Comparative structural studies of peptide transporters and their roles in physiological processes.

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Certificate of Examination

This to certify that the dissertation titled **"Comparative structural studies of peptide transporters and their roles in physiological processes"** submitted by **Mr. Shubham Bhojane** (Reg. No. MS14020) for the partial fulfilment of BS-MS dual degree programme of the Institute, has been examined by the thesis committee duly appointed by the Institute. The committee finds the work done by the candidate satisfactory and recommends that the report be accepted.

Dr. Debrina Jana Dr. Sanchita Sengupta Dr. Monika Sharma

(Supervisor)

Dated: April --, 2019

Declaration

The work presented in the dissertation has been carried by me under the guidance of Dr.Monika Sharma at the Indian Institute of Science Education and Research Mohali.

This work has not been submitted in part or in full for a degree, or diploma, or a fellowship to any other University or Institute. Whenever contribution of others are involved, every effort is made to indicate this clearly, with due acknowledgement of collaborative research and discussions. This thesis is a bonafide record of original work done by me and all sources listed within have been detailed in bibliography.

Shubham Bhojane

(Candidate)

Dated: April --, 2019

In my capacity as the supervisor of the candidate's project work, I certify that the above statements by the candidate are true to the best of my knowledge

Dr. Monika Sharma

(Supervisor)

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Abstract

The POT family of membrane transporter proteins shows remarkable feature of diverse substrate promiscuity. This promiscuity has led to development of peptide based pro-drugs that us PepT1 and PepT2, mammalian homologues, to improve oral drug delivery[1]. Here I tried to classify 46 POT family transporters on the basis of transmembrane α-helical spanners and to establish evolutionary relationship between POT family members and by sequence alignment technique looked into residues conserved in POT family members.

Contents

Chapter 1: Introduction

1.1 Cell membrane its function and composition

Both prokaryotic and eukaryotic cells are enclosed in a semipermeable membrane also known as the cell membrane or the plasma membrane. cell membrane has four important functions function number one is, it creates a protective barrier between the outside and the inside environment of the cell it basically prevents toxins and other pathogenic agents from entering the cell and it prevents molecules from spontaneously exiting the cell in the first place, now function number two is transport, that is it only allows the Selective movement of certain things outside or into that cell so this is a semipermeable membrane and what that means is the cell actually picks and chooses what to allow into the cell and what to not allow into the cell, function number three is signal transduction what that means is certain molecules for instance hormones can actually interact with the outside portion of the cell membrane and that will create many different types of signals and processes inside the cell, function number four energy storage. Therefore cell membrane is an extremely important type of structural component of the cell. Plasma membrane found in prokaryotes and eukaryotes is a phospholipid bilayer means it has two layers of phospholipid. A phospholipid is a molecule that consists of a polar phosphate group attached to a nonpolar fatty acid tail via a group known as the glycerol group. Inside a cell membrane, we also have proteins which give the cell membrane its functionality. They are embedded in the cell membrane. These proteins are of two types' first integral proteins and second peripheral proteins. Integral proteins extend throughout the entire bilayer membrane and their usual function because they extend through the entire membrane is to transport things from the inner portion to the outer portion of our cell and vice versa from the outside to inside of the cell. Peripheral proteins bind via electric forces to either the integral proteins themselves or they bind to phospholipid bilayer. Because these

proteins do not actually span the entire bilayer that means they usually do not act as transport proteins, so they function in cell recognition, cell signalling or cell communication.

In reality, integral proteins embedded in phospholipid bilayer gives the cell membrane its semipermeable character. Which basically means certain materials will pass across the membrane while others will be blocked. Two factors influence the ease with which any external molecule or atom passes across the cell membrane and these factors include the size of a molecule as well as the polarity of that molecule. Size aspect is a bit intuitive so the larger the molecule less likely it will pass through that cell membrane. Since cell membrane is a phospholipid bilayer that means there are two layers of phospholipids and phospholipids themselves are predominantly fatty acids so that means predominant portion of the cell membrane is nonpolar inside, in fact, the entire intermediate space between these heads is basically nonpolar and so that means nonpolar molecules no matter how large will be able to move across and that's exactly why cholesterol which is a large molecule has no problem moving across our cell membrane but even a very small atom that has a full positive or full negative charge such as the sodium atom will not be able to move across the membrane, because it is very polar and contains a full charge.

1.2 Membrane transport

Membrane transport is about how exactly molecules make their way across the cell membrane from one side to the other side of that cell membrane. In doing so molecules use different transport mechanisms or methods and these methods that they use to cross the membrane really depends on the properties of those molecules. To begin let's focus on nonpolar and small molecules. cell membrane consists predominantly of a hydrophobic region so the entire core of the membrane is hydrophobic nonpolar because of the presence of hydrocarbon tails[2], part of the phospholipid molecules now because a non-polar molecule can easily dissolve in a hydrophobic nonpolar solution what that means is if a small non polar molecule wants to make its way across the cell membrane all it has to do is dissolve inside that cell membrane and this process by which a small nonpolar molecule will move down its concentration gradient from a high to low potential through the core of that membrane by dissolving in that cell membrane this is known as simple diffusion. For example, way cell membrane of the cells found inside our lungs facilitates the movement of O_2 and CO_2 molecules easily. Inside the

cells of our lungs we know we have a high concentration of CO_2 inside and a low concentration on the outside conversely we have a low concentration of O_2 on the inside but a high concentration of O_2 on the outside. Both carbon dioxide and oxygen are small nonpolar molecules and therefore these two molecules will have no problem making their way and dissolving into the hydrophobic core of that membrane. These oxygen molecules will naturally move spontaneously from a high potential concentration to a low potential concentration from the outside to the inside. they will pass and dissolve inside and through membrane likewise these carbon dioxide's being nonpolar will also dissolve and move through that membrane via simple diffusion but they will move from the inside to the outside down their concentration gradient.

Now, what about if the molecule is polar? What if it has some type of charge? For instance, let's say we're looking at ions like sodium ions or chloride ions and molecules that don't have a charge yet they're very polar for instance sugar molecules. Sugar molecules are large enough and polar enough to not be able to pass across the membrane via simple diffusion. In this case, if a molecule is polar and large for example sugars and sodium they will not be able to simply dissolve inside the hydrophobic core of cell membrane[3] and in this particular case they have to use another method and what they use is integral proteins that exist inside the membrane of our cells membrane. These are also known as transport membrane proteins because we find these proteins in the plasma membrane and their function is to transport such polar or charged molecules across the two sides of the membrane.

Now there are two types of transport membrane proteins, membrane channels, and membrane pumps. Membrane channels essentially create a passageway in the plasma membrane which basically lack or doesn’t contain the hydrophobic core. In other words, membrane channel removes that hydrophobic core and facilitate the spontaneous diffusion of ions in some cases molecules, down their electrochemical gradient. This type of transport is known as facilitated diffusion. And since membrane channels don't use any energy molecules for instance ATP molecules to carry out the process this type of transport is known as passive transport. Membrane channels and membrane pumps both transport membrane proteins basically move large and polar molecules but the difference is that channels do not use energy

and they always move molecules down their electrochemical gradient from a high to low potential. But membrane pumps actually use energy to move molecules against their electrochemical gradient from a low potential to a high potential. Therefore such type of molecular transport carried out by protein pumps using energy stored in the chemical bonds of ATP molecules is known as active transport.

Chapter 2: Peptide transporter proteins

Peptide transport may be defined as the process by which peptides of two to eight amino acid residues are transported across the cell membrane into a cell. Transport of peptides into cells is a well-documented process which is carried out by specific, energy dependent transporters found in vide variety of organisms[4] as diverse as bacteria and human including fungi, plants and mammals. Peptide transport is an important route for the cellular acquisition of nitrogen and amino acids[5]. Thus obtained nitrogen and amino acids are subsequently used by cell for metabolism and growth. Therefore cellular uptake of peptides is an important physiological process mediated by the PTR family of proton-coupled peptide transporters[6]. PTR family proteins are members of the major facilitator superfamily (MFS) of secondary active transporters[7]. Proteins of proton-dependent oligopeptide transporter (POT) family also known as peptide transport family (PTR) are of about 450-600 amino acyl residues in length with the eukaryotic proteins in general being longer than the prokaryotic bacterial proteins. They exhibit 12 to 14 established or putative transmembrane α-helical spanners. Remarkable characteristic of POT family protein is their diverse substrate promiscuity meaning POT family proteins recognise and transport diverse library of peptides. This promiscuity has led to development of peptide based pro-drug that use PepT1 and PepT2, the mammalian homologues, to improve oral drug delivery[8]. Therefore interest in peptide transporters of mammalian members increased recently after the discovery that both PepT1 and PepT2 are able to recognise and transport a large number of orally administered drug molecules[9], including beta-lactam antibiotics, antiviral and anticancer drugs. Major challenges in drug delivery system are poor intestinal absorption & distribution of drug molecule, missing desired target eventual side effect or breakdown of drug & excretion, poor bioavailability. A successful strategy to tackle this problem has been to develop prodrug molecules, which could target the intestinal peptide transporter, mammalian members of POT family transporters for active transport into the body[10]. Prodrugs are bioreversible derivatives of drug molecules that undergo an enzymatic or chemical transformation in vivo to release the active parent drug[11]. This ability

Of PepT1 and PepT2 to recognise and transport peptide based prodrug molecules resulted into increased attention of mammalian homologues by pharmaceutical industry.

Chapter 3: Methods used

3.1 Protein sequence alignment: aligned protein sequences of 46 peptide transporter family member proteins using Uniprot database.

In bioinformatics sequence alignment is considered as basic fundamental procedure to compare given sequence with other sequence available in biological database either it can be RNA, DNA or Protein. By sequence alignment we can understand about sequence homology whether the sequence is ortholog or paralog? Or whether the given sequence has very good sequence identity with other sequence in database? Or sequence conservation whether the active site residues are conserved? Or motifs are conserved? Such information we get by sequence alignment. Protein sequence alignment gives more information than DNA sequence alignment because protein sequence contain 20 different characters like 20 Amino Acid having each different chemical properties therefore protein sequence alignment is more complicated as compare to DNA sequence alignment[12], where only 4 characters A,T,G,C are present. Which can be easily analysed but information we get by DNA sequence alignment is may not be reliable as compare to that of protein sequence alignment.

Why we need sequence alignment? By sequence alignment we can identify changes or differences at the individual base level or amino acid level between two or more sequences. Sequence alignment helps us to organise and analyse sequence data to check the sequence homology and identity between sequences[13]. Sequence alignment help us to phylogenetic trees from homologues sites. It helps use to estimate and establish evolutionary relationship. And we can identify and highlight the conserved and variable sites and regions. It also used to test and hypotheses about protein fold, motifs, domains and their three dimensional structures.

Uniprot which stands for universal protein resource is an online freely accessible database. It aims to provide various types of information about proteins for example protein sequence including isoforms and variants if present. It also provides detailed information on

protein function, interaction, pathways, involvement in diseases and other such biological areas of interest. It also provides stable identifiers and accessions. Uniprot provides "Align" tool for multiple sequence alignment. End result of sequence alignment depends upon algorithms used for alignment. Uniprot website can be accessed at the URL http://www.uniprot.org/.

3.2 Protein structure prediction:

Used web based tool Phyre2 to predict structure of PepT1 and PepT2 proteins. This server can be accessed at the URL http://www.sbg.bio.ic.ac.uk/~phyre2/html/page.cgi?id=index .

Phyre2 or a Protein Homology/Analogy Recognition Engine is an online web service to predict three dimensional structures of proteins[14]. At present we have around fifteen thousand structures of proteins in protein data bank, on the other hand the available information regarding protein sequences in Uniport database is about eighty nine million sequences. If we compare the availability of amino acid sequences and structures available, sequences are about six thousand fold than the availability of the structures. The protein structures is helpful in understanding function, identifying active sites, antigenic sites and different binding sites with other complexes. Therefore it is very important to have the structures of proteins than sequence information. Due to the availability of more number of sequences and less number of structures it is important to predict the structures of proteins from just amino acid sequence. Deciphering the native conformation of protein from amino acid sequence is called a protein folding problem. From the unfolded state, protein finally folds into the stable three dimensional structure. So how to obtain 3D structure from the amino acid sequence. There are various methods to predict the 3D structures just from amino acid sequence. One of the most popular methods is homology modelling. Which is also used by Phyre2 an online 3D structure predicting web service. Homology modelling is based on the principle that if two sequences share high sequence identity or sequence similarity then the assumption is that the structures are also similar.

3.3 Phylogenetic tree: used Uniprot to establish evolutionary relationship between 46 POT family members.

All species are related to one another. Which could be easily observed by looking at the species in itself. There are similarities which are progressing in a hierarchical way from a unicellular organism to multicellular organisms. When we observe, we could see there is a hierarchical progress in several levels which eventually ends up with evolved organisms like humans or other animals. Having explained in a qualitative way it is also possible to explain this relationship between the species in quantitative manner. A tree structure representing this relationship in a quantitative manner is called as a phylogenetic tree. In earlier studies morphological characteristics were recorded from existing or fossilized species which were used to obtain this quantitative relationship and was represented by means of phylogenetic trees. Recently revolution in sequencing technologies and development of efficient bioinformatics algorithms has allowed us to use DNA or protein sequences for phylogenetic analysis. So earlier morphological traits were used for building phylogenetic trees but with the various bioinformatics methods and sequencing methodologies that we have today we can use molecular information and describe similarities and dissimilarities between sequences in terms of phylogeny. With the set of DNA or protein sequences from different species we are able to infer the phylogenetic relationship among the species. This follows an underlying assumption that the sequence considered has evolved from a common ancestral gene such set of sequences which comes out from a common ancestor gene are known as orthologous sequences[15]. It is also possible that two sequences considered are similar because of some gene duplication events and it could be present in the same species such sequences are called as paralog they might even have the same function but they don't have a common ancestor. Therefore phylogenetic informations are usually derived from an ortholog a set of gene.

Chapter 4: Result

1] Classification of POT family proteins based on number of transmembrane α- helical spanners

No of transmembrane α-helical spanners	Protein name	Organism	Gene
8	Uncharacterized protein	Rhizophagus irregularis	GLOINDRAFT_34 3346

Table 1.

Figure 3: structure of U9UKY5_RHIID Uncharacterized protein OS=Rhizophagus irregularis modelled using Phyre2.

No of transmembrane α-helical spanners	Protein name	Organism	Gene
9	Nitrate transporter	Oryza sativa (Rice)	NRT1

Table 2

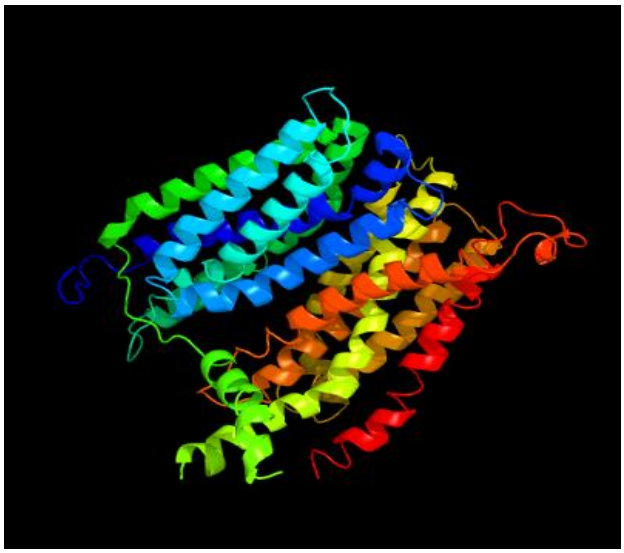


Figure 4: structure of Q9SPU1_ORYSA Nitrate transporter OS= Oryza sativa (Rice) modelled using Phyre2.

No of transmembrane α-helical spanners	Protein name	Organism	Gene
10	Probable peptide transporter ptr2	Schizosaccharomyces pombe (Fungus)	ptr2
	Protein NRT1/ PTR FAMILY 8.1	Arabidopsis thaliana (Mouse-ear cress)	NPF8.1
	Protein NRT1/ PTR FAMILY 8.2	Arabidopsis thaliana (Mouse-ear cress)	NPF8.2
	Protein NRT1/ PTR FAMILY 1.2	Arabidopsis thaliana (Mouse-ear cress)	NPF1.2
	Peptide transporter PTR3-A	Aegilops tauschii (Tausch's goatgrass)	F775_27357
	Peptide transporter family 1	Drosophila melanogaster (Fruit fly)	yin

Table 3

No of transmembrane α-helical spanners	Protein name	Organism	Gene
11	Peptide transporter PTR2	Saccharomyces cerevisiae (Baker's yeast)	PTR2
	Putative peptide transporter	Trichoderma harzianum (Fungus)	ptr2
	Ptr22p	Candida albicans (Yeast)	PTR22
	Protein NRT1/ PTR FAMILY 8.3	Arabidopsis thaliana (Mouse-ear cress)	NPF8.3
	RCH2 protein	Brassica napus (Rape)	N/A
	Protein NRT1/ PTR FAMILY 5.2	Arabidopsis thaliana (Mouse-ear cress)	NPF5.2
	Solute carrier family 15 member 5	Homo sapiens (Human)	SLC15A5
	Protein NRT1/ PTR FAMILY 2.12	Arabidopsis thaliana (Mouse-ear cress)	NPF2.12
	Protein NRT1/ PTR FAMILY 7.3	Arabidopsis thaliana (Mouse-ear cress)	NPF7.3
	Oligopeptide transporter PEPT1	Fundulus heteroclitus macrolepidotus	SLC15A1b
	Peptide transporter family 1	Caenorhabditis elegans (Roundworm)	pept-1

Table 4

No of transmembrane α-helical spanners	Protein name	Organism	Gene
12	Di-/tripeptide transporter	Lactococcus lactis (Bacteria)	dtpT
	Di-tripeptide ABC transporter	Geobacillus kaustophilus	GK2020
	Protein NRT1/ PTR FAMILY 6.3	Arabidopsis thaliana	NPF6.3
	Protein NRT1/ PTR FAMILY 2.7	Arabidopsis thaliana	NPF2.7
	Protein NRT1/ PTR FAMILY 3.1	Arabidopsis thaliana	NPF3.1
	Solute carrier family 15 member 3	Homo sapiens (Human)	SLC15A3
	Solute carrier family 15 member 4	Homo sapiens (Human)	SLC15A4
	Protein NRT1/ PTR FAMILY 4.2	Arabidopsis thaliana	NPF4.2
	Protein NRT1/ PTR FAMILY 2.13	Arabidopsis thaliana	NPF2.13
	Protein NRT1/ PTR FAMILY 4.6	Arabidopsis thaliana	NPF4.6
	Protein NRT1/ PTR FAMILY 2.10	Arabidopsis thaliana	NPF2.10
	Protein NRT1/ PTR FAMILY 6.2	Arabidopsis thaliana	NPF6.2
	Protein NRT1/ PTR FAMILY 2.11	Arabidopsis thaliana	NPF2.11
	Solute carrier family 15 member 1	Rattus norvegicus (Rat)	Slc15a1
	Peptide transporter family 2	Caenorhabditis elegans	pept-2
	Solute carrier family 15 member 2	Mus musculus (Mouse)	Slc15a2
	Solute carrier family 15 member 2	Danio rerio (Zebrafish)	slc15a2
	Solute carrier family 15 member 2	Homo sapiens (Human)	SLC15A2
	Solute carrier family 15 member 1	Homo sapiens (Human)	SLC15A1
	Peptide transporter 3	Caenorhabditis elegans	pept-3

Table 5

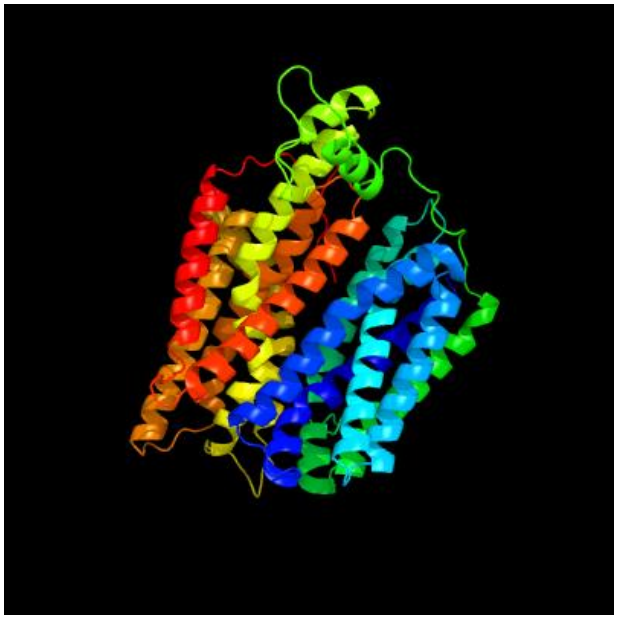


Figure 5: P46059|S15A1_HUMAN Solute carrier family 15 member (PepT1) protein structure modelled using Phyre2.

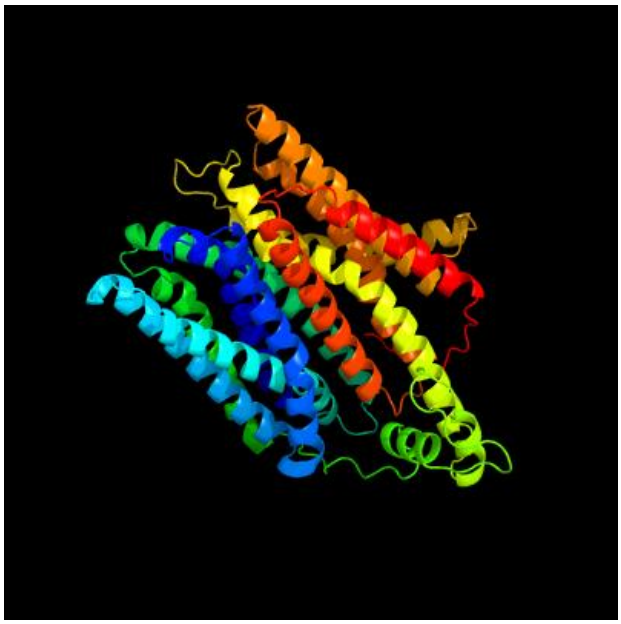


Figure 6: Q16348|S15A2_HUMAN Solute carrier family 15 member 2 (PepT2) protein 3D structure modelled using Phyre2.

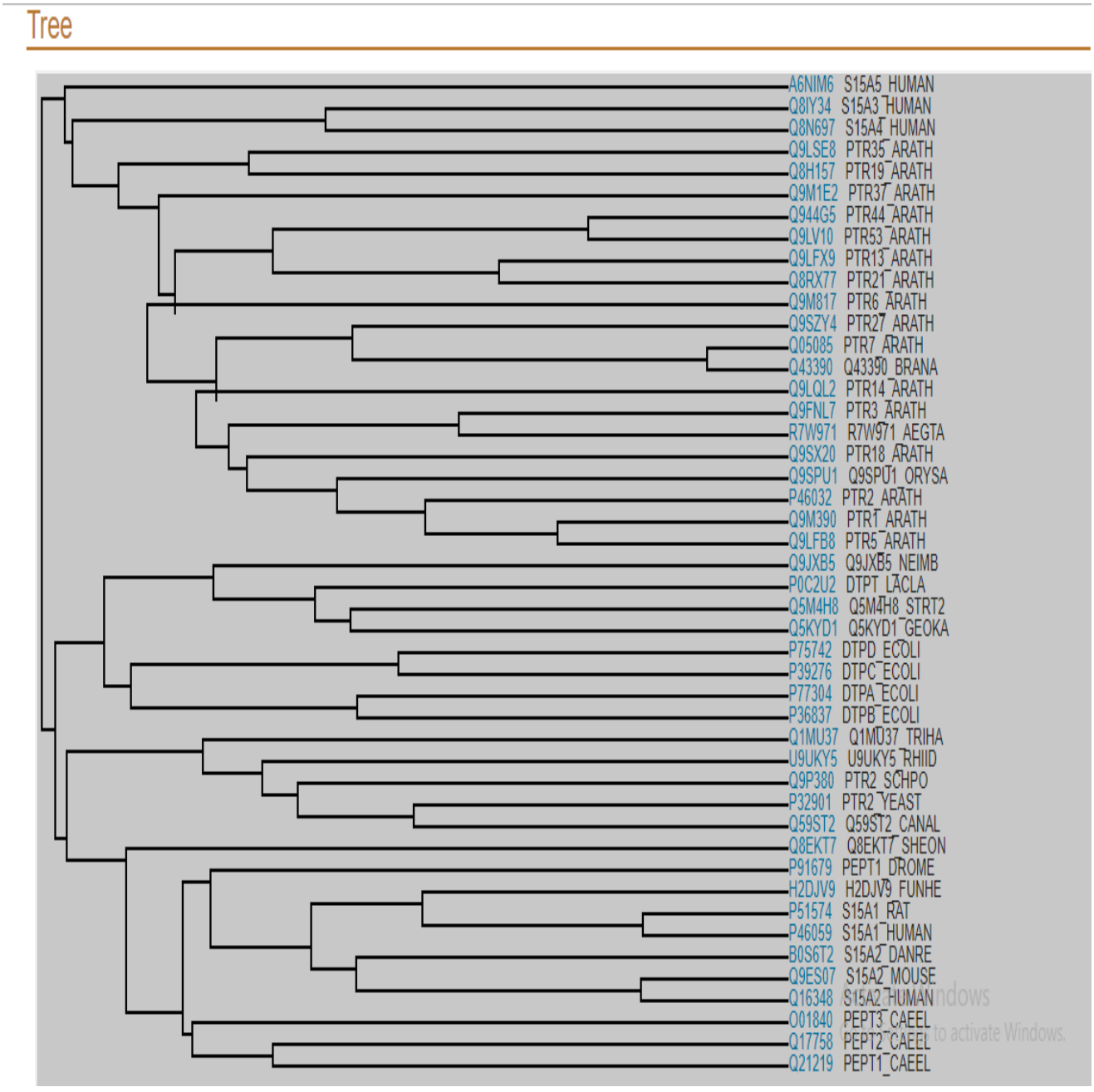
No of transmembrane α-helical spanners	Protein name	Organism	Gene
13	Di-or tripeptide:H+ symporter	Streptococcus thermophiles (Bacteria)	dtpT
	Glutathione uptake transporte	Shewanella oneidensis (Bacteria)	SO_0002

Table 6

No of transmembrane α-helical spanners	Protein name	Organism	Gene
14	Dipeptide and tripeptide permease A	Escherichia coli (Bacteria)	dtpA
	Dipeptide and tripeptide permease B	Escherichia coli (Bacteria)	dtpB
	Dipeptide permease D	Escherichia coli (Bacteria)	dtpD
	Dipeptide and tripeptide permease C	Escherichia coli (Bacteria)	dtpC
	Peptide transporter	Neisseria meningitidis serogroup B (Bacteria)	NMB2136

Table 7

2] Phylogenetic tree establishing evolutionary relationship between POT family members.



As we can see in above phylogenetic tree, peptide transporter protein which is root protein in this case has evolved mainly into two branches. From tree we can deduce POT members of

eukaryotic organisms are more closely related to one another as compare to prokaryotic organisms.

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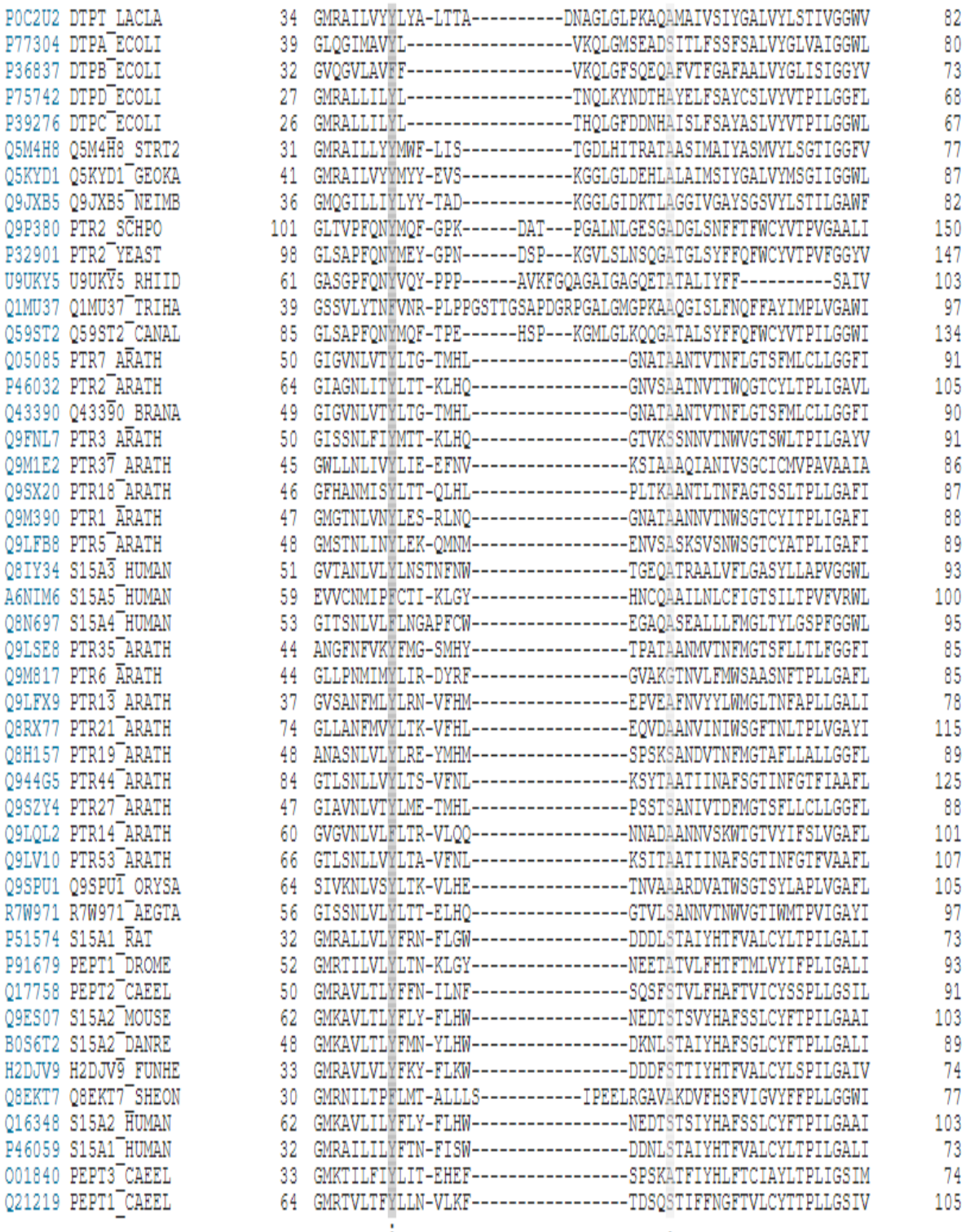
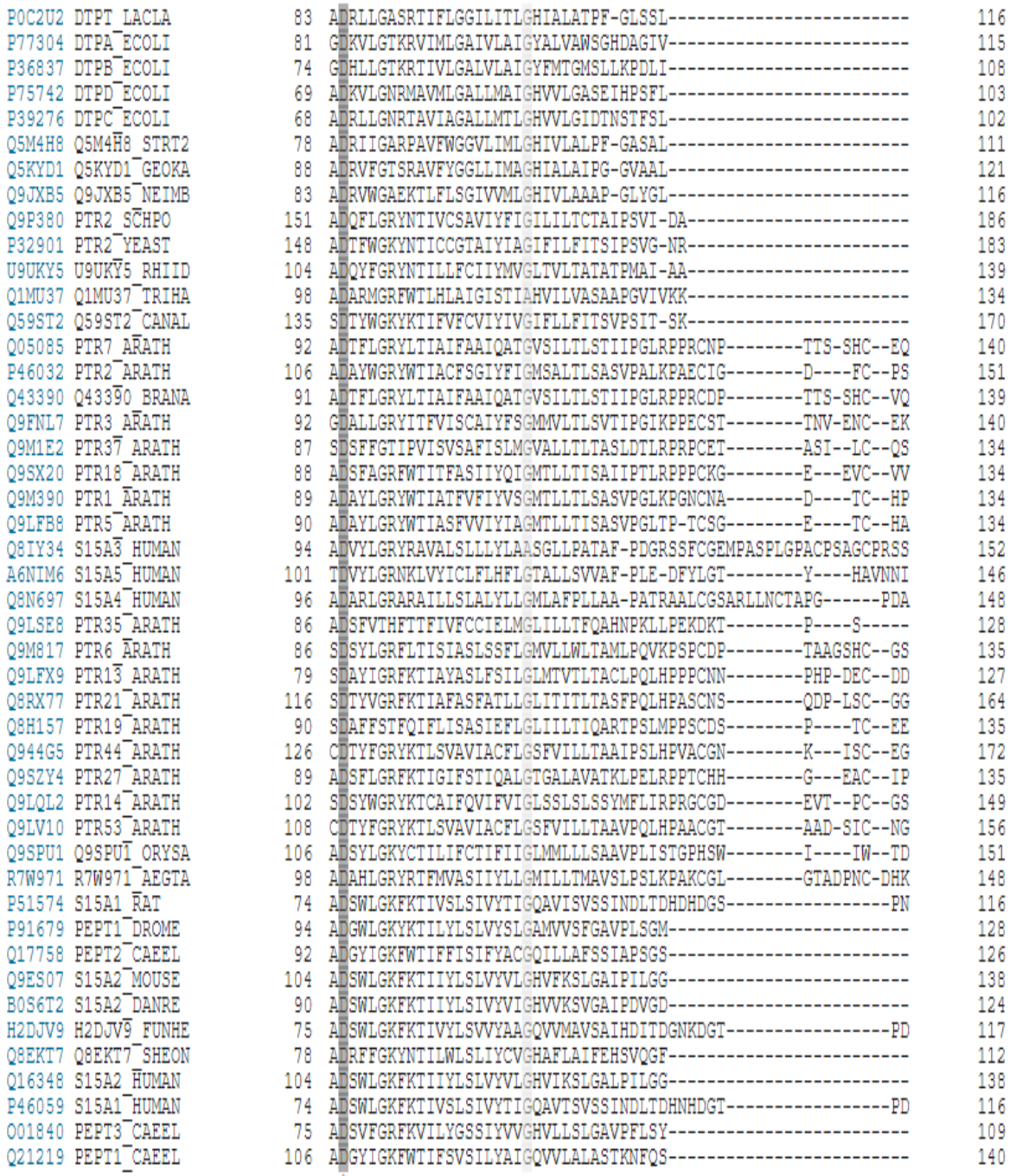
Detailed sequence alignment of 46 POT family transporters highlighting conserved residues.




P0C2U2 DTPT_LACLA 83 ADRLLGASRTIFLGGILITLGHIALATPF-GLSSL---------- 116
P77304 DTPA_ECOLI 81 GDKVLGTKRVIMLGAIVLAIGYALVAWSGHDAGIV---------- 115
P36837 DTPB_ECOLI 74 GDHLLGTKRTIVLGALVLAIGYFMTGMSLLKPDLI---------- 108
P75742 DTPD_ECOLI 69 ADKVLGNRMAVMLGALLMAIGHVVLGASEIHPSFL---------- 103
P39276 DTPC_ECOLI 68 ADRLLGNRTAVIAGALLMTLGHVVLGIDTNSTFSL---------- 102
Q5M4H8 Q5M4H8_STRT2 78 ADRIIGARPAVFWGGVLIMLGHIVLALPF-GASAL---------- 111
Q5KYD1 Q5KYD1_GEOKA 88 ADRVFGTSRAVFYGGLLIMAGHIALAIPG-GVAAL---------- 121
Q9JXB5 Q9JXB5_NEIMB 83 ADRVWGAEKTLFLSGIVVMLGHIVLAAAP-GLYGL---------- 116
Q9P380 PTR2_SCHPO 151 ADQFLGRYNTIVCSAVIYFIGILILTCTAIPSVI-DA---------- 186
P32901 PTR2_YEAST 148 ADTFWGKYNTICCGTAIYIAGIFILFITSIPSVG-NR---------- 183
U9UKY5 U9UKY5_RHIID 104 ADQYFGRYNTILLFCIIYMVGLTVLTATATPMAI-AA---------- 139
Q1MU37 Q1MU37_TRIHA 98 ADARMGRFWTLHLAIGISTIAHVILVASAAPGVIVKK---------- 134
Q59ST2 Q59ST2_CANAL 135 SDTYWGKYKTIFVFCVIYIVGIFLLFITSVPSIT-SK---------- 170
Q05085 PTR7_ARATH 92 ADTFLGRYLTIAIFAAIQATGVSILTLSTIIPGLRPPRCNP--------TTS-SHC--EQ 140
P46032 PTR2_ARATH 106 ADAYWGRYWTIACFSGIYFIGMSALTLSASVPALKPAECIG--------D----FC--PS 151
Q43390 Q43390_BRANA 91 ADTFLGRYLTIAIFAAIQATGVSILTLSTIIPGLRPPRCDP--------TTS-SHC--VQ 139
Q9FNL7 PTR3_ARATH 92 GDALLGRYITFVISCAIYFSGMMVLTLSVTIPGIKPPECST--------TNV-ENC--EK 140
Q9M1E2 PTR37_ARATH 87 SDSFFGTIPVISVSAFISLMGVALLTLTASLDTLRPRPCET--------ASI--LC--QS 134
Q9SX20 PTR18_ARATH 88 ADSFAGRFWTITFASIIYQIGMTLLTISAIIPTLRPPPCKG--------E---EVC--VV 134
Q9M390 PTR1_ARATH 89 ADAYLGRYWTIATFVFIYVSGMTLLTLSASVPGLKPGNCNA--------D----TC--HP 134
Q9LFB8 PTR5_ARATH 90 ADAYLGRYWTIASFVVIYIAGMTLLTISASVPGLTP-TCSG--------E----TC--HA 134
Q8IY34 S15A3_HUMAN 94 ADVYLGRYRAVALSLLLYLAASGLLPATAF-PDGRSSFCGEMPASPLGPACPSAGCPRSS 152
A6NIM6 S15A5_HUMAN 101 TDVYLGRNKLVYICLFLHFLGTALLSVVAF-PLE-DFYLGT--------Y----HAVNNI 146
Q8N697 S15A4_HUMAN 96 ADARLGRARAILLSLALYLLGMLAFPLLAA-PATRAALCGSARLLNCTAPG------PDA 148
Q9LSE8 PTR35_ARATH 86 ADSFVTHFTTFIVFCCIELMGLILLTFQAHNPKLLPEKDKT--------P----S----- 128
Q9M817 PTR6_ARATH 86 SDSYLGRFLTISIASLSSFLGMVLLWLTAMLPQVKPSPCDP--------TAAGSHC--GS 135
Q9LFX9 PTR13_ARATH 79 SDAYIGRFKTIAYASLFSILGLMTVTLTACLPQLHPPPCNN--------PHP-DEC--DD 127
Q8RX77 PTR21_ARATH 116 SDTYVGRFKTIAFASFATLLGLITITLTASFPQLHPASCNS--------QDP-LSC--GG 164
Q8H157 PTR19_ARATH 90 SDAFFSTFQIFLISASIEFLGLIILTIQARTPSLMPPSCDS--------P----TC--EE 135
Q944G5 PTR44_ARATH 126 CDTYFGRYKTLSVAVIACFLGSFVILLTAAIPSLHPVACGN--------K---ISC--EG 172
Q9SZY4 PTR27_ARATH 89 ADSFLGRFKTIGIFSTIQALGTGALAVATKLPELRPPTCHH--------G---EAC--IP 135
Q9LQL2 PTR14_ARATH 102 SDSYWGRYKTCAIFQVIFVIGLSSLSLSSYMFLIRPRGCGD--------EVT--PC--GS 149
Q9LV10 PTR53_ARATH 108 CDTYFGRYKTLSVAVIACFLGSFVILLTAAVPQLHPAACGT--------AAD-SIC--NG 156
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B0S6T2 S15A2_DANRE 90 ADSWLGKFKTIIYLSIVYVIGHVVKSVGAIPDVGD---------- 124
H2DJV9 H2DJV9_FUNHE 75 ADSWLGKFKTIVYLSVVYAAGQVVMAVSAIHDITDGNKDGT----------------PD 117
Q8EKT7 Q8EKT7_SHEON 78 ADRFFGKYNTILWLSLIYCVGHAFLAIFEHSVQGF---------- 112
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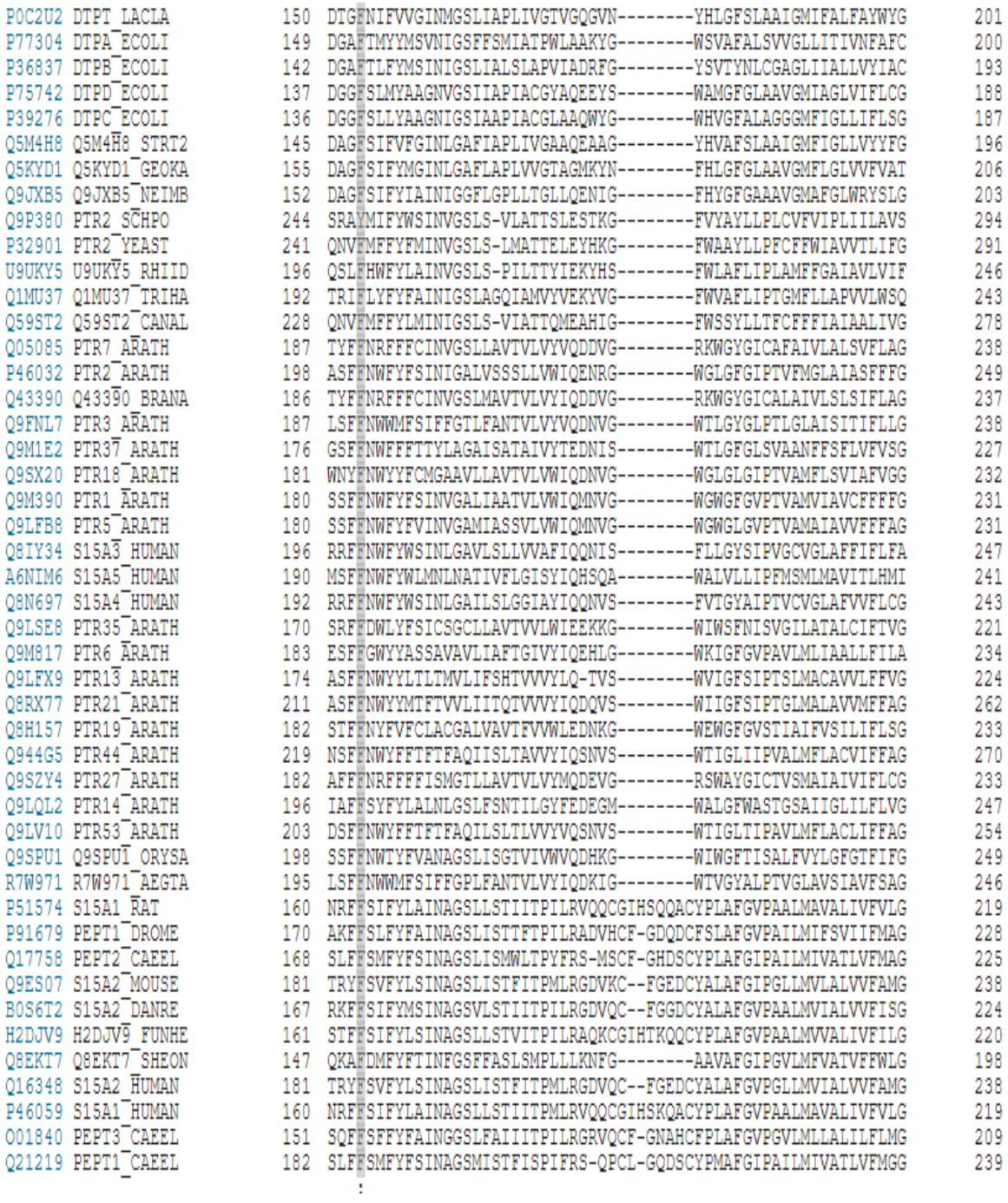
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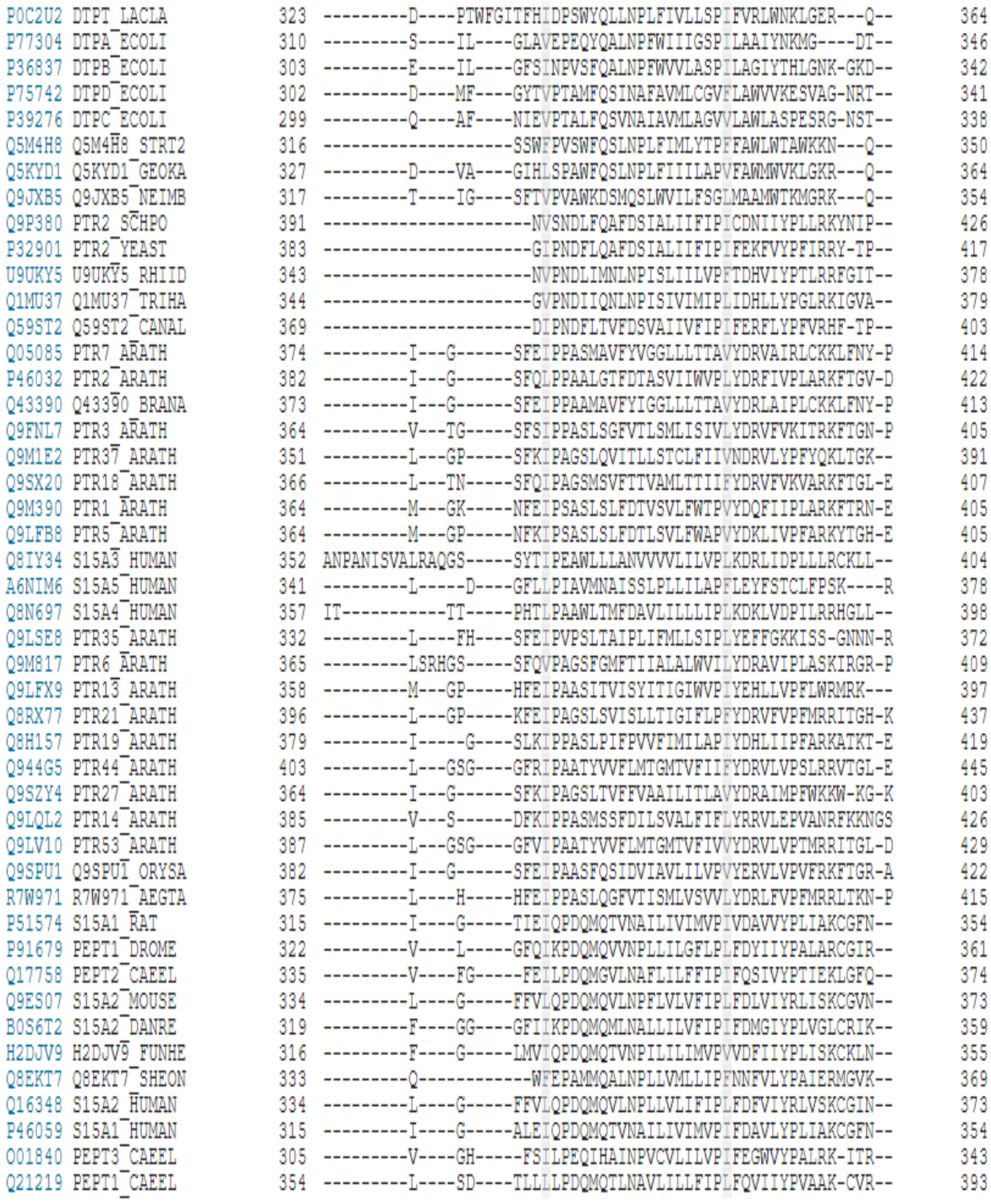
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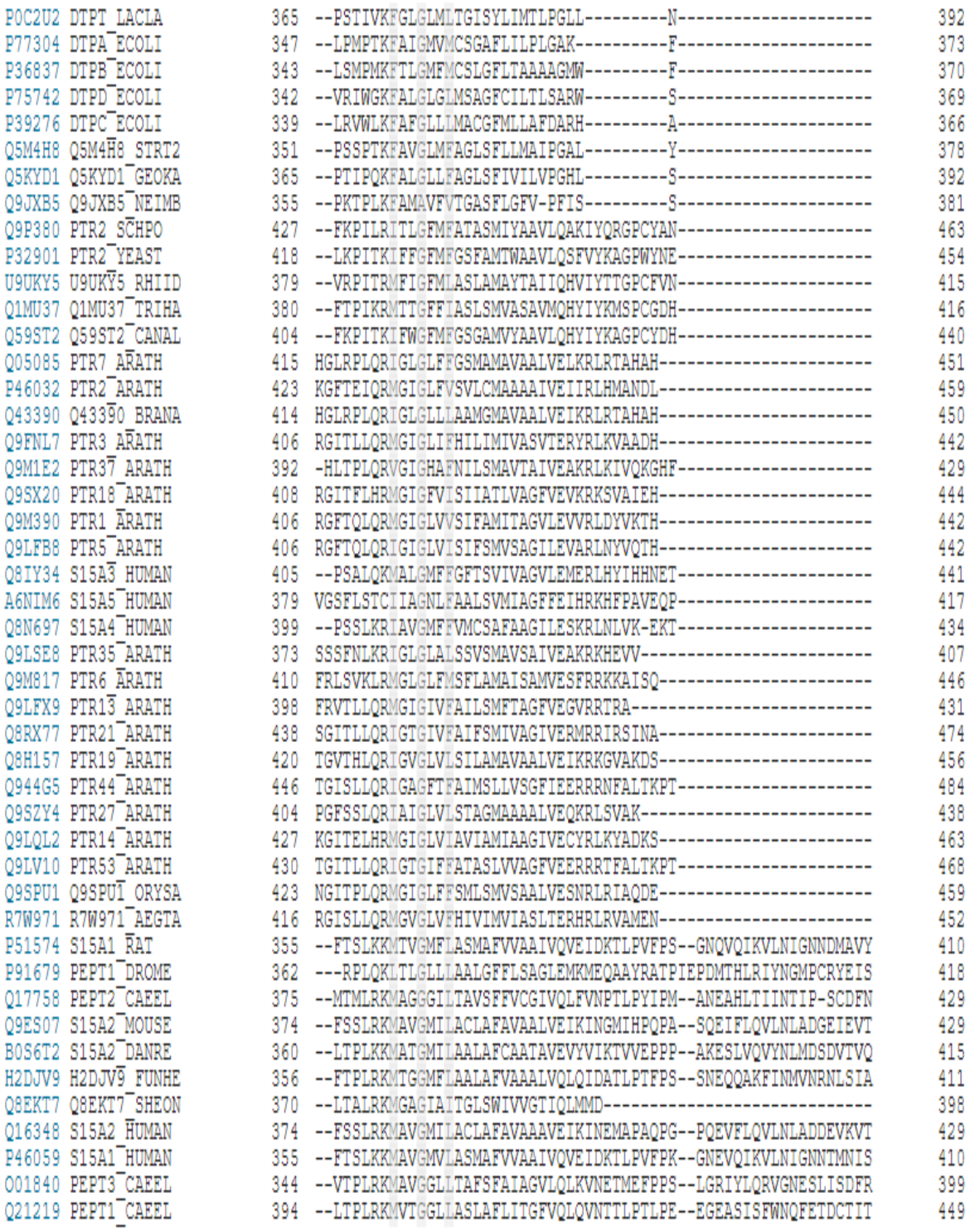
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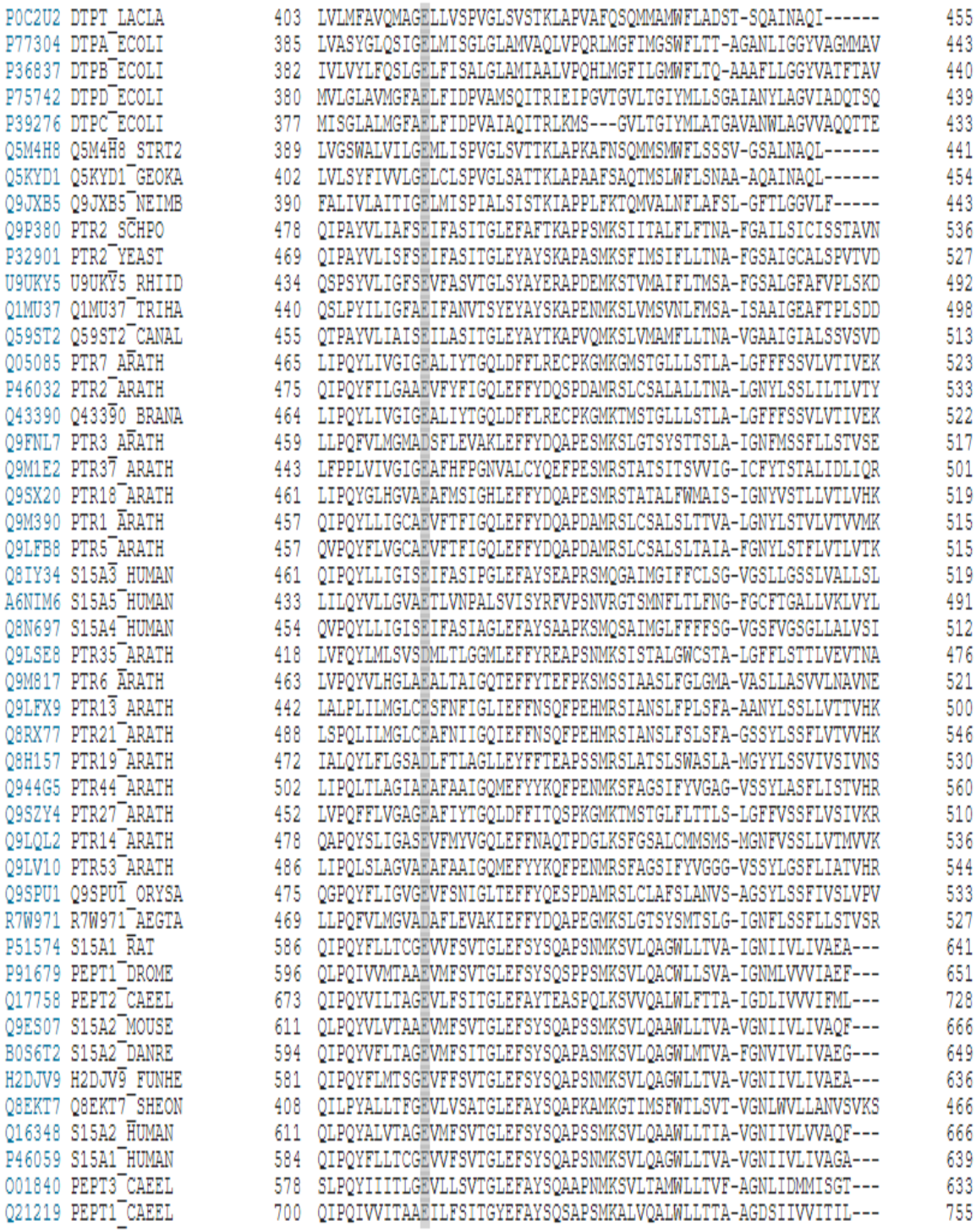
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Q8N697 S15A4_HUMAN 454 QVPQYLLIGISEIFASIAGLEFAYSAAPKSMQSAIMGLFFFFSG-VGSFVGSGLLALVSI 512
Q9LSE8 PTR35_ARATH 418 LVFQYLMLSVSDMLTLGGMLEFFYREAPSNMKSISTALGWCSTA-LGFFLSTTLVEVTNA 476
Q9M817 PTR6_ARATH 463 LVPQYVLHGLAEALTAIGQTEFFYTEFPKSMSSIAASLFGLGMA-VASLLASVVLNAVNE 521
Q9LFX9 PTR13_ARATH 442 LALPLILMGLCESFNFIGLIEFFNSQFPEHMRSIANSLFPLSFA-AANYLSSLLVTTVHK 500
Q8RX77 PTR21_ARATH 488 LSPQLILMGLCEAFNIIGQIEFFNSQFPEHMRSIANSLFSLSFA-GSSYLSSFLVTVVHK 546
Q8H157 PTR19_ARATH 472 IALQYLFLGSADLFTLAGLLEYFFTEAPSSMRSLATSLSWASLA-MGYYLSSVIVSIVNS 530
Q944G5 PTR44_ARATH 502 LIPQLTLAGIAEAFAAIGQMEFYYKQFPENMKSFAGSIFYVGAG-VSSYLASFLISTVHR 560
Q9SZY4 PTR27_ARATH 452 LVPQFFLVGAGEAFIYTGQLDFFITQSPKGMKTMSTGLFLTTLS-LGFFVSSFLVSIVKR 510
Q9LQL2 PTR14_ARATH 478 QAPQYSLIGASEVFMYVGQLEFFNAQTPDGLKSFGSALCMMSMS-MGNFVSSLLVTMVVK 536
Q9LV10 PTR53_ARATH 486 LIPQLSLAGVAEAFAAIGQMEFYYKQFPENMRSFAGSIFYVGGG-VSSYLGSFLIATVHR 544
Q9SPU1 Q9SPU1_ORYSA 475 QGPQYFLIGVGEVFSNIGLTEFFYQESPDAMRSLCLAFSLANVS-AGSYLSSFIVSLVPV 533
R7W971 R7W971_AEGTA 469 LLPQFVLMGVADAFLEVAKIEFFYDQAPEGMKSLGTSYSMTSLG-IGNFLSSFLLSTVSR 527
P51574 S15A1_RAT 586 QIPQYFLLTCGEVVFSVTGLEFSYSQAPSNMKSVLQAGWLLTVA-IGNIIVLIVAEA--- 641
P91679 PEPT1_DROME 596 QLPQIVVMTAAEVMFSVTGLEFSYSQSPPSMKSVLQACWLLSVA-IGNMLVVVIAEF--- 651
Q17758 PEPT2_CAEEL 673 QIPQYVILTAGEVLFSITGLEFAYTEASPQLKSVVQALWLFTTA-IGDLIVVVIFML--- 728
Q9ES07 S15A2_MOUSE 611 QLPQYVLVTAAEVMFSVTGLEFSYSQAPSSMKSVLQAAWLLTVA-VGNIIVLIVAQF--- 666
B0S6T2 S15A2_DANRE 594 QIPQYVFLTAGEVMFSITGLEFSYSQAPASMKSVLQAGWLMTVA-FGNVIVLIVAEG--- 649
H2DJV9 H2DJV9_FUNHE 581 QIPQYFLMTSGEVFFSVTGLEFSYSQAPSNMKSVLQAGWLLTVA-VGNIIVLIVAEA--- 636
Q8EKT7 Q8EKT7_SHEON 408 QILPYALLTFGEVLVSATGLEFAYSQAPKAMKGTIMSFWTLSVT-VGNLWVLLANVSVKS 466
Q16348 S15A2_HUMAN 611 QLPQYALVTAGEVMFSVTGLEFSYSQAPSSMKSVLQAAWLLTIA-VGNIIVLVVAQF--- 666
P46059 S15A1_HUMAN 584 QIPQYFLLTCGEVVFSVTGLEFSYSQAPSNMKSVLQAGWLLTVA-VGNIIVLIVAGA--- 639
O01840 PEPT3_CAEEL 578 SLPQYIIITLGEVLLSVTGLEFAYSQAAPNMKSVLTAMWLLTVF-AGNLIDMMISGT--- 633
Q21219 PEPT1_CAEEL 700 QIPQIVVITAAEILFSITGYEFAYSQSAPSMKALVQALWLLTTA-AGDSIIVVITIL--- 755