II) ions, water molecules and carbonate ions, all involved in
6 urease activation, is highlighted here, and their potential role in the urease activation mechanism
7 is discussed.

8

9 **INTRODUCTION**

10 Transition metal ions are needed by all living organisms as essential micronutrients.¹⁻² Their
11 essentiality, coupled with their limited environmental availability and toxicity, has stimulated all
12 life forms to develop mechanisms for selective metal ions accumulation and utilization.³
13 Accordingly, all organisms possess metal homeostasis networks that ensure the availability and
14 the correct localization of metal ions in metallo-proteins and sub-cellular compartments.⁴ In
15 parallel, intracellular metal trafficking mechanisms maintain the concentration of free metal ions
16 in the cytoplasm under the physiological limits.⁵⁻⁷ Despite their biological and biophysical
17 relevance, metal trafficking processes in the cell and inside the proteins are still poorly
18 understood.⁵⁻⁶

19 Ni(II) ions are essential for the survival of several and often deadly pathogenic strains of
20 *Helicobacter*, *Staphylococcus*, *Clostridium*, *Vibrio*, *Mycobacterium*, *Yersinia*, *Escherichia*,
21 *Proteus*, *Ureaplasma*, *Klebsiella*, *Pseudomonas*, *Corynebacterium*, *Providencia*, *Morganella*,
22 and *Cryptococcus*. These ureolytic bacteria rely on the activity of the enzyme urease (urea

1 amidohydrolase; EC 3.5.1.5) to colonize and survive the host organism.⁸⁻⁹ Urease catalyzes urea
2 degradation to yield ammonia and bicarbonate and causing a local pH increase to values suitable
3 for bacterial survival. This is especially true in the case of *Helicobacter pylori*, a spiral-shaped
4 neutrophilic bacterium able to survive in the highly acidic gastric niche.¹⁰ The Center for Disease
5 Control and Prevention estimates that approximately two-thirds of the world's population
6 harbors *H. pylori*, whose infection can lead to stomach cancer and cause gastric mucosa-
7 associated lymphoid tissue lymphoma.¹¹ In 1994, the International Agency for Research on
8 Cancer classified *H. pylori*, uniquely among bacteria, as a class-I carcinogen in humans. The
9 importance of this bacterium has been emphasized by the award of the Nobel Prize in Medicine
10 to Marshall and Warren in 2005, for their studies on the link between *H. pylori* infection with
11 gastritis and peptic ulcers. Moreover, the rising antibiotic resistance that affects the most
12 commonly used *H. pylori* eradication treatments requires the identification of new drug targets.¹²⁻
13 ¹³

14 The knowledge of the activation mechanisms that lead from the inactive apo-urease to its active
15 holo-form, with the insertion of two essential Ni(II) ions in the active site of the enzyme, is thus
16 essential for the development of new drugs able to eradicate *H. pylori* infections. In particular, it
17 is fundamental to understand, at the molecular detail, the structure-function relationships for the
18 proteins that play key roles in this mechanism. The available crystal structures of ureases from
19 several bacteria and higher plants show a typical quaternary structure formed by a functional
20 minimal trimeric assembly.⁸⁻⁹ Each monomer is in turn composed by a single chain in ureases
21 from higher plants, as in the cases of jack bean (*Canavalia ensiformis*)¹⁴ and pigeon pea
22 (*Cajanus cajan*),¹⁵ by two chains in the case of *H. pylori*,¹⁶ and by three chains in the cases of
23 *Sporasarcina pasterurii* and *Klebsiella aerogenes*⁸⁻⁹. The minimal trimeric assembly eventually

1 forms dimers in higher plants or nearly spherical tetramers in *H. pylori* (Fig. 1A)¹⁶. Each
2 trimeric assembly hosts three conserved active sites, each containing two Ni(II) ions (Fig. 1B).⁹
3 Urease is produced in vivo in an inactive form, and its activation necessitates the carbamylation
4 of a key lysine in the active site to render this residue able to bind and bridge the two Ni(II)
5 through the carbamate moiety, and the delivery of Ni(II) into the active site, two steps that
6 apparently require GTP hydrolysis and CO₂ uptake.⁸ This activation process is carried out
7 through the action of four accessory proteins, named UreD (called UreH in *H. pylori*), UreF,
8 UreG, and UreE.⁸ UreD appears to be the first protein that binds apo-urease, although little is
9 known about its functional properties.¹⁷ UreF is proposed to bind the urease-UreD complex
10 through a direct interaction with UreD,¹⁸ facilitating the formation of the complex between apo-
11 urease and the UreD-UreF-UreG complex (UreDFG hereafter).¹⁹ UreG is a GTPase proposed to
12 couple GTP hydrolysis to the process of urease activation, and its putative role has been
13 proposed to be linked to the formation, in the presence of CO₂, of carboxyphosphate, an
14 excellent carbamylation agent for the conserved metal-binding lysine in the enzyme active site.¹⁹
15 UreG is the first reported case of an intrinsically disordered enzyme,²⁰ which can retain
16 enzymatic activity because of the rigidity of the GTP binding site region while possessing
17 disordered regions involved in protein-protein recognition mechanisms, prodromal to a disorder-
18 to-order transition.²¹ UreF has also been proposed to act as a GTPase-activating protein (GAP) to
19 regulate the folding and the function of UreG.²² Finally, UreE is known to be the metallo-
20 chaperone²³ in charge of delivering and transferring Ni(II) ions to the apourease-UreDFG
21 complex in a GTP-dependent activation process.²⁴ The urease activation mechanisms proposed
22 so far involve either the sequential binding of UreD, UreF, and UreG to apo-urease⁸ (Fig. 1C), or
23 the direct interaction of a preformed UreDFG protein complex to the inactive form of the

1 enzyme, to build a pre-activation complex that prepares apo-urease for nickel binding. Ni(II)
2 ions were suggested to be directly delivered by UreE to apo-urease in the final step of the
3 process²⁴ (Fig. 1C). However, a recent study indicated the occurrence of a preliminary step of
4 Ni(II) translocation from UreE to UreG when the latter is not yet bound to the UreF and UreD
5 accessory proteins.²⁵ According to this scheme, UreG subsequently separates from UreE to join
6 the preformed UreD-UreF assembly and form the Ni(II)-bound UreDFG complex. The latter
7 would finally interact with apo-urease completing the insertion of two Ni(II) ions into the
8 enzyme following GTP hydrolysis and through activation by carbonate²⁵ (Fig. 1C).

9 The recent publication of the apo-UreDFG crystal structure from *H. pylori* (*HpUreDFG*, Fig.
10 1D),²⁶ devoid of metal ions, represents a crucial breakthrough for the understanding of Ni(II)
11 ions delivery to the apo-urease active site. The *HpUreDFG* structure features a central core
12 composed by *HpUreF* in the same dimeric form as previously observed for *HpUreF* itself.²⁷ A
13 monomeric chain of *HpUreD* is bound to each *HpUreF* monomer in the same arrangement found
14 in the UreD-UreF crystal structure from *H. pylori* (*HpUreDF*).²⁸ In the *HpUreDFG* complex, the
15 *HpUreG* dimer is bound to the *HpUreDF* complex interacting with a large concave region
16 formed on the *HpUreF* dimer surface and flanked, on each side, by one *HpUreD* monomer. In
17 the crystal structure of this super-complex, a GDP molecule is bound to each *HpUreG* monomer.
18 A recent study on the metal-binding properties of recombinant *HpUreF*, determined using site-
19 directed mutagenesis and isothermal titration calorimetry, indicated that His229 and Cys231 in
20 *HpUreF* are involved in Ni(II) binding in vitro, and are critical for urease activation in vivo.²⁹
21 This result prompted a detailed analysis of the structure of the *HpUreDFG* complex, which
22 revealed the presence of a large cavity at the interface between *HpUreF* and *HpUreG*, containing
23 several internal water molecules interconnected through a network aligned along the long

1 horizontal axis of the UreD-UreF₂-UreD portion of the structure (Fig. 1E).²⁹ This internal water
2 network encompasses two nearly identical and symmetric tunnels going from the central cavity
3 in the complex and exiting near the *HpUreD* C-terminal, passing through *HpUreF* in the vicinity
4 of His229 and Cys231, located at the interface between *HpUreF* and *HpUreD*.²⁹ This observation
5 prompted the proposal for a role of UreF in the metal ion transport through these tunnels during
6 urease activation.²⁹ In particular, this hypothesis entails that Ni(II) ions, known to bind to a
7 conserved Cys-Pro-His (CPH) motif on the surface of the *HpUreG* dimer^{8, 30-31} facing *HpUreF* in
8 the *HpUreDFG* complex structure, can proceed through the tunnels in order to reach the apo-
9 urease active site.²⁹ This hypothesis has subsequently received support by in vivo assays using
10 site-directed mutagenesis coupled with bioinformatics and atomistic molecular dynamics (MD)
11 simulations on UreD from *K. aerogenes* (*KaUreD*), of.³²

12 Here, we use atomistic 200 ns-long MD simulations in explicit solvent to extend the
13 investigation to the structural fluctuations and the stability of the full *HpUreDFG* complex,
14 focusing the analysis on the dynamic behavior of the internal tunnels that encompass the entire
15 protein super-complex. Our findings indicate that the tunnels are persistent during the
16 investigated time of the MD simulation, further suggesting alternative routes for Ni(II) and
17 carbonate ions during the urease activation process. The results of this study represent the
18 starting point for atomistic simulations of Ni(II) permeation through the tunnels in the full
19 *HpUreDFG* complex by using enhanced sampling algorithms.

20

21 MATERIALS AND METHODS

1 The *HpUreDFG* crystal structure from *H. pylori* strain 26695 (PDB code: 4HI0)²⁶ was used. The
2 most probable protonation state of titratable amino acids, and the tautomeric state of histidine
3 residues at neutral pH, were assigned through the Protein Preparation wizard tool of the
4 Schrödinger suite 2015.4.³³ The complex was embedded into a truncated octahedron water box
5 using an 11-Å buffer zone of solvent around the protein complex. The resulting system consisted
6 of ca. 337,000 atoms. The Amber ff99SB force fields³⁴ for the protein and the TIP3P model³⁵ for
7 water were used, while known parameters were applied to the GDP molecule found in the crystal
8 structure.³⁶ The systems were neutralized by adding Na⁺ and Cl⁻ ions using the *genion* program
9 of the GROMACS 4.6.2 package.³⁷⁻³⁹ Analogously, additional Na⁺ and Cl⁻ ions were placed in
10 the water box to achieve the physiological ionic strength (150 mM). A total of 350 Na⁺ and 316
11 Cl⁻ ions were added. The system was energy-minimized and then equilibrated at 300 K and 1 atm
12 by performing 1 ns of gradual annealing using GROMACS 4.6.2. The geometry optimization
13 was performed in four cycles. In the first two cycles, which comprised 800 steps of steepest
14 descent followed by 3000 steps of conjugate gradient, the water molecules were relaxed while
15 the protein was constrained using a harmonic potential with a force constant of 1,000 J mol⁻¹ Å⁻².
16 In the third and in the fourth cycles the procedure was repeated without applying any constraint.
17 During this equilibration phase, positional constraints were applied on the protein atoms and on
18 GDP (force constant of 1,000 J mol⁻¹ Å⁻²). The temperature and pressure was controlled using a
19 Berendsen thermostat and barostat,⁴⁰ respectively. An integration step of 1 fs was used, and the
20 structures were sampled every 0.1 ps. Periodic boundary conditions (PBC) were applied. The
21 Particle Mesh Ewald (PME) method was used to calculate electrostatic interactions.⁴¹ The cut-off
22 values for the real part of the electrostatic interactions and for the van der Waals interactions
23 were set to 10 Å. In the 200 ns-long production run, the temperature and pressure coupling was

1 made using a Nose-Hoover thermostat⁴²⁻⁴³ and a Parrinello-Raman barostat,⁴⁴⁻⁴⁵ respectively.

2 The calculations were performed using the Eurora and the PLX supercomputers at CINECA
3 (Italy).

4 The program CAVER 3.0⁴⁶ was used to calculate all pathways departing from the *HpUreG* CPH
5 motif region within 2,000 superimposed MD snapshot of the *HpUreDFG* complex. All water
6 molecules were removed before the tunnel calculation. The starting point of the tunnel search
7 was calculated as the average position between the *HpUreG* Cys66 S γ atoms from each *HpUreG*
8 monomer. The tunnel search was performed using a probe of 0.9-Å radius. This probe was
9 selected for two reasons: i) it is the CAVER 3.0 default value for the determination of molecular
10 tunnels using molecular dynamics simulations,⁴⁶ and ii) it provides a reasonable agreement with
11 the shape of the water density inside the tunnels (see below). The GDP molecules were
12 considered in the computation in order to avoid bias due to the *HpUreG* GTP/GDP solvent
13 exposed cavity. Each tunnel is determined as an ensemble of beads of radii selected to fit the
14 tunnel diameter. The identified tunnels were clustered by hierarchical average link by calculating
15 the pairwise distances (i.e. dissimilarities) among the centers of the beads for all the computed
16 tunnels.

17 *HpUreD* residue conservation was analyzed using the ConSurf server.⁴⁷ The server calculates
18 conservation on the basis of a PSI-BLAST analysis⁴⁸ that retrieved the best 150 *UreD* sequences
19 with more than 15% and less than 90% sequence identity with respect to *HpUreD*. Residue
20 conservation was mapped on the *HpUreD* structure found in the *HpUreDFG* complex (PDB
21 code: 4HI0)²⁶. Molecular graphics and analyses were performed using the UCSF Chimera
22 package⁴⁹ and VMD.⁵⁰

1 Solvent molecules passing through or in the vicinity of the tunnel bottleneck characterized by
2 *HpUreD* residues Arg95 and Asp140 (see Results and Discussion section below) were filtered
3 out from the remaining part of the solvent by selecting the water molecules passing within 3.2 Å
4 of the tunnel-facing atoms of Arg95 and Asp140 along the entire trajectory. The volumetric
5 density map of the selected water molecules was then created using the VolMap plugin in VMD.
6 VolMap replaced each oxygen atom of the selected water molecules with a normalized Gaussian
7 distribution of width corresponding to the oxygen atomic radius. The superimposition of all the
8 trajectory frames were used to compute the resulting density map. An in-house tcl script was
9 used to calculate the time spent inside the tunnels by the selected water molecules.

10

11 **RESULTS AND DISCUSSION**

12 To gain a deeper understanding of the structural and dynamic behavior of the *HpUreDFG*
13 complex, we ran one 200 ns-long MD simulation in explicit solvent, using an atomistic force
14 field. The root-mean-square-deviation (RMSD) of the C α atoms of the complex from the initial
15 conformation stabilizes after ca. 25 ns and then oscillates around 2.0 Å for the remaining time of
16 the simulation (Fig. 1-SI in the Supplementary Information). The RMSD of each protein forming
17 the complex stabilizes after a short period (less than 25 ns) and remains stable around values of
18 ca. 1.0, 1.0 and 1.5 Å for *HpUreF*, *HpUreD*, and *HpUreG*, respectively (Fig. 2-SI). This
19 observation, together with the constant secondary structure content of the complex (Fig. 3-SI)
20 indicates that the simulation was long enough to relax and equilibrate each protein within the
21 *HpUreDFG* complex. In particular, the *HpUreG* dimer remains well-folded and stable along the
22 simulation (Fig. 4-SI), especially in those regions that were predicted to be intrinsically unfolded

1 through bioinformatics predictions²⁰ and MD calculations conducted on the *HpUreG* model
2 structure before the release of the *HpUreG* crystal structure.²¹ Apparently, the interaction
3 between *HpUreF* and the predicted intrinsically unfolded region of *HpUreG* (residues 38-94,
4 128-137, and 155-176) stabilizes the latter in the simulation time scale, consistently with the
5 hypothesis that *UreF* acts as a GTPase activator (GAP) for *UreG*.²²

6 *Analysis of the tunnels.* Following the assessment of the overall structure stability of the
7 *HpUreDFG* complex, the tunnels departing from the cysteine residues in the conserved CPH
8 motif of the *HpUreG* dimer, and able to pass through the entire complex in order to eventually
9 transport the Ni(II) ions needed for urease activation to *HpUreG* to *HpUreD*, were then
10 examined. The software CAVER 3.0 was used for the analysis of 2,000 snapshots from the 200
11 ns-long trajectory of *HpUreDFG*. In each snapshot, all possible pathways with a bottleneck
12 radius equal or larger than 0.9 Å were identified, leading to a set of ca. 58,000 pathways along
13 the simulation. These pathways were clustered, using the average-link algorithm based on the
14 pairwise distances of the pathways, to yield 2,081 clusters. Considering the symmetry of the
15 *HpUreDFG* complex and the position along the major vertical axis of the starting point of the
16 tunnels (Fig. 2A), in principle each cluster of tunnels could have a symmetrically corresponding
17 tunnel. Moreover, considering further the symmetry of the system, each side of the *HpUreDFG*
18 complex along the vertical axis can be considered independent from the other side. In other
19 words, by running 200 ns of simulation on the *HpUreDFG* structure, we sampled a total of 400
20 ns of the tunnels dynamics. The analysis of the cluster of tunnels revealed that the largest portion
21 of the tunnels departing from the CPH motif passes through only *HpUreG* itself or *HpUreF* (Fig.
22 2A). On the other hand, it is possible to identify five pairs of symmetric clusters of tunnels
23 passing through both *HpUreF* and *HpUreD* (Table 1). Tunnels 1-3 are present in about 30% of

1 the analyzed frames, while tunnels 4 and 5 are closed for the large part of the simulation time.
2 We thus concentrate on tunnels 1-3 (Fig. 2B-D, Table 1 and 2), while tunnels 4 and 5 are
3 reported in the SI (Fig. 5-SI and Table 1-SI). From Table 1, it appears that the tunnels going
4 through the *HpUreDF* monomer located on the left in Fig. 2B-D are more present and active
5 during the MD trajectory as compared to the tunnel on the *HpUreDF* monomer on the right. The
6 analysis of the tunnels' bottlenecks (i.e. the region of each tunnel showing the smallest tunnel
7 radius, Table 2 and Fig. 6,7,8-SI) revealed that the *HpUreD* residues Arg95 and Glu140 are
8 among those more frequently found in a single bottleneck. Glu140 was also identified in a recent
9 study on *KaUreD* (Asp142 in *K. aerogenes* numeration) as one of the crucial residues in urease
10 maturation.³² The analysis of the distance between *HpUreD* Arg95 C ζ and Glu140 C δ shows that
11 the side chains of these two residues are at different distances in the left and in the right
12 *HpUreDF* monomer, respectively, as shown in Fig. 3A. In particular, in the *HpUreD* monomer
13 on the right side of the *HpUreDFG* complex, the Arg95 C ζ - Glu140 C δ distance is less than 6 Å
14 for the 95% of the simulation time, while in the monomer on the left side this happens only for
15 only 21% of the time. Consistently, *HpUreD* Arg95 and Glu140 side chains are involved in the
16 formation of a H-bond for 98% and 30% of the simulation time in the right and in the left
17 *HpUreDF* monomer, respectively. When *HpUreD* Glu140 is not forming a H-bond with Arg95,
18 it can form a H-bond with the O η atom of the *HpUreD* Tyr138 residue. The analysis of the H-
19 bonds formed by the side chains of *HpUreD* Tyr138 and Glu140 showed that one H-bond is
20 present between these residues for 54% and 5% of the simulation time in the left and in the right
21 *HpUreDF* monomer, respectively. A conservation analysis conducted using PSI-BLAST⁴⁸
22 showed that Glu140 is conserved in 50% of the *HpUreD* most similar sequences, while in the
23 remaining cases this residue is conservatively mutated with an aspartate. Arg95 is present in only

1 1% of the cases, while in 96% of the sequences it is mutated with a glutamine, which is
2 nevertheless able to form a H-bond with the residue in the position of Glu140 through its $-NH_2$
3 group. Moreover, the residue in position 94 is not largely conserved, and is present as a tyrosine
4 in 36% of the cases, and as an arginine in 17% of the cases. Finally, in *K. aerogenes* UreD and
5 only in the 3% of the considered sequences, position 96 is again mutated with an arginine.³² In
6 the case of the model structure of *Ka*UreD used for MD simulations,³² position 96 does not
7 correspond to an arginine because of possible misalignment between the structure of *Ka*UreD
8 and *Hp*UreD, for which the crystal structure has been experimentally determined. Tyr138 is
9 present in 47% of the cases, while in the remaining sequences it is mostly mutated with a
10 glycine. On the other hand, *Hp*UreD Ser139 is frequently mutated with a tryptophan residue that
11 can ensure the formation of an H-bond with Glu140 through the nitrogen atom in the indole
12 group. Taken together, these results show that the formation of the Glu140-Tyr138 H-bond
13 opens the tunnels passing through *Hp*UreF and *Hp*UreD (Fig. 3B), while the presence of the
14 Arg95-Asp140 salt bridge closes the tunnels (Fig. 3C). In the present simulation, the Arg95-
15 Asp140 bottleneck in the left side of the structure is open for ca. 95% of the simulation time, but
16 only for ca. 70% of time on the right side. No correlation has been identified between the
17 open/close behaviour of the tunnels on the left with the respect of the tunnels on the right,
18 suggesting a completely stochastic situation.

19 Tunnels 1, 2 and 3 coincide from the starting CPH motif at the interface of the *Hp*UreG dimer
20 until they reach the *Hp*UreD Arg95-Asp140 bottleneck (Fig. 2B-D). In this region, these three
21 most populated tunnels split to reach different regions on the *Hp*UreD surface. Tunnels 1 and 2
22 emerge in highly conserved region of the *Hp*UreD surface, while tunnel 3 flows into a less
23 conserved zone (Table 2). *Hp*UreD is composed by 17 β -strands and 2 α -helices. The structure is

1 characterized by two mixed strand β -sheets with β -strands β 1, β 2, β 5, β 8, β 11, β 13, and β 14
2 forming β -sheet I and β -strands β 3, β 4, β 6, β 7, β 9, β 10, β 12, and β 15- β 17 forming β -sheet II
3 (Fig. 4A). Helix α 1 and α 2 are packed against anti-parallel β -strands β 15- β 17 to form an α/β -like
4 motif located at the C-terminus of β -sheet II. The C-terminal regions of both β -sheets I and II
5 constitute the interacting region with *HpUreF*. Tunnel 1 passes through β -strand β 9, β 10 and β 12
6 in β -sheet II and emerges in the space between helix α 2 and β -strand β 6 (Table 2 and Fig. 4A).
7 Tunnel 1 is characterized by a second bottleneck located at the *HpUreF*-*HpUreD* interface and
8 involving Ala233, Val235, Lys237 and Asp238 on the *HpUreF* side together with *HpUreD*
9 Asp174, Thr176, Tyr197 and Asn199 residues. In the vicinity of this bottleneck, the two *HpUreF*
10 residues His229 and Cys231 were experimentally found to be involved in Ni(II) binding events
11 critical for urease activation in vivo.²⁹ Indeed, all the most populated tunnels pass through this
12 region, and *HpUreD* Asp174 was among the identified residues in *KaUreD* to be crucial for
13 urease activation,³² while Asn199 mutation resulted only in a small but recognizable reduction of
14 urease activation. The mouth of tunnel 1 remains open for all the simulation time and is
15 stabilized by the formation of one salt-bridge between the side chains of *HpUreD* Arg76 and
16 Glu251 (Fig. 4B). Tunnel 2 passes through the space between β -sheets I and II and emerges in
17 the vicinity of β -strands β 1, β 3, β 4, and β 6 (Table 2 and Fig. 4A). Also in this case, the exit
18 mouth of tunnel 2 remains open for all the simulation time and is stabilized by a dense H-
19 bonding network involving *HpUreD* Ser54, Asp61, Gln63, and Glu83 (Fig. 4C). Among these
20 residues, *HpUreD* Asp61 and Glu83 are in the list of crucial residues for urease activation
21 identified in a mutagenesis/MD study on *KaUreD*,³² while Ala52, Met57, Gln63, and Lys84
22 mutations did not alter the *K. aerogenes* urease activity with respect of the level of active
23 enzyme obtained using the wild type *KaUreD*. Moreover, the exit mouth of tunnel 2 is located in

1 a highly conserved surface region of *HpUreG*, and this region has been proposed to act as the
2 UreD/urease binding interface.³² Finally, tunnel 3 passes through the space between β -sheets I
3 and II, and crosses the entire length of the *HpUreDF* complex exiting between β -strands β 1 and
4 β 2 (Table 2 and Fig. 4A). The tunnel mouth is open for the largest part of the simulation time
5 even if some hydrophobic residues (*HpUreD* Ile24, Leu35, and Ala37) can close at times the
6 access to the bulk of the solvent (Fig. 4D). Indeed, these three residues are also found among the
7 most frequent bottleneck residues for tunnel 3 (Table 2 and Fig. 8-SI). As for the residues
8 identified in this region (Table 2), Leu35 mutation in *KaUreD* didn't produce large changes in
9 urease activation levels with respect to the wild type, while the mutation of Tyr40 resulted in a
10 small reduction.³² All the remaining mutated *KaUreD* residues that didn't show any relevant
11 activity on urease maturation (Asp44, Ala46, Glu47, His86, Asn87, Phe109, Thr126, Arg146,
12 Glu151, Lys161, Ser163, Glu167, and Arg213 in *HpUreD* numeration) are not involved in any of
13 the tunnels identified in the present study.

14 These results shows that the tunnels observed in the *HpUreDFG* crystal structure and passing
15 through each *HpUreDF* monomer are stable in the simulation time scale and can open and close
16 in the nanoseconds – tens of nanoseconds time scale. The three most present tunnels, observed
17 during the simulation, feature openings in different regions of the *HpUreD* structure. The exit of
18 tunnel 2 is found in a conserved region proposed to be in contact with apo-urease³² and thus
19 tunnel 2 should be the preferred pathway for Ni(II) ions during urease maturation. However, the
20 role of tunnel 1 and 3 has not been elucidated yet. Even when the *HpUreD* Arg95-Glu140
21 bottleneck is closed, the tunnels mouths are open for the largest part of the simulation time and
22 can theoretically be navigated by water molecules coming from the tunnels or from the bulk of
23 the solvent. In order to gather additional information on the role of the three tunnels passing

1 through the *HpUreDF* monomers, we analyzed the dynamic behavior of water molecules present
2 inside the tunnels.

3 *Water molecules trafficking inside the tunnels.* The presence and persistence of the identified
4 tunnels passing through each *HpUreDF* dimer in the simulation time scale is not enough to
5 demonstrate the effective passage of water molecules together with Ni(II) ions through the
6 tunnels during the urease activation process. We thus focused our attention on the water
7 molecules passing at H-bond distance from the *HpUreD* Arg95-Asp140 bottleneck of tunnels 1-
8 3. This analysis resulted in 511 out of the initial 108,896 water molecules. The density of water
9 molecules calculated from the trajectory of these 511 specimens retraces with very good
10 agreement the shape of the tunnels (Fig. 5A). We then concentrated only on those water
11 molecules that are able to enter in the tunnels from the bulk of the solvent or that escape from the
12 tunnels during the simulation. For this analysis we developed an in-house algorithm built on the
13 following assumptions/approximations: i) a total number of fourteen overlapping spheres of
14 radius equal to 15 Å were used to encompass the water molecules density map contoured at
15 0.025 oxygen atoms Å⁻³ (Fig. 12-SI). This step allowed us to unambiguously define the edges of
16 the tunnels in a computationally efficient way; ii) a water molecule entering the tunnels was
17 defined as a molecule moving from the bulk of the solvent (i.e. from outside the spheres defined
18 above) to the interior of at least one of the spheres and spending no less than 5 consecutive ps
19 inside the tunnels; vice versa, a water molecule exiting the tunnels was defined when the same
20 movement occurred in the opposite direction; iii) in order to avoid artifacts due to the way the
21 spheres were defined, only water molecules with a persistence inside the tunnels greater than 1
22 ns were considered. This analysis allowed us to identify a subset of 370 water molecules moving
23 from or into the tunnels during the course of the simulation and spending an average time of ca.

1 52 ns inside the tunnels. Ca. 30% of these water molecules spent less than 10 ns inside the
2 tunnels, but a considerable amount of them (ca. 20%) remained inside the tunnels for more than
3 half of the simulation time (Fig. 13-SI). The visual inspection of these 370 water molecules
4 revealed that the majority of them explore only a small portion of the tunnels. On the other hand,
5 46 water molecules were able to cover almost one half of the tunnels inside almost one of the
6 monomers composing the *HpUreDFG* complex (Fig. 14-SI). Among these water molecules, only
7 two passed in the proximity of the Arg95-Asp140 bottleneck on the right side, possibly due to
8 the persistent closure of that gateway during the simulation. On the other hand, in the remaining
9 44 cases, 13 water molecules were able to pass from *HpUreF* to *HpUreD* or vice versa. Fig. 5B-E
10 reports selected examples of such water molecules, able to traverse a large part of tunnel 1.
11 These water molecules started their journey from the inside of the protein complex (Fig. 5B,C),
12 or come from the bulk of the solvent and enter the tunnels at the *HpUreG-HpUreF* interface (Fig.
13 5D) or from the mouth of tunnel 1 (Fig. 5E). Among the selected solvent molecules, there are
14 cases of water molecules entering/exiting the tunnel from the mouth of tunnel 2 (6 cases) and
15 tunnel 3 (3 cases), demonstrating the feasibility of these routes for the trafficking of water
16 molecules within the *HpUreDFG* protein supercomplex.

17

18 **CONCLUSIONS**

19 The *HpUreDFG* complex and the tunnels observed in the crystal structure appear to be stable in
20 solution in the hundreds of nanoseconds time scale. The traffic of water molecules inside the
21 tunnels that start from the proposed Ni(II) binding site located at the *HpUreG-HpUreF* interface
22 and pass through *HpUreF* and *HpUreD* can be regulated by the opening of two main bottlenecks,

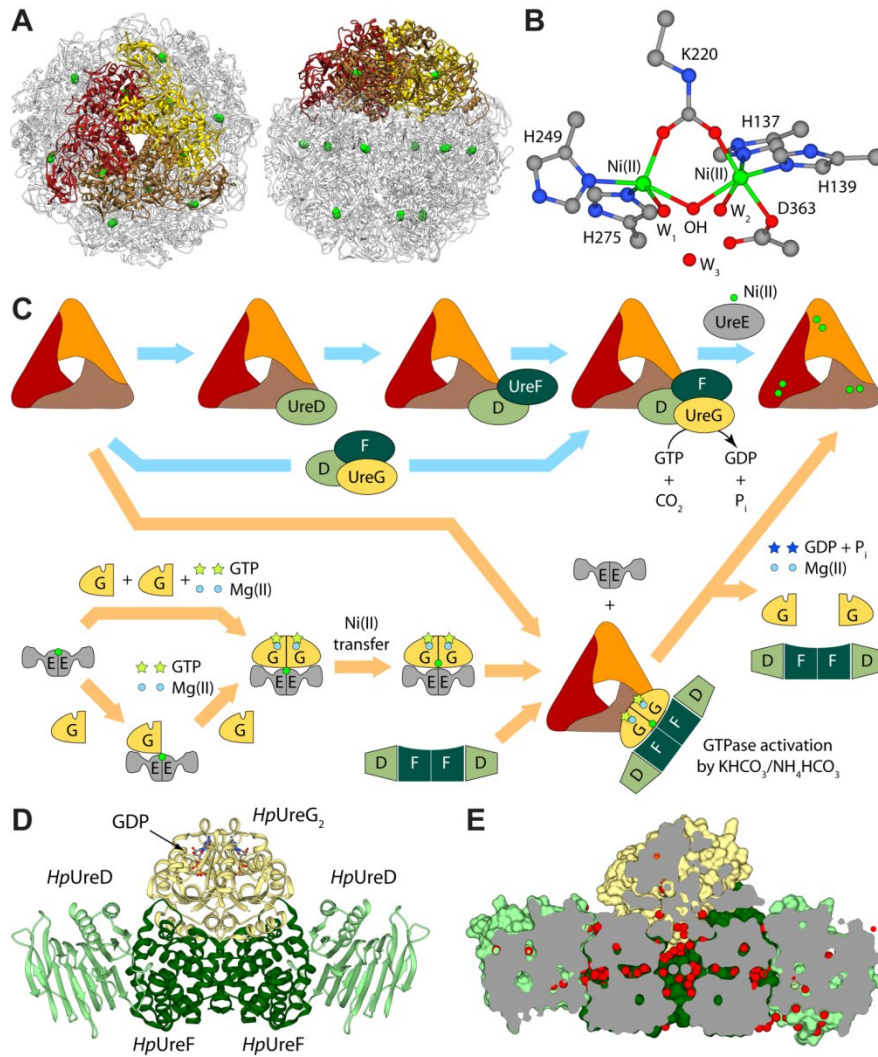
1 the first located at the *HpUreF-HpUreD* interface (bottleneck 1), which remains always open,
2 and the second in the core of *HpUreD* (bottleneck 2). The latter appears to be of particular
3 importance because it is able to control the flow of water molecules as well as Ni(II) ions.
4 Indeed, Ni(II) ions can travel through the tunnels either in their hydrated form, or directly
5 establishing bonds with the atoms found on the tunnels' walls, as reported for other ions,⁵¹⁻⁵³
6 Ni(II) ions have a smaller radius (0.83 Å)⁵⁴ with respect to water molecules, but their movement
7 can be stopped by the closure of bottleneck 2. The latter can further regulate the access to three
8 different tunnel openings on the *HpUreD* surface. In particular, the exit of tunnel 2 is in the
9 vicinity of *HpUreD* Asp61 and Glu83, two crucial residues for urease activation,³² suggesting
10 that this route is favorable for Ni(II) ions trafficking from *HpUreG* to the apo-urease reaction site
11 (see Scheme 1). On the other hand, tunnel 1 is the most stable along the simulation and its
12 opening mouth is also located in a highly conserved region on the *HpUreD* surface. Considering
13 that i) Ni(II) insertion in the urease reaction site should be subsequent to the carbamylation of a
14 conserved lysine residue, ii) a carbonate/bicarbonate ion cannot pass through the bottlenecks of
15 the tunnels inside the *HpUreDFG* complex because of size constraints, and iii) the opening of
16 tunnel 1 shows the largest diameter with respect of the exits of tunnels 1 and 3, we put forth the
17 hypothesis of the possible involvement of the terminal part of tunnel 1 in the
18 carbonate/bicarbonate transport inside the reaction site of apo-urease through the terminal part of
19 tunnel 2 (see Scheme 1).

20 The present study highlights the presence of potential distinct routes for the traffic of Ni(II) ions,
21 water molecules, and carbonate ions, all necessary for the activation of urease through
22 incorporation of the metal ions and the carbamylation of the conserved lysine residue that is
23 essential for Ni(II) binding and positioning in the active site. The identified bottlenecks can

1 represent potential new targets for drugs aimed at eradicating infections by ureolytic human
2 pathogens as alternative to the currently used antibiotic treatments. The present results, together
3 with the development of a multi-site model of Ni(II) ions currently underway in our laboratories,
4 pave the way to the atomistic simulations of Ni(II) permeation through the *HpUreDFG* tunnels.

5

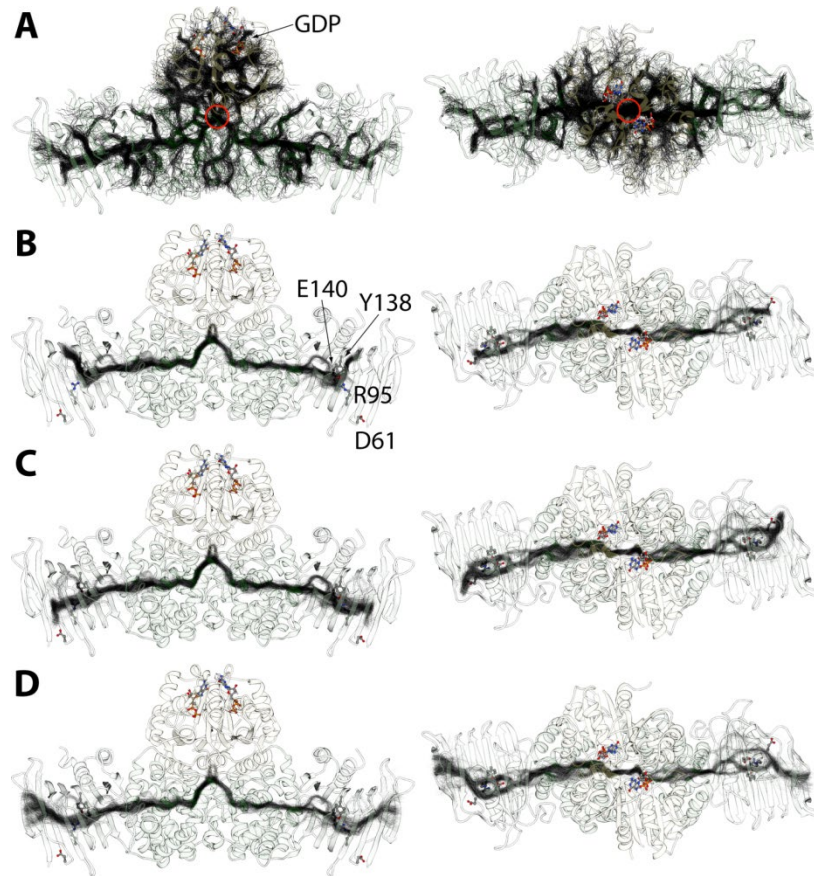
1 FIGURES



2

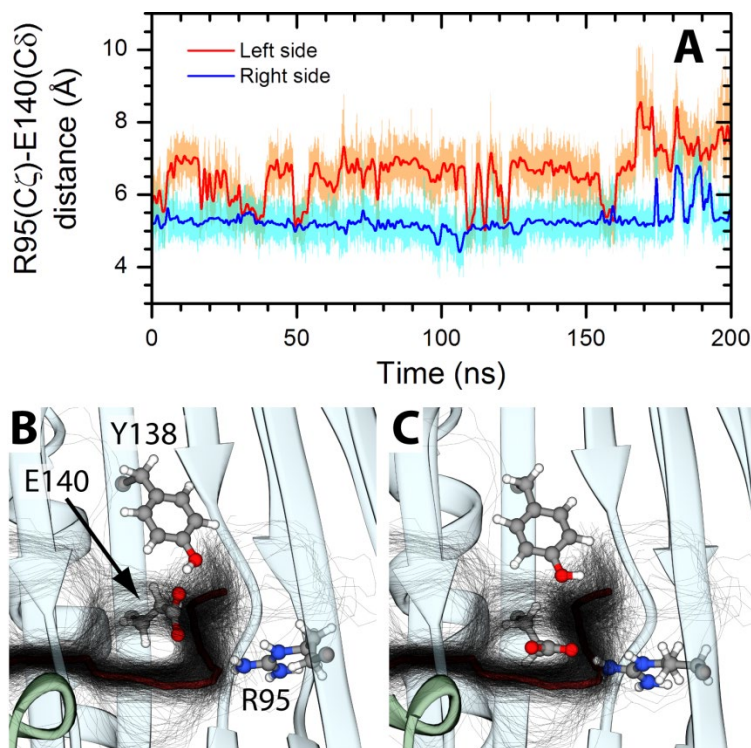
3 **Figure 1.** (A) Ribbon diagram of urease from *H. pylori* (PDB code: 1E9Z). Ribbon colors
 4 highlight the chains composing the trimer of oligomers constituting the minimal quaternary
 5 structure of urease. Ni(II) ions are reported as green spheres. The right panel is rotated by 90°
 6 around the horizontal axis vs. the left panel. (B) Coordination geometry of the Ni(II) ions in
 7 native urease active site (source *Sporosarcina pasteurii*, PDB code 4CEU). Color scheme:
 8 nickel, green; carbon, gray; nitrogen, blue; oxygen, red. (C) Schematic representation of the
 9 proposed mechanisms for urease activation. (D) Ribbon diagram and (E) longitudinal section of

1 the solvent-excluded surface of the apo *HpUreDFG* crystal structure (PDB code 4HI0). *HpUreD*,
2 *HpUreF*, and *HpUreG* chains are colored as in panel (C). Water molecules are depicted as red
3 spheres, GDP is reported as balls-and-sticks and colored according to atom type.



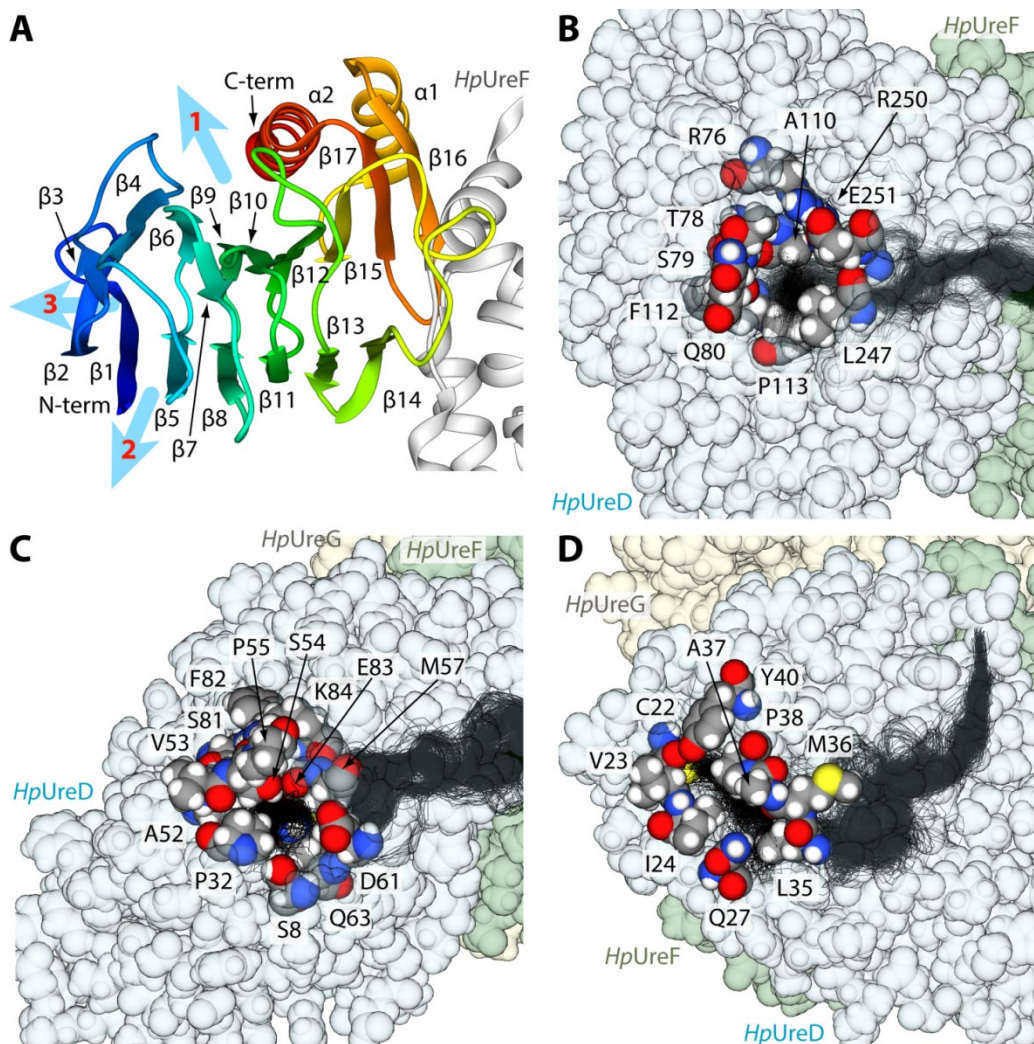
4

5 **Figure 2.** Ribbon diagram of the *HpUreDFG* complex and tunnels identified throughout the
6 MD simulation by CAVER 3.0, all depicted in one frame as the tunnel centerlines. In the right
7 panels, the *HpUreDFG* complex is rotated by 90° around the horizontal axis with respect to the
8 orientation in the left panels. In panel (A) all the tunnels identified in the protein complex are
9 reported (only one frame per ns was considered for clarity reasons). The red circles identify the
10 starting point position of the tunnels. Tunnels 1-3 are depicted in panels (B-D), respectively (see
11 Table 1 and 2). Residues cited in the text are reported as balls-and-sticks.



1
 2 **Figure 3.** (A) *HpUreD* Arg95 C ζ and Glu140 C δ distance plotted as a function of time. The
 3 orange and light blue lines represent the effective sampling during the simulation, while the red
 4 and blue lines have been obtained by applying a Fast Fourier Transform filter in order to cut-off
 5 noise. (B, C) Selected snapshot showing *HpUreD* Arg95, Tyr138 and Glu140 in different
 6 arrangements during the simulation. In panel (B), tunnel 1 (black lines) is open, while in (C) it is
 7 closed.

8



1

2 **Figure 4.** (A) Ribbon diagram of *HpUreD* as found in the *HpUreDFG* complex. The

3 ribbons are colored from blue in the proximity of the N-terminal to red at the C-terminus. Tunnel

4 openings are indicated by light blue arrows. Details of tunnel 1 (B), 2 (C) and 3 (D) exits.

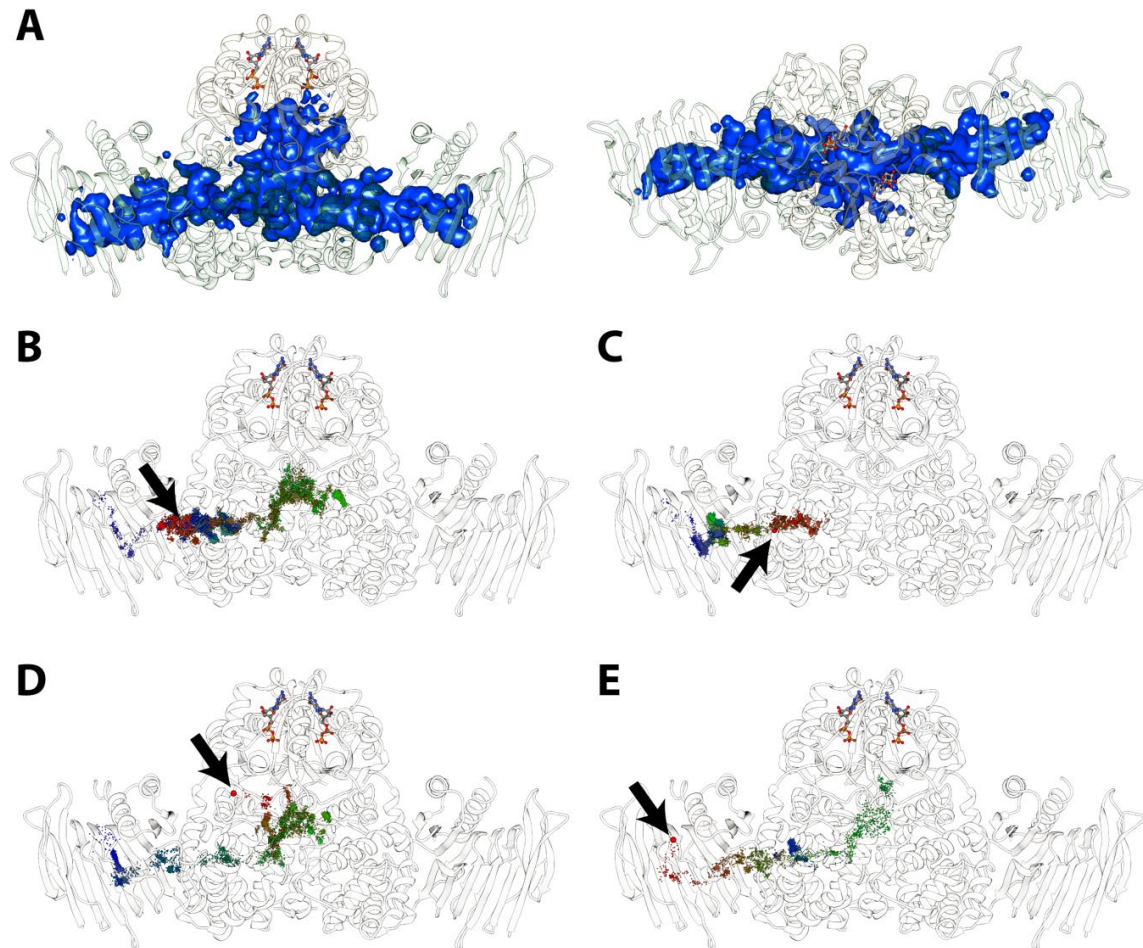
5 *HpUreD*, *HpUreF* and *HpUreG* atoms are reported as spheres and are colored in light blue, light

6 green and light yellow, respectively. Residues located next to each tunnel exit are colored

7 according to atom type. The tunnels identified throughout the MD simulation by CAVER 3.0 are

8 depicted as the tunnel centerlines.

9

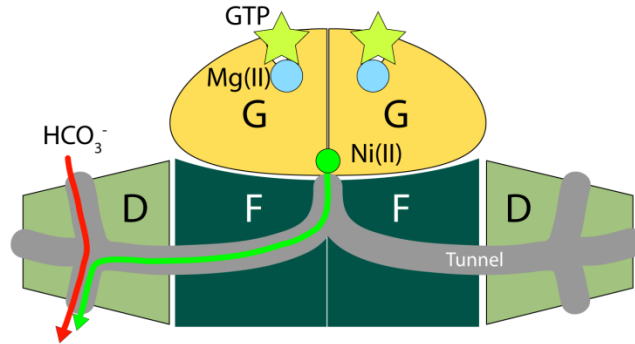


1
2 **Figure 5.** (A) Density isosurface of the water molecules found inside the *HpUreDFG*
3 tunnels contoured at 0.025 oxygen atom \AA^{-3} (blue). In the right panel, the *HpUreDFG* complex is
4 rotated by 90° around the horizontal axis with respect to the orientation in the left panel. (B-E)
5 Trajectory of four selected water molecules inside the *HpUreDFG* tunnels. In each frame, the
6 water molecule is reported as a sphere colored from red to green and finally to blue, accordingly
7 to the simulation time. The starting frame is indicated by a red sphere of larger radius with
8 respect to the others, and by a black arrow. The *HpUreDFG* complex is reported as white ribbons
9 and GDP is depicted as balls-and-sticks.

10

1 SCHEMES

2



3

Apo Urease

4 **Scheme 1.** Schematic representation of the pathways followed by Ni(II) ions (green arrow)

5 and by the carbonate/bicarbonate ion (red arrow) inside the *HpUreDFG* tunnels.

TABLES

Table 1. Analysis of the tunnels identified by CAVER 3.0 and passing through both *HpUreF* and *HpUreD* during the MD simulation (Fig. 2B-D and 5-SI).

Tunnel #	Cluster #	# of snapshots		Average bottleneck	Maximum bottleneck	Average length
	(left side / right side)	(left side / right side)	Total snapshots	radius (left side / right side) (Å)	radius (left side / right side) (Å)	(left side / right side) (Å)
1	17 / 63	1745 / 534	2279 (57%)	1.00 ± 0.08 / 0.96 ± 0.07	1.28 / 1.32	78 ± 6 / 80 ± 7
2	35 / 72	1457 / 678	2135 (53%)	0.97 ± 0.06 / 0.94 ± 0.04	1.28 / 1.14	86 ± 6 / 89 ± 7
3	73 / 135	831 / 331	1162 (29%)	0.95 ± 0.05 / 0.93 ± 0.03	1.26 / 1.16	95 ± 6 / 98 ± 7
4	105 / 119	228 / 103	331 (8%)	0.94 ± 0.04 / 0.94 ± 0.05	1.15 / 1.22	77 ± 7 / 69 ± 6
5	157 / 737	269 / 20	289 (7%)	0.94 ± 0.03 / 0.92 ± 0.02	1.11 / 0.97	97 ± 7 / 115 ± 14

Table 2. Relevant regions in tunnels 1-3 identified by CAVER 3.0 and passing through both *HpUreF* and *HpUreD* during the MD simulation (Fig. 2B-D).

Tunnel #	<i>HpUreD</i> residues (and conservation ^a) at tunnel exit	Most frequent bottleneck residues
1	Arg76 (8), Thr78 (9), Ser79 (9), Gln80 (9), Ala110 (6), Phe112 (9), Pro113 (9), Leu247 (8), Arg250 (6), Glu251 (3)	<u><i>HpUreF</i></u> : Ala233, Val235 <u><i>HpUreD</i></u> : Arg95, Leu114, Glu140, Ile141, Ile142, Thr160, Asp174, Thr176, Tyr197, Asn199, Lys237
2	Ser8 (8), Pro32 (9), Ala52 (9), Val53 (9), Ser54 (9), Pro55 (9), Met57 (7), Asp61 (9), Gln63 (9), Ser81 (8), Phe82 (9), Glu83 (7), Lys84 (9)	<u><i>HpUreD</i></u> : Phe33, Ala52, Gln63, Glu83, Arg95, Pro111, Phe112, Leu114, Glu140
3	Cys22 (9), Val23 (6), Ile24 (6), Gln27 (5), Leu35 (7), Met36 (9), Ala37 (9), Pro38 (8), Tyr40 (9)	<u><i>HpUreD</i></u> : Leu12, Ile24, Gln27, Leu35, Met36, Ile48, Ile77, Arg95, Pro111, Glu140

^a Conservation calculated by the ConSurf server.⁴⁷ The score goes from 0 (variable) to 5 (average) to 9 (highly conserved).

ASSOCIATED CONTENT

Supporting information. RMSD and RMSF of the *HpUreDFG* complex along the simulation; diagrams and relevant regions of tunnels 4 and 5; analysis of bottleneck residues found in tunnels 1-5; multiple sequence alignment of UreD sequences and ConSurf analysis; distribution of the time spent inside the tunnels by water molecules; and trajectory of selected water molecules inside the *HpUreDFG* tunnels.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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Protein tunnels: the case of urease accessory proteins

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SUPPLEMENTARY INFORMATION

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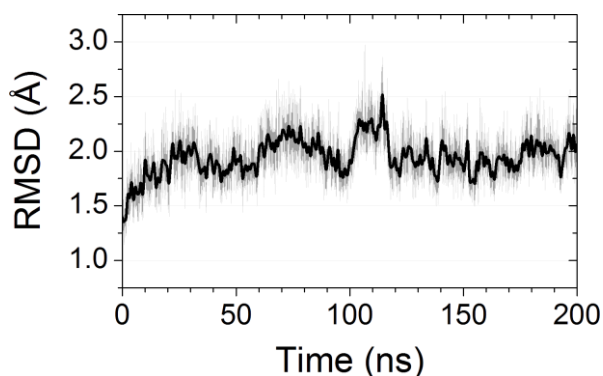


Figure 1-SI. Calculated root mean square deviations (RMSD) of the *HpUreDFG* C α from the initial X-ray structure plotted as a function of time. The grey line represent the effective sampling of RMSD during the simulation, the black line has been obtained by applying a Fast Fourier Transform filter in order to cut-off noise.

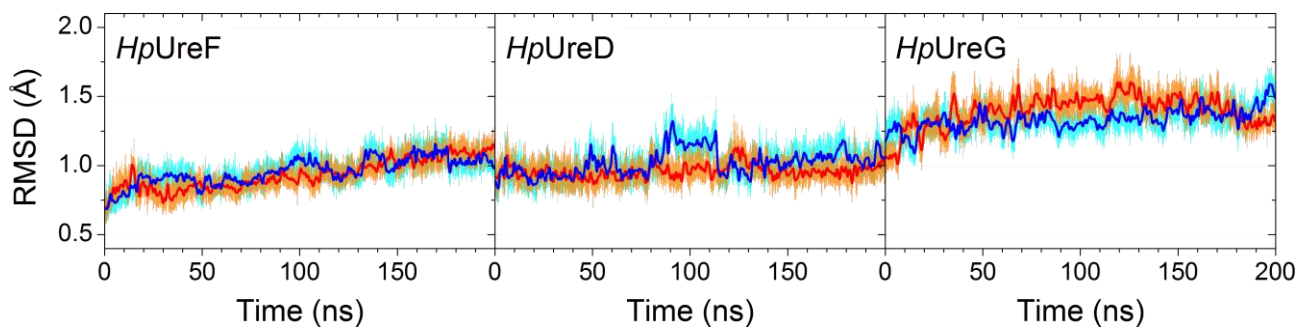


Figure 2-SI. Calculated RMSD of the monomeric *HpUreF* (left panel), *HpUreD* (central panel) and *HpUreG* (right panel) C α from the initial X-ray structure plotted as a function of time. The RMSD plots of the different monomers of the same protein are in light blue and orange. The blue and red lines have been obtained by applying a Fast Fourier Transform filter in order to cut-off noise.

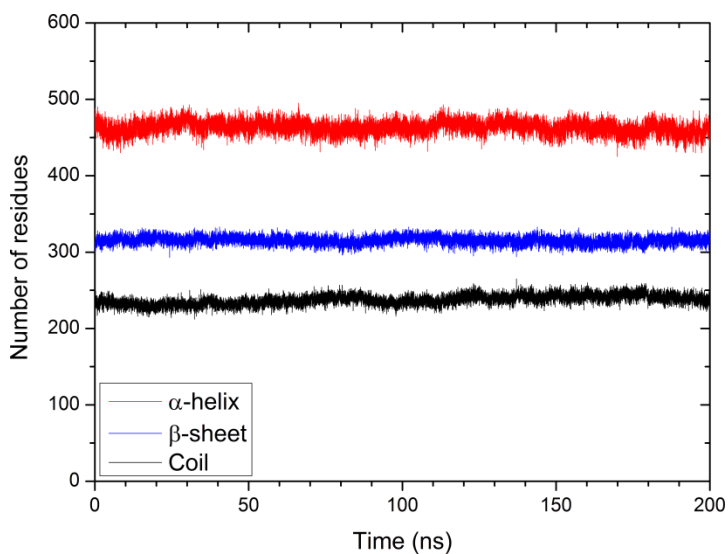


Figure 3-SI. Secondary structure content of the *HpUreDFG* complex plotted as a function of time.

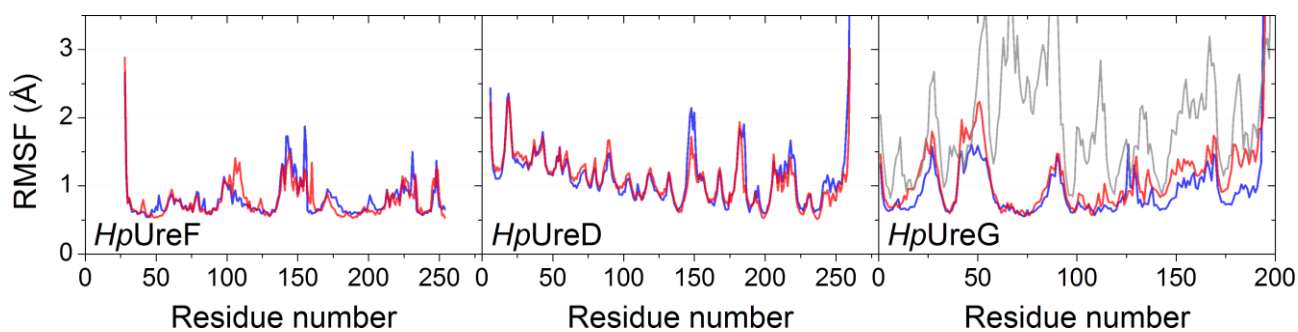


Figure 4-SI. Calculated root mean square fluctuations (RMSF) of the monomeric *HpUreF* (left panel), *HpUreD* (central panel) and *HpUreG* (right panel) C α during the simulation. The RMSF plots of the different monomers of the same protein are blue and red. In the right panel, the gray line represent the average RMSF obtained from replica exchange MD simulations performed on the *HpUreG* model structure (1).

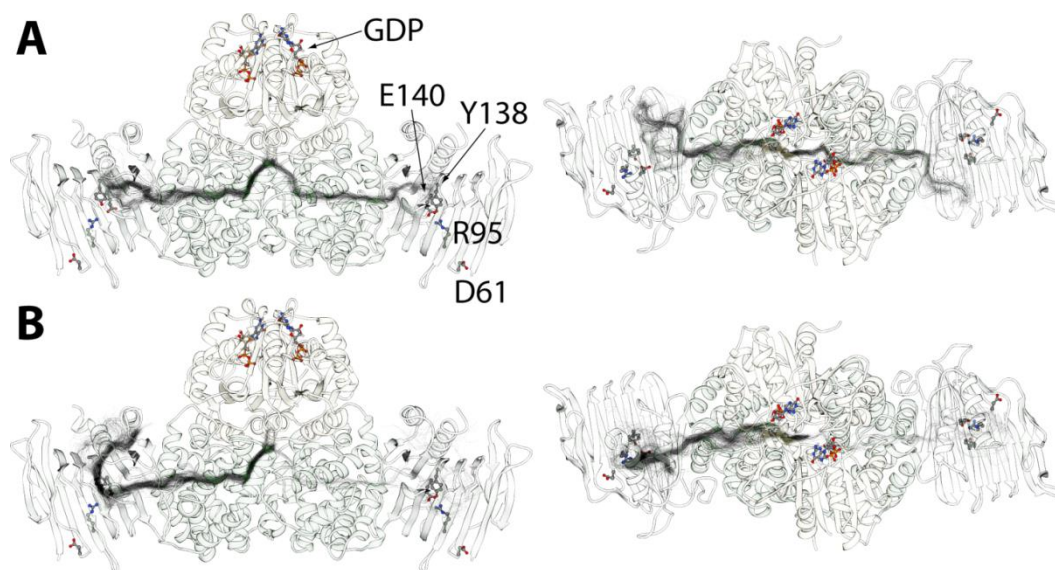


Figure 5-SI. Ribbon diagram of *HpUreDFG* complex and tunnels 4 (A) and 5 (B) identified throughout the MD simulation by CAVER 3.0 all depicted in one frame as the tunnel centerlines (see Table 1 and 1-SI). In the right panels, the *HpUreDFG* complex is rotated by 90° around the horizontal axis with respect to the orientation in the left panels.

Table 1-SI. Relevant regions in tunnels 4 and 5 (Table 1) identified by CAVER 3.0 and passing through both *HpUreF* and *HpUreD* during the MD simulation (Fig. 5-SI).

Tunnel #	<i>HpUreD</i> residues (and conservation ^a) at tunnel exit	Most frequent bottleneck residues
4	Ser132 (2), Ser133 (3), Ser134 (8), Gln135 (4), Gln166 (7), Asn204 (4), His233 (7)	<i>HpUreF</i> : Leu113 <i>HpUreD</i> : Leu130, Leu136, Ile164, Gln166, Ile171, Tyr172, Tyr173, Val201, Val203, His233
5	Ile216 (7), Glu217 (1), Ser219 (1), Val222 (1), Asp223 (1)	<i>HpUreD</i> : Ser139, Ile141, Leu198, Leu200, Val236, Leu246, Leu249, Arg250, Ile253,

^a Conservation calculated by the ConSurf server (2). The score goes from 0 (variable) to 5 (average) to 9 (highly conserved).

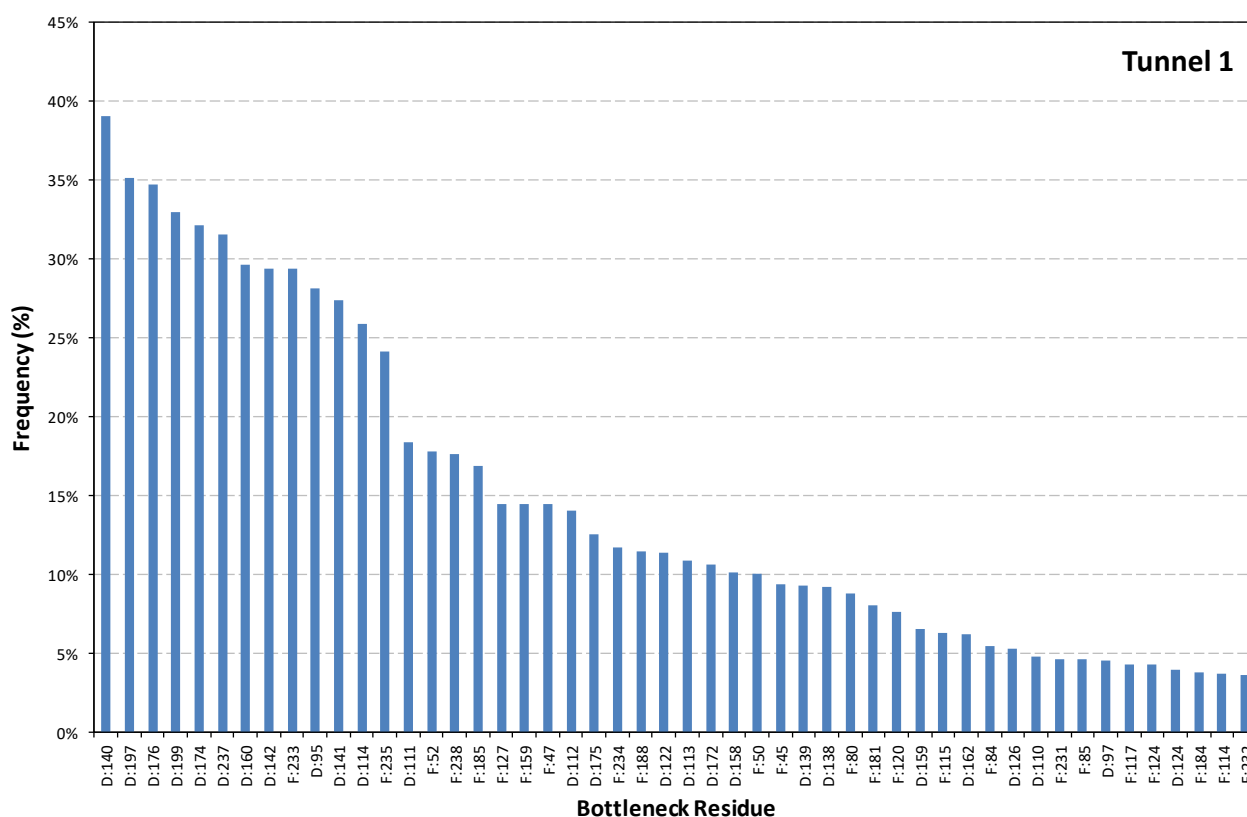


Figure 6-SI. Analysis of bottleneck residues found in tunnel 1 (Table 1).

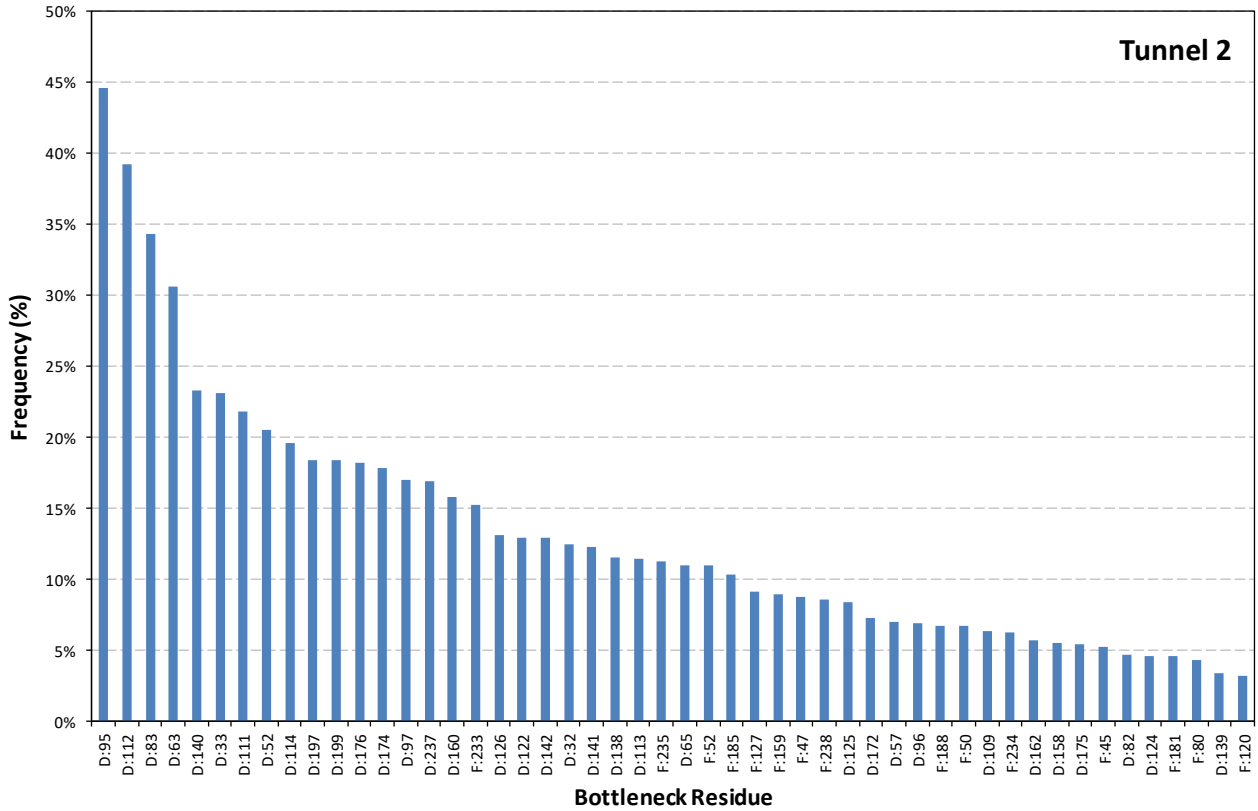


Figure 7-SI. Analysis of bottleneck residues found in tunnel 2 (Table 1).

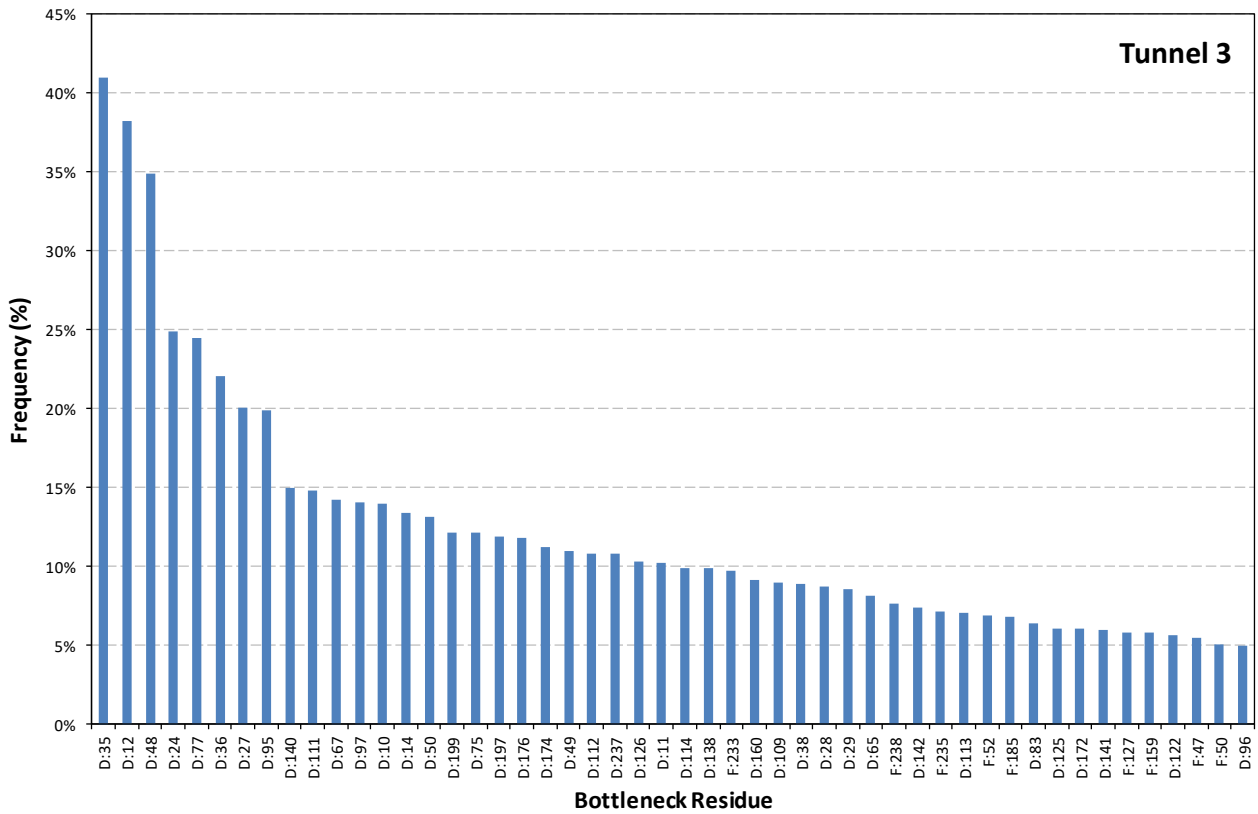


Figure 8-SI. Analysis of bottleneck residues found in tunnel 3 (Table 1).

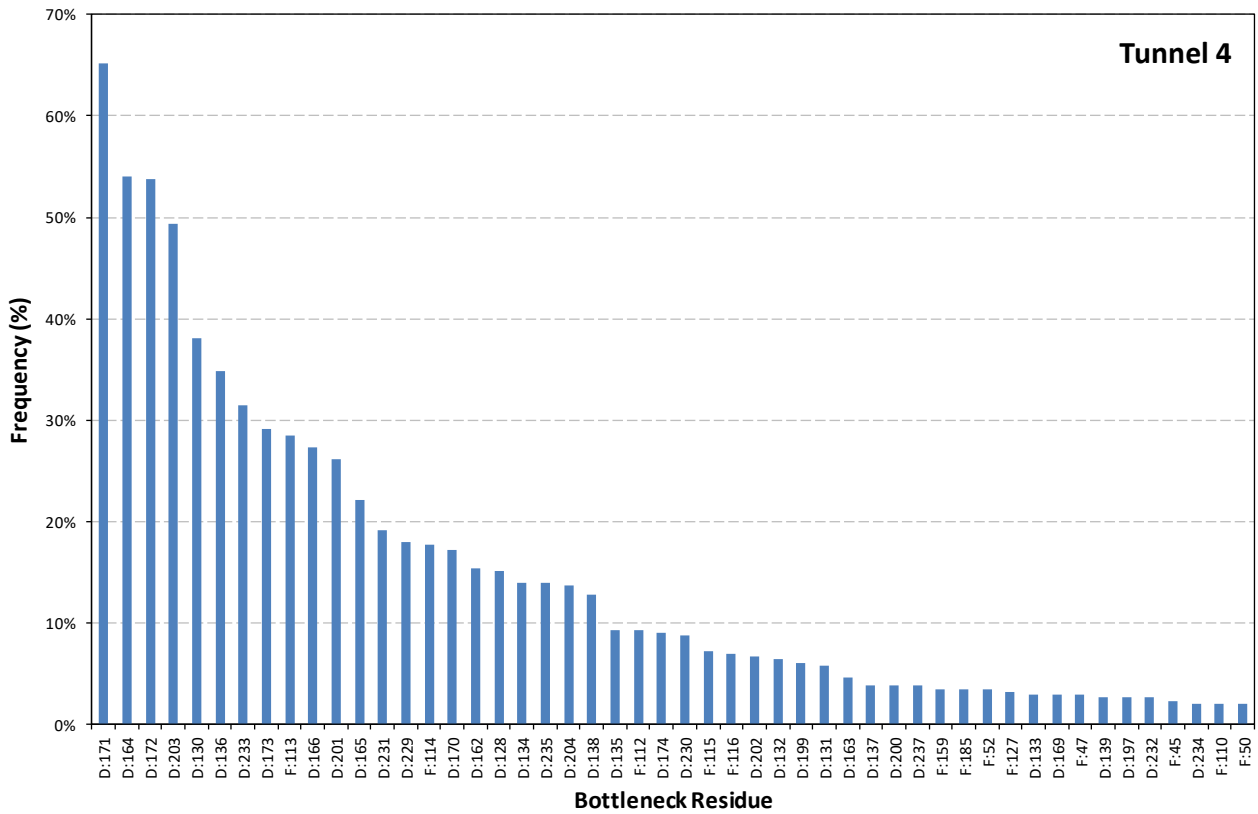


Figure 9SI. Analysis of bottleneck residues found in tunnel 4 (Table 1).

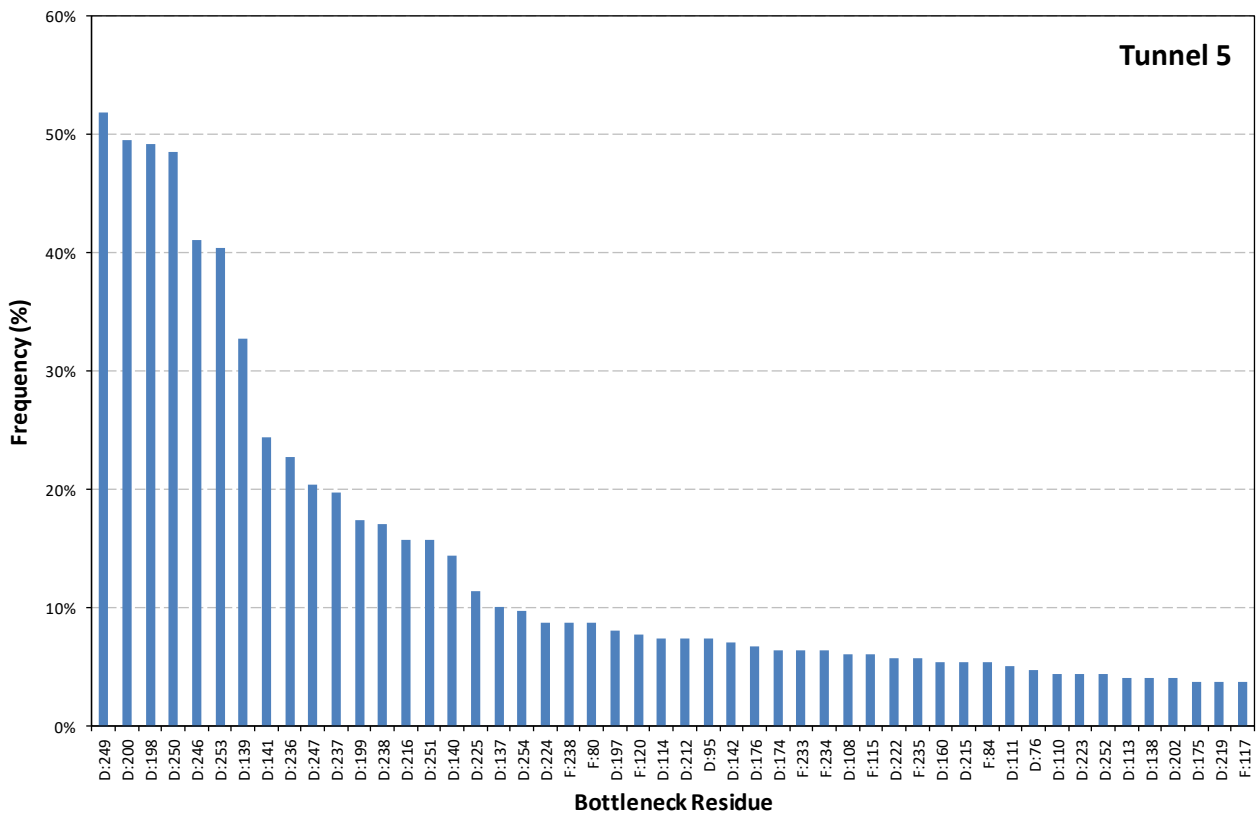


Figure 10-SI. Analysis of bottleneck residues found in tunnel 5 (Table 1).

Figure 11-SI. Multiple sequence alignment obtained by using PSI-BLAST and considering the 150 *UreD* best sequences with more than 15% and less than 90% sequence identity with respect to *HpUreD*.

	1	10	20	30	40	50
<i>HpUreD</i>	---	MNTYAQESKLRRLKTKIGADGRCVIEDNFFTPPFKLMAPFY	-----	PKD-DLAEIML		
UniRef90_A0A0K9H6B6_4_266	-----	WTGILRLLEAE-DRGKKTVAKNVYFQGAFKVMRPIY	-----	HDDSGQPCYYI		
UniRef90_A0A0K9GXZ4_4_265	-----	WTGTLRLDVE-ERQGKTVAKNVYFQGALKVMRPVY	-----	HDDSGQACYYI		
UniRef90_A0A0A3IXZ5_4_264	-----	WTGILSLDLE-NRNGKTVAKRAYFQGALKVMRPIY	-----	HDDSGQVCYYL		
UniRef90_K9ZPZ7_7_273	VNSPIDKNWHGRNLNLYA-KRQDSTQLIYNHHQAPFNIQRPFY	-----	PEGQEVCHSVI			
UniRef90_A0A0C1XDA3_13_272	-----	GWHGKLNLYA-DRLGTALISNSHQAPLKVQRPFY	-----	PEGQQICHSVI		
UniRef90_UPI000379D7E3_4_266	-----	WTGSLSLLELE-DRNGKTVAKRVYFQGAFKVMRPIY	-----	TDDSGQVCYYL		
UniRef90_UPI0002DF3930_13_277	-----	SWHGKLDLLYA-NRQGITQLIHAHHQAPLKVQRPFY	-----	PEGKAVCHSVI		
UniRef90_A0A0M0W0K1_1_266	-----	MNDWTGSLSLDLE-DRNGKTVAKRVYFQGAFKVMRPIY	-----	ADDSGQVCYYL		
UniRef90_UPI000422C885_4_265	-----	WTGTLRLDVE-VRQGKTVAKNVYFQGALKVMRPIY	-----	HDNSGQACYYI		
UniRef90_B4W160_8_270	-----	WQGSLELYA-NDQGKTRLVRDRITSPPLKVQRPFY	-----	PEGQGVCHTVV		
UniRef90_Q8YQZ4_10_269	-----	GWHGKLNLYA-DRNSTQLIYNHQAPLKVQRPFY	-----	PEGEKVCHSVI		
UniRef90_A0A0P1BUZ9_3_269	VNSPIDKTHWGKLNLYA-HRLNSTQLIHSHHQAPLKIQKPFY	-----	PEGEKICHSVI			
UniRef90_A0A0M1JRC4_17_282	---	VRQAGWQGIILNLYA-NHQGKTQVTDSYMKAPLKIQRPFY	-----	PEGTICHSVV		
UniRef90_UPI0007108B5C_4_266	-----	WTGVLRLGAE-ERNKKTVAKNVYFQGAYKVMRPIY	-----	HDESQGVCCYYI		
UniRef90_UPI0006A76A92_4_265	-----	WTGSLDLE-NRNGKTVARNVYFQGAFKVMRPIY	-----	HDSGQVCYYL		
UniRef90_W4ETC9_4_265	-----	WTGVLSDLE-ERRGKTVAKNVYFQGALKVMRPIY	-----	HDNSGQVCYYL		
UniRef90_A0A0D6KKC6_12_271	-----	TWHGKLNLYA-DRKNATQLIYNHQAPLKVQRPFY	-----	PEGEKVCHSVI		
UniRef90_A0A0D8ZYE2_11_271	-----	WHGSLNLYA-QHQGKTQVIHAQVKAPLKVQRPFY	-----	PE-DGVCHSVV		
UniRef90_B2IT63_10_269	-----	GWHGKLNLYA-DRQGATQLIYNHQAPLKVQRPFY	-----	PEAEKVCHSVI		
UniRef90_UPI000308766C_11_271	-----	TGWYKGLSLVYA-ERLQNTTTLIHNQAPLKVQRPFY	-----	PEGQVCHSVI		
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UniRef90_A0A0M2SWM6_4_265	-----	WTGELSDLE-NRNGKTVAGNVYFQGAFKVMRPIY	-----	HDDSGQVCYYL		
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UniRef90_A0A0J6GPD8_11_270 -----TPSWDAELDLGYG-RFGESTRPTLRRHAGPLRVQKHL Y-----AEGPVCQHII
UniRef90_Q4KJ05_11_269 -----TPSWHAELDLGYA-RCGATRPVLRHHLGPLRVQKHL Y-----AEGPEVCQHII
UniRef90_A0A0V7ZQT1_2_281 -----LNLTYA-SRQKKTIVVEQQNAQPLKVQRPLYPEEQTDPEGQKICHSII
UniRef90_A0A075PF54_11_269 -----TPSWHAELDLGYA-RFGATRPVLRHHLGPLRVQKHL Y-----AEGPEVCQHII
UniRef90_A0A0D5Y774_11_269 -----TPSWHAELDLGYA-RYGDSTRPVLRHSGPLRVQKHL Y-----AEGPEVCQHII
UniRef90_A0A0Q5EC30_11_271 -----TPSWHAELDLGYA-RFGDSTRPVQRHHLGPLRVQKHL Y-----AEGPEVCQHII
UniRef90_I4N4V9_11_269 -----APSWHAELDLGYA-RFGDTRPTLRRHLGPLRVQKHL Y-----AEGPEVCQHII
UniRef90_D4TUH6_7_266 -----SWHGKLELVYA-QRQNSTQLMFSHNQAPLKVQRPFY-----PEGEKICHSVI
UniRef90_UPI00048AE6EC_1_266 -----MNTWTGNLQKLEIE-NKRGKSI PKDIYFQGAFKLMRPKY-----FDDSGQPCFYI
UniRef90_UPI0007398261_11_285 -----WQGRALALTFE-DRQGETYLSRCFVQAPLKVQRPFY-----PEGRGVCHGVM
UniRef90_B0C790_12_273 -----SWHGRLSLTYE-KKAHQTVQVQSSYHQAPLNLQRPFY-----PEG-FVCHSVL
UniRef90_A0A066UMR7_26_298 -----GWQANLNLTFE-DRGDKTVLKHRYQLGPLAVQRPLY-----PDG-KTCHSYL
UniRef90_A0A0Q9XW12_4_265 -----WTGILQLDVE-NRQDKSVTKNLHFQGAFKIMRPVY-----HQSQKPCYYI
UniRef90_A0A0S7ZTJ9_14_276 ---MQANGWHAQLDLDFE-QRESRTVLRARQHFGPLVVQKPFY-----PEG-AVCHVYI
UniRef90_A6SZ04_26_286 -----QARLSLAFD-DDAGTTRMTERS HFGPLRVQKTL Y-----PEHPAVCHAI I
UniRef90_U3H3U5_9_267 -----TPSWHAELDLGYA-RRDERTIPVLRHHLGPLRVQKHL H-----AEGPEVCQHII
UniRef90_A0A073CY52_6_272 ---INPSQWQGLELDYQ-KINNSTQLVKAYSQAPLKIQRSFY-----PEGEEICHNSV I
UniRef90_U6ZYX1_11_270 -----TPSWHAELDLGYA-CTGNATRPVLRHSGPLRVQKHL Y-----AEGPVCQHII
UniRef90_UPI00067CF5D4_26_284 -----VARLRLGFS-DDAGVTRMTERS HFGPLRVQKPLY-----PEHPSICHAI I
UniRef90_A0A0K2BGW7_26_288 -----KARLTLGFA-DDAGTTRMTERS HFGPLRVQKPLY-----PEHPAVCHAVI
UniRef90_A0A011QEK6_40_302 -----RPGWQARLALAFE-RAGETSALVRHEHFGPLRVQKALY-----PEGPDVCHAIL
UniRef90_G4T117_15_272 ---SRQGWQAE LRLGFA-KNESRTVLRHRAHRGPLTVQRPFY-----PEG-DVCHLYL
UniRef90_Q87VP5_11_271 -----TPSWHAELDLGYG-RFYDCTRPVQRHKGPLRVQKHL Y-----AEGPEVCQHII
UniRef90_A0A089YS31_11_269 -----TPSWHARLELGYA-RFGDSTRPTLRRHLGPLRVQKHL Y-----AEGPEVCQHII
UniRef90_UPI0004174C9A_9_267 -----TPHWQAELELGYA-RFGATRPVLRHSGPLRVQKHL Y-----AEGPEVCQHIV
UniRef90_UPI000379F3E4_11_286 -----GWQGSNLNIYA-NRTGTSQLVGERVGA PLKVQRPFY-----PEGAAVCHSVI
UniRef90_A4VQU8_9_267 -----TPHWQAELELGYT-RIGDATRPVLRHSGPLRVQKHL Y-----PEGSEVCQHII
UniRef90_A0A0M3V4J1_7_297 ----TATAWQGKLNLYE-NCQNSTQLIYNHHQAPLKVQRPFY-----PEGEQVCHSVI
UniRef90_A0A098ESZ3_4_266 -----WTGILRLDVAE-DRYGKTVARNVYFQGALKVMRPIY-----HDNSGQACYYI
UniRef90_UPI000345DD51_13_277 ----NDSAWHARLTLGFA-DDAGTTRLVERS HAGPLRVQKPLY-----PEGGAVCHAI V
UniRef90_UPI00047D06E7_9_270 ----SSGWKAKLELAVY-ARPERTVLARSSRRGPLAVQRAF Y-----PED-GVCHSYV
UniRef90_I3BUX5_1_262 ---MAASGWQAE LSLGFA-CRGGKTVLAERRQGPLAVQRPFY-----PEG-DVCHAYV
UniRef90_UPI000780B9AB_11_271 -----TPSWHAELDLGYG-RFGDSTRPIQRHKGPLRVQKHL Y-----AEGPEVCQHII
UniRef90_UPI000255752C_11_273 -----TPSWHAELDLGYA-RDTRTPVMMRHHGPLRVQKHL Y-----AEGPVCQHII
UniRef90_UPI000484E5E1_11_269 -----TPSWHAELDLGYA-RFGDSTRPILRRHSGPLRVQKHL Y-----AEGPVCQHII
UniRef90_A0A0D6AS13_1_264 ---MSGQNWQGKINLVE-YQEGKTKIKSAYHQAPLKIQRSFY-----PEGDSICHSVI
UniRef90_UPI00034A425D_18_281 -----WHGKLELDFA-NRDGATHVKHSYSQAPWLKQRPFY-----PEGDRICHSVL
UniRef90_UPI00046A7B93_11_269 -----TPSWHAELDLGYA-RFGATRPVLRHHLGPLRVQKHL Y-----AEGPVCQHII
UniRef90_I3YAM1_6_262 -----PGWNARLALGFA-ERAGRTRLVERHRQGPLAVQRPFH-----PEG-APCHCYL
UniRef90_A0A0D9AIT7_9_267 ----TPHWNAELDLGYA-RFDHVTRPVLRHSGPLRVQKHL Y-----PEGPEVCQHII
UniRef90_UPI0003FDB5F5_4_265 -----WTGVLDLVME-NRDLGRSVAKSVYFQGAFKVMRVPY-----FNKNSYPCYYL
UniRef90_K9SBL5_6_267 ----TTQPWCGLDLVYA-QRQGITQPIHNLALAPLKIQRPFH-----PEG-AVCHSVL
UniRef90_UPI00040AC544_17_274 ----SAQGWEAKLALGFA-RQHGKTVLAHRRHYGPLTVQRPFY-----PEG-GVCHVYI

UniRef90_A6D6Q9_31_296 ----TQFGWKASLDLTFI-DRGDKTVLKHRSQQGPLAIQRPLY-----PEG-NPCHTYL
 UniRef90_B8HW54_12_274 -----SWQGNLCLKFA-RKQDTTQLIHCLGKAPLKLQRPFY-----PEGPQICHGVI
 UniRef90_A0A0J6H3B0_11_269 -----TPHWLAELELGYG-RFGDSTRPTLRRHCGPLRVQKHLY-----AEGPQVCQHI I

	51	60	70	80	90	100
<i>HpUreD</i>	LAVSPGMMRGDAQDVQLNIGPNCKLRITSQSFEKIHNTEDGF	-----	ASRDMHIVVVG			
UniRef90_A0A0K9H6B6_4_266	LNPGGGYLDGDRYRMQIALDKQAKMTLTTSQATKVKYKTPNNY	-----	VYQETEISLK			
UniRef90_A0A0K9GXZ4_4_265	LNPGGGYLDGDRYNLQFSLKEKTKLTLTTSQATKVKYKTPNQH	-----	AYQETEFLK			
UniRef90_A0A0A3IXZ5_4_264	LNPGGGYLDGDRYRMEISVDAGAIEVLTTSQATKVKYKTPKSL	-----	AYQETEITLK			
UniRef90_K9ZPZ7_7_273	LHTAGGIVGGDRLSDDIHLKEDSQALITTTAAAGKVYRSNGLP	-----	AKQTVNIQIG			
UniRef90_A0A0C1XDA3_13_272	LHTAGGIVGGDRLSLNFHLQPNQALITTTAAASKIYRSNGTQ	-----	AKQSVNIQVD			
UniRef90_UPI000379D7E3_4_266	LNPGGGYLDGDRYKMDISADEGSKVTLTTSQATKVKYKTPKNY	-----	AYQETVIRLK			
UniRef90_UPI0002DF3930_13_277	LHTAGGIVGGDKLSCNFQLQEPESQVLTITTTAAAGKIYRSNGRQ	-----	ATQONIEVVS			
UniRef90_A0A0M0W0K1_1_266	LNPGGGYLDGDRYKMQISADEGSKVTLTTSQATKIYKTPKSH	-----	AYQETEINLK			
UniRef90_UPI000422C885_4_265	LNPGGGYLDGDRYKQLQFSLKEQAKLTLTTSQATKVKYKTPNQH	-----	AYQETEFLK			
UniRef90_B4W160_8_270	LHTAGGIVGGDRLSQTIHLQEDSQALITTTAAASKIYRSNGQR	-----	ANQRIHIHVE			
UniRef90_Q8YQZ4_10_269	LHTAGGIVGGDRLSYNLHLQPNQAALITTTAAAGKVYRSNGLQ	-----	ARQTIIEKID			
UniRef90_A0A0P1BUZ9_3_269	LHTAGGIVGGDRLSKMEISADEGSKVTLTTSQALITTTAAASKIYRTNGLQ	-----	ARQNETIIRLQ			
UniRef90_A0A0M1JRC4_17_282	LHTAGGIVGGDRLAQNPHLRENAKALITTTAAASKIYRSNGNN	-----	AQQTINIKVD			
UniRef90_UPI0007108B5C_4_266	LNPGGGYLDGDRYQMKISLEKQAKLTLTTSQATKIYKTPNSH	-----	AYQEAENLKL			
UniRef90_UPI0006A76A92_4_265	LNPGGGYLDGDRYRMIISAENSKVTLTTSQATKVKYKTPTDH	-----	VYQETEISLK			
UniRef90_W4ETC9_4_265	LNPGGGYLDGDRYKMEISANEGAKVTLTTSQATKVKYKTPKSF	-----	AYQETIISLK			
UniRef90_A0A0D6KKC6_12_271	LHTAGGIVGGDRLSLNFHLQPHAQALITTTAAASKIYRSNGLQ	-----	AKQIIDIKVD			
UniRef90_A0A0D8ZEY2_11_271	LHTAGGIVGGDRNTLSFHLQPSQALITTTAAASKIYRSNGSS	-----	ASQNVQIQVD			
UniRef90_B2IT63_10_269	LHTAGGIVGGDRLSNHLQPPQAALITTTAAASKIYRSNGLQ	-----	ARQTIQMQVD			
UniRef90_UPI000308766C_11_271	LHTAGGIVGGDRLSKMFHLSQFNALITTTAAASKIYRSNGTQ	-----	ARQNETIIRVD			
UniRef90_K9R6Q0_10_280	LHTAGGIVGGDRLSDFHLQPDKALITTTAAANKIYRSNGLQ	-----	ARQNIIDIKID			
UniRef90_A0A127D3L2_4_264	LNPGGGYLDGDRYKIQITLEKQARLTLTTSQATKVKYKTPNTH	-----	AYQETEIIILQ			
UniRef90_UPI00028931D6_4_266	LNPGGGYLDGDRYQLKISLEKQAKLTLTTSQATKIYKTPKHH	-----	AYQETEINLK			
UniRef90_A0A0M0ENP6_4_266	LNPGGGYLDGDRYKMEISADEGSKVTLTTSQATKVKYKTPKGY	-----	AYQETIHLQ			
UniRef90_A0A0S3PHU6_16_275	LHTAGGIVGGDRLSYNFHLQPNQAALITTTAAASKIYRSNGLL	-----	AKQITINIKID			
UniRef90_A0A081NYG6_3_264	LNPGGGYLDGDRYKLDIELAEADAKLLLTTSQSTKVKYKTRNTA	-----	PVQDMEIRMK			
UniRef90_A0A0K9GPB1_4_266	LNPGGGYLDGDRYHLHIALEEQARVTLTTSQATKVKYKTPQSY	-----	AYQETEIFLK			
UniRef90_UPI000717378B_2_265	LNPGGGYLDGDRYRMEIAVEEGAKVTLTTSQATKVKYKTPNDH	-----	VYQETEISLK			
UniRef90_K9W1V1_14_278	LHTGGVGGDRLSLNFHLQPNTHALITTTAAAGKVYRSNGLE	-----	ARQVEMRVE			
UniRef90_K9U4Q1_17_272	LHTAGGIVGGDCLSLNQLQPRSQALVTTTAAASKIYRSNGLQ	-----	ARQIVEIQID			
UniRef90_A0A0M2SWM6_4_265	LNPGGGYLDGDRYRMIISADEGSKVTLTTSQATKVKYKTPKDH	-----	VYQESEIILK			
UniRef90_UPI0003652A48_11_275	MHTAGGIVGGDRLTFDFHLSAGSQALITTTAAASKIYRTNGRE	-----	AHQVINDVA			
UniRef90_UPI00047A812C_16_286	LHTAGGIVGGDRLSYHLHLQPNQAALITTTAAAGKIYRSNGTT	-----	ARQTIIEKVD			
UniRef90_K9TKA4_12_277	LHTAGGIVGGDSLQSIHVQENAHALITTTAAAKIYRSTGEV	-----	ARQSIKINVD			
UniRef90_M7NKH7_1_269	LNPGGGYLDGDRYRMDITAEPPARVTLTTSQATKVKYKTPKDH	-----	AYQETTMTLK			
UniRef90_K6DR39_4_265	LNPGGGYLDGDRYSYQMKISLAENARVTLTTSQATKVKYKTPNKY	-----	AYQESDISLK			
UniRef90_A0A0B4RFS1_1_265	LNPGGGYLDGDRYRMIISADEGSKVTLTTSQATKVKYKTPKGY	-----	AYQETIYLE			
UniRef90_A0A168N9T6_4_266	LNPGGGYLDGDRYKMEISADEGSKVTLTTSQATKVKYKTPSY	-----	AYQEAENLKL			
UniRef90_A0A139X4D9_7_274	LHTAGGIVGGDRLSYKHLQPKAALITTTAAASKIYRSNGAQ	-----	ARQNIIDIQVD			
UniRef90_UPI00030AB192_16_277	LHTAGGIVGGDRLSYDFHLQPHAQALITTTATAGKIYRTNGMT	-----	AKQMEIEKVD			
UniRef90_K7W9H0_9_269	LHTAGGIVGGDRLSHHLQPDNALITTTAAAGKIYRSNGLP	-----	ARQTVNIQVD			
UniRef90_UPI00034A5E0C_10_263	LHTAGGIVGGDRLSKIHLPDAQAVITTTAAASKIYRSNGLP	-----	ATQITINLKID			
UniRef90_A0A0A0E4Q3_4_265	LNPGGGYLDGDRYQMKIQLGENAKLTLTTSQATKVKYKTPNRF	-----	AYQESEISLQ			
UniRef90_UPI000717263C_4_266	LNPGGGYLDGDRYKLEFADDEGSKVTLTTSQATKVKYKTPKSH	-----	AYQETIHLK			
UniRef90_K9QPZ4_10_269	LHTAGGIVGGDRLSKTIHLQPNQAVITTTAAAGKIYRSNGLQ	-----	ARQTIIDIQID			
UniRef90_UPI0002D28249_14_276	LHTAGGIVGGDRLSNLFHLQPHAQALITTTAAASKIYRTNGLR	-----	ARQITINIQID			
UniRef90_F9DU20_4_266	LNPGGGYLDGDRYRMEITLDEQAQLTLTTSQATKVKYKTPTRQ	-----	VYQESVFHMK			
UniRef90_UPI00047933CA_3_266	LNPGGGYLDGDRYKMKISLEKNARVMTTTSQATKVKYKTPKNH	-----	AYQEAFFLE			
UniRef90_W7RFE8_4_266	LNPGGGYLDGDRYRMEITLLEEQALTLTTSQATKVKYKTPHTP	-----	VLQNETIILK			
UniRef90_UPI0007441C40_4_265	LNPGGGYLDGDRYRMIISAAENSKVTLTTSQATKVKYKTPKDH	-----	VYQESEIFLK			
UniRef90_A0A0T7BRT9_7_268	LHTAGGIVGGDRLSNHLQPSQVLLTTAAASKIYKSNGLQ	-----	ARQDVTIHD			
UniRef90_UPI0006A78357_4_266	LNPGGGYLDGDRYQMKISLEKQARLTLTTSQATKIYKTPKNH	-----	AYQETEITLK			
UniRef90_UPI0007C7BB46_4_266	LNPGGGYLDGDRYRMEITLLEEQALTLTTSQATKVKYKTPHTP	-----	VLQNETIILK			
UniRef90_UPI000472611B_4_265	LNPGGGYLDGDRYQMQVTVQEEARLTLTTSQATKIYKSPRSF	-----	SYSEMEFTLK			
UniRef90_UPI0002ACBA0D_11_270	LHTAGGIVGGDRNLSFHLQPHSQSLITTTATASKIYRSNGLL	-----	AKQNIQMQVD			
UniRef90_A0A0C2KR59_11_269	LHTAGGIVGGDRLSNLFHLQRNAQALITTTAAASKIYRSNGTQ	-----	ARQSEIETVD			
UniRef90_K9WE93_4_277	LHTAGGIVGGDRLSQTIHLSPHAHALITTTAAASKIYSGKGRACPPQGPQAKQTIQIQID	-----	AKQVIEIKVE			
UniRef90_A0A0M0SP30_16_277	LHTAGGIVGGDRLSYDFHLQPDQAALITTTATAGKIYRSNGMI	-----	AKQVIEIKVE			
UniRef90_K9Q9K1_10_268	LHTAGGIVGGDRLSHFLHLQPNQALITTTAAASKIYRSNGLQ	-----	ARQTIIDIQID			
UniRef90_A0A0S3TTX4_17_278	LHTAGGIVGGDRLSYNFHLQPHAQALITTTATAGKIYRSNGTI	-----	AKQNIIEKVD			
UniRef90_K9VQF3_56_323	LHTAGGIVGGDRLSGFHLQPNKALITTTAAAGKIYRSNGLE	-----	SQNKIIDIQLD			
UniRef90_W1SM28_4_265	LNPGGGYLDGDRYQMKLSLLEKAKLTLTTSQATKVKYKTPNNF	-----	AYQEAESLQ			
UniRef90_A0A0C1N935_15_285	LHTAGGIVGGDRLSCKVHLQPKAALITTTAAASKIYRSNGAQ	-----	ARQNIIEIQID			
UniRef90_A0A139SK67_11_275	LHPAGIVGGDSLAIQVLAAGAHALLTPGAGKWRYSGGPS	-----	ASLTQITVVG			
UniRef90_UPI00041C7CDC_4_265	LNPGGGYLDGDRYHLQFSLKEQARLTLTTSQATKVKYKTPSY	-----	AYQETEIFLK			
UniRef90_K9XHH8_15_275	LHTAGGIVGGDKLSLNFHLQQAHTLITTTAAASKIYRSNGWE	-----	ARQNIQVQVD			
UniRef90_UPI0002E7D901_4_265	LNPGGGYLDGDTYRMYKVTLAEDSRLTLTTSQSTKVKYKTPVSY	-----	AYQETEFLK			
UniRef90_A0ZB05_10_269	LHTAGGIVGGDRLSNHLQNTAQAALITTTAAASKIYRTNGLQ	-----	ARQNIIDIQVD			
UniRef90_D4ZSS4_5_270	LHTAGGIVGGDRLSNHLQADTKVLLTTAAASRVYRSTGKT	-----	ASQNVKIKLE			
UniRef90_A0A0F5YFY1_6_271	LHTAGGIVGGDRLLQEIHLQPKTQAVITTTASASKIYRSNGKQ	-----	AKQTVKIKVD			
UniRef90_K9T9Y9_59_322	LHTAGGIVGGDRLSQTIHLRENANTLITTTAAAGKVYRSNGKL	-----	AKQIVRIKIE			

UniRef90_K9VAD2_10_273 LHTAGGVVGGDKLSYDVHLQDNSQALITTAASKIYRSNGYQ-----AKQDIKIKLD
UniRef90_W7Z4J7_4_265 LNPPGGYLDGDRYQMKISLNERARLTQTQSATKIYKTPNQL-----AYHETEINLK
UniRef90_Q47G52_13_278 LHPPSGIAGGDHLAISAEVGECSHAQLTTPGAGKWYRSGGAE-----ASQRVAFTVG
UniRef90_UPI0004024FB0_3_269 LHTAGGILGGDRLTSDIHLQPQTNALITTAASKIYRSQGLP-----ARQIVNIQVN
UniRef90_K8GMD3_12_265 LHTAGGVVGGDRLFLNLELQPAHALITTAAGKIYRSNGLE-----AQQIVTVKVA
UniRef90_A0A0S3UB12_16_269 MHTAGGIVGGDRLSFEFRLAADSRLITTPAASKIYRTNGRE-----AHQTIQIDIE
UniRef90_A0A0F7D4R9_4_265 LNPPGGYLDGDRYRMRVSLVGDNSRLTTPGASTKVKYKTPKSY-----AQYQTEFHLK
UniRef90_A0YQS4_5_271 LHTGGGIVGGDRLQEIHLQPQTQALITTAASKIYRSNGKQ-----AKQITINIQVD
UniRef90_A0A0Q8RCL2_14_276 VHPPGGVVGDELRLIDASVGNAGALITTPGAACKWYKANGHI-----SRQDVHLQAG
UniRef90_UPI0005625009_5_271 LHPPGGVVGDSLIDIVHVESGAQALITTPGATKFYRSNGRL-----ATQIQTLTSLVA
UniRef90_UPI000305E365_16_284 LHTAGGVVGGDRLSINFLQPHAQALITTPATAGKIYRSNGMT-----AKQIIEIKVD
UniRef90_UPI0002E38242_11_269 VHPPGGIAGGDRLDIRASVERDAWAQLTSPGAACKWYRATGS-----ASQTLTSLKVA
UniRef90_G8Q511_12_270 VHPPGGIAGGDRLDISAHVGPDAWAQLTSPGAACKWYRAAGP-----AYQQLTSLVA
UniRef90_A0A168IUL4_4_266 MSFGGGIVGGDRYKLEIHLGEQAQMLTTQSATKIYKTINRP-----AMQEMNIVLE
UniRef90_UPI0004799FB1_14_281 LHPPSGIAGGDRLDISAVDNSHAQLTTPGAGKWYRSGGAA-----ASQVTLNLVA
UniRef90_Q3KIS7_11_269 VHPPGGIAGGDRLDISARVAQGAWAQITSPGAACKWYRAAGP-----AYQSLNLHVA
UniRef90_K9XZ09_12_271 LHTAGGIVGGDRLSQIKVQPNASHLITTAASKIYRSNGRE-----AKQILTIEIE
UniRef90_A0A090RU86_25_288 LHPPGGVVGDDTLQIKAKAERGASVLITTPGATKFYRSNKY-----AKQSQILSVE
UniRef90_A0A0M5LWB1_11_269 VHPPGGIAGGDRLDISARVEPAAWAQLTSPGAACKWYRAAGP-----AYQTLDLKVA
UniRef90_A0A0C2I8A1_11_269 VHPPGGIAGGDRLAISARVEPAAWAQLTSPGAACKWYRATGP-----AYQTLDLKVA
UniRef90_H3SNI3_3_265 MNPPGGVVGDDRYRMELELGEASSLMTTQSSTKIYRTPKEP-----VFQTRIALVA
UniRef90_A0A0Q0XPT8_11_269 VHPPGGIAGGDRLHINAHVGPDAWAQLTSPGAACKWYRAAGP-----AYQTEVELSVA
UniRef90_K4ZJ70_4_265 LNPPGGYLDGDRHLSINFLVLEEGARLTLTQAATKIYKTPKPP-----AYQTEIIRLK
UniRef90_A0A085V951_11_269 VHPPGGIAGGDRLDISASVGNPNAWAQLTSPGAACKWYRAAGP-----AYQQLDLQVA
UniRef90_A0A098SV87_11_271 VHPPGGIAGGDRLDIDVSVGANAWAQLTSPGAACKWYRAAGP-----AYQQLLELSVA
UniRef90_A0A0A1GEL6_9_267 VHPPGGIAGGDRLDISAVGSGAWAQLTSPGAACKWYRAGGP-----AFQNVHLRVE
UniRef90_I4CP19_9_267 LHPPGGIAGGDRLDISASVAGAWAQLTSPGAACKWYRAVGP-----AYQKLDLRVA
UniRef90_A0A0W0P2S5_11_269 VHPPGGIAGGDRLAIHARVDTGAWAQLTSPGAACKWYRANGP-----ASQRLELQVA
UniRef90_C3K5A6_11_269 VHPPGGIAGGDRLDISAHVAGAWAQLTSPGAACKWYRAGGP-----AYQQLDLQVA
UniRef90_A0A078LV36_9_267 VHPPGGIAGGDRLDISAHAGRNVAWVQLTSPGAACKWYRSNGP-----ASQTLNLHVE
UniRef90_J3GGT8_11_269 LHPPGGIAGGDRLDISASVGNNAWAQLTSPGAACKWYRAAGP-----AYQKLDLRVA
UniRef90_A5L5M9_32_304 LHPPGGVVGDDTLNINVNLEHGAHALITTPGATKFYRSNNKY-----AKQKQTLRVE
UniRef90_A0A0J6GPD8_11_270 VHPPGGIAGGDRLNIRASVGPDAWAQLTSPGAACKWYRAAGP-----AYQTEVELKVA
UniRef90_Q4KJ05_11_269 VHPPGGIAGGDRLAISARVDSGAWAQLTSPGAACKWYRATGP-----ASQTLNLQVA
UniRef90_A0A0V7ZQT1_2_281 LHTAGGVVGGDRLSDFLQPNQALITTAASKIYRSNGSQ-----ARQKLEINVD
UniRef90_A0A075FP54_11_269 VHPPGGIAGGDRLDITAHLAQGAWAQLTSPGAACKWYRASGP-----AYQQLALTVE
UniRef90_A0A0D5Y774_11_269 VHPPGGIAGGDRLQIRASVDRDAWAQLTSPGAACKWYRATGP-----AYQTELELTA
UniRef90_A0A0V5EC30_11_271 LHPPGGIAGGDRLAISAVVGPQAWAQLTSPGAACKWYRAAGP-----AFQHLDLHVE
UniRef90_I4N4V9_11_269 VHPPGGIAGGDRLINVNVDGAWAQLTSPGAACKWYRAAGP-----AYQTLNLHVA
UniRef90_D4TUH6_7_266 LHTAGGVVAGDRLSSNIHLQSETDVLTITTAASKIYRSNGLY-----AKQTVSIXID
UniRef90_UPI00048AE6EC_1_266 LNPPGGYLDGDRYRMDLNLEEKAEALLTTPQAATKVKYKTPNQS-----VIQETNISMG
UniRef90_UPI0007398261_11_285 LHTAGGIVGGDRLSTTLQLEANAHALITTPATAGKVYRSNGQE-----AQQEVQISLA
UniRef90_BOC790_12_273 MHTAGGMVGGDRLSINVTLQEPQTHALITTTAGKIVYRSNGHG-----AQQTVCQQLD
UniRef90_A0A066UMR7_26_298 LHPPGGVVGDDRLNIDISAESGAHTLITTPGATKFYRSNAKY-----AKQKQMLHVA
UniRef90_A0A0Q9XWI2_4_265 LNPPGGYLDGDRYRMEVSVQEEAKALTTQSATKIYKTPSKH-----AYQETEIHLK
UniRef90_A0A0S7ZTJ9_14_276 IHPPGGVVGDDTLINVTSCERSQTLITTPAANKFYRSNGPV-----ARLEQILTLK
UniRef90_A6SZ04_26_286 VHPPGGIVGGDQLITARVGDRAHALITTPGAGKWYRANGQL-----SQQVVSLEVG
UniRef90_U3H3U5_9_267 VHPPGGIAGGDRLDLSARVGDGAWAQLTSPGAACKWYRARGP-----AFQTLALRVE
UniRef90_A0A073CY52_6_272 LHTAGGMVGGDRLSQTINLQPETQVLLTTPAASKIYRSNGET-----AQNTINIEIQ
UniRef90_U6ZYX1_11_270 VHPPGGIAGGDRLAIRARVDSGAWAQLTSPGASKWYRAASP-----ASQLELQVA
UniRef90_UPI00067CF5D4_26_284 VHPPGGIVGGDELHIDATLGDQAHALITTPGAGKWYRANGNL-----SHQYVTLQAA
UniRef90_A0A0K2BGW7_26_288 LHPPGGIAGGDRLNIDISAVGNNAWAQLTTPGAGKWYRANGFV-----SQQKSLTAT
UniRef90_A0A011QEK6_40_302 LHPPGGIAGGDSLEISLHVAGAHALITTPGAGKWYRSNGRP-----ARQSLSVRVG
UniRef90_G4T117_15_272 LHPPGGVVGDDRLTIEVKAHEGSHALITTPAAGKFYRSEGDG-----ASQSVTMTIE
UniRef90_Q87VP5_11_271 VHPPGGIAGGDRLDISVNVGAHAWAQLTSPGAACKWYRAASP-----AFQQLLEHVA
UniRef90_A0A089YS31_11_269 VHPPGGIAGGDRLDISAVQVNAWAQLTTPGAACKWYRALS-----AYQTELELHVA
UniRef90_UPI0004174C9A_9_267 VHPPGGIAGGDRLAIRAVGDGAWTQLTSPGAACKWYRAAGP-----AFQTELELRVG
UniRef90_UPI000379F3E4_11_286 LHTAGGVVGGDRLCFDITLHPDTRALITTAAGKIYRTNGLE-----AKQTALIKIA
UniRef90_A4VQU8_9_267 VHPPGGIAGGDRLDISVTLGPGAWAQLTSPGAACKWYRAASP-----AFQDLQLRVE
UniRef90_A0A0M3V4J1_7_297 LHTAGGVVGGDRLSHFHLKPNQALITTAASKIYRSNGLQ-----ARQTIIDIQID
UniRef90_A0A098ESZ3_4_266 LNPPGGYLDGDRYRMOFLLEENAKLITTTQSATKVVYRTPRLH-----AYQETIEVMK
UniRef90_UPI000345DD51_13_277 VHPPGGVVGDDQLSISARVGPAAHALITTPGAACKWYKANGKV-----SRQVVYLQAG
UniRef90_UPI00047D06E7_9_270 LHPPGGVVGGDDELIDHVTVEAEHALITTPGATKFYRSAGPF-----AEQIQQFKVE
UniRef90_I3BUX5_1_262 LHPPGGVVGDDLHLDFVNDAAHALITTPGATKFYRSAGMQ-----AAHQQDFHIS
UniRef90_UPI000780B9AB_11_271 VHPPGGIAGGDRLDISASVGPQAWAQLTSPGAACKWYRAASP-----AYQKLELQVA
UniRef90_UPI000255752C_11_273 VHPPGGIAGGDRLDIDHILGENAWAQLTSPGAACKWYRAAGP-----AYQQLNITVA
UniRef90_UPI000484E5E1_11_269 VHPPGGIAGGDRLDISASVERDAWAQLTSPGAACKWYRANS-----AYQQLLELHVA
UniRef90_A0A0D6AS13_1_264 LHTAGGIVGGDRLSQTILHSSNSQVITTPAATKIYRTEQEK-----AQQLEIINLE
UniRef90_UPI00034A425D_18_281 LHTAGGMVGGDRLSAEINLAENTHALITTAASKIYRSNGLI-----AQQSTRIQIA
UniRef90_UPI00046A7B93_11_269 VHPPGGIAGGDQLAISARVNDGAWAQLTSPGAACKWYRANGP-----AGQTLALQVA
UniRef90_I3YAM1_6_262 LHPPGGIVGGDRLDISAVSDGSAHALITTPGATKLYRSNGAE-----AHQTLHLRVA
UniRef90_A0A0D9AIT7_9_267 VHPPGGIAGGDRLDISATVGDGAWAQLTSPGAACKWYRAAGP-----AFQTLALRVE
UniRef90_UPI0003FDB5F5_4_265 LNPPGGYLDGDRYQMKVTLGERAMLTTPQSSTKVVYRTPK-----VYQETIFHMK
UniRef90_K9SBL5_6_267 LHTAGGIVGGDRLTIRARLEPESHALLITTAASKLYRSNGFE-----AQQRVHLQAG
UniRef90_UPI00040AC544_17_274 LHPPGGIVAGDHLSEIDAEAGSHALITTPAAGKFYRSAGGL-----ARQDVSITVA
UniRef90_A6D6Q9_31_296 LHPPGGVVGDDTLQISVHAIQGAKSLITTPGATKFYRSSESKY-----AKQKQTLHVA
UniRef90_B8HW54_12_274 LHTAGGVVGGDRLSLDIDLDTQVLLTQAASKIYRSEGLE-----AHQQVRLITVA
UniRef90_A0A0J6H3B0_11_269 VHPPGGIAGGDQLDIRASVGNPNAWAQLTSPGAACKWYRAAGP-----AYQRIELTVA

	110	120	130	140	150	160
<i>HpUreD</i>	ENAF	LDFA	FPFL	IPFEN	AHFK	NGNTT
UniRef90_A0A0K9H6B6_4_266	EGSY	LEYI	PDPL	IAYRH	ARYK	QKNI
UniRef90_A0A0K9GXZ4_4_265	KGSY	LEYI	PDPL	IMYRN	ARYK	QKNI
UniRef90_A0A0A3IXZ5_4_264	KGSL	EYLP	PDPL	IAYQ	NAHY	KQKN
UniRef90_K9ZPZ7_7_273	ANAC	EYLP	PQET	ILFN	GAIY	RQDL
UniRef90_A0A0C1XDA3_13_272	AGAC	LEWFP	PQET	IVFN	GAIY	RQDL
UniRef90_UPI000379D7E3_4_266	KGSY	EYLP	PDPL	IAYQ	NAHY	KQKN
UniRef90_UPI0002DF3930_13_277	TGAT	LEWLP	PQET	IVFD	GAIY	RQDR
UniRef90_A0A0M0W0K1_1_266	KGSY	EYLP	PDPL	IAYQ	NAHY	KQKN
UniRef90_UPI000422C885_4_265	KGSY	LEYI	PDPL	IMYR	DAQY	VQKN
UniRef90_B4W160_8_270	AGAC	LEWLP	PQET	IVFN	GADY	QQMT
UniRef90_Q8YQZ4_10_269	AGAC	LEWLP	PQET	ILFN	GAIY	RQDL
UniRef90_A0A0M1BUZ9_3_269	AGAC	LEWLP	PQET	ILFN	GAIY	RQDL
UniRef90_A0A0M1JRC4_17_282	NDAC	LEFIP	PQET	IVFN	QALY	RQDL
UniRef90_UPI0007108B5C_4_266	EGSY	LEYI	PDPL	IGYQ	DARY	KQKN
UniRef90_UPI0006A76A92_4_265	KGSY	EYLP	PDPL	IAYEN	AHYK	QKNV
UniRef90_W4ETC9_4_265	RGSY	EYLP	PDPL	IAYEN	AHYK	QKNV
UniRef90_A0A0D6KKC6_12_271	AGAC	LEWLP	PQET	ILFN	SAIY	RQDL
UniRef90_A0A0D8ZEY2_11_271	ANAC	LEWLP	PQET	IVFN	GAIY	RQDL
UniRef90_B2IT63_10_269	PGAC	LEWLP	PQET	ILFN	DAIY	RQDL
UniRef90_UPI000308766C_11_271	SGAC	LELLP	PQET	IVFN	GAIY	RQDL
UniRef90_K9R6Q0_10_280	KNAC	LEWLP	PQET	IVFS	GASFR	QDIK
UniRef90_A0A127D3L2_4_264	SGCY	EYLP	PDPL	IMYQ	DARY	KQKN
UniRef90_UPI00028931D6_4_266	EGSY	LEYI	PDPL	IGYK	DARY	KQKN
UniRef90_A0A0M0ENP6_4_266	KGSY	EYLP	PDPL	IAYEN	AHYK	QKNV
UniRef90_A0A0S3PHU6_16_275	AGAC	LEWLP	PQET	ILFN	GAIY	RQDL
UniRef90_A0A081NYG6_3_264	KGSF	EYV	PDPL	IAYR	HAQY	KQKT
UniRef90_A0A0K9GPB1_4_266	AGSY	EYLP	PDPL	IAYQ	HAHY	KQKN
UniRef90_UPI000717378B_2_265	KGSY	EYLP	PDPL	IAYEN	AHYK	QKNV
UniRef90_K9W1V1_14_278	AGAC	LEWLP	PQENI	IFND	ANYR	QDLR
UniRef90_K9U4Q1_17_272	EGAC	LEWLP	PQET	IVFN	GANY	RQDL
UniRef90_A0A0M2SWM6_4_265	KGSY	EYLP	PDPL	IAYEN	AHYK	QKNV
UniRef90_UPI0003652A48_11_275	EGAC	LEWLP	LD	SIVFN	QAIY	RQMQ
UniRef90_UPI00047A812C_16_286	AGAC	LEWLP	PQET	IVFN	SALY	RQDL
UniRef90_K9TKA4_12_277	SGAI	CEWLP	PQESI	IFNG	AIYR	QDLR
UniRef90_M7NKH7_1_269	AGSY	EYLP	PDPL	IAYK	DAAY	RQKN
UniRef90_K6DR39_4_265	AGSY	EYLP	PDPL	IAYQ	NAHY	KQKN
UniRef90_A0A0B4RFS1_1_265	KGSY	EYLP	PDPL	IAYEN	AHYK	QKNV
UniRef90_A0A168N9T6_4_266	KGSY	EYLP	PDPL	IAYEN	AHYK	QKNV
UniRef90_A0A139X4D9_7_274	AGAS	LEWLP	PQET	IVFN	GAIY	RQDL
UniRef90_UPI00030AB192_16_277	DGAC	LEWLP	PQET	IVFD	GALY	RQDI
UniRef90_K7W9H0_9_269	SHAC	EYLP	PQET	ILFN	DGIY	RQDL
UniRef90_UPI00034A5E0C_10_263	TGAC	LEWLP	PQET	ILFN	DGIY	RQDL
UniRef90_A0A0A0E4Q3_4_265	AGSY	EYFP	PDPL	IAYQ	NAHY	KQKN
UniRef90_UPI000717263C_4_266	KDSY	EYLP	PDPL	IAYEN	AHYK	QKNV
UniRef90_K9QPZ4_10_269	AGAC	LEWLP	PQET	ILFN	GAIY	RQDL
UniRef90_UPI0002D28249_14_276	ANAC	LEWLP	PQET	IVFN	SALY	RQDL
UniRef90_F9DU20_4_266	KDSY	EYLP	PDPL	IAYK	DAKY	QKNV
UniRef90_UPI00047933CA_3_266	AGSY	EYLP	PDPL	IAYQ	HAHY	KQKN
UniRef90_W7RFE8_4_266	EGSY	LEYI	PDPL	IGYQ	DARY	KQKN
UniRef90_UPI0007441C40_4_265	KGSY	EYLP	PDPL	IAYEN	AHYK	QKNV
UniRef90_A0A0T7BRT9_7_268	SHAC	EYLP	PQET	IVFN	SALY	RQDR
UniRef90_UPI0006A78357_4_266	EGSF	EYLP	PDPL	IAYR	DARY	KQKN
UniRef90_UPI0007C7BB46_4_266	KGSY	LEYI	PDPL	IAYQ	DARY	KQKN
UniRef90_UPI000472611B_4_265	NGSY	EYLP	PDPL	IGYR	DARY	KQKT
UniRef90_UPI0002ACBA0D_11_270	TDAC	LEWLP	PQET	IVFD	GAIY	RQDL
UniRef90_A0A0C2KR59_11_269	AGAC	LEWLP	PQET	IVFN	GAIY	RQDL
UniRef90_K9WE93_4_277	QAAC	LEWLP	PQET	IVFN	GAIY	RQDL
UniRef90_A0A0M0SP30_16_277	DGAC	LEWLP	PQET	IVFD	GALY	QDLR
UniRef90_K9Q9K1_10_268	AGAC	LEFLP	PQET	ILFN	GADY	RQDL
UniRef90_A0A0S3TTX4_17_278	DHAY	LEWLP	PQET	IVFD	GALY	RQEN
UniRef90_K9VQF3_56_323	TGAN	LEWLP	PQET	IVFD	GAIY	RQNL
UniRef90_W1SM28_4_265	PGSY	EYLP	PDPL	IAYQ	NAKY	QKNI
UniRef90_A0A0C1N935_15_285	AGAC	LEWLP	PQETI	IFNG	AIYR	QDVR
UniRef90_A0A139SK67_11_275	DGAV	CEWLP	PQET	ILVFD	GARG	GQTE
UniRef90_UPI00041C7CDC_4_265	AGSY	EYFP	PDPL	IAYQ	DARY	KQKN
UniRef90_K9XHH8_15_275	SNAC	LEWFP	PQET	IVFN	GAIY	RQDL
UniRef90_UPI0002E7D901_4_265	KGSY	EYLP	PDPL	IAYK	DAKY	VQKN
UniRef90_A0ZB05_10_269	AGAC	LEWLP	PQET	IVFN	GAIY	RQDL
UniRef90_D4ZSS4_5_270	KGAY	EYLP	PRETI	IFNG	AIYR	QDLR
UniRef90_A0A0F5YFY1_6_271	ENAC	CEYLP	PRETI	IFNG	AIYR	QDLQ
UniRef90_K9T9Y9_59_322	SGAC	LEWVP	PQETI	IFNG	AIYQ	DLR
UniRef90_K9VAD2_10_273	SNSY	LEWLP	PQETI	IFND	AEYS	QKLR
UniRef90_W7Z4J7_4_265	KGSY	LEYI	ITDPL	IGYQ	DARY	KQKT
UniRef90_Q47G52_13_278	EGAT	LEWLP	PQET	IVFD	GARAR	MTQV
UniRef90_UPI0004024FBO_3_269	DHSY	EYLP	PQET	ILFN	GAIY	RQDL

UniRef90_K8GMD3_12_265 PNACLEWLPQETIVFQAQYRQMQIDLAPGALWIGWEITRFGRRTARGEKFFAGWEWRSRT
UniRef90_A0A0S3UB12_16_269 NGACLEWLPDLAIVFNQASFRQEMMINLAPGAEWIGWEITRFGRSARGERFVEGNWRSQT
UniRef90_A0A0F7D4R9_4_265 KNSYLEYLPDALIAYKDAKYIQKNVVYMEKGTLLYSIDIVTPGWSPEGDAFSVDTLRLKS
UniRef90_A0YQS4_5_271 SEACCEYLPRETIVFNQAIYRQDLYVELAQNATWLGWEITRFGRRTARGEQFTAGWEWRSCT
UniRef90_A0A0Q8RCL2_14_276 DSATLEWLPQETIFFDAAHVRLDTAIELGTDATYIGTEILCFGRRTASGESFDSGMVEQKT
UniRef90_UPI0005625009_5_271 KGGMLEWMPQENIFFPDANARIETHIALEPGAFFIGWDIQCLGRPVNDEPFDIGSMASAT
UniRef90_UPI0004799FB1_14_281 EHACLEWLPQETIFFDGAARYQDLRVNLAATEASYIGWEITRFGRRTARGEKFFLQGEWRSHT
UniRef90_UPI0002E38242_11_269 AGATLEWLPQETIVFSAQAELATRIELEGDARLFYWDIVALGRPASGERFDRGRHFQAHL
UniRef90_G8Q511_12_270 PGATLEWLPQETIVFSAQAELSTSIDLQDGRFLFYWDMVALGRPASGERFDLGHFQSQL
UniRef90_A0A168IUL4_4_266 KGSYLEYMPDPIIAYEHAKYLQNTIVHMNPGSAMIYGDIIITPGWSPDGKWFYHTLQIKT
UniRef90_UPI0004799FB1_14_281 AGATLEWLPQESIVFDGAIARMTHVTLAADSRYLQWIDILCLGRAAAGERFDDHGRFLDHC
UniRef90_Q3KIS7_11_269 DGATLEWLPQETIVYSAQAELTTSIELEGDARLFYWDVVALGRPASGERFDLGHFQAHL
UniRef90_K9XZ09_12_271 PGATLEYLPQENIVFSAIYRQDLRIQLAPGANWIGWEINRFGRSARGEQFIAGWEWRSYT
UniRef90_A0A090RU86_25_288 KGARLEWLPQENIFFPDHVRLDQVHLEKDAQFLGEMHCFGRPALNEGFSGHLVQKT
UniRef90_A0A0M5LWB1_11_269 AGATLEWLPQETIVFSAQAELSTRIDLEGDARLFYWDMVALGRVALGRPASGERFDLGHFQSQL
UniRef90_A0A0C2I8A1_11_269 AGATLEWLPQETIVFSAQAELRTTIDLEGDARLFYWDMVALGRPASGERFDRGRHFHSQL
UniRef90_H3SNI3_3_265 AGSYLEWLPDSVIAYRDSRYRQQTDIRMHSSAALILGEIVTPGWSPDGEHFSYDEITLKT
UniRef90_A0A0Q0XPT8_11_269 AGATLEWLPQETIVFSAQAELSTQIELEGDARLFYWDMVALGRMASGERFECGHFQSQL
UniRef90_K4ZJ19_4_265 KGSYLEYITDPIIYGEHARYKQKTVIWMKGANLLYSEIVTSGWSPDGRQDFHGRFLDHC
UniRef90_A0A085V951_11_269 PGATLEWLPQETIVFSAQAELTTRIELEGDARLFYWDVVALGRPASGERFEGGHFQSQL
UniRef90_A0A098SV87_11_271 SGGTLEWLPQETIVFSAQAELTTRINLQDGRFLFYWDVVALGRPASGERFDQGHFQSQL
UniRef90_A0A0A1GEL6_9_267 AGATLEWLPQETIVYCAAQAELSTSIDLEGDARLFYWDIIALGRPASGERFDAGHFQSQL
UniRef90_U4CP19_9_267 TGATLEWLPQETIVYSAQAELSTVIELEGDARLFYWDMVALGRPASGERFDLGHFQSQL
UniRef90_A0A0W0P2S5_11_269 PGATLEWLPQETIVFSAQAELTTCIELEGDARVYWDIIALGRPASGERFAQGYLQAHL
UniRef90_C3K5A6_11_269 AGATLEWLPQETIVFSAQAELTTRIELHGDARLFYWDVVALGRPASNERFDLGHFQSQL
UniRef90_A0A078LV36_9_267 AGGTLEWLPQETIVYSAQAELKTCIDLEADARLFYWDMVALGRPAATERFDDGYFQSQL
UniRef90_U3GGT8_11_269 AGATLEWLSQETIIFSDAQAELSTRIDLEGDARLFYWDVVALGRPASGERFDLGHFQSQL
UniRef90_A5L5M9_32_304 KGARLEWMPQENIFFPNAHVRLDTEIRLEKGAQFWGEMHCFGRPAQNEGFEHGLVQKT
UniRef90_A0A0J6GPD8_11_270 AGATLEWLPQETIVFSAQAELSTRIDLEGDARLFYWDMVALGRQASDEHFDLGHFQSQL
UniRef90_Q4KJ05_11_269 PGATLEWLPQETIVFSAQAELTTRIELEGDARLFYWDIIALGRPASGERFEQGHFQSQL
UniRef90_A0A0V7ZQT1_2_281 ERACLEWLPQETIVFNADYRQDLRVLDLANNASFLGWEINRFGRRTARGEKFFVQGNWRSHT
UniRef90_A0A075PF54_11_269 AGATLEWLPQETIVFSAQAELRTRIDLEGDARLFYWDVVALGRPASGERFDLGHFQSQL
UniRef90_A0A0D5Y774_11_269 AGATLEWLPQETIVFSAQAELSTRIDLEGDARLFYWDVVALGRPASDERFEQGHFQSQL
UniRef90_A0A0Q5EC30_11_271 PGATLEWLPQETIVFSAQAELQTHIELQDGRFLFYWDMVALGRPASGERFAGYFQSQL
UniRef90_U4N4V9_11_269 PGATLEWMPQETIVYSAQAELQTHIELQDGRFLFYWDMVALGRPAADERFAGYFQSQL
UniRef90_D4TUH6_7_266 RGSCLYLPQETIVFNGGARYRQDVRIELGEGSSFIGWEISRLGRRTARGEKFFLEGEMLSHT
UniRef90_UPI00048AE6EC_1_266 KDSTLEYVDPDPIIAYRSADYIQHNNIHMESGATLIYSIDILTPGWSPDGLSFSYDNIQVKN
UniRef90_UPI0007398261_11_285 SGACLEWLPQETIVFNQAEFRQLRVLDLEPGALWMMGWEIARLGRSARGERFVCGNWRSHS
UniRef90_B0C790_12_273 TNAILEWLPDPIIYFNQAEFRQLRVLDLEPGALWMMGWEIARLGRSARGERFVCGNWRSHS
UniRef90_A0A066UMR7_26_298 KDRARLEWMPQENIFFPDHVRLDTEIYLEKGAQFWGEMHCFGRPAQNEGFEHGLVQKT
UniRef90_A0A0Q9XWI2_4_265 QGSYLEYLPDPLIAYKDAKYVQKNIVRMEKGAFFLYTDILTPGWSPGKHFYSYSLRLIN
UniRef90_A0A0S7ZTJ9_14_276 QHASLEWLPQETILFNQCEVSTTCINLSDNSRFIIGWEISCLGRPASGEAFDYSRVRQRF
UniRef90_A6SZ04_26_286 ADAALEWLPQETIIFNEADVRLEHNVTLAADARYIGGEILCFGRRTASGETFDSGRVQRF
UniRef90_U3H3U5_9_267 AGATLEWLPQETIVFSAQAELSTRIDLEGDARLFYWDVVALGRPASGERFAGHFQSQL
UniRef90_A0A073CY52_6_272 EQAYLEFIPREIIFNGAIFSONLRVNDPNACYLGWEITRFGRRTARGEIFNQGWKSCST
UniRef90_U6ZYX1_11_270 PGATLEWLPQETIVFSAQAELTTRIELHGDARLCYWDIVALGRPASGERFVQGHFQSQL
UniRef90_UPI00067CF5D4_26_284 AGARLEWLPQETIIFNEADVRLEHNVTLAVDASYIGGEILCFGRRTASGESFDSGRVQRF
UniRef90_A0A0K2BGW7_26_288 AGAALEWLPQETIIFNEADVRMEHSVLDAAADACYIGGEILCFGRRTASGESFNSGRVQRF
UniRef90_A0A011QEK6_40_302 EGGVVEYLPQETIVFDGAEAQMQTQVELAAGALFCGWWEILCLGRRTASGERFRHGRQLLAT
UniRef90_G4T117_15_272 ENAVLEWLPQETIVYEGARFTSETTIKIDTGSRFIAWEVIVLGRPASGEFELGELALNW
UniRef90_U87VP5_11_271 PGATLEWLPQETIVYSAQAELTTRIELHGDARLCYWDVVALGRPASGERFEHGHFQSQL
UniRef90_A0A089YS31_11_269 AGATLEWLPQETIVYSAQAELTTRIHQDGRFLFYWDIVAVGRPAAGERFAGHFQSQL
UniRef90_UPI0004174C9A_9_267 AGATLEWLPQETIVYAGAQPDLTRISLEDDARLFYWDMVALGRPASGERFDSGRLLRRL
UniRef90_UPI000379F3E4_11_286 GGACLEWLPQETIVYNNAIYRQDLRVELEPGASILIWEITRFGRSARGEQFLQGFWRSHS
UniRef90_A4VQU8_9_267 AGATLEWLPQETIVYSAQAELNTRIELHGDARLFYWDIVALGRPAAGERFDAGHFQSQL
UniRef90_A0A0M3V4J1_7_297 AGACLELLPQETIIFNGADYRQDLRVELAPGACFLAWEITRFGRSARGEKFFLQGEWRSHT
UniRef90_A0A098ESZ3_4_266 KGSYLEYLPDPLIAYRNKYLQKNIFRMEKGTALFYTDIIITPGWSPDGKLFYSYMLQLIN
UniRef90_UPI000345DD51_13_277 AGASVEWLPQESIFFDQARVALEQTVVLEADASYIGCEILCLGRRASGETFNSGKIAQRT
UniRef90_UPI00047D06E7_9_270 EGGALEWLPQETIIFPGACAGLKTQIQLHPKASYLQWVHCLGRPTNQETFDSEGLLFQT
UniRef90_U3BUX5_1_262 DG-CLEWLPQENIFFSANALLSSEVHLHGTAQYLGWEIHCLGRPVIGETFAAGRALFKT
UniRef90_UPI000780B9AB_11_271 AGGTLEWLPQETIVFSEAKAELTTRIDLECDARLLFWDVVALGRPASGERFEQGHFQSQL
UniRef90_UPI000255752C_11_273 AGATLEWMPQETIVYSAHAELVSNIELIGDGKLFYWDIVALGRPASDERFDLGHFQSQL
UniRef90_UPI000484E5E1_11_269 AGATLEWLPQETIVFSAQAELNTSIDLQDGRFLFYWDVIALGRPASDERFEHGHFQSQL
UniRef90_A0A0D6AS13_1_264 NDTYLEYLPQETIVFNKQYQQLRVNLRNRENATWLGWEIIRFRGRSARGEIIFTHGQWLNQT
UniRef90_UPI00034A425D_18_281 AGAYLEWLPQDSIIFDGAIIYQHLHVELAPQATWCGWEVCRYGRRTARGESFSLSQVRSHT
UniRef90_UPI00046A7B93_11_269 PGATLEWLPQETIVFSAQAELSTQVDLQDGRFLFYWDVVALGRPASGERFAGHFQSQL
UniRef90_I3YAM1_6_262 ADGILEWLPQENILFAGTHARLATQVDLDPGARFIGWEVQALGRPANGERLTGTADLSL
UniRef90_UPI00049AIT7_9_267 PGATLEWLPQETIVYSAQAELMSIELQDGRFLFYWDIVALGRPASGERFAGHFQSQL
UniRef90_UPI0003FDB5F5_4_265 KDSYLEYLPDALIAYKDAKASYQKNSIYMEKGTALLYSIDILTPGWSPGKHFYSYMLRLKKT
UniRef90_K9SBL5_6_267 AGACVEWLPQESIVFDGAVYRQDLRVELAPDAWFWGELTRLGRSARGERFVQGNWRSHS
UniRef90_UPI00040AC544_17_274 EGALEWLPQETIIFEGARLRSTRVRELASKARFIGWEILSLGRPACGERFDEGLADLDW
UniRef90_A6D6Q9_31_296 SGRSLEWLPQENIFFPDHVRLDTEIHLERGAQFLGEMHCFGRPALNEGFSAGHLLGKT
UniRef90_B8HW54_12_274 PGAWLEWLPRETIVFNQAHYHQLRVELAPGAVWLGWEITRGRRTARGEQFLQGHWRSHS
UniRef90_A0A0J6H3B0_11_269 AGATLEWLPQETIVFSAQAELSTRIDLEGDARLFYWDMIALGRQASGERFERGRHFQSQL

	170	180	190	200	210
<i>HpUreD</i>	SILQDEKPIIYDNTILDPKTTDLNNMCMFDGYTHYLNVLVNCPIEL----	SGVRECIEE			
UniRef90_A0A0K9H6B6_4_266	ELYVDDELAVYDHIKLNPRNQDMNTIGFMEGFSHLGSMIIVVGEQTDS----	DLLDRLHEA			
UniRef90_A0A0K9GXZ4_4_265	EVYMDDELVMYDHIKLNPAEQDMKAIKFMEGYTHLGSMIIVIGEQTNA----	DLLDRLYNS			
UniRef90_A0A0A3IXZ5_4_264	EIYLDGQLGVFDHIKLTGPKHSISGIGFMEGYTHLGSMIIVVSELTNN----	SLLDELYEM			
UniRef90_K9ZPZ7_7_273	EIWQNGIPQWIDRQILPGSEEVFHSPLGLAGYPVVGSLVWVGSVSR----	EIEEKARSL			
UniRef90_A0A0C1XDA3_13_272	EIWQQGKPLWIDRQWLPGNEEVFHSPLGLAGQPITGNLVWVGGVVSAAAA--	EIVDKARNL			
UniRef90_UPI000379D7E3_4_266	EIYWDGKLGVDHIKLMFQQQTISGLFMEGYTHLGSMIIVAVSEQTEP----	EYLDDELYEA			
UniRef90_UPI0002DF3930_13_277	EVWQQGKPLWVDRQWLPGSEEIFYSPHALNGQPVVGTFIYIGSTVSP----	EIEEKASSY			
UniRef90_A0A0M0W0K1_1_266	EIYWNGLGVFDHIKLVFQQQKISGLFMEGYTHLGSMAIAISEQMDA----	ALLDELYDA			
UniRef90_UPI000422C885_4_265	EIYMDELVVYDHIKVNPAEQDMQSIGFMEGYTHLGSFMVIGEQTNA----	ELLDKHLHL			
UniRef90_B4W160_8_270	EIWQQGHPLWIDRQWLPGGEAVLDSPLGLAGPIVGTLIWVGPPVSS----	EIIDNARSL			
UniRef90_Q8YQZ4_10_269	EIWQQGVPLWIDRQWLPGNDAVFHSPLGLAGQPIVGSVLVWLGSPIST----	EIEEKARNL			
UniRef90_A0A0M1BUZ9_3_269	EIWQQGVPLWIDRQILKLPQKQVLFHSPLGLAGQPIAALTWVGTSTVSP----	ELLDKARNL			
UniRef90_A0A0M1JRC4_17_282	EVWQAGEPLWIDRQCLFGSEEMFHSPLNALKGYPLVGTLFWIGQPVSA----	DAIASARNF			
UniRef90_UPI0007108B5C_4_266	EIYMENELVVYDHIKLSPATQNIINGLGMEGYSHLGSMIIVVDEKTDH----	DLLDRLYEA			
UniRef90_UPI0006A76A92_4_265	EIYLDGKLGVDHIKLVFQKSPMTGLFMEGFTHLGSMAIVASEDTTN----	ELLDLCEI			
UniRef90_W4ETC9_4_265	EIHLDGKLGVDHIKLVFPHNQKISGLFMEGYTHLGSMAIVASEDTTN----	ALLDELYET			
UniRef90_A0A0D6KKC6_12_271	EIWQQGVPLWIDRQYLPGSEEVFHSPLGLAGQPIVGSVLVWVGNPVDS----	EILAKARNL			
UniRef90_A0A0D8ZEY2_11_271	EVWQQGKPLWIDRQWLPATETIINSHHGLNGQPIVGSFAWIGQPVTK----	EIVEQARNL			
UniRef90_B2IT63_10_269	EIWQQSVPLWIDRQCLRGSEIDFHSPLGLAGKPIVGSVLVWVGGAVSA----	EIVEKTRSL			
UniRef90_UPI00030817378E_11_271	EIWQQGVPLWIDRQILKLPQKQVLFHSPLGLAGQPLVGSVLVYVQGVVSP----	ELLDKARNL			
UniRef90_K9R6Q0_10_280	EIWQNNKPLWIDRQYLPGSEEVFHSPLHALAGKPIVGTLIYIGKPVSP----	EIVQKIRTL			
UniRef90_A0A127D3L2_4_264	EIYMDELAVYDHIQLNPAEQNIIEKIGFMEGFSHLGSMLVVGGEQTSP----	DLLDRLYQA			
UniRef90_UPI00028931D6_4_266	EIYMENELVVYDHIKLNPAEQNMEKLGMEGYSHLGSMLVIVIDEKANH----	ALLDRLYQA			
UniRef90_A0A0M0BNP6_4_266	EVYLNGLKGVFDHIKLMPEKQVLFHSPLGLAGQPIAALTWVGTSTVSP----	ELLDKARNL			
UniRef90_A0A0S3PHU6_16_275	EVYQEGVPLWIDRQWLPGNEGVFHSPLGLAGQPIVGSFVWVGSVAVTE----	EFVQKARDL			
UniRef90_A0A081NYG6_3_264	EIYVDGDLAVYDQVRLNPSEQDLTGIGLLEGYTHFGSLIVVGEQMTS----	DFLDQLYEA			
UniRef90_A0A0K9GPB1_4_266	EIYMDELISFDHIKLNPAEQNIIEALFMEGFSHLGSMMVISEQMSPT----	DLLDRLYHA			
UniRef90_UPI000717378E_2_265	EIYLDGKLGVDHIKLVFPHNQKISGLFMEGYTHLGSMAIVASEDTTN----	ALLDELYEM			
UniRef90_K9W1V1_14_278	EIWRQGDPLWIDRQWLPGGEAVLDSPLGLAGQPIVGSFVWVGSVAVTE----	DLIEKARNC			
UniRef90_K9U4Q1_17_272	EVWQQGQPLWIDRQWLPGEEAILNSPHGLAGHSIVASLTWIGCEVSP----	ELVTCKRDV			
UniRef90_A0A0M2SWM6_4_265	EIYLDGKLGVDHIKLVFPHNQKISGLFMEGFTHLGSMAIVASEDTTN----	QLLDELYDK			
UniRef90_UPI0003652A48_11_275	EVWQAGKPIWIDRQWMPGSEEVFHSPLGLAGCPVVGSAFVWVGVVTP----	ELVEKARSL			
UniRef90_UPI00047A812C_16_286	EIWQQGKPLWIDRQWVPGSEEIFYSPHLAGQPIVGSVLVWVGSVAVSV----	EIEEKARNI			
UniRef90_K9TKA4_12_277	EIWQQGRPLWIDRQHLQSGESAVSSNSALAGFPVATLAWIGDPVTP----	ELVQEARSL			
UniRef90_M7NKH7_1_269	EIYVDGEPVFDNIIRLSPSDQVVGGLFMEGYTHLGSMAIAGEQTND----	DLIDILHDL			
UniRef90_UPI0006A78357_4_266	EIYMDELVVYDHIKLVFQKQNIITGLFMEGYTHLGSMAIVASDQMDN----	VLLDALYEM			
UniRef90_A0A0B4RFS1_1_265	EIYVDGDLAVFDHIKLVFQKQNIISGVMMEGYSHIGSMIVIGEQTTK----	ELLDLCEI			
UniRef90_A0A168N9T6_4_266	EIYWDGKLGVDHIKLVFQKQNIITGLFMEGYTHLGSMAIVASDQMDN----	VLLDALYEM			
UniRef90_A0A139X4D9_7_274	EVWQMGVPLWIDRQWLPGSEEVFHSPLGLAGQPIVGSFVWVGSVAVTE----	ELVHKARNL			
UniRef90_UPI00030AB192_16_277	EIWQQDKPLWIDRQWLPGSEEVFHSPLGLAGQPIVGSVLVYIGQKISP----	ELVHQARNL			
UniRef90_K7W9H0_9_269	EIWQNGIPLWIDRQILVPGSEEVFHSPLGLRDNVVGSAFVWVGFPIISP----	EIIHQARSL			
UniRef90_UPI00034A5E0C_10_263	EIWQHNIPLWIDRQWLPGNQDVFHSPLGLSGKPIVGTFFVWVGDVVSAAAA--	EIVETARNL			
UniRef90_A0A0A0E4Q3_4_265	EIYMDGELVVYDHIKLVFQKQNIIRGLFMEGYTHLGSMAIVASDQMDN----	SFLDQLYSL			
UniRef90_UPI000717263C_4_266	EIYVDGQIGVFDHIKLVFQKQSVSGLFMEGYTHLGSMLVVSSEYTNK----	AFIDELYEA			
UniRef90_K9QPZ4_10_269	EIWQEGVPLWIDRQYLPGSEEVFHSPLGLAGQPIAGNFYILGSPVSS----	EITIEKARSL			
UniRef90_UPI0002D28249_14_276	EIWQQGKPLWIDRQWLPGSDKIFHSPLGLNGQAIAGSLVWVQGAVSQ----	DMIEKARDL			
UniRef90_F9DU20_4_266	EIYMEDELVVYDHIKLVFQKQNIIRGLFMEGYTHLGSMAIVASEDTTN----	DLLDRLHET			
UniRef90_UPI00047933CA_3_266	EIYMDELVVYDHIKLVFQKQNIIRGLFMEGFSHLGSMAIVIGEQTNS----	VLLDQLYSV			
UniRef90_W7RFE8_4_266	EIYMENELAVYDHIKLVFQKQNIIRGLFMEGYSHLGSMAIVINENVDH----	DLLDRLYQA			
UniRef90_UPI0007441C40_4_265	EIYLDGVLGVFDHIKLAPEKNSIAGLGMEGYTHLGSMAIVASEDTTN----	GLLDMLYET			
UniRef90_A0A0T7BRT9_7_268	EIWRDNQPLWIDRQYLPGDMVVFHSPLGLNSQAIAGSFYILGKQISP----	QLITQIRQM			
UniRef90_UPI0006A78357_4_266	EIYMENELVVYDHIKLVFQKQNIIRGLFMEGYSHLGSMAIVIDEKSNQ----	DLLDRLYQA			
UniRef90_UPI0007C7BB46_4_266	EIYLDGKLGVDHIKLVFQKQNIIRGLFMEGYTHLGSMAIVASEDTTN----	VLLDQLYSV			
UniRef90_UPI000472611B_4_265	EIYMDDELVVYDHIKLVFQKQNIIRGLFMEGFSHMGSMAIVIGEKSNA----	ALLDLVYQE			
UniRef90_UPI0002ACBA0D_11_270	EVWQQGLPLWIDRQWLPAGEKIIDSPHGLAGLPIVGSFAWIGQPVVTP----	EIVEKARVL			
UniRef90_A0A0C2KR59_11_269	EIWQQGVPLWIDRQWLPGRVEVFHSPLGLAGQPLAGSLVYVQGVVSS----	DLVEKARSL			
UniRef90_K9WE93_4_277	EVWQQGRPLWIDRQWLPGEQVLDSPHGLAGKPIVAGSLAWVGGVAVSP----	EMIEKARLI			
UniRef90_A0A0M0SP30_16_277	EIWQQNKPLWIDRQSLPASEEVFHSPLGLAGQPIVGSVLVYIGQETSP----	ELVNKARNL			
UniRef90_K9Q9K1_10_268	EIWQQGVPLWIDRQWLPGNQDVFHSPLGLSGKPIVGTFFVWVGDVVSAAAA--	EIEEQVRSR			
UniRef90_A0A0S3TTX4_17_278	EIWQQGKPLWIDRQWLPGRVEVFHSPLGLAGQPIVGSVLVYIGREISP----	EIVEKARNL			
UniRef90_K9VQF3_56_323	EVWQENSPLWIDRQQLRGLGKEMLESPHGLAGKPIVATLAWVGEVPTA----	EFVEKVRDL			
UniRef90_W1SM28_4_265	EVYVDNELVVYDHIKLVFQKQNIIRGLFMEGFSHLGSMLVVGKQNTS----	SLLDQLYSA			
UniRef90_A0A0C1N935_15_285	EVWQMGVPLWIDRQWLPGRVDFVHSPLGLAGQPIVGSFVWVGSVAVTE----	ELVHKARSL			
UniRef90_A0A139SK67_11_275	RIRRDGQTLWLERGRVTGNSPLLASPIGLAGQPVVATMWWVAPQVNE----	GLRDACRAI			
UniRef90_UPI00041C7CDC_4_265	EIYLDDELVVYDHIKLVFQKQNIIRGLFMEGYSHLGSMAIVASEDTTN----	ELLDRLYYA			
UniRef90_K9XHH8_15_275	EVWQQQRPLWIDRQQLRPDVKVIDSPHGLAGKSIIGSFVWVIGQPVSA----	DVVEKVRML			
UniRef90_UPI0002E7D901_4_265	EIYMDELVVYDHIKLVFQKQNIIRGLFMEGYTHLGSMAIVASEDTTN----	DLLDQLYEA			
UniRef90_A0ZB05_10_269	EIWQQGVPLWIDRQYLPGSEEVFHSPLGLAGQPIVGSVLVWVGSVAVTE----	EFLAKARSL			
UniRef90_D4ZSS4_5_270	EIYLDGKLGVDHIKLVFQKQNIIRGLFMEGYTHLGSMAIVASEDTTN----	ELLDKARNL			
UniRef90_A0A0F5YFY1_6_271	EIWQNGKPLWIDRQWLPASEEILTSPHGLAGQAIVGTLAWVGHVSVSE----	EMLKEIRQL			
UniRef90_K9T9Y9_59_322	EIWQQGQPLWIDRQWLPAGEAIIINSSLGLAGQPIVAGSLIWIWIKPVSS----	NIIEAQTLL			
UniRef90_K9VAD2_10_273	EIWHLQKPLWIDRQWLPAGEEIVFHSPLGLAGQAIVGTLAWVGHVSVSE----	EITDQVRNL			
UniRef90_W7Z4J7_4_265	EIYLDGKLGVDHIKLVFQKQNIIRGLFMEGYTHLGSMAIVASEDTTN----	ALLDQLYEA			
UniRef90_Q47G52_13_278	QVNRDQRPIWIERGGFDGSDPMLISPAWAGATVCGTLLCAFFPEWPMQAS----	ALLEACKRI			
UniRef90_UPI0004024FBO_3_269	EIWQNDIPLWIDRQIIPGNEEVFHSPLGLAGNVPVGTLLVWVGNVSVSG----	EMIDKARSL			

UniRef90_K8GMD3_12_265 EVWQQGRPLWIDRQWLPGNEETFSSPHGLANCPVVGSGFAVIGQTVNP----DLIEKIRAT
UniRef90_A0A0S3UB12_16_269 EVWQSGKPIWIDRQWLPGSEATFNPSPHGLAGCPVVASFAWIGKTVDS----ECVEKARSL
UniRef90_A0A0F7D4R9_4_265 EIYMDGELVVDHVKLQPEQQNMTGLGFMEGYTHLGSFIVIGEKTD----ALIDRLYEY
UniRef90_A0YQS4_5_271 EIWQNGKPLWIDRQWLPANVEILTSPHGLAGQAIIVGTLAWVGHVSE----EMLKEIRQL
UniRef90_A0A0Q8RCL2_14_276 SIRRDKLWLFEEQGMALAGSAAAMTSPILGLAGNTVCAITLAVGKPLAA----SMMATLREA
UniRef90_UPI0005625009_5_271 HISIDGELVLIDQLRTEG-RALLDAAAGLRGYPMQASLFIVPGEACRVSLTDLLEHIRE
UniRef90_UPI000305E365_16_284 EIWQDKPLWIDRQWLPGSEEIFHSLHGLAGQPIVGSLLIYIGQEISP----EIVEKARSL
UniRef90_UPI0002E38242_11_269 DIRRDGQPLWHERQRIEGDDGLLDSPIGLDGQPVFATLLVTGE-IDS----ELLERCRL
UniRef90_G8Q511_12_270 DIRRDGQLLWHERQRIVGGDGLLDSPIGLDGQPVFATLLVTGE-IDS----ELLEQCRL
UniRef90_A0A168IUL4_4_266 QVYLEDKLVVFDHLQLRPANDPMEGIGLLEGYTHLGSMLIVIGERTDP----ELIERLSDS
UniRef90_UPI0004799FB1_14_281 RIERAGKPLWIERGVSAGDAMLHSPAGWAGATVCGTLLCSFPPELPPQAA--ALLEALRTL
UniRef90_Q3KIS7_11_269 DIRRDGRLWHERQRIVGGDGLLDSPIGLDGHPVFATLLVTGE-IDA----ELLERCRL
UniRef90_K9XZ09_12_271 EVWQNNRLLWIDRQWLPGAEELINSINGLAGKPVIGTFSYLKGKPVDK----ELLEKINNL
UniRef90_A0A090RU86_25_288 EIYLDGQRLLEGLNVRGDKLLKD-KGLLYQMMGTLYISID--DE----DFYQLVQSL
UniRef90_A0A0M5LWB1_11_269 DIRRDGQLLWHERQRIVGGDGLLDSPIGLDGQPVFATLLVTGE-IDS----ELLEKICRL
UniRef90_A0A0C2I8A1_11_269 DIRRDGQLFWHERQRIVGGDGLLDSPIGLDGQPVFATLLVTGE-IDS----ELLERCRLSV
UniRef90_H3SNI3_3_265 MIEMDGVVFLDHLRLRPGEQPIHGLGRMDGHTHIGSLYVVGPLATR----AFIEELAEK
UniRef90_A0A0Q0XPT8_11_269 DIRRDGQLLWHERQRIVGGDGLLDSPIGLDGHPVFATLLVTGE-IST----ELLHTCRSL
UniRef90_UPI0004799FB1_14_281 EIYLDGVLAIHDHIKLDPAAHRTSLGFMGYSHLGSMMMISEQVDQ----DLEDRLYLE
UniRef90_A0A085V951_11_269 DIRRDGTLWHERQRIVGGDGLLDSPIGLDGKTVFGTLLVTGE-IES----ELLEACRSL
UniRef90_A0A098SV87_11_271 DIRRDGRLWHERQRIVGGDGLLDSPIGLDGKPVFATLLVTGE-IDP----ELMERCCEL
UniRef90_A0A0A1GEL6_9_267 NISRDGELLWHERQRIVGGDGLLDSPIGLDGHPVFATMIVSGE-ISA----ELLERCRL
UniRef90_U4CP19_9_267 DIRRDGQLLWHERQRIVGGDGLLDSPIGLDGHSVFATLIVSGE-IDA----ELMERCCEL
UniRef90_A0A0W0P2S5_11_269 DIRRDGRLWHERQRIEGDDGLLESPLVGLDGHVPVFATLLITGQ-AED----DLLERCRL
UniRef90_C3K5A6_11_269 DIRRDGQLLWHERQRIVGGDGLLDSPIGLDGQPVFATLLVTGE-IDP----ELLEHCRL
UniRef90_A0A078LV36_9_267 DIRRDGKLLWHERQRIVGGDGLLDSPIGLDGQPVFATLLVTGE-IDA----DLLERCRL
UniRef90_U3GGT8_11_269 DIRRDGQLLWHERQRIVGGDGLLDSPIGLDGQPVFATLLVTGE-IDP----ELLEKICRL
UniRef90_A5L5M9_32_304 EIYLDNRQLLLETFDFHGGDKLMLN-MGLLDYAMMGTFYLTSN--EK----QDLELVQSL
UniRef90_A0A0J6GPD8_11_270 DIRRDGRLWHERQRIVGGDGLLDSPIGLDGHPVFATLLVTGE-IDP----ELLETCRSL
UniRef90_Q4KJ05_11_269 DLYRDGRPLWHERQRIVGGDGLLDSPIGLDGQPVFATLLVTGE-IDS----ELLERCRL
UniRef90_A0A0V7ZQT1_2_281 EIYQEGIPLWIDRQWLPGSEEIFYSPNGLAGQAVIGSLIFVVGKTSK----DIVEQVRS
UniRef90_A0A075PF54_11_269 DIRRDGQLLWHERQRIVGGDGLLDSPIGLDGQPVFATLLVTGE-IDS----ELLEQCRL
UniRef90_A0A0D5Y774_11_269 DIRRDGQLLWHERQRIVGGDGLLDSPIGLDGQPVFATLLASGE-IDA----ELLERCRL
UniRef90_A0A0Q5EC30_11_271 EIRRDGRLWHERQRIVGGDGLLDSPIGLDGKTVFATLLMTGE-AGS----ELLETCRSL
UniRef90_I4N4V9_11_269 DIRRDGELLWHERQRIVGGDGLLDSPMGLDGHVVFATLLVTAD-ISP----ELLEQCRGF
UniRef90_D4TUH6_7_266 EIWQGEVPLWIDRQHIPPGEAFYFNPHSLKGNPVIIGSFVVCVGLPISE----ERIEKRSRG
UniRef90_UPI00048AE6EC_1_266 QIFMNGRRVVDHLLRKPNSQDITGGIGLMEGFTHVGSMLVICDQVSK----EFMERIKEH
UniRef90_UPI0007398261_11_285 QVWQAGRLIWDVDPQWVAGGSEMESLHGLAGYPIVIAFALLGHPVSG----ELVETVRS
UniRef90_B0C790_12_273 EIWQGAPLWIDRQWLPGQPDITWESPHGLAGQPVVGSFVLWVGQVGP----NLVQARDL
UniRef90_A0A066UMR7_26_298 EIYLDNKKLLTEGFNFHGGDKLMLN-MGLLDYAMMGTFYITAD--EP----QDLELVQSL
UniRef90_A0A0Q9XW12_4_265 EIYLDNDEIVVFDHLHLSPRNKAMNGLGHMEGYTHLGSLLIAISEKVND----AFIETLYNT
UniRef90_A0A0S7ZTJ9_14_276 ELYKHEKPLFIERALLEGGQPTLAAHWGLQSFVTATMIAYP--ADK----AVLELARKS
UniRef90_A6SZ04_26_286 SIRRGGKLLWFEQALQARSTSMHSPSLLAGYTVCAITLAVGKTMNG----AFLNELREB
UniRef90_U3H3U5_9_267 DIRRDGRALWHERQRIVGGDGLLDSPIGLAGQPVFATLLVTGE-LDP----ELLERCRL
UniRef90_A0A073CY52_6_272 EIWQNGCPVWIDRQGFIANEEILNSPHGLGGKPVIAITLWVGGQPVSE----DIVKNIRQL
UniRef90_U6ZYX1_11_270 DIRRDGRPLWHERQRIVGGDGLLDSPVGLDQPVFATLLVTGE-IDA----QLLERCRL
UniRef90_UPI00067CF5D4_26_284 SIRRDKLWLFEEQGVLAHAASMSHSPSLLAGYTVCAITLAVGKTMTP----AFLQTLREB
UniRef90_A0A0K2BGW7_26_288 SIRRGGKLVWFEQGLTLLHAASMSMTSPLALAGFTVSATLAVGLPINA----AFLSELREQ
UniRef90_A0A011QEK6_40_302 RIERQGRPLWLERGRLLGASSWLDAAAPLAGFPVVASLLLAGRAVEP----EWLAACRAL
UniRef90_G4T117_15_272 RIVLGDQPIYLERLRDLDA--QAFARWGLSRHSSCGTLFAYP--ASA----EVLEIVRNV
UniRef90_Q87VP5_11_271 DIRRDGTLWHERQRIVGGDGLLDSPIGLDGKTVFATLLVTGE-VDS----DLEVCRL
UniRef90_A0A089YS31_11_269 EIRRDGELLWHERQRIVGGDGLLDSPVGLGKPVFATLLVTGE-IDP----ELLERCRL
UniRef90_UPI0004174C9A_9_267 DIRRDGRLWHERQRIVGGDGLLDSPIGLAGQPVFATLLASGE-IDA----DLLERCRL
UniRef90_UPI000379F3E4_11_286 EIWQGRPLWIDRQQLIGGEETLNSPHGLAGKPVVGSRAWIGVRVTP----ELVEKARSL
UniRef90_A4VQU8_9_267 DIRRDRLIWHERQRIAGDALLDSPIGLDGRSVFATLLASGE-LDA----DLLERCRL
UniRef90_A0A0M3V4J1_7_297 EIWQGVPLWIDRQFLPNPEIFHSPHGLFGQPIVGSLLIWLGHVPSV----EIEKARSL
UniRef90_A0A098ESZ3_4_266 EIYMEDELAADFHIKLVPSVQNISGLGFLENHHLGSMIVIGEQANR----EFLDHLQNE
UniRef90_UPI000345DD51_13_277 QIHRDGKLVWVWQCALAGGEMLRSPGLDGHVSVCAITLAVGKVLPA----AALASLREA
UniRef90_UPI00047D06E7_9_270 DIQRDGEPLYKEHLQLDNFWD-LQGMAGLSGYPMATMLALP--AGN----DALELARQA
UniRef90_I3BUX5_1_262 ALYRDGKPLLLDRLLIQGERD-IQLAAGLRGNPVFATLLATP--ATP----ELLEQARSL
UniRef90_UPI000780B9AB_11_271 DIRRDGKLLWHERQRIVGGDGLLDSPVGLGKPVFATLLVTGE-VDA----ELMERCRL
UniRef90_UPI000255752C_11_273 NIRRDELLWYERQRIVGGDGLLDSPIGLDGYPVFATLLLSAE-IAP----ELLEQCRL
UniRef90_UPI000484E5E1_11_269 NIRRDELLWYERQRIVGGDGLLDSPIGLDGQPVFATLLVTGE-IDG----ELLERCRL
UniRef90_A0A06AS13_1_264 EVWYKDKPLWIDRQQLLQGESAINGLANKPVIIGNLTLISAKIN----DIIREIREL
UniRef90_UPI00034A425D_18_281 EVWQGRPLWIDRQRLSGGADTIHSPHALAGQPVVANLAFIVGQVIPT----EIVEQARTL
UniRef90_UPI00046A7B93_11_269 DIRRDGKPLWHERQRIVGGDGLLDSPIGLDGHPVFATLLATGE-ISA----ELLEHCRL
UniRef90_I3YAM1_6_262 AIQAGRPLLLDRLRIDAGTG-LDGPAGLRGFAVTGTLVATG--IDR----EDLAVRGL
UniRef90_A0A0D9AIT7_9_267 NITRDGEWLWHERQRIVGGDGLLDSPIGLDGNPVFATLLVTGE-IDA----ELMERCCEL
UniRef90_UPI0003FDB5F5_4_265 EIYMENQLVAFDHIKLPASQHMNELGFMEGYTHLGSLLIVVGEKTS--ALLDRLYET
UniRef90_K9SBL5_6_267 EVWRQGQPLWIDRQWLPGNPAWLDSPHGLHGRSLVGSFAVVGQPIAP----ELVAEARAL
UniRef90_UPI00040AC544_17_274 QVYCRDQPLLLERKLKDA--RAFAARWGLQGCACGTLFAYP--AGA----ETLAAVQSL
UniRef90_A6D6Q9_31_296 EYVLDKQLLLEGLNVRGNDKLLKS-RGLLDYAMMGTFYVVSID--DE----DFYQLVQTL
UniRef90_B8HW54_12_274 EVWQGTPLWIDPQWLPGGEEELKSYHGLSGYPVVGTLVLIQQAEEA----ELIAQIRQL
UniRef90_A0A0J6H3B0_11_269 DIRRDGQLLWHERQRIVGGDGLLDSPIGLDGNPVFATLLVTGE-VSP----ELLDACRSL

HpUreD
 UniRef90_A0A0K9H6B6_4_266
 UniRef90_A0A0K9GXZ4_4_265
 UniRef90_A0A0A3IXZ5_4_264
 UniRef90_K9ZPZ7_7_273
 UniRef90_A0A0C1XDA3_13_272
 UniRef90_UPI000379D7E3_4_266
 UniRef90_UPI0002DF3930_13_277
 UniRef90_A0A0M0W0K1_1_266
 UniRef90_UPI000422C885_4_265
 UniRef90_B4W160_8_270
 UniRef90_Q8YQZ4_10_269
 UniRef90_A0A0P1BUZ9_3_269
 UniRef90_A0A0M1JRC4_17_282
 UniRef90_UPI0007108B5C_4_266
 UniRef90_UPI0006A76A92_4_265
 UniRef90_W4ETC9_4_265
 UniRef90_A0A0D6KKC6_12_271
 UniRef90_A0A0D8ZYE2_11_271
 UniRef90_B2IT63_10_269
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 UniRef90_K9R6Q0_10_280
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 UniRef90_UPI00028931D6_4_266
 UniRef90_A0A0M0ENP6_4_266
 UniRef90_A0A0S3PHU6_16_275
 UniRef90_A0A081NYG6_3_264
 UniRef90_A0A0K9GPB1_4_266
 UniRef90_UPI000717378B_2_265
 UniRef90_K9W1V1_14_278
 UniRef90_K9U4Q1_17_272
 UniRef90_A0A0M2SWM6_4_265
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 UniRef90_K9TKA4_12_277
 UniRef90_M7NKH7_1_269
 UniRef90_K6DR39_4_265
 UniRef90_A0A0B4RFS1_1_265
 UniRef90_A0A168N9T6_4_266
 UniRef90_A0A139X4D9_7_274
 UniRef90_UPI00030AB192_16_277
 UniRef90_K7W9H0_9_269
 UniRef90_UPI00034A5E0C_10_263
 UniRef90_A0A0A0E4Q3_4_265
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 UniRef90_K9QPZ4_10_269
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 UniRef90_UPI000472611B_4_265
 UniRef90_UPI0002ACBA0D_11_270
 UniRef90_A0A0C2KR59_11_269
 UniRef90_K9WE93_4_277
 UniRef90_A0A0M0SP30_16_277
 UniRef90_K9Q9K1_10_268
 UniRef90_A0A0S3TTX4_17_278
 UniRef90_K9VQF3_56_323
 UniRef90_W1SM28_4_265
 UniRef90_A0A0C1N935_15_285
 UniRef90_A0A139SK67_11_275
 UniRef90_UPI00041C7CDC_4_265
 UniRef90_K9XHH8_15_275
 UniRef90_UPI0002E7D901_4_265
 UniRef90_A0ZB05_10_269
 UniRef90_D4ZSS4_5_270
 UniRef90_A0A0F5YFY1_6_271
 UniRef90_K9T9Y9_59_322
 UniRef90_K9VAD2_10_273
 UniRef90_W7Z4J7_4_265
 UniRef90_Q47G52_13_278
 UniRef90_UPI0004024FBO_3_269

SE-----GVDGAVSETASSHLCVKA
 IHV--NTN-----EYRIGLSLLPVPGFITRV
 MSH--DEN-----EYRMGLSMLPVKGFITRV
 IQE--EST-----DFKFGLSRLPVSGLSIRI
 VT--NNLTGVSRLQ--NGFLCRY
 WC-----G-----KGEAGVTRLE--NGFLCRY
 IRS--EES-----DFSFGLSHLAIPGFCIRI
 TQ-----HSVLST-----QYSFGVTRLE--HGFLCRY
 VMT--VEA-----DFTFGISEVSLIPGFCIRI
 MDQ--NEQ-----DYKFGLSMLS VKGFSIRV
 WT-----ADQR-----QGEAGVTQTQAQGLLCRY
 GN-----T-----QGEAGVTSLE--NGFLCRY
 WH-----G-----SGQVGAIRLE--NGFLCRY
 WY-----NRKG-----EGEAGVTQIL--NGLVCRY
 VPN--QTK-----EYKIGLSLLPVPGFITRV
 IHS--EEQ-----NFKFGISRLAIPGLSIRI
 IQI--EEA-----DFKFGISRLAIPGFSIRI
 WD-----G-----AGEVGVSRLE--HGFLCRY
 WQ-----PTNC-----HSLTGVTRLE--TGLLCRY
 WN-----G-----EGEVGASRLQ--HGFLCRY
 WN-----G-----KGEAGVTRLS--CGLLCRY
 FI-----PPSPPLPIP-----PSSQGVTRIE--NGLLCRY
 ING--NTD-----RYKIGLSLLSVPGFITRI
 IDA--NTK-----EYKVGLSFLSIPGFITRV
 IQI--EES-----SFKFGISRLAIPGFSIRI
 WD-----G-----VGEVGVTLQ--NGFLCRY
 MDA--ETV-----PCRMGLSMLPVSGFSVRV
 LNS--KTN-----AYEIGLSLLPVKGFITRV
 MKG--IES-----NFTFGLSRLAIPGFSIRV
 WQ-----AGEY-----QGESGVTTLL--EGMLCRY
 TC-----NVSTTIP-----ITNYGVTRLE--HGFLCRY
 IYS--EQA-----NIKFGLSKLAIPGLSIRV
 WA-----GS-----SGEIGVTRLS--IGLLCRY
 WQ-----PIPPSPSLPLPL-----SSQIGVTRLE--HGFLCRY
 WE-----GRSSSS-----EGEAGVTRLE--HGFLCRY
 LAGTLEED-----QVKFGISRLAIPGFSIRI
 LSK--STY-----ECKVGLSLLSVPGFITRV
 ILS--QEA-----DVKFGLSSELVVSGLSIRI
 IQA--EEA-----DFSFGISNLAIPGFSIRI
 FL-----S-----PTPHSLLPTPSVGVTRLS--CGLLCRY
 WK-----PTLT-----HSQIGVTRLE--HGFLCRY
 II-----Q-----NSDAGVTRLE--HGFLCRY
 WN-----G-----EGETGVTLT--HGFLCRY
 LDK--NTL-----DYKVGLSLLPVSGFTARV
 IQL--EQA-----DFKAGISKLAIVSGFSIRI
 FT-----P-----HALIGVTRLE--NGFLCRY
 WH-----G-----EGEVGTRLE--HGFLCRY
 IQK--EAG-----DFAFGLSRLAIPGFTIRI
 IEM--NTN-----DYKVGLSLLSVPGFITRV
 IDT--QTK-----EYKIGLSLLPVPGFSVRV
 IHS--EQS-----NFKFGLSRLAIPGLSIRV
 WG-----ENS-----PSAVGVTALE--HGFLCRY
 IDP--NAK-----EYKVGLSALPVPGFITRI
 IGK--DLD-----ECKAGLSLLIEGGFTLRI
 LHE--NST-----DFKIGLSALSVPGFITRV
 FP-----NNS-----SSQGGVTRLE--MGLLCRY
 WR-----G-----EGQAGVTRLS--CGLLCRY
 WA-----TQER-----QGEAGVTQLM--SGLLCRY
 GK-----PTLS-----HSQIGVTRLE--HGFLCRY
 FT-----KHLTGVTLQ--HGFLCRY
 WQ-----LPII-----HPQIGVTRLE--HGFLCRY
 PS-----EATIYPG-----NSTVGVTRIP--NGLLCRY
 IDM--NSD-----EYKLGSLILSVPGLTIRV
 FL-----SSTAPNPSFSIPSPQVGVTRLS--CGLLCRY
 LPE-----VGAGGVTLPLGGVLLARW
 LNP--KTD-----AYDVGFSLLPVEGGFTLRI
 ST-----VD-----QGETGVTRLE--TGLLCRY
 VDG--MEG-----DFEFGISRLTIPGFTIRI
 WD-----G-----SGEVMGTRLE--NGFLCRY
 WG-----EHQS-----EGEAGATQLL--SGLLCRY
 WN-----PPDT-----LGEVGVTLQ--SGLLCRY
 WS-----DKQY-----LGEAGVTQTQARGLLCRY
 WQ-----G-----KGEVGVTRLE--HGFLCRY
 IHE--DTN-----EYKVGLSLLPVAGLIVRV
 -----VPAD-----GAQHGLSALP--GVLIARY
 II-----E-----NNFSGVTRLE--QGFLLCRY

UniRef90_K8GMD3_12_265	WN-----GA-----VGQTGITRLQ-SGILCRY
UniRef90_AOA0S3UB12_16_269	WA-----GT-----SGEIGVTRLP-LGLLCRY
UniRef90_AOA0F7D4R9_4_265	VHA--ESG-----DFEFGISKLTVPGFTRI
UniRef90_AOYQS4_5_271	WN-----HSDT-----LGEVGVTOQLL-SGFCLRY
UniRef90_AOA0Q8RCL2_14_276	DVS-----DGAFGVTOQMK-SVIVARY
UniRef90_UPI0005625009_5_271	IS-----SVDS---IALEVGTQVD-GVLVVRV
UniRef90_UPI000305E365_16_284	WQ-----LPITHHPLPIT-----HPQIGVTRLE-HGLLCRY
UniRef90_UPI0002E38242_11_269	-----ST---AVRGDLSQLP-GLLVARC
UniRef90_G8Q511_12_270	-----GH---DVRGDLTQLP-GLVVARC
UniRef90_AOA168IUL4_4_266	LKC--CTS-----SAHIGLSTLMVPGFSLRV
UniRef90_UPI0004799FB1_14_281	-----TPGD---GARHGITAPP-GLLIARY
UniRef90_Q3KIS7_11_269	-----GH---EVRGDLTQLP-GLLVARC
UniRef90_K9XZ09_12_271	RK-----TREN-----KGEFGVTELM-SGLLCRY
UniRef90_AOA090RU86_25_288	LT-----NMQQE-----NKKG---AVLIAASQLE-NLLVIRA
UniRef90_AOA0M5LWB1_11_269	-----PG---PVRADLTQLP-GLLVARC
UniRef90_AOA0C2I8A1_11_269	-----PA---RVRGDLTQLP-NLLVARC
UniRef90_H3SNI3_3_265	LDL--NRM-----EGCIGLSELIIPGFGVRM
UniRef90_AOA0Q0XPT8_11_269	-----PN---PVRGDLTQLP-GLLVARC
UniRef90_K4ZJ70_4_265	IDG--KYE-----DCRIGLSLLPVSGLMARV
UniRef90_AOA085V951_11_269	-----PA---QVRGDLTQLP-GLLVARC
UniRef90_AOA098SV87_11_271	-----AEHS---PVRGDLTQLP-GLLIARC
UniRef90_AOA0A1GEL6_9_267	-----PN---RVRGDLTQLP-GMLVGRV
UniRef90_I4CP19_9_267	-----PS---RVRGDLTQLP-GLVVARC
UniRef90_AOA0W0P2S5_11_269	-----QH---PVRGDLTQLP-GLLLARC
UniRef90_C3K5A6_11_269	-----PH---TVRGDLTQLP-GLLVARC
UniRef90_AOA078LV36_9_267	-----PG---RVRGDLTQLP-GLLVGRV
UniRef90_J3GGT8_11_269	-----PN---DVRGDLTQLP-GLLVARC
UniRef90_A5L5M9_32_304	LL-----SITQQASQQSDSSKISSDP---TLILGATQIE-GLIVVRA
UniRef90_AOA0J6GPD8_11_270	-----PN---PVRGDLTQLP-GLLVARC
UniRef90_Q4KJ05_11_269	-----AH---PVRGDLTQLP-GLLVARC
UniRef90_AOA0V7ZQT1_2_281	WK-----SNPHMTLSRHAALTPIPNK-----SPNQGVTRLN-NGFLCRY
UniRef90_AOA075PF54_11_269	-----PH---AVRGDLTQLP-GLLVARC
UniRef90_AOA0D5Y774_11_269	-----GH---AVRGDLTQLP-GLLVARC
UniRef90_AOA0Q5EC30_11_271	-----NMPN---PVRGDLTQLP-GLIVARC
UniRef90_I4N4V9_11_269	-----KG---KVRGDLTQLP-GLLVARC
UniRef90_D4TUH6_7_266	IA-----N-----GWDAGVTRLE-QGILCRY
UniRef90_UPI00048AE6EC_1_266	YSE--DDQ-----KYKMGISLVLIPGFSVRI
UniRef90_UPI0007398261_11_285	WE-----ALPEQEVRSQHGVPNRV-----LTQVGVTRLM-SGLLCRY
UniRef90_BOC790_12_273	WQ-----PTTD-----GAEMGVTRLP-LGVLCRY
UniRef90_AOA066UMR7_26_298	LL-----SITQQASLQPVHFGSSSKS---SLIMGATQIE-GLIVIRA
UniRef90_AOA0Q9XWI2_4_265	LEQ--MEG-----NFKIGISRLATEGLSIRI
UniRef90_AOA0S7ZTJ9_14_276	T-----AAHT---TALCSATLVD-EVLVCRY
UniRef90_A6SZ04_26_286	SS-----ALAQ---GGRSGATQMK-QVLVARY
UniRef90_U3H3U5_9_267	-----PS---AVRGDLTQLP-GLLVARC
UniRef90_AOA073CY52_6_272	WS-----QRET-----SSQAGVTQLI-SGLLCRY
UniRef90_U6ZYX1_11_270	-----EH---PVRGDLTQLP-GLLLARC
UniRef90_UPI00067CF5D4_26_284	TA-----VAAE---DGRSGATQMK-QVLVARY
UniRef90_AOA0K2BGW7_26_288	TG-----ALTRDS---NDRTGATQMK-QVVLRY
UniRef90_AOA011QEK6_40_302	-----PVAD---GLLTGVTALP-ELLVARC
UniRef90_G4T117_15_272	IGE-----APGRGVTRID-DLLICRA
UniRef90_Q87VP5_11_271	-----SMPS---PVRGNLTQLP-GLIVARC
UniRef90_AOA089YS31_11_269	-----TT---RVRGDLTQLP-GLLVARC
UniRef90_UPI0004174C9A_9_267	-----DT---PVRGDLTQLP-GLLVARC
UniRef90_UPI000379F3E4_11_286	RT-----PLSLDGSFGGGEARGV-----HHQAGATRLT-DGLLCRY
UniRef90_A4VQU8_9_267	-----PS---RVRGDLTQLP-GLIVARC
UniRef90_AOA0M3V4J1_7_297	FTPYLALSEKLRAGVPPVEQTSVTQHSALST-----QHLVGVTOLE-HGLLCRY
UniRef90_AOA098ESZ3_4_266	IQN--KSP-----AAAIGISMLPIPGFTVRI
UniRef90_UPI000345DD51_13_277	-----GLDG---AGKFGVTQMK-GVLSARY
UniRef90_UPI00047D06E7_9_270	CK-----AFGG---EGYTAPTLTD-DVLVRY
UniRef90_I3BUX5_1_262	C-----AEAG---MGTAGATLFN-GVLVRY
UniRef90_UPI000780B9AB_11_271	-----AEHS---PVRGDLTQVP-GLIARC
UniRef90_UPI000255752C_11_273	-----AADNRLELRGDLTQLP-GILVARC
UniRef90_UPI000484E5E1_11_269	-----DH---PVRGDLTQLP-GLLVARC
UniRef90_AOA0D6AS13_1_264	IE-----SKFT-----NLIICITTLQ-QGLLCRY
UniRef90_UPI00034A425D_18_281	VK-----TAIKGEM-----QGEFGVTRLE-QGIICRY
UniRef90_UPI00046A7B93_11_269	-----EH---PVRGDLTQLP-GLLVARC
UniRef90_I3YAM1_6_262	A-----ATDS---DILWGATLTD-DLLVARC
UniRef90_AOA0D9AIT7_9_267	-----SS---RVRGDLTQLP-GLVIGRC
UniRef90_UPI0003FDB5F5_4_265	IQQ--EAG-----EFTFGLSKLAVPGFTTIRI
UniRef90_K9SBL5_6_267	WQ-----G-----RGEVGVTRLM-AGMLCRY
UniRef90_UPI00040AC544_17_274	IGD-----ATGRGVTRMD-DLLVCRA
UniRef90_A6D6Q9_31_296	LD-----NMQQE-----HNEG---AVLIAASQLE-NLLVIRA
UniRef90_B8HW54_12_274	WN-----AEKF-----EGETGVTRLM-SGLLCRY
UniRef90_AOA0J6H3B0_11_269	-----PH---PVRGDLTQLP-GLLVARC

	240	250	260	265
HpUreD				
UniRef90_A0A0K9H6B6_4_266	LAKGSEPLLHLREK	IARLV	TQTTQKV	
UniRef90_A0A0K9GXZ4_4_265	LANKTQ	TIERLFTECHRI	I	ISEEWFNK-
UniRef90_A0A0A3IXZ5_4_264	LAHSTQ	LIERIFDNCHRL	IKKSWF---	
UniRef90_K9ZPZ7_7_273	RGNSTSEVRN	WFTNVWQ	ILRVSL	LNR-
UniRef90_A0A0C1XDA3_13_272	RGSSSTSEVRN	WFIDVWQ	LLRMSF	SSR-
UniRef90_UPI000379D7E3_4_266	QANATQ	TIERIFNQCHT	I	ISKKNHR-
UniRef90_UPI0002DF3930_13_277	RGSSSTSEVRN	WFTA	AAWQLLRQ	SLLER-
UniRef90_A0A0M0W0K1_1_266	QANTTQ	TIERI	INQCHAIL	SEKWNHR-
UniRef90_UPI000422C885_4_265	LANKTQ	TIERIFSECHQ	L	ISEDWFN--
UniRef90_B4W160_8_270	RGSSSTSEVRN	WFTQVWQ	CLRLTYLGR-	
UniRef90_Q8YQZ4_10_269	RGASTSEVRN	WFTSVWQ	LLRGEFFSR-	
UniRef90_A0A0M0W0K1_3_269	RGSSSTSEVRN	WFTSVWQ	LLRVSLHR-	
UniRef90_A0A0M1JRC4_17_282	RGNSTSEVRS	WFIDVWHLLR	LSYLG--	
UniRef90_UPI0007108B5C_4_266	LANGTQ	TIERIFSEFHNI	I	SQEWFNK-
UniRef90_UPI0006A76A92_4_265	LANKTQ	LIERIFN	NCHRI	I
UniRef90_W4ETC9_4_265	LANSTQ	LIERIFNSCHK	I	SEKWTN--
UniRef90_A0A0D6KKC6_12_271	RGASSSEVRN	WFTSVWQ	MLRVN	FLSR-
UniRef90_A0A0D8ZYE2_11_271	RGSSSTSEVR	HWFTNVWQ	LIRSSYLER-	
UniRef90_B2IT63_10_269	RGSSSTSEVRN	WFIDVWQ	LLRVSLNR-	
UniRef90_UPI000717378B_11_271	RGSTTSEVRN	WFTAVWQ	LLRQSF	LAR-
UniRef90_K9R6Q0_10_280	RGDSTAKVRN	WFISVWQ	LLRISFLNR-	
UniRef90_A0A127D3L2_4_264	LANKTQ	EIEKIFTECHRI	I	SQEWF---
UniRef90_UPI00028931D6_4_266	LANN	TQAIENIFSEFH	HI	I
UniRef90_A0A0M0ENP6_4_266	LAHSTQ	VIERILDQCQK	I	SEKWNNR-
UniRef90_A0A0S3PHU6_16_275	RGLSTSEVRN	WFTVWQ	LLRVSLHR-	
UniRef90_A0A081NYG6_3_264	LASSTQ	DIERLFAACQ	RLVREQ	WLG--
UniRef90_A0A0K9GPB1_4_266	LANKTQ	TIEQLFTECH	CM	I
UniRef90_UPI000717378B_2_265	LANSTQ	LIERIFANCHK	DITQ	KWFG--
UniRef90_K9W1V1_14_278	RGYSTLEARN	WFIRVWELLR	L	AYLGK-
UniRef90_K9U4Q1_17_272	RGSSSIEVRN	WFTSVWQ	-----	
UniRef90_A0A0M2SWM6_4_265	LANKTQ	IIEERIFNDCHK	I	SRKLNH--
UniRef90_UPI0003652A48_11_275	RGHSSSEARR	WFLAVWQ	LIRVSYFQR-	
UniRef90_UPI00047A812C_16_286	RGSSSTAEVR	RHWFIGVWQ	LLRMSFLNR-	
UniRef90_K9TKA4_12_277	RGSSSTPEVRN	WFSEVWQ	LLRSLF	IGR-
UniRef90_M7NKH7_1_269	LGRSTGRIE	KMLNACHKR	I	SEEWLG--
UniRef90_K6DR39_4_265	LANKTQ	MIKIFSEIHQ	M	ISREWFG--
UniRef90_A0A0B4RFS1_1_265	LANKTQ	VIEKI	INECHRI	I
UniRef90_A0A168N9T6_4_266	QANATQ	TIERILNQCHT	I	SEKWNNR-
UniRef90_A0A139X4D9_7_274	RGSGTTEVRN	WFTSAWQ	LLRQSVLTR-	
UniRef90_UPI00030AB192_16_277	RGYSTTEVRN	WFIGVWQ	LLRIFL	LSR-
UniRef90_K7W9H0_9_269	RGNSTSQVR	SWFTNIWQ	MLRV	SCLNR-
UniRef90_UPI00034A5E0C_10_263	RGDSTSEVRN	WFMAVWQ	MLR-----	
UniRef90_A0A0A0E4Q3_4_265	FANTTQ	VIERIFSEIHRH	I	SEHFQ--
UniRef90_UPI000717263C_4_266	LANKTQ	VIERILN	NCHKLI	SEKWLNR-
UniRef90_K9QPZ4_10_269	RGASTSEVR	RHWFTSVWQ	MLRV	DYFKR-
UniRef90_UPI0002D28249_14_276	RGSSSTAEVRN	WFISVWQ	LLRVSFLSRV	
UniRef90_F9DU20_4_266	MANYTQ	VIERI	SACHH	V
UniRef90_UPI00047933CA_3_266	LANKTQ	VIEKMFSEFHQ	I	SQEWFNK-
UniRef90_W7RFE8_4_266	LANKTQ	I	VERL	FSEFHHLNQEWFNK-
UniRef90_UPI0007441C40_4_265	LGNSTQ	LIERIFNQCHK	I	SEKWNNR--
UniRef90_A0A0T7BRT9_7_268	RGNSTSEVRN	WFISVWQ	LLRQSIGNR-	
UniRef90_UPI0006A78357_4_266	LAKNTQ	TIESMFFDFHH	I	SQEWFNK-
UniRef90_UPI0007C7BB46_4_266	LAHSTQ	KIEELMAAC	SSFLRKEWYDR-	
UniRef90_UPI000472611B_4_265	LANTTQ	VIEALFAKCH	M	VNKEWYD--
UniRef90_UPI0002ACBA0D_11_270	RGSSSIEVRN	WFTI	WQ	LLRSPYLNR-
UniRef90_A0A0C2KR59_11_269	RGSTTSEVRN	WFIGVWQ	LLRQSF	---
UniRef90_K9WE93_4_277	RGSSSTSEVRN	WFTSVWQ	LLRSLFGR-	
UniRef90_A0A0M0SP30_16_277	RGSSSTAEVRN	WFIGVWQ	LLRMSFLSR-	
UniRef90_K9Q9K1_10_268	RGASTSEVRN	WFTAVWQ	ILR	SFLSR-
UniRef90_A0A0S3TTX4_17_278	RGSSSTAEVRN	WFIGVWQ	LLRMSFLNR-	
UniRef90_K9VFQ3_5_323	RGTSTTAARD	WVFN	IWQ	LLRSLFSQR-
UniRef90_W1SM28_4_265	LANTTQ	VIEKLFSEIHR	V	SQEWFN--
UniRef90_A0A0C1N935_15_285	RGSGTTEVRN	WFTSVWQ	LLRQSVLAR-	
UniRef90_A0A139SK67_11_275	LGPACE	PGRAWFARL	WAVLRP	PALSGRA
UniRef90_UPI00041C7CDC_4_265	LANKTQ	I	I	E
UniRef90_K9XHH8_15_275	RGDSTTEVR	QWFTEVWHL	LR	SSLGK-
UniRef90_UPI0002E7D901_4_265	LADKTQ	LIESIVSACH	LAVSEK	WHQ--
UniRef90_A0ZB05_10_269	RGASTSEVRN	WFTVWQ	LLR	GDFLHR-
UniRef90_D4ZSS4_5_270	RGPSQEAIA	WFTQIWQ	LLRPNLSGK-	
UniRef90_A0A0F5YFY1_6_271	RGNTTQ	EVINWFTVWQ	LIRQNHQGRV	
UniRef90_K9T9Y9_59_322	RGSSSTADVRN	WFTGVWQ	LLRSLMKR-	
UniRef90_K9VAD2_10_273	RGSGSSEVRN	WFTD	VWQ	LLRMSYLHRV
UniRef90_W7Z4J7_4_265	LANKTQ	VIEKIH	TKCHHI	I
UniRef90_Q47G52_13_278	LGNSSEAR	LWF	FAELWT	ILRPACCGR-
UniRef90_UPI0004024FB0_3_269	RGHSISIEVRN	WFTNIWQ	SLRIN	YQNR-

UniRef90_K8GMD3_12_265 RGHSTSEARRWFIQVWQ-----
UniRef90_AOA0S3UB12_16_269 RGHSSTEARRWLIIVWSMVR-----
UniRef90_AOA0F7D4R9_4_265 IADKTQVIERVTAACHAAISEEWQ--
UniRef90_AOYQS4_5_271 RGNTTQEVINWFTNIWQFIRQNYQGRV
UniRef90_AOA0Q8RCL2_14_276 LGHSSQTARRLMMHTWQRLRPALTGR-
UniRef90_UPI0005625009_5_271 LGQRTESILRLFTAIWRRVRPEI----
UniRef90_UPI000305E365_16_284 RGSSTTEVRNWFIVGWQLLRMSFLSR-
UniRef90_UPI0002E38242_11_269 LAGQALHARAWLIELWRLLRPALLGR-
UniRef90_G8Q511_12_270 LASEALLARGWLIELWRLLRPALLGR-
UniRef90_AOA168TUL4_4_266 LAYSTQEIEKIFRSVQQLIREQWFGK-
UniRef90_UPI0004799FB1_14_281 LGDNSEARLWFAELWKILRPACCGR-
UniRef90_Q3KIS7_11_269 LASEALLARAWLIDLWRLLRPALLGR-
UniRef90_K9XZ09_12_271 RGYSTTEAKEWLSQVWQILRSEI----
UniRef90_AOA090RU86_25_288 LGNWSEVILDCFQVWQVAREHWTG--
UniRef90_AOA0M5LWB1_11_269 LAVEALQARAWLIELWRLLRPALLGR-
UniRef90_AOA0C2I8A1_11_269 LAGEALHARAWLIELWRLLRPALLGR-
UniRef90_H3SNI3_3_265 LGNSTQAIETLFGRIANAVRESWFG--
UniRef90_AOA0Q0XPT8_11_269 LATEALQARAWLIELWRLLRPALLGR-
UniRef90_K4ZJ70_4_265 LANSTQTEAIFACCHRFINQSI FN--
UniRef90_AOA085V951_11_269 LADEALHARAWMIELWKLRLPAVLGR-
UniRef90_AOA098SV87_11_271 LADEALHARAWLIELWKLRLPALLGR-
UniRef90_AOA0A1GEL6_9_267 LAGEALHARAWLIDLWRLLRPELLDR-
UniRef90_I4CP19_9_267 LADEALHARAWLIDLWRLLRPELLGR-
UniRef90_AOA0W0P2S5_11_269 LASEALHARAWLIDLWHLRLLPALLGR-
UniRef90_C3K5A6_11_269 LASEALLARGWLIIDLWKLRLPVMFGR-
UniRef90_AOA078LV36_9_267 LANEALHARSWLIALWQLLRPELLER-
UniRef90_J3GGT8_11_269 LASEALLARGWLIIDLWRLLRPALLGR-
UniRef90_A5L5M9_32_304 LGNWSEDIQAFGQIWKQATRSHTLYG--
UniRef90_AOA0J6GPD8_11_270 LAEALQARGWLIIDLWHLRLLPALLGRA
UniRef90_Q4KJ05_11_269 LASEALQARAWLIELWRLLRPALLGR-
UniRef90_AOA0V7ZQT1_2_281 RGNSTAEVRNWFIVWLLLRSTFSLSR-
UniRef90_AOA075PF54_11_269 LAGETLQARAWLIALWRLLRPALLGR-
UniRef90_AOA0D5Y774_11_269 LASETLARAWLIDLWRLLRPALLGR-
UniRef90_AOA0Q5EC30_11_271 LADEALHARAWLIELWRLLRPALLGR-
UniRef90_I4N4V9_11_269 LAHEGLHARDWLI GLWKLRLRPEALGK-
UniRef90_D4TUH6_7_266 RGNSTSWAKKWFNTNVWQDLRQSLNLR-
UniRef90_UPI00048AE6EC_1_266 LSHDTQTEIEEVFNIIHQTI RKELLQK-
UniRef90_UPI0007398261_11_285 RGTSTQEARRWFTTVVHLLRWELLNR-
UniRef90_BOC790_12_273 RGPSSQAARQWFIQVWNLRLRSTHLGR-
UniRef90_AOA066UMR7_26_298 LGHWSEDIQAFGQIWKQATRSHTLGC--
UniRef90_AOA0Q9XWI2_4_265 MANSTQLIERIFTACHHTISM EWFQ--
UniRef90_AOA0S7ZTJ9_14_276 LGHHGEQAKKVFSTVWSAIRPACVNR-
UniRef90_A6SZ04_26_286 LGHSSETARLWMTRAWQIRPELMQR-
UniRef90_U3H3U5_9_267 LASEALHARAWLIDLWRLLRPALLGR-
UniRef90_AOA073CY52_6_272 RGNSTQEVINWFTDVWQLLRQNYTGK-
UniRef90_U6ZYX1_11_270 LASEALQARAWLMDLWRLLRPALLGRA
UniRef90_UPI00067CF5D4_26_284 LGHSSSESARHWMTRAWQIRPELM---
UniRef90_AOA0K2BGW7_26_288 LGNSSQAARQWLTHAWQIRPELMQR-
UniRef90_AOA011QEK6_40_302 LAPGAEARGWLREVWQQLRPLALGK-
UniRef90_G4T117_15_272 LDHRADKLRDFNEVWTSIREATVGR-
UniRef90_Q87VP5_11_271 LADEALHARAWLIEIWKRLRLLPALLGR-
UniRef90_AOA089YS31_11_269 LADEALHARDWLIQLWTLRLLPALLGR-
UniRef90_UPI0004174C9A_9_267 LASEALHARAWLIELWRLLRPALLGR-
UniRef90_UPI000379F3E4_11_286 RGNSTAEVRNWFIVGWQLLRQSFWGR-
UniRef90_A4VQU8_9_267 LADEALHTRAWLIDLWRLLRPALLGR-
UniRef90_AOA0M3V4J1_7_297 RGASTSEVRNWFITAVWQILRSTFSLSR-
UniRef90_AOA098ESZ3_4_266 MAHSTQAIIEGIFSEYHHIISRDFWFK-
UniRef90_UPI000345DD51_13_277 LGDDSEQARRVMLAVWQRLRPFLLEA
UniRef90_UPI00047D06E7_9_270 LGNSTEQAHHLFRKIWLAI RPLVNGRL
UniRef90_I3BUX5_1_262 LGDSTAQAHRLEFRSLWQAIRPLLTGRA
UniRef90_UPI000780B9AB_11_271 LADEALHARAWLIELWKLRLPALLGR-
UniRef90_UPI000255752C_11_273 LAREALHARAWLIQLWQLLRPAVLGR-
UniRef90_UPI000484E5E1_11_269 LASEALLARGWLIIDLWRLLRPALLGR-
UniRef90_AOA0D6AS13_1_264 HGNSVSEAKTCLTAIWQLLRQY---
UniRef90_UPI00034A425D_18_281 RGASSLEARTWLIIVWQMLRVSFMG--
UniRef90_UPI00046A7B93_11_269 LASEALLARAWLIDLWRLLRPALLGR-
UniRef90_I3YAM1_6_262 LAPFAEPARRLFAAIWGI LRPRLL---
UniRef90_AOA0D9AIT7_9_267 LASEALHARAWLIDLWRLLRPALLGR-
UniRef90_UPI0003FDB5F5_4_265 LANYTQVIERIISVCHHVISDEWYQ--
UniRef90_K9SBL5_6_267 RGDSTEEARAWMLRVWDLRQALIQR-
UniRef90_UPI00040AC544_17_274 LDCRSDRLRVFFERVWAVVRPDCVRR-
UniRef90_A6D6Q9_31_296 LGNWSEVILACFQKIWQLVRGHWTG--
UniRef90_B8HW54_12_274 RGFSTQSARNWFMQVWHLRLRHRHQ-
UniRef90_AOA0J6H3B0_11_269 LAGEAFQARGWLIIDLWRLLRPALLGR-

Table 2-SI. ConSurf analysis of the multiple sequence alignment obtained using PSI-BLAST.

<i>HpUreD</i> sequence number	A	C	D	E	F	G	H	I	K	L	M	N	P	Q	R	S	T	V	W	Y	Most conserved residue (%)	ConSurf Grade
1								8		8	38		23					23			M 38.462	6
2	8		4					12				31	4	4	23	15					N 30.769	3
3	10		6			1	1		1	1	4	1	4	4	3	12	48	1			T 47.826	3
4	3				3	1	1		4			4	47	12		12	12			1	P 47.368	2
5	7		2	2		33	6	1				2	1	3	1	36	6				S 36.275	3
6														1					99		W 99.315	9
7		1	1	1			47		3	1		2	14				28	1		3	H 46.980	6
8	35					64										1					G 64.430	9
9	1		1	26				8	18	2		7		3	9	10	3	11		1	E 26.174	2
10								1		99											L 99.333	9
11	4	1	10	26			7		1			21		3	13	12	3				E 26.000	2
12								1		99	1										L 98.667	9
13	9		19	3		27		3	5	1		2		1		3	5	25			G 26.667	1
14	8				17			2		9	2						1	6		55	Y 55.333	6
15	52	1		30		7		1	1			1		1		2	2	3			A 52.000	6
16										100											I 100.000	6
17	1	4	22	7	1	1	7		6	1		13	1	6	24	2		1	2		R 24.000	1
18	2	3	7	1	15		3	2	5			1		2	53	2	1	1		1	R 52.667	3
19	7		5	3		26	3		7	5		12	1	23	4	2	1			1	G 26.000	1
20	3		20	5		51	1		1			16	1			2					G 51.333	1
21	8	3		2		3		3	35					3	11	17	13	1			K 35.333	2
22		1														5	94				T 94.000	9
23	4			1		1	1	4	3					25	27		2	33		1	V 32.667	6
24	23					1		5		37	3		24			1	1	5			L 37.333	6
25	3		1	1		1		26	23	1	1	1		1	5	3	11	22			I 26.000	3
26			5	9	4	1	15		4	13	1	15		8	11	5	1			9	HN 14.667	1
27	7	1	1	1				2	1	1		19		2	32	9	1	23			R 32.000	5
28	1			1	3		11		1	2				15	28	5	1			31	Y 31.333	4
29	1				25	3	39	1			3	9		7	1	3	1	5		2	H 39.333	5
30	1	1		1	4	1	1	1	9	9		1		59	5	5	3			1	Q 58.667	5
31	36					61						1	1				1	1			G 61.333	9
32	27												73								P 72.667	9
33					19					77									1	3	L 77.333	7
34	5								63			2			27		1	1			K 63.333	9
35								11		5	1							84			V 84.000	7
36	1								1	25				72				1			Q 72.000	9
37	1								29				1		69	1					R 69.333	9
38	3						21						71			3	1				P 71.333	8
39					42		1	17	1	31								8			F 42.000	7
40							3													97	Y 97.333	9
41	20				3		17			4			55				1				P 55.333	7
42			25	71		1			1			2	1	1							E 70.667	9
43	1		17	3		69	2		1			5		1	1						G 69.128	5
44	8		6	28		30			9			2	1	9	1	5	1				G 30.000	1
45							2	15	2	1			2	21	1		1	53	2		V 53.333	6
46	9	72											7				12				C 72.000	7
47		26		1			51							23							H 50.667	9
48	6	1			1	1	21	1		1		1				33	5	1	27		S 33.333	7
49	1				1			29		1	1							35	33		V 34.667	8
50	1							64		23	1							10			I 64.000	6
51								1		71	3							25			L 70.667	8
52	1					72						27					1				H 72.000	9
53					1								61					37	1		P 61.333	9
54	36					29							35				1				A 36.000	9
55	1												1				1				G 97.333	9
56						100															G 100.000	9
57								42		1	4							26	27		I 42.000	7
58	23									26	1							50			V 50.000	9
59	2		25	1		71						1			1						G 70.667	8
60							99										1				G 99.333	9
61			100																		D 100.000	9
62	1	1		2			3	1	2					3	78	4	5	1			R 78.000	6
63										71		1		1						27	L 70.667	9
64	7	1	15	1	1	1	3	1	7	2		5		9	11	32	4				S 32.000	4
65	1	4			2	1		35		13	21			7		7	2	1	7		I 35.333	5
66	1	1	13	11			5		14			18		7	5	18	5				NS 18.000	1
67	23				19			35		8								16			I 34.667	3
68	4		2	3		1	35		1	1		5		4	9	25	10				H 35.333	1
69	11							1		57							1		30		L 57.333	7
70	8	1	11	18		23	1	1	3	1		1		30	1	2					Q 30.000	2
71	10		5	25			1		6			1	35	3	4	6	3				P 35.333	1

148	71									27				1	1			A 70.667	9			
149	5	1	9	7		1		1	1	1		5	1	37	30			R 37.333	6			
150	1		4			88			1			5	1			1		G 88.000	6			
151			3	87		1			5					1	1	1		E 87.333	8			
152	1			1		3	3	2	33	3		2	1	8	35	3	3	1	R 35.333	2		
153					98						1							F 98.000	9			
154	6	1	16	9	1	1		1	1	19	1	2		2	25	6	7	3	S 24.667	1		
155	7	1	1	5	1	1	7	1	1	6				27	3	7	3	27	QY 27.333	2		
156			18	1		72	2		1			3		1	1	1		G 72.000	6			
157	1		3	26	1		21	1	5	3	4	7		3	7	4	13	3	E 26.000	2		
158	3				23			8		19	3						11	33	W 33.333	5		
159	3		3	1		1	2		3	4				41	40	1	1	2	Q 41.333	6		
160	11				3	3		1		27	1	2		4	46	1	1		S 46.000	6		
161	1	3	1	1	1		37	9	13	3	2	3		9	9	1		5	3	H 36.667	2	
162		1			1			1		23		16			2	56		1		T 56.000	8	
163	1		18	66			1		1		1	3		4	3	3				E 66.000	7	
164							79			3							18			I 79.333	7	
165				2	1		1			1		1	1	23	1	1	1	36	32	W 36.000	6	
166		1					1	1	1	12	13			35	31		4	2	1	Q 34.667	7	
167	3		50	8		3	1		1	1	1	9		22	1	1				D 50.000	5	
168			13	4		71			1			9		1	1					G 70.667	3	
169	1	1	3	19			1	3	25	1				17	15	1	2	11		K 25.333	1	
170	1						1	1	47			47		2		1		1		P 47.333	6	
171	5			1	7		7		63				1			17				L 63.333	6	
172	2			1			1		7	2						1		21	64	2	W 64.000	6
173				19		21	39	1	5								3	1	1	11	I 38.667	6
174			67	33																	D 67.333	9
175						3	27					1	1	5	63						R 63.333	8
176	1			1	6		21		10					59		1	1				Q 58.667	8
177	1	1	1	1	1	3	3	23	3	1	2			3	28	1	1	1	23	3	R 28.000	3
178				3			18		67	1							1	11			L 67.333	5
179	5	1	5	4	1	1	4	3	2	1	1	7	31	5	5	7	5	13			P 30.667	1
180	9					61						1	29								G 61.333	7
181	15	1	8	7		25	1		3	1		13	1	2	4	19	1				G 25.170	1
182	3		28	32		1	1	1	4	1	1	3	2	6	2	7	5	3	1		E 31.757	1
183	10		7	21		21	1		6			3	2	22	1	3	3	1			Q 22.000	3
184	4		5			1	1	12	1	28	4	13	2		1	5	5	16	1		L 27.891	1
185					25			16		41	15							3	1		L 40.667	4
186	4		27	9		2	21	2	3			10		2	3	7	7			3	D 26.667	1
187	6		1	1		20			1	1		3			66	1					S 66.000	7
188	3			1			2	9		21	1	1	58		1	1		1	1		P 58.219	4
189	4	1				27	33	19	1	4	2	3	1		1	1		3	2		H 33.333	6
190	4		1		20	65	1		5	1				1	2				1		G 65.333	6
191					1					73	25									1	L 72.667	9
192	33		19	27	1	4	1		1	3		4		1	3	3					A 32.667	5
193			1			93						3		1	1						G 93.333	7
194	1	3	1	1	11		9		11	1		6		27	1				1	29	Y 29.333	1
195	5												53	1		15	26				P 52.667	6
196	1					28	19		3	3					1		45				V 45.333	8
197	5	5			23		7		24	4			1		1	3	27		1		V 26.667	4
198	36					63			1												G 63.333	6
199												3			53	44					S 52.667	8
200				15					61	24							1				L 60.667	6
201	10			4			35		23	3					1	3	17	1	3		I 35.333	4
202	18	2			2	1		3		5	1							37	22	9	V 37.333	3
203	1						27		6	1						6	20	37		2	V 36.667	3
204	3	1	2		1	73		1	1			1	4	1		11					G 73.333	4
205	1	1	10	42	1	3	3		9	1		3	3	15	1	5	1	1			E 41.667	2
206	7		2	11		1			9	2		3	23	23	2	5	6	5		2	PQ 23.148	1
207	8						27		3	6						3	15	36	1		V 36.301	3
208	2	1	26	7		2					16	3			33	10					S 33.333	2
209	19		4	7		3	3		7	1	1	7	24	5	3	13	3	1			P 24.000	1
210	11		21	54		1	1					1		4		5					E 54.000	3
211	2	1	2		11	1		17		56	4				1		2	3	1	1	L 56.000	2
212							18		57	4					1			19		1	L 56.667	5
213	7		28	49		3		2				3		5	1	1	2				E 48.667	5
214	6			13		3	2	24	5	1	1		13	24	2	5	1				KR 24.000	1
215	26	25					7		30						1	1	11				L 30.000	5
216	1	1				1	3	1	1			1		5	66	1			21		R 66.000	7
217	9		6	23		3	1		1	2	1	13		9		26	4	1		1	S 26.000	1
218	12	1		4	1	1	1	5	1	59	3			1		3	5	5	1		L 58.667	1
219	1	2	1		6	2		26		12	4		1		2	3	4	5	31	1	W 30.702	1
220	5	2	13	5		5	7	3	7	5	1	10	3	15	2	7	7	1		2	Q 15.315	1
221	9		13	15		5	5	1	5	3	1	7	11	7	6	8	3	2			E 15.333	1
222	5	3	1		11	25	2	1		4		1	4			7	2	24	1	11	G 24.667	1
223	3	1	3	21	1	1	1	2	17	7		1		9	27	3	3				R 26.667	1

224	12	1		14	23	1	15		1	3		1	1	3	7	17	1	1	G 22.667	1		
225	3	1	21		75					1				1					G 74.667	8		
226	10			1			11		40	1		1				37			L 40.000	6		
227															37	63			T 62.667	8		
228	4			3	1		1	1	4	11	3	1		35	33	2	2		Q 35.333	4		
229					1			4		86	4		1				2	3	L 86.000	7		
230	9		4	15				2	3	3	4	1	37	7		9	4	1	P 36.667	2		
231	4			2			33									2	2	53	V 53.333	5		
232	1	3	3	3		27	11	1	2	1	1	9	19	5	1	11	1		G 26.667	1		
233					65	1	1		26	1							7		G 64.667	7		
234				33				7	57	1							2		L 56.667	5		
235		2			1		5		37	1					11	13	29		L 37.333	6		
236	27	39			2		17		6								9		C 39.333	6		
237								1						99					R 99.333	9		
238	5	23					13		1							14	1	44	Y 44.000	7		
239				1		1	1		57	2			2	37					L 57.333	8		
240	48		1		50										1				G 50.000	8		
241	5	1	11		1	3	11		1	1		32	3	1	1	23	2	1	3	N 32.000	2	
242	2		1	21	1	4	1		3	1		2		1	2	53	5		3	1	S 52.667	6
243	21	1			1			1							15	61	1				T 60.667	7
244	6		1	11	1	1		1		22		1	33		17	7					Q 32.667	6
245	6		3	34			12	2	2	9	1		2	8	1	2	9	9	1		E 34.000	2
246	38				1		29		2								1	29			A 38.000	8
247				27		1		3	3	4					62						R 62.000	8
248	19		3	2		5	4		7	2		26		4	21	3	2	1			N 26.000	2
249	1	2			1		18		10	2							3	63			W 62.667	5
250				63		1	3		27	5				1		1	1				F 62.667	6
251	7		1	1	1	2		33	2	3	8		1	3	9	27	1				I 33.333	3
252	15	1	15	23		6	1		3			8		11	5	9	1	2		1	E 22.667	1
253	3	19			3			13		23							1	37		1	V 36.667	6
254	1					24							2		1			72			W 72.000	8
255	3	1	1	2		1	9		9	2	1	2		43	21	2	3				Q 43.333	4
256	5	1	1		2		1	18		52	6			1	5	1	1	4			L 52.027	2
257	1						30		61								1	6			L 61.486	7
258		1				1		1			2				75	19	1			1	R 75.000	8
259	1		1	14		2	1	2	3	7	5		33	15	2	4	2	7	1		P 32.877	1
260	25		3	21	1		3		8	2		4	1	2	1	25	2	1			AS 24.658	4
261	1	3			17		1	3		32	1					1	1	3	27	9	L 32.192	1
262		2			19	1	1	1		50	3	6		3	1	3	5	2	1	3	L 49.650	1
263	1		2	3		45	6		1			22		11	1	7	1				G 44.928	1
264								16							1	83					R 82.727	8
265	45								9								45				AV 45.455	7

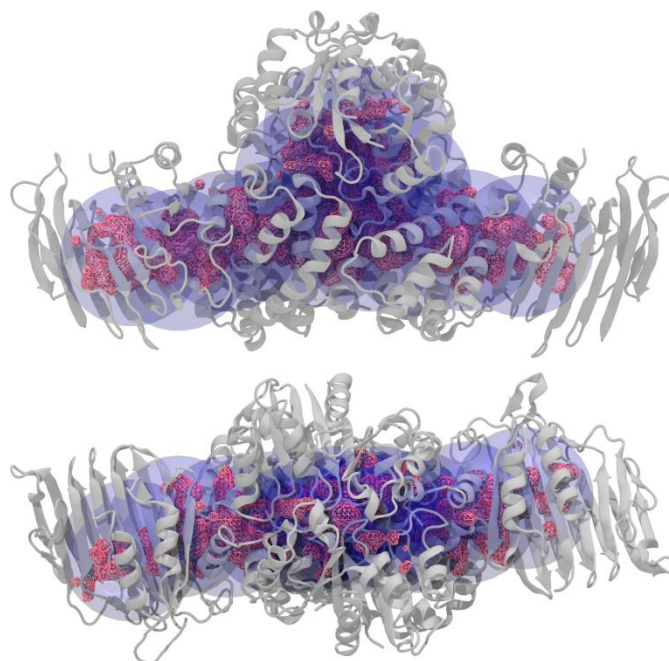


Figure 12-SI. Density isosurface of the water molecules found inside the *HpUreDFG* tunnels contoured at 0.025 oxygen atom \AA^{-3} (purple mesh) superimposed on the fourteen spheres (light blue) used to discriminate the time frames in which selected waters lied inside or outside the tunnels. The *HpUreDFG* complex is reported as white ribbons. In the bottom panel, the *HpUreDFG* complex is rotated by 90° around the horizontal axis with respect to the orientation in the top panel.

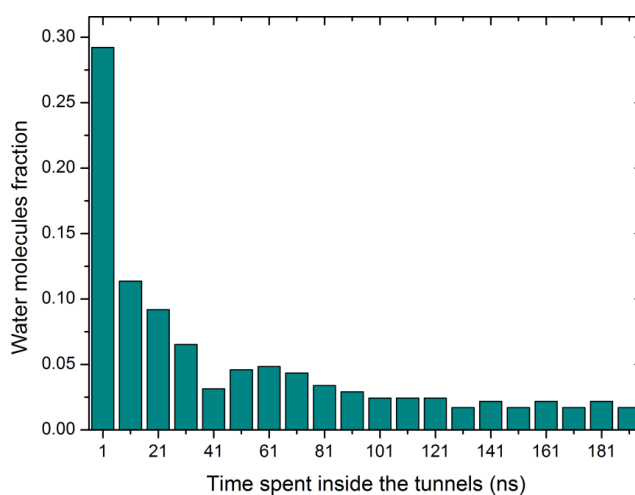


Figure 13-SI. Distribution of the time spent inside the tunnels of the 370 water molecules that are able to enter in the tunnels from the bulk of the solvent or that escape from the tunnels during the course of the simulation (see main text for details).

Figure 14-SI (part one). Trajectory of selected water molecules inside the *HpUreDFG* tunnels (see main text for details). In each frame, the water molecule is reported as a sphere colored from red to green and finally to blue, accordingly to the simulation time. The starting frame is indicated by a red sphere of larger radius with respect to the others and a black arrow. The *HpUreDFG* complex is reported as white ribbons and GDP is depicted as balls-and-sticks.



Figure 14-SI (part two).



Figure 14-SI (part three).



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