## Sweet Taste Receptor Gene Variation and Aspartame Taste in Primates and Other Species

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#### Abstract

Aspartame is a sweetener added to foods and beverages as a low-calorie sugar replacement. Unlike sugars, which are apparently perceived as sweet and desirable by a range of mammals, the ability to taste aspartame varies, with humans, apes, and Old World monkeys perceiving aspartame as sweet but not other primate species. To investigate whether the ability to perceive the sweetness of aspartame correlates with variations in the DNA sequence of the genes encoding sweet taste receptor proteins, T1R2 and T1R3, we sequenced these genes in 9 aspartame taster and nontaster primate species. We then compared these sequences with sequences of their orthologs in 4 other nontasters species. We identified 9 variant sites in the gene encoding T1R2 and 32 variant sites in the gene encoding T1R3 that distinguish aspartame tasters and nontasters. Molecular docking of aspartame to computer-generated models of the T1R2 + T1R3 receptor dimer suggests that species variation at a secondary, allosteric binding site in the T1R2 protein is the most likely origin of differences in perception of the sweetness of aspartame. These results identified a previously unknown site of aspartame interaction with the sweet receptor and suggest that the ability to taste aspartame might have developed during evolution to exploit a specialized food niche.

Key words: aspartame, modeling, primates, sweet taste, taste receptor, T1R2, T1R3

#### Introduction

The ability to perceive sweet taste is a common trait in a range of animals that probably reflects the importance of simple carbohydrates as a dietary energy source (Kare and Beauchamp 1984). However, not all compounds that taste sweet are sugars and within the last 2 centuries, researchers have discovered several nonsugar sweeteners, such as saccharin and aspartame. These sweeteners are desirable because they are potentially safer for use among people who metabolize simple sugars poorly, for example, diabetics, and among people who wish to avoid the extra calories of sugar, for example, in sweetening coffee or tea. Some of types of high-potency sweeteners are large proteins found in plants, but many were synthesized, often by accident, in the laboratory (Dubois 2008).

One high-potency sweetener, aspartame, is apparently not sweet to most mammals other than humans and closely related primates (Hellekant et al. 1980, 1981, 1994; Naim et al.

1982; Sclafani and Abrams 1986; Thomsen et al. 1988; Glaser et al. 1992; De Francisco and Dess 1998; Bachmanov, Tordoff, and Beauchamp 2001; Schilling et al. 2004; Li et al. 2009). We say apparently since we do not know what an animal perceives, but we judge their ability by their behavior when offered aspartame-sweetened water to drink or food to eat. The differences among species in their behavior toward aspartame correspond to differences in afferent sensory responses of the chorda tympani and glossopharyngeal gustatory nerves. For example, aspartame does not elicit gustatory neural responses in the aspartame nontaster species: mice (Inoue et al. 2001), gerbils (Jakinovich 1981), hamsters (Nowlis et al. 1980; Hellekant and Danilova 1996; Danilova, Hellekant, Tinti, and Nofre 1998), rats (Hellekant and Walters 1993), cows, (Hard af Segerstad and Hellekant 1989a, 1989b; Hellekant et al. 2010), pigs (Hellekant and Danilova 1996; Glaser et al. 2000), prosimians and New World simians (Hellekant et al. 1980, 1981, 1993; Glaser et al. 1995; Nofre et al. 1996; Danilova et al. 2002). However, in Old World monkeys and apes, aspartame evokes both behavioral preference and responses in gustatory nerves (Sato et al. 1977; Glaser et al. 1992, 1995, 1996; Hellekant and Danilova 1996; Hellekant et al. 1996). The term aspartame "taster" and "nontaster" is used here to distinguish between species that prefer aspartame-flavored food or water to plain food or plain water or which have a vigorous taste nerve response to aspartame and those that do not. This term is adopted for simplicity but not all members of a species are necessarily the same in their behavioral response to aspartame. For instance, some mice prefer aspartame to water (Meliska et al. 1995; Bachmanov, Tordoff, and Beauchamp 2001). Likewise, there are exceptions to the observation that only humans and closely related primates prefer aspartame, for instance one species related to the raccoon is an aspartame taster (Li et al. 2009), as are fruit flies (Gordesky-Gold et al. 2008). These observations notwithstanding, the main point is that most mammals except for humans and Old World primates are indifferent to aspartame. The explanation for the species difference is unknown.

Recent advancements in our understanding of the molecular mechanisms of taste perception allowed us to form a hypothesis. Differences in taste perception among species, strains, or even among members of a population are often due to variant sites in specific receptor genes (Chandrashekar et al. 2000; Bachmanov, Li, et al. 2001; Kitagawa et al. 2001; Max et al. 2001; Montmayeur et al. 2001; Sainz et al. 2001; Jordt and Julius 2002; Kim et al. 2003; Reed et al. 2004; Bufe et al. 2005; Reed et al. 2010). Therefore, to understand species differences in aspartame sensitivity, we focused on the known sweet receptor, a heterodimer of 2 proteins, T1R2 and T1R3 (Max et al. 2001; Nelson et al. 2001, 2002; Li et al. 2002; Ariyasu et al. 2003; Damak et al. 2003; Zhao et al. 2003). From cell-based assays, we have learned that the human receptor (as opposed to the mouse receptor) is required for aspartame responsiveness (Xu et al. 2004).

Introduction of the human receptor into a mouse or cell line humanizes its response to aspartame (Jiang et al. 2004; Xu et al. 2004). The preponderance of the evidence indicates that the logical first step toward understanding aspartame sensitivity would be to examine the T1R2 + T1R3 dimer, but we acknowledge that T1R homodimers or unknown heterodimers may comprise an alternative aspartame receptor in some species.

These lines of evidence led us to formulate the hypothesis that disparate aspartame taste responses among primates and other species might be due to species variation in sequences of orthologs of the known sweet receptor genes. To test this hypothesis, we sequenced genes encoding T1R2 and T1R3 in 9 aspartame taster and nontaster primate species. We then compared these sequences with sequences of their orthologs in 4 other nontasters species and determined which of these differences were liable to disrupt the interaction of the sweet receptor to aspartame using computer-assisted modeling. Our goal was to identify the most likely DNA variant sites within the sweet receptor that account for aspartame sensitivity.

#### Materials and methods

#### Selection of primate species to sequence

We selected the primate species for sequencing based on the availability of results from previous behavioral and electrophysiological studies that determined whether the species was an aspartame taster or nontaster (Table 1). We included 4 additional nonprimate species because their responses to aspartame were known from previous studies and also because full-length sequences of the sweet taste receptor genes were available. Cats were eliminated from consideration because their aspartame insensitivity extends to all sweeteners tested (Li et al. 2005).

#### Obtaining DNA and preparing DNA from primates

Genomic DNA samples from 6 primate species were available through 2 commercial sources 1) Coriell Institute for Medical Research: chimpanzee (Pan troglodytes, chimpanzee); gorilla (Gorilla gorilla, western lowland gorilla); orangutan (Pongo pygmaeus abelii, Sumatran orangutan); patas monkey (Erythrocebus patas, patas monkey); tamarin (Saguinus labiatus, red-bellied tamarin) and 2) Therion International, LLC: rhesus monkey (Macaca mulatta, rhesus monkey). The San Diego Frozen Zoo provided genomic DNA from 2 species: squirrel monkey (Saimiri sciureus, squirrel monkey) and marmoset (Cebuella pygmaea, Pygmy marmoset). The Texas Biomedical Research Institute provided us with baboon DNA (Papio hamadryas, baboon). Genomic DNA was measured for concentration and purity using conventional spectrophotometer and diluted to a concentration of 25 ng/µL as a prerequisite for polymerase chain reaction (PCR)-based sequencing.

Species name	Preference	Electrophysiology	References
Humans (Homo sapiens)	+	NA	Mojet et al. (2001, 2003, 2004)
Chimpanzee (Pan troglodytes)	+	+	Glaser et al. (1992, 1995), Hellekant et al. (1996, 1998); Hellekant, Danilova, and Ninomiya (1997)
Gorilla (Gorilla gorilla)	+	NA	Glaser et al. (1992, 1995, 1996)
Orangutan (Pongo pygmaeus abelii)	+	NA	Glaser et al. (1992, 1995, 1996)
Patas monkey ( <i>Erythrocebus patas</i> )	+	NA	Glaser et al. (1992, 1995, 1996)
Baboon ( <i>Papio hamadryas</i> )	+	NA	Glaser et al. (1992, 1995, 1996)
Rhesus monkey ( <i>Macaca mulatta</i> )	+	+	Thomsen et al. (1988), Glaser et al. (1992, 1995, 1996), Hellekant, Danilova, and Ninomiya (1997)
Marmoset ( <i>Cebuella pygmaea</i> )	_	_	Glaser et al. (1992, 1995, 1996), Danilova, Hellekant, Roberts, et al. (1998), Danilova et al. (2002)
Squirrel monkey (Saimiri sciureus)	_	NA	Glaser et al. (1992, 1995, 1996)
Tamarin (Saguinus labiatus)	_	NA	Glaser et al. (1992, 1995, 1996)
Cow (Bos taurus)	_	_	Hard af Segerstad and Hellekant (1989a, 1989b), Hellekant et al. (1994)
Dog (Canis lupus familiaris)	_	NA	Glaser (2002)
Rat ( <i>Rattus norvegicus</i> )	_	-	Sclafani and Abrams (1986), Thomsen et al. (1988), Hellekant and Walters (1992), De Francisco and Dess (1998)
Mouse ( <i>Mus musculus</i> )	_	_	Bachmanov, Tordoff, and Beauchamp (2001), Inoue et al. (2001)

 Table 1
 List of species used in this study and their aspartame taster/nontaster status

Preference refers to the case when consumption of aspartame solution is more than 50% of the total fluid intake in a 2-bottle test with aspartame and water. Electrophysiology refers to the case when responses in chorda tympani or glossopharyngeal nerves are observed when stimuli are applied to the oral cavity. +, a species prefers or responds to aspartame; –, a species does not prefer or does not respond to aspartame. NA, data not available.

#### Selection of genes to sequence

We selected the 2 known sweet receptor genes, *Tas1r2* and *Tas1r3*, for DNA sequencing. All the primate species tested have functional sense of other tastes. Therefore, we thought it was unlikely that variation in genes involved in perception of more than one taste quality (e.g., gustducin, TRPM5) would contribute to the aspartame taster/nontaster species differences. We use *Tas1r2* and *Tas1r3* as the gene symbols (in some cases generically, when referring to multiple species) and T1R2 and T1R3 as the protein symbols, as applicable. Gene or protein symbols with a prefix refer to the specific species, for example, mT1R2 is mouse T1R2 and hT1R3 is human T1R3.

#### Amplification of Tas1r2- and Tas1r3-coding regions by PCR

The sequences corresponding to the validated exons of the human *Tas1r2* and *Tas1r3* genes were amplified. Because mouse and human genes have the same intron–exon structure, we assumed that the primate gene structure would be the same as human too. We confirmed this assumption by sequencing the cDNA from one primate species, with the method as follows: we collected circumvallate and foliate papillae from a postmortem tongue tissue sample taken from a female Baboon (*Papio anubis*). We extracted total RNA from the taste papillae by using TRIZOL reagent (Invitro-

gen), total RNA was transcribed to cDNA using Superscript III kit (Invitrogen), and reverse transcriptasepolymerase chain reaction (RT-PCR) was conducted using intron-spanning primers designed using baboon genomic sequences of *Tas1r2* and *Tas1r3*. Sequencing of RT-PCR products revealed that the exon–intron junctions of T1R2 and T1R3 from baboon are the same as those of humans. Collection of tongue tissue was approved by the animal care and use committee at the University of Pennsylvania and the Monell Chemical Senses Center.

We used a walk-down procedure for designing primers to amplify nonhuman DNA: we first designed primers based on human Tas1r2 and Tas1r3 sequences to obtain primatespecific sequences and then used the resulting primate sequence to design additional primate-specific primers. After PCR amplification, the products were purified and sequenced by the DNA sequencing facility at the University of Pennsylvania. Both strands were sequenced and assembled using Sequencher (version 4.0.5, Gene Codes). In cases where primate sequences became available through public sequencing efforts during the data collection phase of this project, we compared our sequencing against that of the published sequence to check for sequencing errors or gaps. In cases where we could fill gaps in our own sequencing with public sequence, we assembled all available sequences and used these data in the alignments.

human	MGPRAKTICSLFFLLWVLAEPAENSDFYLPGDYLLGGLFSLHANMKGIVHLNFLQVP	57
chimpanzee	MGPRAKTICSLFFLLWVLAEPAENSDFYLPGDYLLGGLFSLHANMKGIVHLNFLQVP	57
gorilla	MGTRATTICSLFFLLWVLAEPAENSDFYLPGDYLLGGLFSLHANMKGIVHLNFLQVP	57
orangutan	MGPRATTICSLFFLLWVLAEPAENSDFYLPGDYLLGGLFSLHANMKGIVHLNFLQVP	57
patas_monkey	XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX	57
baboon	MRPRATTICSLFFLLKVLABPAKNSDFILFGDYLLGGLFTLHANMKGIVHLDYLQVP	57
rnesus monkey	MRPRATTICSDFFLDRVLABFARNSDFTLFGDYLLGGDFTLHAMMRGTVHLDTLQVP MRDDVDTVCPL PPLLDVLAPDARNSDFTLFGDYLLGOL PTLHAMMRGTVHLMPLOVD	57
marmoset	MGPRARTVCPLFFLLWVLARL AENSDPHI.DODVI.LOGI.PTI.NANMKOTUNI NDI OVD	57
tamarin	MGPRARTVYFLFFLLEVLAEP AKNSDFYLPGDYLLGGLFTLHANMKGTVHLNFLOVP	57
COW	MGPOGRAACSLLFLLQALAEP AENSEFFLPGDYLLGGLFTLHANVKGIVHLNYLKVP	57
dog	MGPRAKAVCSLFILLOVLAEP AENSDFYLPGDYLLGGLFTLHANVKGTVHLSFLOVP	57
rat	MGPOARTLCLLSLLLHVLPKPGKLVENSDFHLAGDYLLGGLFTLHANVKSISHLSYLOVP	60
mouse	MGPOARTLHLLFLLLHALPKPVMLVGNSDFHLAGDYLLGGLFTLHANVKSVSHLSYLOVP	60
human	MCKEYEVKVIGYNLMQAMRFAVEEINNDSSLLPGVLLGYEIVDVCYISNNVQPVLYFLAH	117
chimpanzee	MCKEYEVKVIGYNLMQAMRFAVEEINNDSSLLPGVLLGYEIVDVCYISNNVQPVLYFLAH	117
gorilla	MCKEYEVKVIGYNLMQAMRFAVEEINNDSSLLPGVLLGYEIVDVCYISNNVQPVLYFLAH	117
orangutan	MCKEYEVKVIGYNLMQDMRFSVEBINNDSSLLPGVLLGYEMVDVCYVSNNVQPVLYFLAH	117
patas_monkey	XXXXXEVKVIGYNLMQAMRFAVEEINNDSSLLPDVLLGYEMVDVCYVSNNVQPVLYFLAQ	117
baboon	MCKEYETKVIGYNLMQAMRFAVEEINNDSSLLPDVLLGYEMVDVCYVSNNVQPVLYFLAQ	117
rhesus_monkey	MCKEYETKVIGYNLMQAMRFAVEEINNDSSLLPDVLLGYEMVDVCYVSNNVQPVLYFLAQ	117
squirrel_monkey	MCKEYEVKL <b>S</b> GYNLMQAMRFAVEEINNDSSLLPDVRLGYEMVDVCYVSNNVQPVLYFLAQ	117
marmoset	MCKEYEMKVSGYNLMQAMRFAVEBINNDSSLLPDVLLGYEMVDVCYISNNVQPALYFLAQ	117
tamarin	MCKEYEMKVSGYNLMQAMRFAVEBINNDSSLLPDVLLGYEMVDVCYISNNVQPALYFLAQ	117
cow	KCKETEMKVDGINLMQAMKFAVEEVNNDSSLLPNVLLGIEMVDSCIMSNNVQPVLIFLSQ	117
dog	QUARTERAVEGINERQAREPAVEEINNRSDEEPGVEIGIEIVDVCTISNRVQPVEIFEAR	11/
Idu	VONEY INVEGUNI NORMORAVERINACISLIPGALIGUEN OVCILISMAINPOLITENQ VONEYNMYJEGYNI NORMORAVERINACISLIPGALI GYEMUDYCYLENNI ODGLYFI.	120
niouse	CARLINALADIALAQAARTAVEETAACSSLLPGALLSTEMADACIDSAATQPOLIFLSQ	120
human	EDNLL PTORDYSNYTSRVVAVIGPDNSRSVMTVANRI, SLFLI, DOTTY SATE OPT OPT VOD	177
chimpanzee	EDNLLPIOEDYSNYISRVVAVIGPDNSESVMTVANFLSLFLLPOTTYSATCOPLODVUDP	177
gorilla	EDNLLPIOEDYSNYISRVVAVIGPDNSESVMTVANFI.SLFLLPOTTYSATSDELODY	177
orangutap	EDNLLPIOEDYSDYVSRVVAVIGPDNSESVMTVANFLSLFLLPOITYSATSDELODKUOP	177
patas morkey	EDDLLPIOENYSNYVPRVVAVIGPDNSDAVXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX	177
baboon	EDDLLPIOENYSNYVSRVVAVIGPDNSDAVMTVANFLSLFLLPOITYSAISDELPDKVPP	177
rhesus monkey	EDDLLPIOENYSNYVPRVVAVIGPDNSDAVMTVANFLSLFLLPOITYSAISDELEDKVRF	177
squirrel monkev	EDNLLPIQEDYSNYVPRVVAVIGPENSESVTTVANFLSLFLLPOITYSAISDOLRDKORF	177
marmoset	EDNLLPIQEDYSNYVPRVVAVIGPENSESVMTVAHFLSLFLLPOITYSAISDOLODKORF	177
tamarin	EDNLLPIQEDYSNYVPRVVAVIGPENSESVMTVAHFLSLFLLPOITYSAISDELXXXXX	177
COW	DDYFLPIQEDYSQYVPRVVAIIGPDNSESTKTVANFLSLFLLPOXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX	177
dog	EDYSLPIQEDYSHYVPRVLAVIGPDNSESTTTVAHFLSLFLLPOITYSAISDDLRDKOHF	177
rat	DDDLLPILKDYSQYMPHVVAVIGPDNSESAITVSNILSHFLIPOITYSAISDKLRDKRHF	180
mouse	IDDFLPILKDYSQYRPQVVAVIGPDNSESAITVSNILSYFLVPOVTYSAITDKLRDKRFF	180
Contraction (Charleston)		
human	PALLRTTPSADHHVEAMVQLMLHFRWNWIIVLVSSDTYGRDNGQLLGERVA-RRDICIAF	236
chimpanzee	PALLRTTPSADHHVEAMVQLMLHFRWNWIIVLVSSDTYGRDNGQLLGERLA-RRDICIAF	236
gorilla	PALLRTTPSADHHVEAMVQLMLHFRWNWIIVLVSSDTYGRDNGQLLGERLA-RRDICIAF	236
orangutan	PALLRTTPSADHHIEAMVQLMLHFRWNWIIVLVSSDTYGRDNGQLLGERLA-RRDICIAF	236
patas_monkey	XXXXXXAPSADHHIEAMVQLMLYFHWNWIIVLVSGDTYGRDNGQLLGDRLA-RGDICIAF	236
baboon	PALLRTAPSADHHIEAMVQLMLHFRWNWIIVLVSGDTYGRDNGQLLGDRLA-RGDICIAF	236
rhesus_monkey	PALLRTAPSADHHIEAMVQLMLHFRWNWIIVLVSGDTYGRDNGQLLGDRLA-RGDICIAF	236
squirrel_monkey	PALLRTTPSAKHHIEAMVQLMLHFRWNWISVLVSSDTYGRDNGQLLGDRLA-GGDICIAF	236
marmoset	PALLRTTPSAKHHIEAMVQLMLHFHWNWISVLVSSDTYGRDNGQMLGDRLA-GGDICIAF	236
tamarin	XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX	236
COW	XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX	236
dog	PALLRTVAGADHQIEAMVQLLLHFNWNWIIVLVSSDDYGRYNSQLLNDRLA-TGDICIAF	236
rat	PSMLRTVPSATHHIEAMVQLMVHFQWNWIVVLVSDDDYGRENSHLLSQRLTKTSDICIAF	240
mouse	PAPERTVPSATARTEARVQUAVARQWAWIVVUVSDDDIGKENSHLUSQKUTNIGDICIAF	240
mouse	PAREKIVPSAINNIEARVQURVNEQWARIVVUVSDDDIGKEASHLLSQKLINGODICIAF	240
human	QETLPTLQPNQMMTSEERQRLVTIVDKLQQSTARVVVVSSPDLTLYHFFMEVLRQNFTGA	240
human chimpanzee	QETLPTLQPNQNMTSEERQRLVTIVDKLQQSTARVVVVPSPDLJLVPFPNEVLRQNPTGA QETLPTLQPNQNMTSEERQRLVTIVDKLQQSTARVVVVPSPDLJLVPFPNEVLRQNPTGA	240 296 296
human chimpanzee gorilla	ORTLPTLOPHOMMISSERVOLUTIVDKLOQSTARVVVVPSDLJUVGRBARLLAQULINGUULAP ORTLPTLOPHOMMISSERVOLUTIVDKLOQSTARVVVVPSDLJUVPNOVLOPHOVLRONFIGA ORTLPTLOPHOMMISSERVOLUTIVDKLOQSTARVVVVPSDLJUVPPNOVLRONFIGA ORTLPTLOPHOMMISSERVOLUTIVDKLOQSTARVVVVPSDLJUVPPNOVLRONFIGA	240 296 296 296
human chimpanzee gorilla orangutan	ORTIFLE/PROGRATSER/ORL/TIVD/LOGSTAR/VVVPSDL/LV/PFI/VL/OPTA/ ORTIFLE/OPTOPRISER/ORL/TIVD/LOGSTAR/VVVPSDL/LV/PFI/VL/OPTA/ ORTIFLE/OPTOPRISER/ORL/TIVD/LOGSTAR/VVVPSDL/LV/PFI/VL/OPTA/ ORTIFL/DPOGRATSER/ORL/TIVD/LOGSTAR/VVPSDL/LV/PFI/VL/OPTA/ ORTIFL/DPOGRATSER/ORL/TIVD/LOGSTAR/VVPSDL/LV/PFI/VL/OPTA/ ORTIFL/DPOGRATSER/ORL/TIVD/LOGSTAR/VVPSDL/LV/PFI/VL/OPTA/	240 296 296 296 296
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human chimpanzee gorilla orangutan patas_monkey baboon rhesus_monkey	ORTLPFLOPNORMISSERVOLLWINGUNARY VURSUDUTVORSSELLSQVITINGUTCAR ORTLPFLOPNORMISSERVOLLWINDUNACY VURSUSUUTVORSSELLSQVITINGUTCAR ORTLPFLOPNORMISSERVOLLWINDUNACY VURSUSUUTVORSSELLSQVITINGURAN ORTLPFLOPNORMISSERVOLLWINDUNCLOGSTARVVVVPSPDLILVDFFRVLARVITOR ORTLPFLOPNORMISSERVOLLWINDUNCLOGSTARVVVPSPDLILVDFFRVLARVITOR ORTLPFVORMORMISSERVOLLVITVDILLOGSTARVVVPSPDLILVDFFRVLARVITOR ORTLPFVORMORMISSERVOLLVITVDILLOGSTARVVVPSPDLILVDFFRVLARVITOR ORTLPFVORMORMISSERVOLLVITVDILLOGSTARVVVPSPDLILVDFFRVLARVITOR ORTLPFVORMORMISSERVOLLVITVDILLOGSTARVVVPSPDLILVDFFRVLARVITOR	240 296 296 296 296 296 296 296 296
human chimpanzee gorilla orangutan patas_monkey baboon rhesus monkey squirrel_monkey	ORT.PTLOPNORMTSBERIGHLYTIVDLOGSTARVVVPSPDLTLYHPFBVLLRONTGA ORT.PALOPMUTSBERIGHLYTIVDLOGSTARVVVPSPDLTLYHPFBVLLRONTGA ORT.PALOPMUTSBERIGHLYTIVDLOGSTARVVVPSPDLSLVDPFBVLLRONTGA ORT.PTLOPMORMTSBERIGHLYTIVDLOGSTARVVVPSPDLTLVDPFBVLLRONTGA ORT.PTLOPMORMTSBERIGHLYTIVDLOGSTARVVVPSPDLTLVDPFBVLLRONTGA ORT.PTLOPMORMTSBERIGHLYTIVDLOGSTARVVVPSPDLTLVDPFBVLLRONTGA ORT.PTVOPMORMTSBERIGHLYTIVDLOGSTARVVVPSPDLTLVDPFBVLLRONTGA ORT.PTVOPMORMTSBERIGHLYTIVDLOGSTARVVVPSPDLTLVDPFBVLLRONTGA	240 296 296 296 296 296 296 296 296 296
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gorilla	HIQDISWHTINNTIPVSMCSKRCQSGQKKKPVGIHVCCFECIDCLPGTFLNHTEDEYECQ	536
orangutan	NIQDISWHTINNTIPVSMCSKRCQSGQKKKPVGIHVCCFECIDCLPGTFLNHTEDEYECQ	536
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rhesus monkey	KIODISWHTINNTIPVSMCSKRCOSGOKKKPVGIHICCFECIDCLPGTFLNOTEDEYECO	536
squirrel_monkey	DIQDISWHTVNNTIPVSMCSKRCQSGQKKKPVGIHTCCFECIDCPPGTFLNQTANEYDCQ	530
marmoset	HIQDISWHTINNTIPVSMCSKRCQSGQKKKPVGIHTCCFECIDCLPGTFLNQTEDEYDCQ	531
tamarın	HIQDISWHTVNNTIPVSMCSKRCQSGQKKKPVGIHTCCFECIDCLPGTFLNQTEXXXXXX	531
dog	ATHNISWHTANNTIPVSMCSKDCHPGORKKPVGIHSCCFECIDCLPGTFLNQTLDEFDCQ ATHNISWHTANNTIPVSMCSKDCHPGORKKPVGIHSCCFECIDCLPGTFLNRTADEFDCQ	535
rat	YINNVSWYTPNNTVPVSMCSKSCQPGQMKKSVGLHPCCFECLDCMPGTYLNRSADEFNCL	540
mouse	YISNVSWYTPNNTVPISMCSKSCQPGQMKKPIGLHPCCFECVDCPPGTYLNRSVDEFNCL	540
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human	A CONNEW CYCOP TO CRY DOLLET RIVER DETAILATE AND CREETE ATT VERHILD CONTY	EQC
chimpanzee	ACPNNEWSIGSEISCFKRQLVFLEWHEAPTIAVALLAALGFLSILAILVIFWRHFQIPIV	596
gorilla	ACPNNEWSYQSETSCFKRQLVFLEWHEAPTIAVALLAALGFLSTLAILVIFWRHFQTPIV	596
orangutan	ACPSNEWSYQSETSCFKRQLAFLEWHEAPTIAVALLAALGFLSTLAILVIFWRHFQTPMV	596
patas_monkey	XXXXXXXXXXEAYCFKRRLAFLEWHEAPTIVVALLATLGFLSTLAILVIFWRHFQTPMV	594
rhesus monkey	ACPSNEWSHQSEASCFKRRLAFLEWHEAPTIVVALLAALGFLSTLATLVIFWRHFQIPMV ACPSNEWSHOSEASCFKRRLAFLEWHEAPTIVVALLAALGFLSTLATLVIFWRHFQIPMV	596
squirrel_monkey	ACPSNEWSHQSETSCFKRRLSFLEWHEAATIAVALLAALGFLSTLAILVIFWRHFETPMV	590
marmoset	ACPSNEWSHQSETSCFKRRLSFLEWHEAATIAVALLAALGFLXXXXXXXXXXXXXXXXXXXX	591
tamarin	XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX	591
cow	PCPSSEWSHRKDTSCFKRQLAFLEWDEAPTIVVVMLASLGFLSTLAIVIIFWRHVRTPVV DCDCVPWCHDNDTSCFKRQLAFLEWDEAPTIVVVMLASLGFLSTLAIVIIFWRHVRTPVV	594
rat	SCPGSMWSYKNDISCFREERFEEWHEVPTIVVAILAALGFFSTLAILFIFWEHFOTPMV	600
mouse	SCPGSMWSYKNNIACFKRRLAFLEWHEVPTIVVTILAALGFISTLAILLIFWRHFQTPMV	600
h		656
chimpanzee	REAGGEMERTINITLLIVAYMVVPVIVGPPKVSTCLCRQALFPLCFTICISCIAVRSFQIV REAGGEMERTINITLLIVAYMVVPVVGPPKVCTCLCPOALEDI.CFTTCTSCTAVRSFQIV	656
gorilla	RSAGGPMCFLMLTLLLVAYMVVPVVVGPPKVSTCLCROALFPLCFTICISCIAVRSFOIV	656
orangutan	RSAGGPMCFLMLTLLLVAYMVVPVYVGPPKVSTCLCRQALFPLCFTICISCIAVRSFQII	656
patas_monkey	RSDGGPMCFLMLTLLLVAYMVVPVYVGPPKVSTCFCRQALFPLCFTICISCIAVRSFQIV	654
baboon	RSAGGPMCFLMLTLLLVAYMVVPVYVGPPKVSTCFCRQALFPLCFTICISCIAVRSFQIV	656
rnesus_monkey	RSAGGPMCFLMLTLLLVAYMVVPVYVGPPKVSTCFCRQALFPLCFTICISCIAVRSFQIV PSAGGPMCFLMLTLLVAYMVVDVVQLDKVSTCLCPOALFDVCFTICISCIAVRSFQIV	650
marmoset	RSAGGPMCFLMLTLLLVAYMVVPVIVGPFKVTTCLCROALFPVCFTICISCITMRSFQIV	651
tamarin	RSAGGPMCFLMLTLLLVAYMVVPVYVGPPKVTTCLCRQALFPICFTICISCITVRSFQIV	651
COW	RSAGGPMCFLMLAPLLMAYTAVPVYVGPPTVWSCIFRQAFFTLCFTICISCITVRSFQIV	654
dog	RSAGGPMCFLMLVPLLLAYAMVPMYIGQPTFFSCLWRQTFFTLCFTICISCITVRSFQIV	655
rat	RSAGGPMCFLMLVPLLLAFGMVPVYVGPPTVFSCFCRQAFFTVCFSICLSCITVRSFQIV	660
niouse	KONGGENEFEMENFEMENTEN INGEFINFOLFCKQAFFINCFONCESCIINKSFQIN	000
human	CAFKMASRFPRAYSYWVRYQGPYVSMAFITVLKMVIVVIGMLATGLSPTTRTDPDDPKIT	716
chimpanzee	CAFKMASRFPRAYSYWVRYQGPYVSMAFITVLKMVIVVIGMLATGLSPTTRTDPDDPKIT	716
gorilla	CAFKMASKFFKAISIWVRIQGFIVSMAFITVLKMVIVVIGMLAIGLSPITRTDPDDPKIT CAFKMASCFFDDAVSVWUDVOGDVVCMAFTTVLKMVIVVIGMLATGLSPITRTDPDDDDKIM	716
patas monkey	CVFKMASRFPRAYSYWVRYOGPYVSMAFITVLKMVTVVIGMLATGLNPTTRIDPDDPKIM	714
baboon	CVFKMASRFPRAYSYWVRYQGPYVSMAFITVLKMVTVVIGMLATGLNPTTRIDPDDPKIM	716
rhesus_monkey	CVFKMASRFPRAYSYWVRYQGPYVSMAFITVLKMVTVVIGMLATGLNPTTRIDPDDPKIM	716
rhesus_monkey squirrel_monkey	CVFKMASRPPRAYSYWVRYQGPYVSMAPITVLKMVTVVIGMLATGLNPTTRIDPDDPKIM CVFKMASRPPRAYSYWVRYQGSYVSVAPITALKMVTVVIGLLATGLNPTTRTDDDDPKIM CVFKMASRPPRAYSYWVRYQGSYVSVAPITALKMVTVVIGLLATGLNPTRTDDDDPKIM	716
rhesus_monkey squirrel_monkey marmoset tamarin	CVFKMASRFPRAYSYWWRYQGPYVSMAFITVLKMVTVVIGMLATGLNPTTRIDPDDPKIM CVFKMASRFPRAYSYWWRYQGSYVSWAFITALKMVTVVISLLATGLNPTTRIDPDDPKIM CVFKMASRFPRAYSYWWRYQGSYVSWAFITALKVVTVVISLLATGLNPTTRIDPDDPKIM CVFKMASRFPRAYSYWWRYGSYVSWAFITALKWVTVVISLLATGLNPTTRIDPDDPKIM	716 710 711 711
rhesus_monkey squirrel_monkey marmoset tamarin cow	CVFKMASRPPRASSYWNYQGPYUSÄAPITVLKMYTVIGMLATGLAPTTRIDPDDPKIM CVFKMASRPPRASSYWNYQGSYUSÄPITALKWYTVVISLLATGLAPTRIDDDPKIM CVFKMASRPPRASSYWNYQGSYUSÄPITALKVYTVVISLLATGLAPTTRADDDPKIM CVFKMASRPPRASSYWNYQGSYUSÄPITALKWYTVVISLLATGLAPTTRADDDPKIM CVFKMASRPPRASGKGNYDAPYVTACVVMLKLIVIASSVLATTMPTRADDDDPKIM	716 710 711 711 714
<u>rhesus_monkey</u> squirrel_monkey marmoset tamarin cow dog	CVFKMASRPPRASSYWPRQGPYVSMAPITYLKMYTVIGMLATGLAPTTRIDPDDFKIM CVFKMASRPPRASSYWPRQGSYVSWAPITALKMYTVVISLLATGLAPTRIDDDDFKIM CVFKMASRPPRASSYWPRQGSYVSWAPITALKMYTVVISLLATGLAPTTRIDDDPKIM CVFKMASRPPRASSYWPRQGSYVSWAPITALKMYTVVISLLATGLAPTTRIDDDFKIM CVFKMASRLPRAYGWRGPYDFWACVMLKLVIVASSVLATTMPTRVDPDDFKIM CIFKMARRLPRAYGYWRCHGPYVFWASFWULKVVIVASVLATTMPTRVDPDDPRIM	716 710 711 711 714 715
rhesus monkey squirrel_monkey marmoset tamarin cow dog rat	CVFINASRPPRAYSYWIFYOGPYVSWAPITVLIMYTVUIMLATCLAPTTRIDPDDPKIM CVFINASRPPRAYSYWIFYOGSYVSWAPITALIMYTVYISLLATCLAPTTRIDDDPKIM CVFINASRPPRAYSYWIFYOGSYVSWAPITALIMYTVYISLLATCLAPTTRIDDDPKIM CVFINASRPPRAYSYWIFYOGSYVSWAPITALIMYTVYISLLATCLAPTTRIDDDPKIM CVFINARRLPRAYSYWIFYOGYYVSWAPITALIMYTVYISLLATCLAPTTRIDDDPKIM CVFINARRLPRAYSYWIFYOGYYVSWAPITALIMYTVYISANLATTINPTRIDDDPKIM CVFINARRLPRAYSYWIFYOFYVSWAPITALIMVLIVYISANLATTINPTRIDDDPKIM	716 710 711 711 714 715 720
rhesus monkey squirrel_monkey marmoset tamarin cow dog rat mouse	CVFKMASREPRAYSYWWRYQGPYUSARFITULKMVTVUIGMLATCLAPTTRIDEDDPKIM CVFKMASREPRAYSYWRYQGSYUSAFITALKWVTVUISLLATGLAPTTRIDDDPKIM CVFKMASREPRAYSYWRYQGSYUSAFITALKWVTVUISLLATGLAPTTRIDDDPKIM CVFKMASREPRAYSYWRYQGSYUSAFITALKWVTVUISLLATGLAPTTRIDDDPKIM CVFKMASREPRAYSYWRYQGSYUSAFITALKWVTVISLLATGLAPTTRIDDDPKIM CVFKMARKLPRAYGYWRYCHGPYUFASFWULKUIVASVLATTMPTRYDDDDPRIM CVFKMARKLPRAYGYWRYCHGPYUFASFWULKUIVASWLATTNAPTAREDDDDPNIM CVFKMARRLPSAYGFWRYHGPYUFAFITAKVALVAGNMLATTINPIGRTDDDDNIM	716 711 711 714 715 720 720
rhesus monkey squirrel_monkey marmoset tamarin cow dog rat mouse human	CVFKMASRPPRAYSYWNYQGPYUSMAFITYLKMYTVUIGHLATGLAPTTRIDPDDPKIM CVFKMASRPPRAYSYWNRYGGSYUSWAFITALKMYTVVISLLATGLAPTTRIDDDPKIM CVFKMASRPPRAYSYWNRYGGSYUSWAFITALKMYTVVISLLATGLAPTTRIDDDPKIM CVFKMASRPPRAYSYWNRYGGSYUSWAFITALKMYTVVISLLATGLAPTTRIDDDPKIM CVFKMASRLPRAYGGWIPHOPYUFYGVYMLKUIVASVLATTNAPTARDDDPRIM CIFKMARRLPRAYGWNRCHGPYUFYAFITALKWALVUGMLATTNAPTARDDDDPNIM CVFKMARRLPRAYGFMRYHGPYUFYAFITAKVALVUGMLATTINPIGRTDPDDPNIM CVFKMARRLPRAYGFMRYHGPYUFYAFITAKVALVUGMLATTINPIGRTDPDDPNIM CVFKMARRLPRAYGFMRYHGPYUFYAFITAKVALVAGMLATTINPIGRTDPDDPNIM IVSCNPNYRNSLLPNTSLDLLLSVUGPSFAYMGKELPTNYNEAKFITLSMTFYFTSSVSL	716 710 711 711 714 715 720 720 720
rhesus_monkey squirrel_monkey marmoset tamarin cow dog rat mouse human chimpanzee	CVFINASERPEASSYWERYOGPYVSÄRFITVLEMVTVUIGHLATGLAPTTEIDEDDEKIM CVFINASERPEASSYWERYOGSYVSAFITALEMVTVUIGLLATGLAPTTEIDEDDEKIM CVFINASERPEASSYWERYOGSYVSAFITALEMVTVUIGLLATGLAPTTERDEDDEKIM CVFINASERPEASSYWERYOGSYVSAFITALEMVTVUIGLLATGLAPTTERDEDDEKIM CVFINASELPEASSYERVERYOGSYVSAFITALEMVTVUIGLLATGLAPTTERDEDDEKIM CVFINASELPEASSYERVERYÖRYVSÄRFITALEMVTVUIGNULATTAINETREDDEDEN CVFINASELPEASSYERVERYÖRYVSÄRFITALEVALVVGMILATTINETGETDEDDEN CVFINASELPEASSYERVERYÖRYVSÄRFITALEVALVVGMILATTINETGETDEDDEN CVFINASELPEASSERVERYÖRFITALEVALVAGMILATTINETGETDEDDEN I IVSCNPNYENSLLPNTSLDLLSVVGFSFAYMGELETMYNEAKFITLSMFYFTSSVSL	716 711 711 714 715 720 720 720 776 776
rhesus_monkey squirrel_monkey marmoset tamarin cow dog rat mouse human chimpanzee gorilla	CVFKMASRPPRASYWWIYQOPYUARFITULKMYTVIONLATCLAPTTRIDPDDPKIM CVFKMASRPPRASYWWIYQOFYUARFITULKMYTVISLLATCLAPTTRIDDDPKIM CVFKMASRPPRASYWWIYQOSYUAPFITALKVYTVISLLATCLAPTTRIDDDPKIM CVFKMASRPPRASYWWIYQOSYUAPFITALKWYTVISLLATCLAPTTRIDDDPKIM CVFKMASRLPRAYCMYKHOPYUYARFITALKWYTVISLLATCLAPTTRIDDDPKIM CVFKMARRLPRAYCMYHOPYUYAFITALKWYTVIAGNULATTINPTRVDDDPRIM CVFKMARRLPRAYCMYHOPYUYAFITALKVALVMANLATTINPIGRTDPDDPNIM CVFKMARRLPSAYSMWIYHOPYUYAFITALKVALVMANNLATTINPIGRTDPDDPNI CVFKMARRLPSAYSMWIYHOPYUYAFITALKVALVMANNLATTINPIGRTDPDDPNI CVFKMARRLPSAYSMWIYHOPYUYAFITALKVALVMANNLATTINPIGRTDPDDPNI IVSCNPNYRNSLLPRISLDLLLSVUGFSPAYMGKELPTNYNBAKFITLSMTFYFTSSVSL IVSCNPNYRNSLLPRISLDLLLSVUGFSPAYMGKELPTNYNBAKFITLSMTFYFTSSVSL	716 710 711 711 714 715 720 720 720 776 776 776
rhesus_monkey squirrel_monkey marmoset tamarin cow dog rat mouse human chimpanzee gorilla orangutan patss_monkey	CVFKMASRPPRAYSYWNYQGPYUSÄAFITULKMYTVIGMLATGLAPTTRIDPDDPKIM CVFKMASRPPRAYSYWNYQGFYUSÄAFITULKMYTVISLLATGLAPTTRIDDDPKIM CVFKMASRPPRAYSYWNYQGSYUSYAFITALKWYTVISLLATGLAPTTRIDDDPKIM CVFKMASRPPRAYSYWNYQGSYUSYAFITALKWYTVISLLATGLAPTTRIDDDPKIM CVFKMASRPPRAYSKWYRYGGSYUSAFITALKWYTVISLLATGLAPTTRUDDDPKIM CVFKMASRLPRAYGCWYRYGGSYUSAFITALKWYTVISLLATGLAPTTRUDDDPKIM CVFKMARRLPRAYGYWYRCHGPYUFYAFITALKWYTVIGKULATTINPIGRTDDDDNIM CVFKMARRLPRAYGWWRYHGPYUFYAFITALKWITVGMLATTINPIGRTDDDDNIM CVFKMARRLPSAYSFWHYRGPYUFYAFITALKVALVGMMLATTINPIGRTDDDDNIN CVFKMARRLPSAYSFWHYRGPYUFYAFITALKVALVGMMLATTINPIGRTDDDDNIN CVFKMARRLPSAYSFWHYRGPYUFYAFITALKVALVGMMLATTINPIGRTDDDDNIN CVFKMARRLPSAYSFWHYRGPYUFYAFITALKVALVGMMLATTINPIGRTDDDDNIN UVSCNNYKNSLLPNTSLDLLLSVUGFSFAYMGKELPTNYNBAKFITLSMTPYFSSVSL IVSCNNYKNSLLPNTSLDLLLSVUGFSFAYMGKELPTNYNBAKFITLSMTPYFSSISL IVSCNNYKNSLLPNTSLDLLLSVUGFSFAYMGKELPTNYNBAKFITLSMTPYFSSISL IVSCNNYKNSLLPNTSLLLLSVUGFSFAYMGKELPTNYNBAKFITLSMTPYFSSISL	716 710 711 711 714 715 720 720 776 776 776 776 776 776
rhesus_monkey squirrel_monkey marmoset tamarin cow dog rat mouse human chimpanzee gorilla orangutan patas_monkey baboon	CVEYMASREPRASSYWURYQGEYUSÄRFITULMYUTVUIGMLATGLAPTTEIDEDDEKIM CVEYMASREPRASSYWURYQGSYUSAFITALMYUTVUIGLATGLAPTTEIDEDDEKIM CVEYMASREPRASSYWURYQGSYUSAFITALMYUTVUIGLATGLAPTTEADTDDEKIM CVEYMASREPRASSYWURYQGSYUSAFITALMYUTVUIGLATGLAPTTEADTDDEKIM CVEYMARRLPRASGYWURYGGSYUSAFFULALMYUTVUIGLATGLAPTTERDTDDEKIM CVEYMARRLPRASGYWURYGGSYUSAFFULALMYUTVUIGLATGLAPTTERDTDDENIM CVEYMARRLPRASGYMURYGGSYUSAFFULALMYUNGMLATTINFIGHTDEDDENIM CVEYMARRLPRASGYMURYGGSYUSAFFULAVUNGMLATTINFIGHTDEDDENIM IVSCNPNYRNSLLPNTSLDLLSYUGFSFAYMGKELPTNYNBAKFILSMTPYFSSVSL IVSCNPNYRNSLLPNTSLDLLSYUGFSFAYMGKELPTNYNBAKFILSMTPYFSSVSL IVSCNPNYRNSLLPNTSLDLLSYUGFSFAYMGKELPTNYNBAKFILSMTPYFTSSVSL IVSCNPNYRNSLLPNTSLDLLSYUGFSFAYMGKELPTNYNBAKFILSMTPYFTSSVSL IVSCNPNYRNSLLPNTSLDLLSYUGFSFAYMGKELPTNYNBAKFILSMTPYFTSTVSL IVSCNPNYRNSLPNTSLDLLSYUGFSFAYMGKELPTNYNBAKFILSMTPYFTSTVSL IVSCNPNYRNSLPNTSLDLLSYUGFSFAYMGKELPTNYNBAKFILSMTPYFTSTVSL IVSCNPNYRNSLPNTSLDLLSYUGFSFAYMGKELPTNYNBAKFILSMTPYFTSTVSL	716 710 711 711 714 720 720 720 776 776 776 776 776 7774 776
rhesus_monkey squirrel_monkey marmoset tamarin ccw dog rat mouse human chimpanzee gorilla orangutan patas_monkey baboon rhesus_monkey	CVFKMASRPRASSYWURYQGPYUSARFITULKMYTVIGMLATGLAPTTRIDPDDPKIM CVFKMASRPRASSYWURYQGSYUSAFITALKWYTVISLLATGLAPTTRIDDDPKIM CVFKMASRPRASSYWURYQGSYUSAFITALKWYTVISLLATGLAPTTRIDDDPKIM CVFKMASRPRASSYWURYQGSYUSAFITALKWYTVISLLATGLAPTTRIDDDPKIM CVFKMASRLPRAYGCMSHHGPYUFYAFUTALKWYTVISLLATGLAPTTRIDDDPKIM CVFKMARLPRAYGYMVRCHGPYUFYAFITALKWYTVIAGSVLATTTMPTRVDDDPRIM CVFKMARLPRAYGYMVRCHGPYUFYAFITALKUVYUMKLATINPIGRTDDDDPNIM CVFKMARRLPRAYGYMVRCHGPYUFYAFITALKUVYUMKLATINPIGRTDDDDPNIM CVFKMARRLPRAYGYMVRCHGPYUFYAFITALKUVYUMKLATINPIGRTDDDDPNII USCONPNYNSLLPNTSLDLLLSVUGFSFAYMGKELPTNYNBAFFILSMTFYFTSSVSL IVSCNPNYNSLLPNTSLDLLLSVUGFSFAYMGKELPTNYNBAFFILSMTFYFTSSVSL IVSCNPNYNSLLPNTSLDLLLSVUGFSFAYMGKELPTNYNBAFFILSMTFYFTSSVSL IVSCNPNYNSLLPNTSLDLLLSVUGFSFAYMGKELPTNYNBAFFILSMTFYFTSSVSL IVSCNPNYNSLLPNTSLDLLLSVUGFSFAYMGKELPTNYNBAFFILSMTFYFTSSVSL IVSCNPNYNSLLPNTSLDLLLSVUGFSFAYMGKELPTNYNBAFFILSMTFYFTSSVSL IVSCNPNYNSLLPNTSLDLLLSVUGFSFAYMGKELPTNYNBAFFILSMTFYFTSSVSL IVSCNPNYNSLLPNTSLDLLLSVUGFSFAYMGKELPTNYNBAFFILSMTFYFTSSVSL IVSCNPNYNSLLPNTSLDLLLSVUGFSFAYMGKELPTNYNBAFFILSMTFYFTSSVSL IVSCNPNYNSLLPNTSLDLLLSVUGFSFAYMGKELPTNYNBAFFILSMTFYFTSSVSL IVSCNPNYNSLLPNTSLDLLLSVUGFSFAYMGKELPTNYNBAFFILSMTFYFTSSVSL	716 710 711 711 714 720 720 720 776 776 776 776 776 776 776 776 776
rhesus_monkey squirrel_monkey marmoset tamarin cow dog rat mouse human chimpanzee gorilla orangutan patas_monkey squirrel_monkey	CVFKMASRPPRASYWWIYQGPYUSAFITULKMYTVIGMLATGLAPTTRIDEDDPKIM CVFKMASRPPRASYWWIYGGYUSAFITALKWYTVISLLATGLAPTTRIDEDDPKIM CVFKMASRPPRASYWWRYGGSYUSAFITALKWYTVISLLATGLAPTTRIDEDDPKIM CVFKMASRPPRASYWWRYGGSYUSAFITALKWYTVISLLATGLAPTTRIDEDDPKIM CVFKMASRPPRASYGWWRYGGYUSAFITALKWYTVISLLATGLAPTTRIDEDDPKIM CVFKMASRLPRAYGWWRYGGYUSAFITALKWYTVIGKULATTINPTRIDEDDPKIM CVFKMARRLPRAYGWWRYGDYYYAFITALKWIYUMKIATTINPIGRTDDDDNIM CVFKMARRLPSAYSFWWRYGPYYYAFITAKVALVAGNMLATTINPIGRTDDDDNIM CVFKMARRLPSAYSFWWRYGUSYUSAFITALKWIYUMKIATTINPIGRTDDDDNIM CVFKMARRLPSAYSFWWRYGUSYUSAFITAKVALVAGNMLATTINPIGRTDDDDNIN CVFKMARRLPSAYSFWWRYGUSYUSAFITAKVALVAGNMLATTINPIGRTDDDDNIN CVFKMARRLPSAYSFWWRYGUSYTYAFITAKVALVAGNMLATTINPIGRTDPDDNIN IVSCNNYKNSLLPNTSLDLLLSVUGFSFAYMGKELTNYNBAKFITLSMTFYFTSSVSL IVSCNNYKNSLFWTSLDLLLSVUGFSFAYMGKELTNYNBAKFITLSMTFYFTSSVSL IVSCNNYKNSLFPNTSLDLLLSVUGFSFAYMGKELTNYNBAKFITLSMTFYFTSSVSL IVSCNNYKNSLFPNTSLDLLLSVUGFSFAYMGKELTNYNBAKFITLSMTFYFTSSVSL IVSCNNYKNSLFPNTSLDLLLSVUGFSFAYMGKELTNYNBAKFITLSMTFYFTSSVSL IVSCNNYKNSLFPNTSLDLLLSVUGFSFAYMGKELTNYNBAKFITLSMTFYFTSSVSL IVSCNNYKNSLFPNTSLDLLLSVUGFSFAYMGKELTNYNBAKFITLSMTFYFTSSVSL IVSCNNYKNSLFPNTSLDLLLSVUGFSFAYMGKELTNYNBAKFITLSMTFYFTSSVSL IVSCNNYKNSLFPNTSLDLLLSVUGFSFAYMGKELTNYNBAKFITLSMTFYFTSSVSL IVSCNNYKNSLFPNTSLDLLLSVUGFSFAYMGKELTNYNBAKFITLSMTFYFTSSVSL IVSCNNYKNSLFPNTSLDLLLSVUGFSFAYMGKELTNYNBAKFITLSMTFYFTSSVSL IVSCNNYKNSLFPNTSLDLLSVUGFSFAYMGKELTNYNBAKFITLSMTFYFTSSVSL	716           710           711           711           711           714           715           720           776           776           776           776           776           776           7774           7776           7776           7776           7776           7776           7776           7776           7776           7776           7776           7776           7776           7776           7776           7776           7776           7776
rhesus_monkey squirrel_monkey marmoset tamarin cow dog rat mouse human chimpanzee gorilla orangutan patas_monkey babcon rhesus_monkey squirrel_monkey marmoset	CVPENASERPEASYSWURYQGPYUSARFITULIMUTVUIGHLATGLAPTTEIDEDDPKIM CVPENASERPEASYSWURYQGSYUSAFITULIMUTVUIGHLATGLAPTTEIDEDDPKIM CVPENASERPEASYSWURYQGSYUSAFITALIMUTVUIGLLATGLAPTTEADTDDPKIM CVPENASERPEASYSWURYQGSYUSAFITALIMUTVUIGLLATGLAPTTEADTDDPKIM CVPENASERPEASYSWURYQGSYUSAFITALIMUTVUIGLLATGLAPTTERDTDDPKIM CVPENARELPEASYGWURYGGSYUSAFITALIMUTVUIGLATGLAPTTERDTDDPKIM CVPENARELPEASYGWURYGGSYUSAFITALIMUTVUIGANLATTINFIGHTDPDPDFIM CVPENARELPEASYSWURYGGSYUSAFITALIMUTVUIGANLATTINFIGHTDPDPDFIM CVPENARELPEASYSWURYGGSYUSAFFITAINVALVUGANLATTINFIGHTDPDPDFIM CVPENARELPEASYSWURYGGSYUSAFFITAINVALVUGANLATTINFIGHTDPDPDFIM IVSCNPNYENSLLPNTSLDLLSVUGFSFAYMGKELPTNYNEAKFITLSMTPYFSSVSL IVSCNPNYENSLLPNTSLDLLSVUGFSFAYMGKELPTNYNEAKFITLSMTPYFSSVSL IVSCNPNYENSLLPNTSLDLLSVUGFSFAYMGKELPTNYNEAKFITLSMTPYFSSVSL IVSCNPNYENSLPRTSLDLLSVUGFSFAYMGKELPTNYNEAKFITLSMTPYFSSVSL IVSCNPNYENSLPRTSLDLLSVUGFSFAYMGKELPTNYNEAKFITLSMTPYFSSVSL IVSCNPNYENSLPRTSLDLLSVUGFSFAYMGKELPTNYNEAKFITLSMTPYFSSVSL IVSCNPNYENSLPRTSLDLLSVUGFSFAYMGKELPTNYNEAKFITLSMTPYFSSVSL IISCNPNYENSLLPNTSLDLLSVUGFSFAYMGKELPTNYNEAKFITLSMTPYFSSVSL IISCNPNYENSLLPNTSLDLLSVUGFSFAYMGKELPTNYNEAKFITLSMTPYFSSVSL IISCNPNYENSLLPNTSLDLLSVUGFSFAYMGKELPTNYNEAKFITLSMTPYFSSVSL IISCNPNYENSLLPNTSLDLLSVUGFSFAYMGKELPTNYNEAKFITLSMTPYFSSVSL IISCNPNYENSLLPNTSLDLLSVUGFSFAYMGKELPTNYNEAKFITLSMTPYFSSVSL IISCNPNYENSLLPNTSLDLLSVUGFSFAYMGKELPTNYNEAKFITLSMTPYFSSVSL IISCNPNYENSLLPNTSLDLLSVUGFSFAYMGKELPTNYNEAKFITLSMTPYFSSVSL IISCNPNYENSLLPNTSLDLLSVUGFSFAYMGKELPTNYNEAKFITLSMTPYFSSVSL IISCNPNYENSLLPNTSLDLLSVUGFSFAYMGKELPTNYNEAKFITSMTPYFTSSVSL IISCNPNYENSLLPNTSLDLLSVUGFSFAYMGKELPTNYNEAKFITSMTPYFTSSVSL IISCNPNYENSLLPNTSLDLLSVUGFSFAYMGKELPTNYNEAKFITSMTPYFTSSVSL	716           710           711           711           711           714           715           720           776           776           776           776           776           776           776           776           776           776           777           777           770           771
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rhesus_monkey squirrel_monkey marmoset tamarin cow dog rat mouse human chimpanzee gorilla orangutan patas_monkey baboon rhesus_monkey marmoset tamarin cow	CVEYKMASREPRASYSYWIRYQGPYUSARFITVLKMYTVIGMLATGLAPTTRIPEDDDPKIM CVEYKMASREPRASYSYWIRYQGPYUSARFITALKWYTVISLLATGLAPTTRIPEDDDFKIM CVEYKMASREPRASYSYWIRYQGSYUSARFITALKWYTVISLLATGLAPTTRIPTDDDPKIM CVEYKMASREPRASYSYWIRYQGSYUSARFITALKWYTVISLLATGLAPTTRIPTDDDDFKIM CVEYKMASREPRASYSYWIRYQGSYUSARFITALKWYTVISLLATGLAPTTRIPTDDDPKIM CVEYKMASREPRASYSYWIRYQGSYUSARFITALKWYTVISLLATGLAPTTRIPTRIDDDPKIM CVEYKMASREPRASYSYWIRYQGYYUSARFITALKWYTVMLKITINSLAFTRUDDDPKIM CVEYKMASREPRASYSWIRYQGYYUSAFFITALKWYTVMLKITINSCHAFDDDPNIN CVEYKMASREPRASYSWIRYQGYYUSAFFITALKWALVGANMLATTINFIGRTDDDDNIN CVEYKMASREPRASYSWIRYQGYYUSAFFITALKVALVGANMLATTINFIGRTDDDDPNIN CVEYKMASREPSASYSWIRYGPYYUSAFFITALKVALVGANMLATTINFIGRTDDDDPNIN CVEYKMASREPSASSFITISLDLLLSVUGFSFAYMGKELPTNYNBARFITLSMTFYFTSSVSL IVSCNPNYRNSLEPNTSLDLLLSVUGFSFAYMGKELPTNYNBARFITLSMTFYFTSSVSL IVSCNPNYRNSLEPNTSLDLLLSVUGFSFAYMGKELPTNYNBARFITLSMTFYFTSSVSL IVSCNPNYRNSLEPNTSLDLLLSVUGFSFAYMGKELPTNYNBARFITLSMTFYFTSSVSL ISCNPNYRNSLEPNTSLDLLLSVUGFSFAYMGKELPTNYNBARFITLSMTFYFTSSVSL ISCNPNYRNSLEPNTSLDLLLSVUGFSFAYMGKELPTNYNBARFITLSMTFYFTSSVSL ISCNPNYRNSLEPNTSLDLLLSVUGFSFAYMGKELPTNYNBARFITLSMTFYFTSSVSL ISCNPNYRNSLEPNTSLDLLLSVUGFSFAYMGKELPTNYNBARFITLSMTFYFTSSVSL ISCNPNYRNSLEPNTSLDLLLSVUGFSFAYMGKELPTNYNBARFITLSMTFYFTSSVSL ISCNPNYRNSLEPNTSLDLLLSVUGFSFAYMGKELPTNYNBARFITSSTFFFYFTSSVSL ISCNPNYRNSLEPNTSLDLLLSVUGFSFAYMGKELPTNYNBARFITSSTFFFSMTFYFTSSVSL ISCNPNYRNSLEPNTSLDLLLSVUGFSFAYMGKELPTNYNBARFITSSTFFFFFYFTSSVSL ISCNPNYRNSLEPNTSLDLLLSVUGFSFAYMGKELPTNYNBARFITSSVSSL ISCNPNYRNSLEPNTSLDLLLSVUGFSFAYMGKELPTNYNBARFITSSTFFFFFYFTSSVSL ISCNPNYRNSLEPNTSLDLLLSVUGFSFAYMGKELPTNYNBARFITSSTFFFFFFFFSSVSL ISCNPNYRNSLEPNTSLDLLLSVUGFSFAYMGKELPTNYNBARFITSSTFFFFFFFFFFFSSVSL ISCNPNYRNSLEPNTSLDLLLSVUGFSFAYMGKELPTNYNBARFITFSMTFYFTSSVSL ISCNPNYRNSLEPNTSLDLLLSVUGFSFAYMGKELPTNYNBARFITFSMTFYFTSSVSL ISCNPNYRNSLEPNTSLDLLLSVUGFSFAYMGKELPTNYNBARFITFSMTFYFTSSVSL ISCNPNYRNSLEPNTSLDLLLSVUGFFAYMGKELPTNYNBARFITFSMTFYFTSSVSL	716 710 711 711 714 715 720 720 720 776 776 776 776 776 776 776 776 776 77
rhesus_monkey squirrel_monkey marmoset tamarin cow dog rat mouse human chimpanzee gorilla orangutan patas_monkey babcon rhesus_monkey squirrel_monkey marmoset tamarin cow dog rat	CVEYMASREPRASYSWURYQQEYUSARTIYULMUTVUIGMLATGLAPTTRIDEDDEKIM CVEYMASREPRASYSWURYQQSYUSARTIALMUTVUIGMLATGLAPTTRIDDEKIM CVEYMASREPRASYSWURYQQSYUSARTIALMUTVUIGLATGLAPTTRADTDDEKIM CVEYMASREPRASYSWURYQQSYUSARTIALMUTVUIGLATGLAPTTRADTDDEKIM CVEYMARRLPRASYSWURYQQSYUSARTIALMUTVUIGLATGLAPTTRADTDDEKIM CVEYMARRLPRASYSWURYQQSYUSARTIALMUTVUIGLATGLAPTTRADTDDENIM CVEYMARRLPRASYSWURYQQSYUSARTIALMUTVUGMULATTANETARDDDEPIM CVEYMARRLPRASYSWURYQQSYUSARTIALMULVUGMULATTANETARDDDEPIM CVEYMARRLPRASYSWURYQQSYUSARTIALMULVUGMULATTANETARDTDDEPIM CVEYMARRLPRASYSWURYQQSYAYARTIALMULVUGMULATTANETARDTDDEPIM CVEYMARRLPRASYSWURYQQSYAYMGRELPTANEAKINTNETARTINETGODDEPIM IVSCNPNYRNSLLPNTSLDLLSVUGFSFAYMGKELPTNYNBAKFITLSMTFYFTSSVSL IVSCNPNYRNSLLPNTSLDLLSVUGFSFAYMGKELPTNYNBAKFITLSMTFYFTSSVSL IVSCNPNYRNSLPNTSLDLLSVUGFSFAYMGKELPTNYNBAKFITLSMTFYFTSSVSL IVSCNPNYRNSLPRTSLDLLSVUGFSFAYMGKELPTNYNBAKFITLSMTFYFTSSVSL IVSCNPNYRNSLPRTSLDLLSVUGFSFAYMGKELPTNYNBAKFITLSMTFYFTSSVSL IISCNPNYRNSLPRTSLDLLSVUGFSFAYMGKELPTNYNBAKFITLSMTFYFTSSVSL IISCNPNYRNSLPRTSLDLLSVUGFSFAYMGKELPTNYNBAKFITLSMTFYFTSSVSL IISCNPNYRNSLLPNTSLDLLLSVUGFSFAYMGKELPTNYNBAKFITLSMTFYFTSSVSL IISCNPNYRNSLLPNTSLDLLLSVUGFSFAYMGKELPTNYNBAKFITSMTFYFTSSVSL IISCNPNYRNSLLPNTSLDLLLSVUGFSFAYMGKELPTNYNBAKFITSMTFYFTSSVSL IISCNPNYRNSLLPNTSLDLLLSVUGFSFAYMGKELPTNYNBAKFITSMTFYFTSSVSL IISCNPNYRNSLLPNTSLDLLLSVUGFSFAYMGKELPTNYNBAKFITSMTFYFTSSVSL IISCNPNYRNSLLPNTSLDLLLSVUGFSFAYMGKELPTNYNBAKFITSMTFYFTSSVSL IISCNPNYRNSLLPNTSLDLLLSVUGFSFAYMGKELPTNYNBAKFITSMTFYFTSSVSL IISCNPNYRNSLLPNTSLDLLLSVUGFSFAYMGKELPTNYNBAKFITSMTFYFTSSVSL IISCNPNYRNSLLPNTSLDLLSVUGFSFAYMGKELPTNYNBAKFITSMTFYFTSSVSL IISCNPNYRNSLLPNTSLDLLSVUGFSFAYMGKELPTNYNBAKFITSMTFYFTSSVSL IISCNPNYRNSLLPNTSLDLLSVUGFSFAYMGKELPTNYNBAKFITSMTFYFTSSVSL IISCNPNYRNSLLPNTSLDLLSVUGFSFAYMGKELPTNYNBAKFITSMTFYFTSSVSL IISCNPNYRNSLLPNTSLDLLSVUGFSFAYMGKELPTNYNBAKFITSMTFYFTSSVSL IISCNPNYRNSLLPNTSLDLLSVUGFSFAYMGKELPTNYNBAKFITSMTFYFTSSVSL	716           710           711           711           711           711           711           711           711           712           720           776           776           776           776           776           776           776           777           771           771           771           773           780
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rhesus_monkey squirrel_monkey marmoset tamarin cow dog rat mouse human chimpanzee gorilla orangutan patas_monkey baboon rhesus_monkey squirrel_monkey marmoset tamarin cow dog rat mouse human	CVPENASERPEASYSWURYQGPYUSARTIYULMYUYUIGHLATGLAPTTEIDEDDPKIM CVFENASERPEASYSWURYQGSYUSARTIALMYUYUIGHLATGLAPTTEIDEDDFKIM CVFENASERPEASYSWURYQGSYUSARTIALMYUYUIGLLATGLAPTTEADTDDPKIM CVFENASERPEASYSWURYQGSYUSARTIALMYUYUIGLLATGLAPTTEADTDDPKIM CVFENASERPEASYSWURYQGSYUSARTIALMYUYUIGLLATGLAPTTEADTDDPKIM CVFENASERPEASYSWURYQGSYUSAFTALMUNYUNGNULATTANPTARDDDPRIM CVFENASERPEASYSWURYQGSYUSAFTALMALWYUNGNULATTANPTARDDDPRIM CVFENASELPEASYSWURYQGSYUSAFTALMALWAGNLATTINPIGKTDPDDPRIM CVFENASELPEASYSWURYQGSYUSAFTALMALWAGNLATTINPIGKTDPDDPRIM CVFENASELPEASYSWURYGDFYUSAFTALMALWAGNLATTINPIGKTDPDDPRIM CVFENASELPEASYSWURYGDFYUSAFTALMALWAGNLATTINPIGKTDPDDPRIM CVFENASELPENSIDLLLSVUGFSFAYMGKELPTNYNBAKFILSMFFYFSSVSL IVSCNNYKNSLLPNTSLDLLLSVUGFSFAYMGKELPTNYNBAKFILSMFFYFTSSVSL IVSCNNYKNSLFPNTSLDLLLSVUGFSFAYMGKELPTNYNBAKFILSMFFYFTSSVSL IVSCNNYKNSLFPNTSLDLLLSVUGFSFAYMGKELPTNYNBAKFILSMFFYFTSSVSL IVSCNNYKNSLFPNTSLDLLLSVUGFSFAYMGKELPTNYNBAKFILSMFFYFTSSVSL IISCNNYKNSLFPNTSLDLLLSVUGFSFAYMGKELPTNYNBAKFILSMFFYFTSSVSL IISCNNYKNSLFPNTSLDLLLSVUGFSFAYMGKELPTNYNBAKFITSMFYFTSSVSL IISCNNYKNSLFPNTSLDLLLSVUGFSFAYMGKELPTNYNBAKFITSMFYFTSSVSL IISCNNYKNSLFPNTSLDLLLSVUGFSFAYMGKELPTNYNBAKFITSMFYFTSSVSL IISCNNYKNSLFPNTSLDLLLSVUGFSFAYMGKELPTNYNBAKFITSMFYFTSSVSL IISCNNYKNSLFPNTSLDLLLSVUGFSFAYMGKELPTNYNBAKFITSMFYFTSSVSL IISCNNYKNSLFPNTSLDLLLSVUGFSFAYMGKELPTNYNBAKFITSMFYFTSSVSL IISCNNYKNSLFPNTSLDLLLSVUGFSFAYMGKELPTNYNBAKFITSMFYFTSSVSL IISCNNYKNSLFPNTSLDLLLSVUGFSFAYMGKELPTNYNBAKFITSMFYFTSSVSL IISCNNYKNSLFPNTSLDLLLSVUGFSFAYMGKELPTNYNBAKFITSMFYFTSSVSL IISCNNYKNSLFPNTSLDLLLSVUGFSFAYMGKELPTNYNBAKFITSMFYFTSSVSL IISCNNYKNSLFPNTSLDLLLSVUGFSFAYMGKELPTNYNBAKFITSMFYFTSSVSL IISCNNYKNSLFPNTSLDLLLSVUGFSFAYMGKELPTNYNBAKFITCMTYFYFTSSVSL IISCNNYKNSLFPNTSLDLLSVUGFSFAYMGKELPTNYNBAKFITSMFYFTSSVSL IISCNNYKNSLFPNTSLDLLLSVUGFSFAYMGKELPTNYNBAKFITCMTYFYFTSSVSL IISCNNYKNSLFPNTSLDLLSVUGFSFAYMGKELPTNYNBAKFITCMTYFYFTSSVSL IISCNNYKNSLFPNTSLDLLSVGFFAYMGKELPTNYNBAKFITCMTYFYFTSSVSL IISCNNYKNSLFPNTSMDLLLSVGFFAYMGKELPTNYNBAKFITCMTYFYFTSSVSL IISCNNYKNSLFPNTSMDLLLSVGFFAYMGKELPTNYNBAKFITCMTYFYFTSSVSL IISCNNYKNS	716 710 711 711 711 715 720 720 720 776 776 776 776 776 776 776 776 776 77
rhesus monkey squirrel_monkey marmoset tamarin cow dog rat mouse human chimpanzee gorilla orangutan patas monkey squirrel_monkey squirrel_monkey marmoset tamarin cow dog rat mouse human chimpanzee	CVEYMASR PPRASY WV:YQG PYUSA PITYLKMYTVIGMLATCIAPTTE IPPDDPKIM CVEYMASR PPRASY WV:YQG PYUSA PITALKVYTVISLLATCIAPTTE IPPDDPKIM CVEYMASR PPRASY WV:YQG SYUSA PITALKVYTVISLLATCIAPTTEADTDDPKIM CVEYMASR PPRASY WV:YQG SYUSA PITALKVYTVISLLATCIAPTTEADTDDPKIM CVEYMASR PPRASY WV:YQG SYUSA PITALKVYTVISLLATCIAPTTEADTDDPKIM CVEYMARRLPRAYGCM;HGPYUYACYVMLKLVIVASVLATTIMPTRTDDDPKIM CVEYMARRLPRAYGYMV:CHGPYUYAFITALKVYTVIAKMLATTINPIGTDDDPNIM CVEYMARRLPRAYGYMV:GYUSAPYMAFTIA CVEYMARRLPRAYGYMV:GYUSAPYMAFTIA CVEYMARRLPRAYGYMV:GYUG SPAYMCKLPTNYNEAKFITLSMTPYFSSVSL IVSCNNYKNSLLPNTSLDLLLSVUG SPAYMCKLPTNYNEAKFITLSMTPYFSSVSL IVSCNNYKNSLLPNTSLDLLLSVUG SPAYMCKLPTNYNEAKFITLSMTPYFSSVSL IVSCNNYKNSLLPNTSLDLLLSVUG SPAYMCKLPTNYNEAKFITLSMTPYFSSVSL IVSCNNYKNSLLPNTSLDLLLSVUG SPAYMCKLPTNYNEAKFITLSMTPYFSSVSL IVSCNNYKNSLLPNTSLDLLLSVUG SPAYMCKLPTNYNEAKFITLSMTPYFSSVSL IVSCNNYKNSLLPNTSLDLLLSVUG SPAYMCKLPTNYNEAKFITLSMTPYFSSVSL IVSCNNYKNSLLPNTSLDLLLSVUG SPAYMCKLPTNYNEAKFITLSMTPYFSSVSL ILSCNNYKNSLLPNTSLDLLLSVUG SPAYMCKLPTNYNEAKFITLSMTPYFSSVSL ILSCNNYKNSLLPNTSLDLLLSVUG SPAYMCKLPTNYNEAKFITLSMTPYFSSVSL ILSCNNYKNSLLPNTSLDLLLSVUG SPAYMCKLPTNYNEAKFITLSMTPYFSSVSL ILSCNNYKNSLLPNTSLDLLLSVUG SPAYMCKLPTNYNEAKFITLSMTPYFSSVSL ILSCNNYKNSLLPNTSLDLLLSVUG SPAYMCKLPTNYNEAKFITSMTPYFSSVSL ILSCNNYKNSLLPNTSLDLLLSVUG SPAYMCKLPTNYNEAKFITSMTPYFSSVSL ILSCNNYKNSLLPNTSLDLLLSVUG SPAYMCKLPTNYNEAKFITSMTPYFSSVSL ILSCNNYKNSLLPNTSLDLLSVUG SPAYMCKLPTNYNEAKFITSMTPYFSSVSL ILSCNNYKNSLLPNTSLDLLSVUG SPAYMCKLPTNYNEAKFITSMTPYFSSVSL ILSCNNYKNSLLPNTSLDLLSVUG SPAYMCKLPTNYNEAKFITSMTPYFSSVSL ILSCNNYKNSLLPNTSLDLLSVUG SPAYMCKLPTNYNEAKFITSMTPYFSSVSL ILSCNNYKNSLLPNTSLDLLSVUG SPAYMCKLPTNYNEAKFITSMTPYFSSVSL ILSCNNYKNSLLPNTSLDLLSVUG SPAYMCKLPTNYNEAKFITSMTPYFSSVSL ILSCNNYKNSLLPNTSNDLLSVUG SPAYMCKLPTNYNEAKFITSMTPYFSSVSL ILSCNNYKNSLLPNTSNDLLSVUG SPAYMCKLPTNYNEAKFITSMTPSTSSISL ILSCNNYKNSLPNSNSLUG SPAYMCKLPTNYNEAKFITSMTPSTSSISL	716           710           711           711           711           711           715           720           776           776           776           776           776           776           776           776           776           776           770           771           771           771           771           771           771           771           771           771           771           771           773           780           8336           836
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<pre>rhesus_monkey squirrel_monkey marmoset tamarin cow dog rat mouse human chimpanzee gorilla orangutan patas_monkey squirrel_monkey marmoset tamarin cow dog rat mouse human chimpanzee gorilla orangutan patas_monkey baboon rat mouse</pre>	CVEYMASREPRASY9WURYQQEYUSAFITULMVUTVUIGMLATCIAPTTEIDEDDEKIM CVEYMASREPRASY9WURYQQEYUSAFITULMVUTVUIGLLATCIAPTTEIDEDDEKIM CVEYMASREPRASY9WURYQQSYUSAFITALKVUTVUIGLLATCIAPTTEADTDDEKIM CVEYMASREPRASY9WURYQQSYUSAFITALKVUTVUIGLLATCIAPTTEADTDDEKIM CVEYMASREPRASY9WURYQQSYUSAFITALKVUTVUIGLLATCIAPTTEADTDDEKIM CVEYMARREDPRASY9WURYQQSYUSAFITALKVUTVUIGLLATCIAPTTEADTDDEKIM CVEYMARREDPRASY8WURYQQSYUSAFITALKVUTVUIGLLATCIAPTTEADTDDENIM CVEYMARREDPRASY8WURYUQSYUSAFITALKVUTVUGKULATTINPIGTDEDDENIM CVEYMARREDPRASY8WURYUQSYEVASFWULKVUIVAGNULATTINPIGTDEDDENIM CVEYMARREDPRASYSFWURYUQFSFAYMGKELTVNINEAKFITLSMTFYFTSSVSL IVSCNNYKNSLLENTSLDLLSVUGFSFAYMGKELTVNINEAKFITLSMTFYFTSSVSL IVSCNNYKNSLLENTSLDLLSVUGFSFAYMGKELTVNINEAKFITLSMTFYFTSSVSL IVSCNNYKNSLEPRTSLDLLSVUGFSFAYMGKELTVNINEAKFITLSMTFYFTSSVSL IVSCNNYKNSLEPRTSLDLLSVUGFSFAYMGKELTVNINEAKFITLSMTFYFTSSVSL IVSCNNYKNSLEPRTSLDLLSVUGFSFAYMGKELTVNINEAKFITLSMTFYFTSSVSL ILSCNNYKNSLEPRTSLDLLSVUGFSFAYMGKELTVNINEAKFITLSMTFYFTSSVSL ILSCNNYKNSLEPRTSLDLLSVUGFSFAYMGKELTVNINEAKFITLSMTFYFTSSVSL ILSCNNYKNSLEPRTSLDLLSVUGFSFAYMGKELTVNINEAKFITLSMTFYFTSSVSL ILSCNNYKNSLEPRTSLDLLSVUGFSFAYMGKELTVNINEAKFITLSMTFYFTSSVSL ILSCNNYKNSLEPRTSLDLLSVUGFSFAYMGKELTVNINEAKFITLSMTFYFTSSVSL ILSCNNYKNSLEPRTSLDLLSVUGFSFAYMGKELTVNINEAKFITLSMTFYFTSSVSL ILSCNNYKNSLEPRTSLDLLSVUGFSFAYMGKELTVNINEAKFITSSVSL ILSCNNYKNSLEPRTSLDLLSVUGFSFAYMGKELTVNINEAKFITLSMTFYFTSSVSL ILSCNNYKNSLEPRTSLDLLSVUGFSFAYMGKELTVNINEAKFITSSVSL ILSCNNYKNSLEPRTSNDLLSVUGFSFAYMGKELTVNINEAKFITLSMTFYFTSSVSL ILSCNNYKNSLEPRTSNDLLSVUGFSFAYMGKELTVNINEAKFITLSMTFYFTSSVSL ILSCNNYKNSLEPRTSNDLLSVUGFSFAYMGKELTVNINEAKFITLSMTFYFTSSVSL ILSCNNYKNSLEPRTSNDLLSVUGFSFAYMGKELTVNINEAKFITLSMTFYFTSSVSL ILSCNNYKNSLEPRTSNDLLSVUGFSFAYMGKELTVNINEAKFITLSMTFYFTSSVSL ILSCNNYKNGLEPTVSNDLLSVUGFSFAYMGKELTVNINEAKFITLSMTFYFTSSVSL ILSCNNYKNGLEPTVSNDLLSVUGFSFAYMGKELTVNINEAKFITLSMTFYFTSSVSL ILSCNNYKNGLEPTVSNDLLSVUGFSFAYMGKELTVNINEAKFITLSMTFYFTSVSUSU TTMSAYGQUVTIVLDLLVTVLILLAISLGYFGFKCVNILFYFERNTPAYFNSNIGGYTM CTFMSAYGQUVTIVLDLLVTVLILLAISLGYFGFKCVNILFYFERNTPAYFNSNIGGYTM	716 710 711 711 711 714 715 720 776 776 776 776 776 776 776 776 776 77
rhesus_monkey squirrel_monkey marmoset tamarin cow dog rat mouse human chimpanzee gorilla orangutan patas_monkey baboon rhesus_monkey squirrel_monkey marmoset tamarin cow dog rat mouse human chimpanzee gorilla orangutan patas_monkey baboon rhesus_monkey	CVEYMASR PPRASY9WINYQQ PYUSA PITYULMVUTVUIGHLATGLAPTTEIDEDDPKIM CVEYMASR PPRASY9WINYQQ PYUSA PITALKVYTVUIGLLATGLAPTTEIDEDDPKIM CVEYMASR PPRASY9WINYQQ SYUSA PITALKVYTVUIGLLATGLAPTTEIDEDDPKIM CVEYMASR PPRASY9WINYQQ SYUSA PITALKVYTVIGLLATGLAPTTEADTDDPKIM CVEYMASR PPRASY9WINYQQ SYUSA PITALKVYTVIGLATGLAPTTEADTDDDPKIM CVEYMASR PPRASY9WINYQQ SYUSA PITALKVYTVIGLATGLAPTTEADTDDDPKIM CVEYMASR PPRASY9WINYQQ SYUSA PITALKVYTVIGASVLATTINPTRVDEDDPKIM CVEYMASR PPRASY9WINYQQ SYUSA PITALKVYTVIGASVLATTINPTRVDEDDPKIM CVEYMASR PPRASY9WINYQU SYAYAS PYULKVYIVAGNULATTINPIGRTDEDDPNIM CVEYMASR PPRASY9WINYQU SYAYANG SYAYANG SANGALATINPIGRTDEDDPNIM CVEYMASR PPRASY9WINYQU SYAYAMG SANGALATINPIGRTDEDDPNIM CVEYMASR PRASY9WINYQU SYAYAMG SANGALATINPIGRTDEDDPNI TVSCNNYNNSLLPNTSLDLLLSVVGFSAYMG SKLPTNYNEAKFILSMTPYFYSSYSL IVSCNNYNNSLLPNTSLDLLLSVVGFSAYMG SKLPTNYNEAKFILSMTPYFYSSYSL IVSCNNYNNSLLPNTSLDLLLSVVGFSAYMG SKLPTNYNEAKFILSMTPYFYSSYSL IISCNNYNNSLLPNTSLDLLLSVVGFSAYMG SKLPTNYNEAKFILSMTPYFYSSYSL IISCNNYNNSLLPNTSLDLLLSVVGFSAYMG SKLPTNYNEAKFILSMTPYFYSSYSL IISCNNYNNSLLPNTSLDLLLSVVGFSAYMG SKLPTNYNEAKFITSMTPYFYSSYSL IISCNNYNNSLLPNTSLDLLLSVVGFSAYMG SKLPTNYNEAKFITSMTPYFYSSYSL IISCNNYNNSLLPNTSLDLLLSVVGFSAYMG SKLPTNYNEAKFITSMTPYFYSSYSL IISCNNYNNSLLPNTSLDLLLSVVGFSAYMG SKLPTNYNEAKFITSMTPYFYSSYSL IISCNNYNNSLLPNTSLDLLLSVVGFSAYMG SKLPTNYNEAKFITSMTPYFYSSYSL IISCNNYNNSLLPNTSLDLLSVVGFSAYMG SKLPTNYNEAKFITCMTPYFYSSYSL IISCNNYNNSLLPNTSLDLLSVVGFSAYMG SKLPTNYNEAKFITCMTPYFYSSYSL IISCNNYNNSLLPNTSLDLLSVVGFSAYMG SKLPTNYNEAKFITCMTPYFYSSYSL IISCNNYNNSLLPNTSMDLLLSVGFSAYMG SKLPTNYNEAKFITCMTPYFYSSYSL IISCNNYNNSLLPNTSMDLLLSVGFSAYMG SKLPTNYNEAKFITCMTPYFYSSYSL IISCNNYNNSLLPNTSMDLLLSVGFSAYMG SKLPTNYNEAKFITCMTPYFYSSYSL IISCNNYNNSLLPNTSMDLLLSVGFSAYMG SKLPTNYNEAKFITCMTPYFYSSYSL IISCNNYNNSLLPNTSMDLLLSVGFSAYMG SKLPTNYNEAKFITLSMTPSTSSISL IISCNNYNNSLPNTSMDLLLSVGFSAYMG SKLPTNYNEAKFITLSMTPSTSSISL IISCNNYNNSLPNTSMDLLLSVGFSAYMG SKLPTNYNEAKFITLSMTPSTSNIGGTM CTFMSAYGGVUTVIULLVTVILLLAISLGYFGPKCYMLLFYPERNTPAYNSMIGGTM CTFMSAYNGVUTVINDLUVTVILLLAISLGYFGPKCYMLFYPERNTPAYNSMIGGTM CTFMSAYNGVUTVINDLUVTVILL	716           710           711           711           711           711           711           711           711           711           711           711           714           715           720           776           776           776           7770           771           774           7780           836
rhesus_monkey squirre1_monkey marmoset tamarin cow dog rat mouse human chimpanzee gorilla orangutan patas_monkey squirre1_monkey marmoset tamarin cow dog rat mouse human chimpanzee gorilla orangutan patas_monkey squirre1_monkey	CVPENASERPEASYSWURYQQEYUSAFITULIMUTVUIGHLATGLAPTTEIDEDDPKIM CVFENASERPEASYSWURYQQSYUSAFITULIMUTVUIGHLATGLAPTTEIDEDDPKIM CVFENASERPEASYSWURYQQSYUSAFITULIMUTVUIGLLATGLAPTTEADTDDPKIM CVFENASERPEASYSWURYQQSYUSAFITULIMUTVUIGLLATGLAPTTEADTDDPKIM CVFENASERPEASYSWURYQQSYUSAFITULIMUTVUIGLLATGLAPTTEADTDDPKIM CVFENASERPEASYSWURYQQSYUSAFITULIMUTVUIGLLATGLAPTTEADTDDPKIM CVFENASERPEASYSWURYQQSYUSAFITULIMUTVUIGLLATGLAPTTEADTDDPKIM CVFENASERPEASYSWURYQQSYUSAFITULIMUTVUIGLATGLAPTTEADTDDPKIM CVFENARELPEASYSWURYQQSYUSAFITULIMUTVURSULATTINFIGHTDPDPHIM CVFENARELPEASYSWURYQQSYUSAFITULIMUTVURSULATTINFIGHTDPDPHIM CVFENARELPEASYSWURYQQSYUSAFITAI:VALVUGMLATTINFIGHTDPDPHIM CVFENARELPEASYSWURYQQSYMUGFEAYMGKELPTNYNEAKFITLSMTFYFSSVSL IVSCNNYKNSLLPNTSLDLLSVUGFEAYMGKELPTNYNEAKFITLSMTFYFTSSVSL IVSCNNYKNSLLPNTSLDLLSVUGFEAYMGKELPTNYNEAKFITLSMTFYFTSSVSL IVSCNNYKNSLPHTSLDLLLSVUGFEAYMGKELPTNYNEAKFITLSMTFYFTSSVSL IISCNNYKNSLPHTSLDLLLSVUGFEAYMGKELPTNYNEAKFITLSMTFYFTSSVSL IISCNNYKNSLPHTSLDLLLSVUGFEAYMGKELPTNYNEAKFITLSMTFYFTSSVSL IISCNNYKNSLPHTSLDLLLSVUGFEAYMGKELPTNYNEAKFITLSMTFYFTSSVSL IISCNNYKNSLLPNTSLDLLLSVUGFEAYMGKELPTNYNEAKFITLSMTFYFTSSVSL IISCNNYKNSLLPNTSLDLLLSVUGFEAYMGKELPTNYNEAKFITSMTFYFTSSVSL IISCNNYKNSLLPNTSLDLLLSVUGFEAYMGKELPTNYNEAKFITSMTFYFTSSVSL IISCNNYKNSLLPNTSLDLLLSVUGFEAYMGKELPTNYNEAKFITSMTFYFTSSVSL IISCNNYKNSLLPNTSLDLLLSVUGFEAYMGKELPTNYNEAKFITSMTFYFTSSVSL IISCNNYKNSLLPNTSLDLLLSVUGFEAYMGKELPTNYNEAKFITSMTFYFTSSVSL IISCNNYKNGLLPNTSLDLLLSVUGFEAYMGKELPTNYNEAKFITSMTFYFTSSVSL IISCNNYKNGLPNTSLDLLLSVUGFEAYMGKELPTNYNEAKFITSMTFYFTSSVSL IISCNNYKNGLPNTSLDLLLSVUGFEAYMGKELPTNYNEAKFITSMTFYFTSSVSL IISCNNYKNGLPNTSLDLLLSVUGFEAYMGKELPTNYNEAKFITSMTFYFTSSVSL IISCNNYKNGLPNTSMDLLLSVUGFEAYMGKELPTNYNEAKFITSMTFYFTSSVSL IISCNNYKNGLPNTSMDLLLSVUGFEAYMGKELPTNYNEAKFITSMTFYFTSSVSL IISCNNYKNGLPNTSMDLLLSVUGFEAYMGKELPTNYNEAKFITSMTFYFTSSVSL IISCNNYKNGLPNTSMDLLLSVUGFEAYMGKELPTNYNEAKFITSMTFYFTSSVSL IISCNNYKNGLPNTVMLLATALAISLGYFORVCVILFYPERNTPAYNSNIQQTM CTFMSAYGGVUVTIVLNLLAISLGYFORVCVILFYPERNTPAYNSNIQQTM CTFMSAYGGVUVTIVLNLLAISLGYFORVCVILFYPERNTPAYNSNIQQTM CTFMSAYMGUVUTNGLLYU	716 711 711 711 714 715 720 776 776 776 776 776 776 776 776 777 771 771
<pre>rhesus_monkey squirrel_monkey marmoset tamarin cow dog rat mouse human chimpanzee gorilla orangutan patas_monkey babcon rhesus_monkey squirrel_monkey marmoset tamarin cow dog rat mouse human chimpanzee gorilla orangutan patas_monkey babcon rat mouse</pre>	CVEYMASR PPRASYSWURYQQ PYUSA PITYULMVUTVUIGMLATCIAPTTEIDPDDPKIM CVEYMASR PPRASYSWURYQQ SYUSA PITALKVYTVUIGLLATCIAPTTEIDPDDPKIM CVEYMASR PPRASYSWURYQQ SYUSA PITALKVYTVUIGLLATCIAPTTEIDPDDPKIM CVEYMASR PPRASYSWURYQQ SYUSA PITALKVYTVUIGLLATCIAPTTEIDPDDPKIM CVEYMASR PPRASYSWURYQQ SYUSA PITALKVYTVUIGLLATCIAPTTEIDPDDPKIM CVEYMARRLPRAYCHRYTVA PITALKVIVUIGKULATINPIGTDDDDPNIN CIFMARRLPRAYCHWRYHOPYUYA PITALKVIVUIGKULATINPIGTDDDDPNIN CVEYMARRLPRAYCHWRYHOPYUYA PITAKVALVAGMLATINPIGTDDDDPNIN CVEYMARRLPRAYSHWRYUG YUYA PITAKVALVAGMLATINPIGTDDDDPNIN CVEYMARRLPRAYSHWRYUG YUYA PITAKVALVAGMLATINPIGTDDDDPNIN CVEYMARRLPRAYSHWRYUG YUYA PITAKVALVAGMLATINPIGTDDDDPNIN CVEYMARRLPRAYSHWRYUG YUYA PITAKVALVAGMLATINPIGTDDDDPNIN CVEYMARRLPRAYSHUD YUYA PITAKVALVAGMLATINPIGTDDDDPNIN CVEYMARRLPRAYSHWRYUG YUYA PITAKVALVAGMLATINPIGTDDDDPNIN CVEYMARRLPRAYSHUD YUYA PITAKVALVAGMLATINPIGTDDDDPNIN USCNNNYNSLLPNTSLLLLSVUG PSAYMGKELPTNNEAKFILSM PYFYSSVSL IVSCNNYNNSLLPNTSLLLLSVUG PSAYMGKELPTNNEAKFILSM PYFYSSVSL IVSCNNYNNSLLPNTSLLLLSVUG PSAYMGKELPTNNEAKFILSM PYFYSSVSL I SCNNYNNSLLPNTSLLLLSVUG PSAYMGKELPTNNEAKFILSM PYFYSSVSL I SCNNYNNSLLPNTSLLLLSVUG PSAYMGKELPTNNEAKFILSM PYFYSSVSL I SCNNYNNSLLPNTSLLLLSVUG PSAYMGKELPTNNEAKFILSM PYFYSSVSL I SCNNYNNSLLPNTSLLLLSVUG PSAYMGKELPTNNEAKFITSM PYFYSSVSL I SCNNYNNSLLPNTSLLLLSVUG PSAYMGKELPTNNEAKFITSM PYFYSSVSL I SCNNYNNSLLPNTSLLLLSVUG PSAYMGKELPTNNEAKFITSM PYFYSSVSL I SCNNYNNSLLPNTSLLLLSVUG PSAYMGKELPTNNEAKFITSM PYFYSSVSL I SCNNYNNSLLPNTSLLLSVUG PSAYMGKELPTNNEAKFITSM PYFYSSVSL I SCNNYNNSLLPNTSLLLSVUG PSAYMGKELPTNNEAKFITSM PYFYSSVSL I SCNNYNNSLLPNTSLLLSVUG PSAYMGKELPTNNEAKFITSM PYFYSVSSISL I SCNNYNNSLLPNTSDLLLSVUG PSAYMGKELPTNYNEAKFITSM PYFYSVSVSL I SCNNYNNSLLPNTSMDLLLSVUG PSAYMGKELPTNYNEAKFITSM PYFYSVSUG CTMSAYGGUVTI VDLLVTVILLLAISLGYFOPKCMILFYPERNTPAYNSNIQGTM CTMSAYMGUVTI NDLLVTVILLLAISLGYFOPKCMILFYPERNTPAYNSNIQGTM CTMSAYMGUVUTINDLLVTVILLLAISLGYFOPKCMILFYPERNTPAYNSNIQGTM CTMSAYMGUVUTINDLLVTVILILLAISLGYFOPKCMILFYPERNTPAYNSNIQGTM CTMSAYMGUVUTINDLLVTVINLLAISLGYFOPKCMILFYPERNTPAYNSNIQGTM CTMSAYMGUVUTINDLVTVINLLAISLGYFOPKCM	716 710 711 711 711 714 715 720 720 720 770 770 770 777 776 776 776 776 7770 7771 7773 780 836 836 836 836 836 836 836 836 836 836
<pre>rhesus_monkey squirrel_monkey marmoset tamarin cow dog rat human chimpanzee gorilla orangutan patas_monkey baboon rhesus_monkey squirrel_monkey marmoset tamarin cow dog rat mouse human chimpanzee gorilla orangutan patas_monkey baboon rhesus_monkey squirrel_monkey marmoset tamarin cow cow</pre>	CVEYMASREPRAYSYWURYQG YUSAFITULMYUTVUIGHLATGLAPTTEIDEDDEKIM CVEYMASREPRAYSYWURYQG YUSAFITULMYUTVUIGHLATGLAPTTEIDEDDEKIM CVEYMASREPRAYSYWURYQG YUSAFITULMYUTVUIGHLATGLAPTTERDEDDEKIM CVEYMASREPRAYSYWURYQG YUSAFITULMYUTVUIGHLATGLAPTTERDEDDEKIM CVEYMASREPRAYSYWURYQG YUSAFITULMYUTVUIGHLATGLAPTTERDEDDEKIM CVEYMASREPRAYSYWURYQG YUSAFITULMYUTVUIGHLATGLAPTTERDEDDENIM CVEYMASREPRAYSYWURYQG YUSAFITULMYUTVUIGHLATGLAPTTERDEDDENIM CVEYMASREPRAYSYWURYQG YUSAFITULMYUTVUSKULATGAPTREDEDDENIM CVEYMASREPRAYSYWURYQG YUSAFITULMYUNYARITTINPIGREDDEDDINI CVEYMASREPRAYSYWURYQG YUSAFITUNYARITUNYARITTINPIGREDEDDENIM CVEYMASREPRAYSYWURYQG YUSAFITUNYARITUNYARITUNPIGREDEDDENIM CVEYMASREPRAYSYWURYGPYYYAFITUNYARITUNYARITUNPIGREDEDDENIM CVEYMASREPRAYSYWURYGPYYYAFITUNYARITUNYARITUNPIGREDEDDENIM CVEYMASREPRAYSYWURYGPYYYAFITUNYARITUNYARITUNYARITUNYARI IVSCNINYKINSLEPINSLDLLLSYUGFSPAYMGKELFINYNBARITILMYFYFTSSVSL IVSCNINYKINSLEPINSLDLLLSYUGFSPAYMGKELFINYNBARITILMYFYFTSSVSL IVSCNINYKINSLEPINSLDLLLSYUGFSPAYMGKELFINYNBARITILMYFYFTSSVSL IVSCNINYKINSLEPINSLDLLLSYUGFSPAYMGKELFINYNBARITILMYFYFTSSVSL IISCNINYKINSLEPINSLDLLLSYUGFSPAYMGKELFINYNBARITILMYFYFTSSVSL IISCNINYKINSLEPINSLDLLLSYUGFSPAYMGKELFINYNBARITILMYFYFTSSVSL IISCNINYKINSLEPINSLDLLLSYUGFSPAYMGKELFINYNBARITILMYFYFTSSVSL IISCNINYKINSLEPINSLDLLLSYUGFSPAYMGKELFINYNBARITILMYFYFTSSVSL IISCNINYKINSLEPINSLLLSYUGFSPAYMGKELFINYNBARITILMYFYFTSSVSL IISCNINYKINSLEPINSLLLSYUGFSPAYMGKELFINYNBARITISMYFYFTSSVSL IISCNINYKINGLLFNYSDLLLSYUGFSPAYMGKELFINYNBARITISMYFYFTSSVSL IISCNINYKINGLLFNYSDLLLSYUGFSPAYMGKELFINNBARITISMYFYFTSSVSL IISCNINYKINGLLFNYSMDLLLSYUGFSPAYMGKELFINNBARITISMYFYFTSSVSL IISCNINYKINGLLFNYSMDLLLSYUGFSPAYMGKELFINNBARITISMYFYFTSSVSL IISCNINYKINGULFUNYNLLLASLGYFGPRCYNLFYFBNIGGYTM CTHMSAYGGUVITUDLLVTUNLLAISLGYFGPRCYNLFYFBNIGYTYNSNIGGYTM CTHMSAYGGUVITUDLLVTUNLLAISLGYFGPRCYNLFYFBRINSAFNNSNIGGYTM CTHMSAYNGUVUTUNDLLVTUNLLAISLGYFGPRCYNLFYFBRINSAFNNSNIGGYTM CTHMSAYNGUVUTUNDLLVTUNLLAISLGYFGPRCYNLFYFBRNTAAYNNSNIGGYTM CTHMSAYNGUVUTUNDLLVTUNLLAISLGYFGPRCYNLFYFBRNTAAYNNSNIGGYTM CTHMSAYNGUVUTUNDLLVTUNLLAISLGYFGPRCY	716 710 711 711 714 715 720 720 720 720 720 720 720 720 720 720
rhesus_monkey squirrel_monkey marmoset tamarin cow dog rat mouse human chimpanzee gorilla orangutan patas_monkey babcon rhesus_monkey squirrel_monkey marmoset tamarin cow dog rat mouse human chimpanzee gorilla orangutan patas_monkey squirrel_monkey marmoset tamarin cow dog rat mouse	CVPENASERPEASYSWURYQGPYUSARTIYULMUTVUIGHLATGLAPTTEIDPDDPKIM CVFWASERPEASYSWURYQGSYUSARTIALKWYTVUIGLLATGLAPTTEIDDDPKIM CVFWASERPEASYSWURYQGSYUSARTIALKWYTVUIGLLATGLAPTTEADTDDPKIM CVFWASERPEASYSWURYQGSYUSARTIALKWYTVUIGLLATGLAPTTEADTDDPKIM CVFWASERPEASYSWURYQGSYUSARTIALKWYTVUIGLLATGLAPTTEADTDDPKIM CVFWASERLPEASYSWURYQGSYUSARTIALKWYTVUGLLATGLAPTTEADTDDPKIM CVFWASERLPEASYSWURYQGSYUSASFULKUVIVAGNULATTINPIGETDDDDPIN CVFWASERLPEASYSWURYQGSYUSASFULKUVIVAGNULATTINPIGETDDDDPIN CVFWASERLPEASYSWURYQGSYUSASFULKUVIVAGNULATTINPIGETDDDDPIN CVFWASERLPEASYSWURYQGSYUSASFULKUVIVAGNULATTINPIGETDDDDPIN CVFWASERLPEASYSWURYQGSYUSASFULKUVIVAGNULATTINPIGETDDDDPIN CVFWASERLPEASYSWURYQGSYUSASFULKUVIVAGNULATTINPIGETDDDDPIN CVFWASERLPEASYSWURYQGSYANGELPTNNEAKFITLSMFYFYSSVSL IVSCNNYKNSLLPNTSLDLLSVUGFSFAYMGKELPTNNEAKFITLSMFYFYSSVSL IVSCNNYKNSLPNTSLDLLSVUGFSFAYMGKELPTNNEAKFITLSMFYFYSSVSL IVSCNNYKNSLPNTSLDLLSVUGFSFAYMGKELPTNNEAKFITLSMFYFYSSVSL IISCNNYKNSLPNTSLDLLLSVUGFSFAYMGKELPTNNEAKFITLSMFYFYSSVSL IISCNNYKNSLPNTSLDLLLSVUGFSFAYMGKELPTNNEAKFITLSMFYFYSSVSL IISCNNYKNSLPNTSLDLLLSVUGFSFAYMGKELPTNNEAKFITSMFYFYSSVSL IISCNNYKNSLPNTSLDLLLSVUGFSFAYMGKELPTNNEAKFITSMFYFYSSVSL IISCNNYKNSLPNTSLDLLLSVUGFSFAYMGKELPTNNEAKFITSMFYFYSSVSL IISCNNYKNSLPNTSLDLLLSVUGFSFAYMGKELPTNNEAKFITSMFYFYSSVSL IISCNNYKNGLPNTSLDLLLSVUGFSFAYMGKELPTNNEAKFITSMFYFYSSVSL IISCNNYKNGLPNTSLDLLLSVUGFSFAYMGKELPTNNEAKFITSMFYFYSSVSL IISCNNYKNGLPNTSLDLLLSVUGFSFAYMGKELPTNNEAKFITSMFYFYSSVSL IISCNNYKNGLPNTSLDLLLSVUGFSFAYMGKELPTNNEAKFITSMTYFYSSVSL IISCNNYKNGLPNTSLDLLLSVUGFSFAYMGKELPTNNEAKFITSMFYFYSSVSL IISCNNYKNGLPNTSDDLLLSVUGFSFAYMGKELPTNNEAKFITSMTYFYSSVSL IISCNNYKNGLPNTSDDLLLSVUGFSFAYMGKELPTNNEAKFITSMTYFYSSVSL IISCNNYKNGLPNTSMDLLLSVIGFSFAYMGKELPTNNEAKFITSMFYFYSNSUG CTFMSAYGGUVTIVULLLAISLGYFGPKCYMLFYPERNTSAYNSMIQGYM CTFMSAYGGUVTIVULKLAISLGYFGPKCYMLFYPERNTSAYNSMIQGYM CTFMSAYGGUVTIVULKULAISLGYFGPKCYMLFYPERNTPAYNSMIQGYM CTFMSAYGGUVTIVULKULAISLGYFGPKCYMLFYPERNTPAYNSMIQGYM CTFMSAYGGUVTIVULKUVTULLAISLGYFGPKCYMLFYPERNTPAYNSMIQGYM CTFMSAYGGUVTIVULLAVYNKLAXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX	716 710 711 711 714 715 720 720 720 776 770 770 770 7776 7776 7
<pre>rhesus_monkey squirrel_monkey marmoset tamarin cow dog rat mouse human chimpanzee gorilla orangutan patas_monkey babcon rhesus_monkey squirrel_monkey marmoset tamarin cow dog rat mouse human chimpanzee gorilla orangutan patas_monkey babcon rat mouse human chimpanzee gorilla orangutan patas_monkey babcon rhesus_monkey squirrel_monkey marmoset tamarin cow dog ratamonkey squirrel_monkey marmoset tamarin cow dog</pre>	CVPENASERPEASYSWURYQQEYUSAFITULGMUTVUIGMLATCIAPTTEIDDDPKIM CVFENASERPEASYSWURYQQEYUSAFITULGWUTVUIGLLATCIAPTTEIDDDPKIM CVFENASERPEASYSWURYQQSYUSAFITALKUVTVUIGLLATCIAPTTEIDDDPKIM CVFENASERPEASYSWURYQQSYUSAFITALKUVTVUIGLATCIAPTTEADTDDPKIM CVFENASERPEASYSWURYQQSYUSAFITALKUVTVUIGLATCIAPTTEADTDDPKIM CVFENASERPEASYSWURYQQSYUSAFITALKUVTVUIGLATCIAPTTEADTDDPKIM CVFENASERPEASYSWURYQQSYUSAFITALKUVTVUIGLATCIAPTTEADTDDPKIM CVFENARELPEASYSWURYQQSYUSAFITALKUVUNGKULATTINPIGTDDDPNIN CVFENARELPEASYSWURYQQSYUSAFITALKUVUNGKULATTINPIGTDDDPNIN CVFENARELPEASYSWURYQQSYUSAFITALKUVUNGKULATTINPIGTDDDPNIN CVFENARELPEASYSWURYQQSYNASENUKLAVINGAKULATTINPIGTDDDPNIN CVFENARELPEASYSWURYQQSYNASENUKLAVINGAKULATINPIGTDDDPNIN CVFENARELPEASYSWURYQVGSFAYMGKELPTNYNEAKFITLSMTFYFSSVSL IVSCNPNYENSLEPTSLDLLSVUGSFAYMGKELPTNYNEAKFITLSMTFYFSSVSL IVSCNPNYENSLEPTSLDLLSVUGSFAYMGKELPTNYNEAKFITLSMTFYFSSVSL IVSCNPNYENSLEPTSLDLLSVUGSFAYMGKELPTNYNEAKFITLSMTFYFSSVSL IVSCNPNYENSLEPTSLDLLSVUGSFAYMGKELPTNYNEAKFITLSMTFYFSSVSL ILSCNPNYENSLEPTSLDLLSVUGSFAYMGKELPTNYNEAKFITLSMTFYFSSVSL ILSCNPNYENSLEPTSLDLLSVUGSFAYMGKELPTNYNEAKFITLSMTFYFSSVSL ILSCNPNYENSLEPTSLDLLSVUGSFAYMGKELPTNYNEAKFITLSMTFYFSSVSL ILSCNPNYENSLEPTSLDLLSVUGSFAYMGKELPTNYNEAKFITSSTFYFYSSVSL ILSCNPNYENSLEPTSDLLLSVUGSFAYMGKELPTNYNEAKFITSSVSL ILSCNPNYENSLEPTSDDLLLSVUGSFAYMGKELPTNYNEAKFITSSVSL ILSCNPNYENSLEPTSDLLLSVUGSFAYMGKELPTNYNEAKFITSSVSL ILSCNPNYENSLEPTSDLLLSVUGSFAYMGKELPTNYNEAKFITSSVSL ILSCNPNYENSLEPTSNDLLLSVUGSFAYMGKELPTNYNEAKFITSSVSL ILSCNPNYENGLEPTSMDLLLSVUGSFAYMGKELPTNYNEAKFITSSVSL ILSCNPNYENGLEPTSMDLLLSVUGSFAYMGKELPTNYNEAKFITSSVSL ILSCNPNYENGLEPTSMDLLLSVUGSFAYMGKELPTNYNEAKFITSSVSL ILSCNPNYENGLEPTSMDLLLSVUGSFAYMGKELPTNYNEAKFITSSVSL ILSCNPNYENGLEPTSMDLLLSVUGSFAYMGKELPTNYNEAKFITSSVSL ILSCNPNYENGLEPTSMDLLSVUGSFAYMGKELPTNYNEAKFITSSVSL ICSCNPNYENGLEPTSMDLLSVUGSFAYMGKELPTNYNEAKFITSSVSL ILSCNPNYENGLEPTSMDLLSVUGSFAYMGKELPTNYNEAKFITSSVFNSNIQGYTM CTFMSAYNGVUVTIVDLLVTVLALLAISLGYFGPECYNLFYPERNTPAYFNSNIQGYTM CTFMSAYNGVUVTIVDLLVTVLALLAISLGYFGPECYNLFYPERNTPAYFNSNIQGYTM CTFMSAYNGVUVTIVDLVTVLALLAISLGYFGPECYNLFYPERNTPAYFNSNI	716 710 711 714 715 720 720 776 776 776 776 776 776 7776 77
<pre>rhesus_monkey squirrel_monkey marmoset tamarin cow dog rat mouse human chimpanzee gorilla orangutan patas_monkey baboon rhesus_monkey squirrel_monkey marmoset tamarin cow dog rat mouse human chimpanzee gorilla orangutan patas_monkey baboon rhesus_monkey squirrel_monkey marmoset tamarin cow dog rat mouse</pre>	CVPENASERPEASYSWURYQGPYCBAPITYLEMYTWIGHLATGLAPTTEIDPDDPKIM CVFENASERPEASYSWURYQGSYGAPITALKWYTWIGLLATGLAPTTEIDDDPKIM CVFENASERPEASYSWURYQGSYGAPITALKWYTWIGLLATGLAPTTERDTDDPKIM CVFENASERPEASYSWURYQGSYGAPITALKWYTWIGLLATGLAPTTERDTDDPKIM CVFENASERPEASYSWURYQGSYGAPITALKWYTWIGLLATGLAPTTERDTDDPKIM CVFENASERPEASYSWURYQGSYGAPITALKWATUNASLATINPTERDTDDPKIM CVFENASERPEASYSWURYQGSYGAPITALKWATUNASKILATGLAPTTERDTDDPKIM CVFENASERPEASYSWURYQGSYGAPITALKWALVUGNELATTINPIGETDDPDPHIM CVFENASERPEASYSWURYGPYCFAFITALKWALVUGNELATTINPIGETDPDDPNIM CVFENASERPEASYSWURYGPYCFAFITALKWALVUGNELATTINPIGETDPDDPNIM CVFENASERPEASYSWURYGPYCFAFITALKVALVAGNELATTINPIGETDPDDPNIM CVFENASERPEASYSWURYGPYCFAFITALKVALVAGNELATTINPIGETDPDDPNIM CVFENASELPEASYSWURYGPYCFAFITALKVALVAGNELATTINPIGETDPDDPNIM CVFENASELPEASYSWURYGPYCFAFITALKVALVAGNELATTINPIGETDPDDPNIM CVFENASELPENSIDLLLSVUGFSPAYMGKELPTNYNEAKFITLSMTFYFTSSVSL IVSCNNYKINSLEPNTSLDLLLSVUGFSPAYMGKELPTNYNEAKFITLSMTFYFTSSVSL IVSCNNYKINSLEPNTSLDLLLSVUGFSPAYMGKELPTNYNEAKFITLSMTFYFTSSVSL IVSCNNYKINSLEPNTSLDLLLSVUGFSPAYMGKELPTNYNEAKFITLSMTFYFTSSVSL IVSCNNYKINSLEPNTSLDLLLSVUGFSPAYMGKELPTNYNEAKFITLSMTFYFTSSVSL IISCNNYKINSLEPNTSLDLLLSVUGFSPAYMGKELPTNYNEAKFITLSMTFYFTSSVSL IISCNNYKINSLEPNTSLDLLLSVUGFSPAYMGKELPTNYNEAKFITLSMTFYFTSSVSL IISCNNYKINSLEPNTSLDLLLSVUGFSPAYMGKELPTNYNEAKFITSS SVEL USCN-NYKINSLEPNTSLDLLLSVUGFSPAYMGKELPTNYNEAKFITSS IISCNNYKINSLEPNTSLDLLLSVUGFSPAYMGKELPTNYNEAKFITSSMTFYFTSSVSL IISCNNYKINGLEPNTSMDLLLSVLGFSPAYMGKELPTNYNEAKFITSSMTFYFTSSVSL IISCNNYKINGLEPNTSMDLLLSVLGFSPAYMGKELPTNYNEAKFITSSMTFYFTSSVSL IISCNNYKINGLEPNTSMDLLLSVLGFSPAYMGKELPTNYNEAKFITSMTFYFTSSISI IISCNNYKINGLEPNTSMDLLLSVLGFSPAYMGKELPTNYNEAKFITLSMTFSFTSSISI IISCNNYKINGLUPYTSMDLLLSVLGFSPAYMGKELPTNYNEAKFITLSMTFSFTSSISI IISCNNYKINGUCYTVULLLAISLGYFGPKCMILFYPBRNTPAYNNSUGGYTM CTFMSAYGGUVTIVDLLVTVLILLAISLGYFGPKCMILFYPBRNTPAYNNSUGGYTM CTFMSAYDGUVTIVDLUVTVLILLAISLGYFGPKCMILFYPBRNTPAYNNSUGGYTM CTFMSAYDGUVTIVDLUVTVLILLAISLGYFGPKCMILFYPBRNTPAYNSNIGGYTM CTFMSAYDGUVTIVDLUVTVLILLAISLGYFGPKCMULFYPBRNTPAYNSNIGGYTM CTFMSAYDGUVTIVDLUVTVLILLAISLGYFGPKCMULFYPBRNTPAY	$\begin{array}{c} \frac{716}{710} \\ 711 \\ 711 \\ 714 \\ 715 \\ 720 \\ 720 \\ 776 \\ 777 \\ 777 \\ 777 \\ 777 \\ 777 \\ 777 \\ 777 \\ 770 \\ 771 \\ 774 \\ 836 \\ 836 \\ 836 \\ 836 \\ 836 \\ 836 \\ 836 \\ 836 \\ 836 \\ 836 \\ 836 \\ 831 \\ 831 \\ 831 \\ 831 \\ 831 \\ 831 \\ 831 \\ 833 \\ 834 \\ 833 \\ 840$
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rhesus_monkey squirrel_monkey marmoset tamarin cow dog rat mouse human chimpanzee gorilla orangutan patas_monkey baboon rhesus_monkey squirrel_monkey marmoset tamarin cow dog rat mouse human chimpanzee gorilla orangutan patas_monkey baboon rhesus_monkey squirrel_monkey marmoset tamarin cow dog rat mouse	CVPENASERPEASYSWURYQGPYCBAPITYLEMYTVUIGHLATGLAPTTEIDPDPKIM CVFENASERPEASYSWURYQGSYGAPITALKWYTVUIGLLATGLAPTTEIDDDPKIM CVFENASERPEASYSWURYQGSYGAPITALKWYTVUIGLLATGLAPTTEADTDDPKIM CVFENASERPEASYSWURYQGSYGAPITALKWYTVUIGLLATGLAPTTEADTDDPKIM CVFENASERPEASYSWURYQGSYGAPITALKWYTVUIGLLATGLAPTTEADTDDPKIM CVFENASERPEASYSWURYQGSYGAPITALKWATVUGHLATTINFIGTDDDDPKIM CVFENASERPEASYSWURYQGSYGAPITALKWATVUGHLATTINFIGTDDDDPKIM CVFENASELPEASYSWURYQGSYGAPITALKWALVUGHLATTINFIGTDDDDPKIM CVFENASELPEASYSWURYQGSYGAPITALKWALVUGHLATTINFIGTDDDDPKIM CVFENASELPEASYSWURYGGSYGAPITALKWALVGGMLATTINFIGTDDDDPKIM CVFENASELPEASYSWURYGGSYGAPITALKWALVGGMLATTINFIGTDDDDPKIM CVFENASELPEASYSWURYGGSYGAPITALKWALVGGMLATTINFIGTDDDDPKIM CVFENASELPEASYSWURYGGSYGAPITALKWALVGGMLATTINFIGTDDDPKIM CVFENASELPEASYSWURYGGSYGAPITALKWALVGGMLATTINFIGTDPDDPKIM CVFENASELPEASYSWURYGGSYGAPITALKWALVGGMLATTINFIGTDDDPKIM CVFENASELPEASYSWURYGGSYGAPITALKWALVGGMLATTINFIGTDDDPKIM CVFENASELPEASYSWURYGGSYGAPITALKWALVGGGFAYMGKELPTNYNEAKFILSMTFYFTSSVSL IVSCNNYKNSLPHYTSLDLLLSVUGFSFAYMGKELPTNYNEAKFILSMTFYFTSSVSL IVSCNNYKNSLPHYTSLDLLLSVUGFSFAYMGKELPTNYNEAKFILSMTFYFTSSVSL IISCNNYKNSLPHYTSLDLLLSVUGFSFAYMGKELPTNYNEAKFITSMTFYFTSSVSL IISCNNYKNSLPHYTSLDLLLSVUGFSFAYMGKELPTNYNEAKFITSMTFYFTSSVSL IISCNNYKNSLPHYTSLDLLLSVUGFSFAYMGKELPTNYNEAKFITSMTFYFTSSVSL IISCNNYKNSLPHYTSLDLLLSVUGFSFAYMGKELPTNYNEAKFITSMTFYFTSSVSL IISCNNYKNSLPHYTSLDLLLSVUGFSFAYMGKELPTNYNEAKFITSMTFYFTSSVSL IISCNNYKNSLPHYTSLDLLLSVUGFSFAYMGKELPTNYNEAKFITSMTFYFTSSVSL IISCNNYKNSLPHYTSNDLLLSVUGFSFAYMGKELPTNYNEAKFITSMTFYFTSSVSL IISCNNYKNSLPHYTSNDLLLSVUGFSFAYMGKELPTNYNEAKFITSMTFYFTSSVSL IISCNNYKNGUPTYNSMCLLLSVUGFSFAYMGKELPTNYNEAKFITSMTFYFTSSVSL IISCNNYKNGUPTYNSMCLLLSVUGFSFAYGKELPTNYNEAKFITSMTFYFTSSVSL IISCNNYKNGUPTYNSMCLLFYFBNTFAYFYFTSSVSL IISCNNYKNGUPTYNGUPTYNSMGUPTM CTFMSAYSGVUVTIVDLUVTVLALLAISLGYFGFCCYMLFYPBNTPAYFNSNIQGYTM CTFMSAYSGVUVTIVDLUVTVLALLAISLGYFGFCCYMLFYPBNTPAYFNSNIQGYTM CTFMSAYGGUVTIVDLUVTVLALLAISLGYFGFCCYMLFYPBNTPAYFNSNIQGYTM CTFMSAYGGUVTIVDLUVTVLALLAISLGYFGFCCYMLFYPBNTPAYFNSNIQGYTM CTFMSAYGGUVTIVDLUVTVLALLAISLGYFGFCCYMLFYPBNTPAYFN	$\begin{array}{c} 716\\ 710\\ 711\\ 714\\ 720\\ 720\\ 776\\ 776\\ 776\\ 776\\ 777\\ 777\\ 777\\ 77$
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<pre>rhesus_monkey squirrel_monkey marmoset tamarin cow dog rat mouse human chimpanzee gorilla orangutan patas_monkey babcon rhesus_monkey squirrel_monkey marmoset tamarin cow dog rat mouse human chimpanzee gorilla orangutan patas_monkey babcon rhesus_monkey squirrel_monkey squirrel_monkey squirrel_monkey squirrel_monkey squirrel_monkey squirrel_monkey squirrel_monkey squirrel_monkey squirrel_monkey marmoset tamarin cow dog rat</pre>	CVPENASERPEASYSWURYQGPYUSAFITULMUTVUIGHLATGLAPTTEIDDDPKIM CVFMASERPEASYSWURYQGSYUSAFITALKUVTVUIGLLATGLAPTTEIDDDPKIM CVFMASERPEASYSWURYQGSYUSAFITALKUVTVUIGLATGLAPTTEADTDDPKIM CVFMASERPEASYSWURYQGSYUSAFITALKUVTVUIGLATGLAPTTEADTDDPKIM CVFMASELPEASYSWURYQGSYUSAFITALKUVTVUIGLATGLAPTTEADTDDPKIM CVFMASELPEASYSWURYQGSYUSAFITALKUVTVUGAULATTANPTARDDDPDFIM CIFMASELPEASYSWURYQGSYUSAFITALKUVUVGAULATTANPTARDDDPDFIM CVFMASELPEASYSWURYQGSYUSAFITALKUVUVGAULATTANPTARDDDPDFIM CVFMASELPEASYSWURYQGSYUSAFITALKUVUVGAULATTANPTARDDDPDFIM CVFMASELPEASYSWURYQGSYUSAFITALKUVUGAULATTANPTARDDDPDFIM CVFMASELPEASYSWURYGGSYUSAFITALKUAUGAULATTANPTARDPDDPDFIN CVFMASELPEASYSWURYGGSYUSAFITALKUAUGAULATTANPTARDPDDPDFIN CVFMASELPEASYSWURYGGSYUGSFANGGELPTNNEAKFITLSMTPYFSSVSL IVSCNNYKNSLLPNTSLDLLLSVUGFSFANGGELPTNNEAKFITLSMTPYFSSVSL IVSCNNYKNSLLPNTSLDLLLSVUGFSFANGKELPTNNEAKFITLSMTPYFSSVSL IVSCNNYKNSLPNTSLDLLLSVUGSFANGKELPTNNEAKFITLSMTPYFTSSVSL IISCNNYKNSLPNTSLDLLLSVUGSFANGKELPTNNEAKFITLSMTPYFSSVSL IISCNNYKNSLPNTSLDLLLSVUGFSFANGKELPTNNEAKFITLSMTPYFSSVSL IISCNNYKNSLPNTSLDLLLSVUGSFANGKELPTNNEAKFITSSTFYFYSSVSL IISCNNYKNSLPNTSLDLLLSVUGSFANGKELPTNNEAKFITSSTFYFYSSVSL IISCNNYKNSLPNTSLDLLLSVUGSFANGKELPTNNEAKFITSSTFYFYSSVSL IISCNNYKNSLPNTSLDLLLSVUGSFANGKELPTNNEAKFITSSTFYFYSSVSL IISCNNYKNSLPNTSLDLLLSVUGSFANGKELPTNNEAKFITSSTFYFYSSVSL IISCNNYKNSLPNTSLDLLLSVUGSFANGKELPTNNEAKFITSSTFYFYSSVSL IISCNNYKNSLPNTSLDLLLSVUGSFANGKELPTNNEAKFITSSTFYFYSSVSL IISCNNYKNSLPNTSLDLLLSVUGSFANGKELPTNNEAKFITSSTFYFYSSVSL IISCNNYKNSLPNTSLDLLLSVUGSFANGKELPTNNEAKFITSSTFYFYSSVSL IISCNNYKNSLPNTSLDLLLSVUGSFANGKELPTNNEAKFITSSTFYFYSSVSL IISCNNYKNSLPNTSNDLLLSVUGSFANGKELPTNNEAKFITSSTFYFYSSVSL IISCNNYKNSLPNTSNDLLLSVUGSFANGKELPTNYNEAKFITSSTFYFYSVSUGUTM CTFMSAVSGVUVTIVLLVIVLALLAISLGYGPKCYMLFYPERNTSAYNSNIGGYTM CTFMSAVSGVUVTIVLSLUTVULLLAISLGYFGPKCYMLFYPERNTSAYNSNIGGYTM CTFMSAVGGVUVTIVLSLUTVULLLAISLGYFGPKCYMLFYPERNTSAYNSNIGGYTM CTFMSAVGGVUVTIVLLUTVLALLAISLGYFGPKCYMLFYPERNTSAYNSNIGGYTM CTFMSAVGGVUVTINDLLVTVLALLAISLGYFGPKCYMLFYPERNTSAYNSNIGGYTM CTFMSAVGGVUVTINDLLVTVLALLAISLGYFGPKCYMLFYPERNTSAYNSNIGGYTM CTFMSA	$\begin{array}{c} 716\\ 710\\ 711\\ 714\\ 720\\ 720\\ 720\\ 776\\ 776\\ 776\\ 776\\ 777\\ 777\\ 778\\ 776\\ 776$

#### Sequence analysis

After we obtained DNA sequences of the coding regions by PCR, we translated the DNA sequences into protein sequences based on the exon-intron junctions of human Tas1r2 and Tas1r3. The nucleotide and predicted protein sequences were aligned to detect nucleic acid and amino acid variants among the species using the ClustalW program (Thompson et al. 1994) (version 1.82; see Electronic Resources). The accession numbers for the primate sequences that we have obtained and deposited are as follows: Chimpanzee, DQ386295 (Tas1r2) and AF545573 (Tas1r3); Gorilla, DQ386296 (Tas1r2) and AF545574 (Tas1r3); Orangutan, DQ386297 (Tas1r2) and DQ381398 (Tas1r3); Patas monkey, DQ386299 (Tas1r2); Baboon, DQ386300 (Tas1r2) and DQ381400 (Tas1r3); Rhesus monkey, DQ386298 (Tas1r2); Squirrel monkey, DQ386301 (Tas1r2) and DQ381399 (Tas1r3); Marmoset, DQ386302 (Tas1r2) and DQ381401 (Tas1r3); and Tamarin, DQ386303 (Tas1r2). The sequences for nonprimate Tas1r3 and Tas1r2 and for rhesus monkey Tas1r3 were obtained from public domain. For some species (e.g., patas monkey), full-length DNA sequences could not be obtained after multiple rounds of primer design and PCR amplification. Consistent with the greater nucleotide diversity of Tas1r3 when compared with Tas1r2, the PCR using Tas1r3-specific primers were more likely to fail. Therefore, complete or nearly complete sequence for the Tas1r2 gene was obtained for most of the species studied, but Tas1r3 sequences for patas monkey and tamarin were not determined. Sequence variants that distinguished taster and nontaster species were identified after sequence alignment. Some areas of the genome of several species were difficult to sequence, and therefore, the data for some species are incomplete. There were no systematic difficulties sequencing particular areas, for example, in no cases was one region of the gene missing DNA sequence in many or all the species tested here. The final list included amino acid locations for which no taster species shared the same amino acids with any nontaster species.

#### Computer-assisted modeling of taste receptor structures

The 3D structures for the amino terminus domain of the mouse and human T1R2 and T1R3 proteins were generated using homology-based techniques. Structures were constructed for the human (aspartame taster) and mouse (aspartame nontaster) sequences. The experimentally determined structure of the rat metabotropic glutamate receptor subtype 1 (rMGR1) in its glutamate-bound (active) conformation

(Protein Data Bank [code 1EWK]) was selected as a template. The taste receptors T1R2 and T1R3 belong to the same class of G protein-coupled receptors (GPCRs) as MGR1 and are expected to share their 3D structure. There are several structures available for MGR1 (Kunishima et al. 2000) in 2 free forms (1EWT at pH 8.5 and 1EWV at pH 7.5), bound to an antagonist (1ISS) and bound to its endogenous agonist glutamate (1EWK). The active conformation of the rMGR1 homodimer shows one chain (chain A) in an active-close conformation, whereas the second chain (chain B) is in an active-open state. The close or open assignment is based on the relative positioning of the lobes of the Venus flytrap (VFT) architecture that forms the active binding site in this class of receptors. Because the relative positioning of the VFT may affect the binding of agonists, we modeled each T1R in both active-close and active-open conformations. Homology modeling was guided by a multiple sequence alignment that included 14 sequences of T1R2 and 11 sequences of T1R3 from different species. The program ClustalX (Thompson et al. 1997) was used to generate the alignments between T1Rs and the template (rMGR1) sequence. The template sequence was aligned to each T1R alignment (Figures 1 and 2), which was kept unchanged during the process. This procedure is referred to as "profile alignment" in ClustalX. The inclusion of T1R sequences other than the ones being modeled increases the quality of the alignment and, hence, the accuracy of the modeled structure. The secondary structures for the template (actual) and for the human T1R (predicted) were used to set structure-dependent gap penalties. The T1R2 alignment was adjusted at region H318-G334 (hT1R2). This segment was originally aligned to a region of the template lying on the surface of the receptor and would have caused a beta-strand in the template, which is part of a 5-strand beta sheet, to be absent in the model for hT1R2. Therefore, the sequence alignment was adjusted to have the H318-G334 (hT1R2) segment aligned to the beta-strand instead, under the assumption that secondary structure elements are more conserved than unstructured regions on the surface. Model building began by copying the backbone coordinates of equivalent residues from the template onto the model structure. Loops not found in the template structure were added by fragment selection using a library of fragments from known 3D structures of proteins. Insertions/deletions in the modeled structure were regularized through localized energy minimization. Side chains were added using an iterative

**Figure 1** ClustalW (1.82) multiple sequence alignment of T1R2. Deduced T1R2 amino acid sequences of 14 animal species. Amino acids that differ between aspartame tasters and nontasters are shown in underlined bold black text with an asterisk (\*) at the end of the aligned residues. Amino acids are numbered for each species and are shown to the right of the alignment. Species above the solid black line are aspartame tasters and those below it are nontasters. "X" denote missing sequence data. The accession numbers for the publicly available sequence are as follows: human, BK000151; cow, NW\_930951; dog, AY916758; rat, AF127390; mouse, NM\_031873. In the color version of this figure, amino acids are in color according to their chemical properties; red, small hydrophobic including those with an aromatic ring; blue, acidic; pink, basic; green, hydroxyl with an amine or that are basic; gray, other. This figure appears in color in the online version of *Chemical Senses*.

rotamer search approach. The complete modeled structure was then fully energy minimized using the CHARMM99 force fields and charges. The resulting model was checked for overall structure quality and validated using experimental data from the literature. Modeling and structural quality checks were performed using the software packages Yasara (www.yasara.org), Quanta (Accelrys, Inc), and MOE (www.chemcomp.com).

#### Molecular docking

Two libraries of ligands were constructed and docked to each of the 3D T1R models: 1) a decoy library of 100 ligands not expected to have affinity for the receptors. These included 6 bitter tastants, such as naringin, salicin and phenylthiocarbamide, 26 medicinal drugs known to be perceived by humans as bitter (e.g., carisoprodol, darvon, and isoptin), and 68 aminoquinolines (antimalaria chelating agents), most of which are well known for their very strong bitter taste. 2) A virtual library of 4 common natural sugars (D-fructose, dextrose [β-D-glucopyranose], sucrose [ $\beta$ -D-fructofuranosyl- $\alpha$ -D-glucopyranoside], and lactose [4-O-alpha-D-galactopyranosyl-D-galactose] and 1 artificial sweetener [aspartame]). The binding interactions between the generated models and these ligands were predicted using an in-house software package called "Orunmila." There are 2 molecular docking protocols implemented in Orunmila: "HierVLS" and "ScanHierDock" (Floriano et al. 2004). HierVLS is a computational protocol that performs a series of steps in order to simulate the molecular docking of each ligand in the virtual library into a potential binding site of the target protein. HierVLS uses a hierarchical scheme that reduces the number of protein-ligand conformers being evaluated from thousands to one in multiple levels of accuracy. The ligands are fully flexible (i.e., all rotatable bonds are allowed to change during docking), and a large number (>10 000) of conformers are generated in the least computationally expensive step for each ligand. Subsequent steps reduce the number of docked conformers, whereas increasing the accuracy of the energy functions used to evaluate binding. ScanHierDock extends the molecular docking to include all potential binding sites within the protein and includes an additional step of all-atoms energy minimization for every ligand-protein complex generated, before the binding energies are calculated. Molecular docking of tastants to binding sites other than the assumed active (orthosteric) site allows the identification of putative allosteric sites. For T1R2 and T1R3, we refer as "active" or "orthosteric" to the site corresponding to where glutamate is found to be bound in the crystallographic structure of the closely related MGR1. This is consistent with current use of the term in the literature (Wellendorph et al. 2009). Binding energies were estimated for the predicted complexes using the Dreiding force field (Mayo et al. 1990), Gasteiger (Gasteiger and Marsili 1980) charges for the ligands, and CHARMM22 (MacKerell et al. 1998) charges for the proteins. The final binding energies include solvation energies calculated using a Generalized Born implicit solvent model (Zamanakos 2002). We used ScanHierDock to perform binding site scanning with hierarchical molecular docking in all T1R models (T1R2 and T1R3, each in active-close and activeopen conformation, for each human and mouse, to a total of 8 modeled structures). Calculated binding energies for the decoy ligands were used to assess whether values could be compared across binding sites within the same model and to determine threshold values to discriminate binders from nonbinders. These results are presented in Table 2 and Figure 3. Calculated binding energies and ligand-bound complexes for the sweet ligands were examined carefully for significance (Table 3) and consistency with experimental data from literature (in Table 4). The aspartame-bound models deemed to be the best representations of the T1R taste receptors bound to aspartame were analyzed to provide insights for the observed inability of mice to respond to this sweetener.

#### Results

#### Sequence comparison for T1R2 and T1R3

The amino acid sequence alignments for T1R2 and T1R3 are displayed, respectively, in Figures 1 and 2. The percent of sequence identity at nucleotide and amino acid levels are listed for T1R2 (Table 5) and T1R3 (Table 6). Results of alignments of T1R2 and T1R3 sequences show that these 2 proteins are conserved among species, and the degree of conservation reflects their known phylogenetic relationship, that is, humans and chimpanzees are much more similar in amino acid sequence than are humans and mice. For nucleotide similarity, the Tas1r3 gene was almost always less conserved compared with the Tas1r2 gene, but this relationship was not true for amino acid similarity. For amino acids, both proteins had approximately the same degree of similarity. This finding is illustrated by comparing chimpanzee and mouse: the percent identity between nucleotides (73%) and amino acids (73%) is the same for T1R3, but for T1R2, the percent identity in amino acid sequence (70%) is lower than in nucleotide sequence (78%).

## Identification of variant sites associated with aspartame taster and nontaster status

From the alignment, we identified 41 DNA variant sites that distinguished aspartame tasters and nontasters, that is, were associated with aspartame taster/nontaster status (these will be referred to as taster/nontaster variant sites throughout the text; Figures 1 and 2). The source of the variations was usually single amino acid substitutions, except for the T1R2 segment aa 348-352 (Table 7), which carries single amino acid deletion for others (squirrel monkey, marmoset, and tamarin). Therefore, the T1R2 segment aa 348-352 was considered a single variant site. Variant sites associations were broadly defined to include any pattern of differences when none of the variant

#### Sweet Taste Rreceptor Gene Variation and Aspartame Blindness 459

human		EO
chimpanzee	MLGPAVLGLSLWALLHPGTGAPLCLSOOLRMKGDYVLGGLFPLGEAEEAGLRSRTRPS	58
gorilla	MLGPAVLGLSLWALLQPGAGAPLCLSQQLRMKGDYMLGGLFPLGEAEEAGFRSRTRPS	58
orangutan	<ul> <li>MLGPAVLGLSLWALLHSGTGAPLCLSQQLRMKGDYVLGGLFPLGEAEEAGLRSRTRPS</li> <li>MLRPAVLGLSLWALLHLGTGAPLCLSQQLRMKGDYVLGGLFPLGEAEEAGLRSRTRPS</li> </ul>	58
rhesus_monkey	MLCPAVLGLSLWALLHLGTGAPLCLSQQLRMKGDYVLGGLFPLGEAEBAGLGSRTRPS	58
squirrel_monkey	MLGSGVLGLSLWTLLHLRTGAPSCLSRQLKMKGDYVLGGLFPLGEAGEAALHSRTRPS	58
COW	MPPAMLGLTFLGLVAALGIRPGAPLCLSQQLSLPGDYILGGLFPLGSADDTGLGDRTQPN	60
dog	MAGEMLLSLMALLGLGAGAPLCLSRQLRMQGDYVLGGLFPLGTAEDTGLSDRTQPN	56
rat	MPGLAILGLSLAAFLELGMGSSLCLSQQFKAQGDYILGGLFPLGTTEEATLNQRTQPN MPALAIMGLSLAAFLELGMGASLCLSQQFKAQGDYILGGLFDLGSTFFATLNQPTODN	58
mouse		50
human	COVCTORSENCE LUST ANYMAURPENNICOL LOCEDLCYDE POTCERDVUAMKDELMPLA	119
chimpanzee	SPVCTRFSSNGLLWALAMKMAVEEINNKSDLLPGLRLGTDLFDTCSEPVVAMKPSLWFLA SPVCTRFSSNGLLWALAMKMAVEEINNKSDLLPGLRLGTDLFDTCSEPVVAMKPSLVFLA	118
gorilla	SPVCTRFSSNGLLWALAMKMAVEEINNKSDLLPGLRLGYDLFDTCSEPVVAMKPSLMFLA	118
orangutan	SPVCTRFSSNGLLWALAMKMAVEEINNKSDLLPGLRLGYDLFDTCSEPVVAMKPSLMFLA SPVCTRFSSNGLLWALAMKVAVERINNKSDLLPGLRLGYDLFDTCSEPVVAMKPSLMFLA	118
rhesus_monkey	SPVCTRFSSNGLLWALAMKMAVEEINNRSDLLPGLRLGHDLFDTCSEPVVAMKPSLMFLA	118
squirrel_monkey	SLVCTRFSWNGLLWALAMKMAVEEINNRLDLLPGLRLGYDLFDTCSEPTVTMKPSLMFLA	118
cow	ATVCTRESWNGLLWALAVMMAVEBINNAPTLLPGLRLGIDLFDTCSESVVIMRPSLMFLA ATVCTRLSAPGLLWALAVMMAVEBINNAPTLLPGLRLGYDLFDTCSEPVVAMKPSLVFMA	120
dog	ATVCTRFSSLGLLWALAMKMAVEEVNNRSTLLPGLRLGYDLFDTCSEPVVAMKPSLMFMA	116
rat	GILCTRFSPLGLFLAMAMKMAVEEINNGSALLPGLRLGYDLFDTCSEPVVTMKPSLMFMA SIPCNRFSPLGLFLAMAMKMAVEEINNGSALLPGLRLGYDLFDTCSEPVVTMKSSLMFLA	118
	*	
human	KAGSRDIAAYCNYTOYOPRVLAVIGPHSSELAMVTGKFFSFFLMPOVSYGASMELLSARE	178
chimpanzee	KAGSRDIAAYCNYTQYQPRVLAVIGPHSSELAMVTGKFFSFFLMPQVSYGASMELLSARE	178
gorilla	KAGSRDIAAYCNYTQYQPRVLAVIGPHSSELAMVTGKFFSFFLMPQVSYGASMELLSARE	178
baboon	KAGSRDIAAYCNYTQYQPRVLAVIGPHSSELADVIGKFFSFFLMPQVSYGASMBLLSARE	178
rhesus_monkey	KADSRDIXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX	178
squirrel_monkey	KANSHDIAAYCNYTQYQPRVLAVIGPHSSELALVTGKFFGFFLMPQVSYGASMDLLSTRE KANSHDIAAYCNYTOYOPRVLAVIGPHSSELALVTGKFFGFFLMPQVSYGASMDLLSTRE	178
cow	KAGSRSIGAYCDYTQYQPRVLAVIGPHSSEVALVTGKFFSFFLMPQVSYGATTDRLSNRE	180
dog	KAGSCDIAAYCNYTQYQPRVLAVIGPHSSELALITGKFFSFFLMPQVSYGASTDRLSNRE	176
mouse	KVGSQSIAAYCNYTQYQPKVLAVIGPHSSELALITGKFFSFFLMPQVSYSASMDRLSDRE KVGSQSIAAYCNYTQYQPRVLAVIGPHSSELALITGKFFSFFLMPQVSYSASMDRLSDRE	178
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human	TFPSFFRTVPSDRVQLTAAAELLQEFGWNWVAALGSDDEYGRQGLSIFSALAAARGICIA	238
chimpanzee	TFPSFFRTVPSDRVQLTAAAELLQEFGWNWVAALGSDDEYGRQGLSIFSALAAARGICIA	238
orangutan	TFPSFFRTVPSDRVQLTAAAELLQEFGWNWVAALGSDDEYGRQGLSIFSALAAARGICIA TFPSFFRTVPSDRVQLTAAADLLOOFGWNWVAALGSDDEYGRQGLSIFSALAAARGICIA	238
baboon	TFPSFFRTVPSDRVQLTAAAELLQEFGWNWVAALGSDDEYGRQGLSIFSALAAARGICIA	238
rhesus_monkey	TFPSFFRTVPSDRVQLVAAAELLQEFGWNWVAALGSDDEYGRQGLSIFSALAASRGICIA	238
marmoset	TFPSFFRTVPSDRVQLMATVELLQQLGWNWVAALGSDDEYGRQGLSIFSGLAAARGICIA	238
cow	TFPSFFRTVPSDRVQATAMVELLRGLHWNWVAAVGSDDEYGRQGLGLFSSLANAKGICIA	240
rat	TFPSFFRTVSSDRVQAVAMVELLQELGWNWVAAVGSDDEIGRQGLSLFSSLANARGICIA TFPSFFRTVPSDRVOLOAVVTLLONFSWNWVAALGSDDDYGREGLSIFSGLANSRGICIA	238
mouse	TFPSFFRTVPSDRVQLQAVVTLLQNFSWNWVAALGSDDDYGREGLSIFSSLANARGICIA	238
human	HEGLVPLPRADDSRLGKVQDVLHQVNQSSVQVVLLFASVHAAHALFNYSISSRLSPKVWV	298
human chimpanzee gorilla	HEGLVPLPRADDSRLGKVQDVLHQVNQSSVQVVLLPASVHAAHALPNYSISSRLSPKVWV HEGLVPLPRADDSRLGKVQDVLHQVNQSSVQVVLLPASVHAAHALPNYSISSRLSPKVWV HEGLVPLPRADDSRLGKVDVLHQVNQSSVQVVLLPASVHAAHALPNYSISSRLSPKVWV	298 298 298
human chimpanzee gorilla orangutan	HEGLVPLPRADDSRLGKVQDVLHQVNQSSVQVVLLPASVHAAHALPNYSISSRLSPKVWV HEGLVPLPRADDSRLGKVQDVLHQVNQSSVQVVLLPASVHAAHALPNYSISSRLSPKVWV HEGLVPLPRADDSRLGKVQDVLHQVNQSSVQVVLLPASVHAAYALPNYSISSRLSPKVWV HEGLVPLPRADDRLGKVQDVLHQVNQSSVQVVLLPASVHAAYALPNYSISSRLSPKVWV	298 298 298 298
human chimpanzee gorilla orangutan baboon rhesus monkey	HEGLVPLPRADDSRLGKVQDVLHQVNQSSVQVVLLPASVHAAHALPNYSISSRLSPKVWV HEGLVPLPRADDSRLGKVQDVLHQVNQSSVQVVLLPASVHAAHALPNYSISSRLSPKVWV HEGLVPLPRADDSRLGKVQDVLHQVNQSSVQVVLLPASVHAAHALPNYSISSRLSPKVWV HEGLVPLPRADDLRLGKVQDVLHQVNQSSVQVVLLPASVHAAYALPNYSISSRLSPKVWV HEGLVPLPRANSPLLGKVQBVLHQVNQSSVQVVLLPASHAAHALPSYSISSRLSPKVWV HEGLVPLPBANSPLLGKVQBVLHQVNQSVQVVLLPASBHALPSYSISSRLSPKVWV	298 298 298 298 298 298
human chimpanzee gorilla orangutan baboon rhesus monkey squirrel monkey	HBGLVPLPRADDSRLGKVQDVLHQVNQSSVQVVLLFASVHAAHALFNYSISSRLSPKVWV HBGLVPLPRADDSRLGKVQDVLHQVNQSSVQVVLLFASVHAAHALFNYSISSRLSPKVWV HBGLVPLPRADDSRLGKVQDVLHQVNQSVQVVLLFASVHAAHALFNYSISSRLSPKVWV HBGLVPLPRADDSRLGKVQDVLHQVNQSSVQVVLLFASVHAAHALFNYSISSRLSPKVWV HBGLVPLPRANSFLGKVQSVLHQVNQSSVQVVLLFASRAAHALFSYSISSKLSRKVWV HBGLVPLPRANSFUGKVQSVLHQVNQSSVQVVLLFASRAAHALFSYSISSKLSRKVWV	298 298 298 298 298 298 298 298
human chimpanzee gorilla orangutan baboon <u>rhesus monkey</u> squirrel_monkey marmoset	HEGLVPLPRADDSRLGKVQDVLHQVNQSSVQVVLLPASVHAAHALPNYSISSRLSPKVWV HEGLVPLPRADDSRLGVQDVLHQVNQSSVQVVLLPASVHAAHALPNYSISSRLSPKVWV HEGLVPLPRADDSRLGKVQDVLHQVNQSVQVVLLPASVHAAHALPNYSISSRLSPKVWV HEGLVPLPRADDSRLGKVQDVLHQVNQSVQVVLLPASVRAAHALPSYSISSRLSPKVWV HEGLVPLPRANSPLLGKVQSVLHQVNQSVQVVLLPASRAAHALPSYSISSKLSRKVWV HEGLVPLPRANSPLJGKVQSULPQLNQTSIQVVLLPASRAAHALPSYSISSKLSRKVWV HEGLVPLPRANSPLGKVQSLLPQLNQTSIQVVLLPASRAAHAHFSPKHISSKLSPKVWV	298 298 298 298 298 298 298 298 298
human chimpanzee gorilla orangutan baboon <u>rhesus monkey</u> squirrel_monkey marmoset cow dog	HEGLVPLPRADDSRLGKVQDVLHQVNQSSVQVVLLPASVHAAHALPNYSISSRLSPKVWV HEGLVPLPRADDSRLGKVQDVLHQVNQSSVQVVLLPASVHAAHALPNYSISSRLSPKVWV HEGLVPLPRADDSRLGKVQDVLHQVNQSVQVVLLPASVHAAHALPNYSISSRLSPKVW HEGLVPLPRADDSRLGKVQDVLHQVNQSSVQVVLLPASVHAAHALPNYSISSRLSPKVWV HEGLVPLPRADSPLGKVQEVLHQVNQSSVQVVLLPASHAAHALPSYSIS HLSRKVWV HEGLVPLPRASSPLGKVQEVLHQVNQSSVQVVLLPASRRAAHALPSYSISSKLSRKVWV HEGLVPLPRASSPLGKVQEVLHQVNQSSVQVVLLPASRRAAHALPSYSISSKLSRKVWV HEGLVPLPRASSPLGKVQEVLHQVNQSVQVVLPASRRAAHALPSYSISSKLSRKVWV HEGLVPLPRASSPLGLQVQSSLQVVLLPASRRAAHALPSYSISSKLSRKVWV YEGLMPLPRASSPLGKVQEVLHQVNQSVQVVLPASRRAAHALPSYSISSKLSRKVWV YEGLMPLPRASSPLGSVQSLLQVNHSSVQVVVPSSAQATYSLFSYSITYRLSPKVWV	298 298 298 298 298 298 298 298 298 300 296
human chimpanzee gorilla orangutan baboon rhesus monkey rhesus monkey marmoset cow dog rat	HEGLVPLPRADDSRLGKVQDVLHQVNQSSVQVVLLPASVHAAHALFNYSISSRLSPKVWV HEGLVPLPRADDSRLGKVQDVLHQVNQSSVQVVLLPASVHAAHALFNYSISSRLSPKVWV HEGLVPLPRADDSRLGKVQDVLHQVNQSVQVVLLPASVHAAHALFNYSISSRLSPKVWV HEGLVPLPRANSPLLGKVQEVLHQVNQSSVQVVLLPASRHAAHALFNYSISSRLSPKVWV HEGLVPLPRANSPLLGKVQEVLHQVNQSSVQVVLLPASRHAAHALFNYSISSRLSPKVWV HEGLVPLPRANSPLGKVQEVLHQVNQSSVQVVLLPASRHAAHALFNYSISSRLSPKVWV HEGLVPLPRANSPLGKVQEVLHQVNQSSVQVVLLPASRHAAHALFNYSISSRLSPKVWV HEGLVPLPRANSPLGKVQEVLHQVNQSSVQVVLLPASRHAAHALFNYSISSRLSPKVWV HEGLVPLPRANSPLGKVQEVLHQVNQSSVQVVLPASRAAHTSPSHISSRLSPKVWV HEGLVPLPRANSFUGSVGLLPQVNQSSVQVVLPASRAAHTSPSHISSRLSPKVWV HEGLVPLPRAGGTRLGSVGLLHQVNQSSVQVVVLPSSRQATYSLPSYSIIVFLSPKVWV HEGLVPLPRAGGTRLGSVGLLHQVNQSSVQVVVLPSSRAATTSPSSIIFDLSPKVWV	298 298 298 298 298 298 298 298 300 296 298
human chimpanzee gorilla orangutan baboon <u>rhesus monkey</u> marmoset cow dog rat mouse	HEGLVPLPRADDSRLGKVQDVLHQVNQSSVQVVLLPASVHAAHALFNYSISSRLSPKVWV HEGLVPLPRADDSRLGKVQDVLHQVNQSSVQVVLLPASVHAAHALFNYSISSRLSPKVWV HEGLVPLPRADDSRLGKVQDVLHQVNQSVQVVLLPASVHAAHALFNYSISSRLSPKVWV HEGLVPLPRADDLRLGKVQDVLHQVNQSSVQVVLLPASRAAHALFPYSISSRLSPKVWV HEGLVPLPRANSPLLGKVQSVLHQVNQSSVQVVLLPASRAAHALFPYSISSRLSPKVWV HEGLVPLPRANSPLGKVQSULHQVNQSSVQVVLLPASRAAHALFPYSISSRLSPKVWV HEGLVPLPRANSPLGKVQSULHQVNQSSVQVVLLPASRAAHALFPYSISSRLSPKVWV YEGLMPLPRADGLWGKVQSLLPQUNQTSVQVVLPASRAAHALFPYSISSRLSPKVWV HEGLVPLPRANSGLUGVNQSLQVVLPASRAAHALFPYSISSRLSPKVWV HEGLVPLPRADGLWGKVQSLLQVNQSSVQVVLPSSAQATYSLPSYSITYRLSPKVWV HEGLVPLPRAGGTRLGSVQSLLHQVNQSSVQVVVLPSSAQATYSLPSYSITYRLSPKVWV HEGLVPLPRAGGTRLGSVQSLLHQVNQSSVQVVVLPSSARATLPSYSILFDLSPKVWV HEGLVPLPRAGGTRLGSVQSLLHQVNQSSVQVVLPSSARATLPSYSILFDLSPKVWV HEGLVPDPHTSGQLGKVLDVLRQVNQSKVQVVVLPSSARAVYSLPSYSILFDLSPKVWV	298 298 298 298 298 298 298 298 300 296 298 298 298
human chimpanzee gorilla orangutan baboon <u>rhesus monkey</u> marmoset cow dog rat mouse human	HBGLVPLPRADDSRLGKVQDVLHQVNQSSVQVVLLPASVHAAHALPNYSISSRLSPKVWV HBGLVPLPRADDSRLGVQDVLHQVNQSSVQVVLLPASVHAAHALPNYSISSRLSPKVWV HBGLVPLPRADDSRLGKVQDVLHQVNQSVQVVLLPASVHAAHALPNYSISSRLSPKVWV HBGLVPLPRADDSRLGKVQDVLHQVNQSVQVVLLPASVHAAYALPNYSISSRLSPKVWV HBGLVPLPRANSPLLGKVQSVLHQVNQSVQVVLLPASARAHALPSYSISSKLSRKVWV HBGLVPLPRANSPLGKVQSVLHQVNQSVQVVLLPASARAHALPSYSISSKLSRKVWV HBGLVPLPRANSPUGKVQSULAQVNQSSVQVVLLPASARAHALPSYSISSKLSRKVWV HBGLVPLPRANSPUGKVQSULAQVNQSSVQVVLPASARAHTPFHISINSRLPPKVWV HBGLVPLPRADGTRLGSVQSLLQVNNQSSVQVVVLPASARAHTPFHSISSRLSPKVWV HBGLVPLPRADGTRLGSVQSLLQVNNQSSVQVVVLPASARAHTPFHSISSRLSPKVWV HBGLVPLPRAGTRLGSVQSLLQVNNQSSVQVVVLPASARAHTPSHSISSRLSPKVWV HBGLVPLPRISSRLGTVQGLLQVNQSSVQVVVLPASARAVYSLPSYSILMGLSPKVWV HBGLVPQHDTSGQQLGKVDVLPQNQSKVQVVVLPASARAVYSLPSYSILMGLSPKVWV ASEAWLTSDLVMGLPQMQMGTVLGPLQRAQL	298 298 298 298 298 298 298 298 298 298
human chimpanzee gorilla orangutan baboon rhesus monkey squirrel_monkey marmoset cow dog rat mouse human chimpanzee comblo 2	HEGLVPLPRADDSRLGKVQDVLHQVNQSSVQVVLLPASVHAAHALPNYSISSRLSPKVWV HEGLVPLPRADDSRLGKVQDVLHQVNQSSVQVVLLPASVHAAHALPNYSISSRLSPKVWV HEGLVPLPRADDSRLGKVQDVLHQVNQSVQVVLLPASVHAAHALPNYSISSRLSPKVWV HEGLVPLPRADDSRLGKVQDVLHQVNQSVQVVLLPASVRAHALPYSISSRLSRKVWV HEGLVPLPRANSPLLGKVQSVLHQVNQSVQVVLLPASRAAHALPSYSISSKLSRKVWV HEGLVPLPRANSPLGKVQSVLHQVNQSVQVVLLPASRAAHALPSYSISSKLSRKVWV HEGLVPLPRANSPLGKVQSVLHQVNQSVQVVLLPASRAAHALPSYSISSKLSRKVWV HEGLVPLPRANSPLGKVQSULHQVNQSSVQVVLLPASRAAHALPSYSISSKLSRKVWV HEGLVPLPRANSPLGKVQSULHQVNQSVQVVLPASRAAHALPSYSIS HEGLVPLPRANSPLGKVQSULHQVNQSVQVVLPASRAAHATPSYSIS HEGLVPLPRAGGTRLGSVQSLLHQVNNSSVQVVVLPSSAQATYSLPSYSI HEGLVPLPRAGGTRLGSVQSLLHQVNQSSVQVVVLPSSAQATYSLPSYSI HEGLVPLPRAGGTRLGSVQSLLHQVNQSKVQVVVLPSSAQATYSLPSYSI HEGLVPQHDTSGQQLGKVLDVLRQVNQSKVQVVVLPSARAXTSPSYSIHEDLSPKVWV ASESMLTSDLVMGLPQMAQMGTVLAFLQRAQCH=PPQVVKTHLALADPARCSALGEBER	298 298 298 298 298 298 298 298 298 298
human chimpanzee gorilla orangutan baboon <u>rhesus monkey</u> guirrel_monkey marmoset cow dog rat mouse human chimpanzee gorilla orangutan	HEGLVPLPRADDSRLGKVQDVLHQVNQSSVQVVLLPASVHAAHALPNYSISSRLSPKVWV HEGLVPLPRADDSRLGKVQDVLHQVNQSSVQVVLLPASVHAAHALPNYSISSRLSPKVWV HEGLVPLPRADDSRLGKVQDVLHQVNQSVQVVLLPASVHAAHALPNYSISSRLSPKVWV HEGLVPLPRADDSRLGKVQDVLHQVNQSVQVVLLPASVHAAYALPNYSISSRLSPKVWV HEGLVPLPRANSPLLGKVQSVLHQVNQSVQVVLLPASAHAHALPYSISSKLSRKVWV HEGLVPLPRANSPLGKVQSVLHQVNQSVQVVLLPASAHAHALPYSISSKLSRKVWV HEGLVPLPRANSPLGKVQSVLLQVNQSVQVVLLPASAHAHALPSYSISSKLSRKVWV HEGLVPLPRANSPLGLGVQLLQVNQSVQVVLPSAQATYSLPSYSISKLSRKVWV HEGLVPLPRANSPLGKVQSVLLQVNQSVQVVLPSAQATYSLPSYSIF HEGLVPLPRANSPLGKVQSVQVVLPSAQATYSLPSYSIF HEGLVPLPRANSPLGKVQSVQVVLPSAQATYSLPSYSIF HEGLVPLPRSGLKVQVVDVLRQVNQSKVQVVVLPSAAHTPSYSIF HEGLVPLPRSGLKQVSVQVLPQNQSKVQVVVLPSAAHTPSYSIF HEGLVPLPRSGLGKVDAVLRQVNQSKVQVVVLPSAAHTPSYSIF HEGLSPEPKVW ASEAMLTSDLVMGLQQAQMGTVLGPLQRQQLHBPPQVVKTHLALADPAPCSALGBRE ASEAMLTSDLVMGLPQAMQMGTVLGPLQRQQLHBPPQVVKTHLALADPAPCSALGBRE ASEAMLTSDLVMGLQAMQMGTVLGPLQRQQLHBPPQVVKTHLALADPAPCSALGBRE	298 298 298 298 298 298 298 298 298 298
human chimpanzee gorilla orangutan baboon rhesus monkey squirrel_monkey marmoset cow dog rat mouse human chimpanzee gorilla orangutan baboon	HEGLVPLPRADDSRLGKVQDVLHQVNQSSVQVVLLPASVHAAHALPNYSISSRLSPKVWV HEGLVPLPRADDSRLGKVQDVLHQVNQSSVQVVLLPASVHAAHALPNYSISSRLSPKVWV HEGLVPLPRADDSRLGKVQDVLHQVNQSVQVVLLPASVHAAHALPNYSISSRLSPKVWV HEGLVPLPRADDSRLGKVQDVLHQVNQSVQVVLLPASVHAAYALPNYSISSRLSPKVWV HEGLVPLPRANSPLLGKVQEVLHQVNQSSVQVVLLPASAHAHALPNYSISSRLSPKVWV HEGLVPLPRANSPLGKVQEVLHQVNQSSVQVVLLPASAHAHALPNYSISSKLSRKVWV HEGLVPLPRANSPLGKVQEVLHQVNQSVQVVLLPASAHAHALPNSISSKLSRKVWV HEGLVPLPRANSPLGKVQSLLQVNQSSVQVVLLPASAHAHALPNSISSKLSRKVWV HEGLVPLPRANSPLGKVQSVLLQVNQSVQVVLPSAAAHALPSYSISSKLSRKVWV HEGLVPLPRANSPLGKVQSVLQVVLPSAAAHALPSHITGRLSPKVWV HEGLVPLPRANSTURGKQGLLQVNQSSVQVVLPSSAATYSLPSYSIIVTSKSKUSKVWV HEGLVPLPRAGTRLGSVQSLLQVNQSVQVVVPSSAATYSLPSYSIIFTSKLGRLSPKVWV HEGLVPLPRAGTRLGSVQSLLQVNQSKVQVVVLPSAAATTPSYSISKLSRKVWV ASLANLTSDLVMGLQGNAQMGTVLGPLQRGAQLHSPPQVVTHLALATDPAPCSALGERE ASEANLTSDLVMGLDGMAQMGTVLGPLQRGAQLHSPPQVVTHLALATDPAPCSALGERE ASEANLTSDLVMGLDGMAQMGTVLGPLQRGAQLHSPPQVVTHLALAADPAPCSALGERE ASEANLTSDLVMGLPGMAQVGTVLGPLQRGAQLHSPPQVVTHLALAADPAPCSALGERE ASEANLTSDLVMGLPGMAQVGTVLGPLQRGAQLHSPPQVVTHLALAADPAPCSALGERE ASEANLTSDLVMGLPGMAQVGTVLGPLQRGAQLHSPPQVVTHLALAADPAPCSALGERE ASEANLTSDLVMGLPGMAQVGTVLGPLQRGAQLHSPPQVVTHLALAAPPRCAAGERE ASEANLTSDLVMGLPGMAQVGTVLGPLQRGAQLHSPPQVVTHLAAAPPRCAAGERE	298 298 298 298 298 298 298 298 298 298
human chimpanzee gorilla orangutan baboon <u>rhesus monkey</u> marmoset cow dog rat mouse human chimpanzee gorilla orangutan baboon <u>rhesus monkey</u>	HBGLVPLPRADDSRLGKVQDVLHQVNQSSVQVVLLPASVHAAHALPNYSISSRLSPKVWV HBGLVPLPRADDSRLGKVQDVLHQVNQSSVQVVLLPASVHAAHALPNYSISSRLSPKVWV HBGLVPLPRADDSRLGKVQDVLHQVNQSVQVVLLPASVHAAHALPNYSISSRLSPKVWV HBGLVPLPRADDSRLGKVQDVLHQVNQSVQVVLLPASVHAAHALPNYSISSRLSPKVWV HBGLVPLPRANSPLLGKVQSVLHQVNQSVQVVLLPASVHAAYALPNYSISSRLSPKVWV HBGLVPLPRANSPLGKVQSVLHQVNQSVQVVLLPASARAHALPSYSISSKLSRKVWV HBGLVPLPRANSPLGKVQSVLHQVNQSVQVVLLPASARAHALPSYSISSKLSRKVWV HBGLVPLPRANSPUGKVQSULAQVNQSSVQVVLPASARAHAPTPSHISTSRLSPKVWV HBGLVPLPRANSPUGKVQSULAQVNQSSVQVVVLPASARAHTPSHISTSRLSPKVWV HBGLVPLPRADGTRLGSVQSLLQVNNQSSVQVVVLPASARAHTPSHISTSRLSPKVWV HBGLVPLPRADGTRLGSVQSLLQVNQSSVQVVVLPASARATYSLSPSISI HBGLVPLPRISSRLGTVQLLQVNQSSVQVVVLPASARATYSLSPSISI HBGLVPQHDTSSQQLGRVVDVLRQVNQSKVQVVVLPASARAYSLSPSISI HBGLVPQHDTSQQLGRVDVLDCLRQVNQSKVQVVVLPASARAYSLSPSISI ASSAMLTSDLVMGLDQMAQMGTVLGPLQGRAQLHEPPQVXTHLALAATDPAFCSALGBRE ASSAMLTSDLVMGLDGMAQMGTVLGPLQGRAQLHEPPQVXTHLALAATDPAFCSALGBRE ASSAMLTSDLVMGLDGMAQMGTVLGPLQGRAQLHEPPQVXTHLALAATDPAFCSALGBRE ASSAMLTSDLIVMGLDGMAQMTVLGPLQGRAQLHEPSQVXTHLALAADPAFCSALGBRE ASSAMLTSDLVMGLDGMAQMTVLGPLQGRAQLHEPSQVXTHLALAADPAFCSALGBRE ASSAMLTSDLIVMGLDGMAQMTVLGPLQGRAQLHEPSQVXTHLALAADPAFCSALGBRE ASSAMLTSDLIVMGLDGMAQMTVLGPLQGRAQLHEPSQVXTHLALAADPAFCSALGBRE ASSAMLTSDLIVMGLDGMAQMTVLGPLQGRAQLHEPSQVXTHLALAADPAFCSALGBRE ASSAMLTSDLIVMGLDGMAQVTVLFPLQGRAQLHEPSQVXTHLALAADPAFCALGBRE ASSAMLTSDLIVMGLDGMAQVTVLFPLQGRAQLHEPSQVXTHLALAADPAFCALGBRE ASSAMLTSDLIVMGLDGMAQVTVLFPLQGRAQLHEPSQVXTHLALAADPAFCALGBRE ASSAMLTSDLIVMGLDGMAQVTVLFPLQGRAQLHEPSQVXTHLALAADPAFCALGBRE	298 298 298 298 298 298 298 298 298 298
human chimpanzee gorilla orangutan baboon <u>rhesus monkey</u> <u>squirrel monkey</u> marmoset cow dog rat mouse human chimpanzee gorilla orangutan baboon <u>rhesus monkey</u> squirrel_monkey	HEGLVPLPRADDSRLGKVQDVLHQVNQSSVQVVLLPASVHAAHALPNYSISSRLSPKVWV HEGLVPLPRADDSRLGKVQDVLHQVNQSSVQVVLLPASVHAAHALPNYSISSRLSPKVWV HEGLVPLPRADDSRLGKVQDVLHQVNQSVQVVLLPASVHAAHALPNYSISSRLSPKVWV HEGLVPLPRADDSRLGKVQDVLHQVNQSVQVVLLPASVHAAHALPNYSISSRLSPKVWV HEGLVPLPRADSPLGKVQDVLHQVNQSVQVVLLPASVHAAHALPSYSISSRLSRKVWV HEGLVPLPRANSPLGKVQULHQVNQSVQVVLLPASARAHALPSYSISSKLSRKVWV HEGLVPLPRANSPLGKVQULHQVNQSVQVVLLPASARAHALPSYSISSKLSRKVWV HEGLVPLPRANSPLGKVQULHQVNQSVQVVLPASARAHALPSYSISSKLSRKVWV HEGLVPLPRANSPUCKVQUSLLPQVNQSSVQVVVLPASARAHTPSHISTBRLSPKVWV HEGLVPLPRADGTRLGSVQSLLHQVNQSSVQVVVLPASARAHTPSHISTBRLSRKVWV HEGLVPLPRADGTRLGSVQSLLHQVNQSSVQVVVLPASARAHTPSHISTBRLSRKVWV ASSANLTSDLVMGLDQVQCLLQVNQSSVQVVVLPASARAVYSLPSYSILQLSPKVWV HEGLVPQHDTSGQDLGKVDVLFQVQNQSKVQVVLPASARAVYSLPSYSILQLSPKVWV ASSANLTSDLVMGLDQMQMOTVLGPLQGAQLHEPPQVKTHLALADPAPCSALGERE ASSANLTSDLVMGLDQMQMOTVLGPLQGAQLHEPPQVKTHLALADPAPCSALGERE ASSANLTSDLVMGLDQMQQVTVLPLQPLQGAQLHEPSQVVKTHLALADPAPCSALGERE ASSANLTSDLVMGLDQMQQVTVLPLQRQAQLHEPSQVVKTHLALADPAPCSALGERE ASSANLTSDLVMGLDQMQQVTVLPLQRQAQLHPSQVVKTHLALADPAPCSALGERE ASSANLTSDLVMGLDQMQQVTVLPLQRQAQLHPSQVVKTHLALADPAPCSALGERE ASSANLTSDLVMGLDQMQQVTVLPLQRQAQLHPSQVVKTHLALADPAPCSALGERE ASSANLTSDLVMGLDQMQQVTVLPLQRQAQLHPSQVVKTHLALADPAPCCALGERE ASSANLTSDLVMGLDQMQQVTVLPLQRQAQLHPSQVVKTHLALADPAPCCALGERE ASSANLTSDLVMGLDQMQQVTVLPLQRQAQLMPSQVVKTHLALADPAPCCALGERE ASSANLTSDLVMGLDQMQQVTVLPLQRQAQLMPSQVVKTHLALADPAPCCALGERE ASSANLTSDLVMGLDQMQQVTVLPLQRQAQLMPSQVVKTHLALADPAPCCALGERE ASSANLTSDLVMGLDQMQQVTVLPLQRQAQLMPSQVVKTHLALADPAPCCALGERE ASSANLTSDLVMGLDQMQQVTVLPLQRQAQLMPSQVVKTHLALADPAPCCALGERE ASSANLTSDLVMGLPQARQVVTVLPLQRQAQLMPSQVVKTHLALADPAPCCALGERE	298 298 298 298 298 298 298 298 298 298
human chimpanzee gorilla orangutan baboon rhesus monkey squirrel_monkey marmoset cow dog rat mouse human chimpanzee gorilla orangutan baboon rhesus monkey squirrel_monkey marmoset cow	HEGLVPLPRADDSRLGKVQDVLHQVNQSSVQVVLLPASVHAAHALPNYSISSRLSPKVWV HEGLVPLPRADDSRLGKVQDVLHQVNQSSVQVVLLPASVHAAHALPNYSISSRLSPKVWV HEGLVPLPRADDSRLGKVQDVLHQVNQSVQVVLLPASVHAAHALPNYSISSRLSPKVWV HEGLVPLPRADDSRLGKVQDVLHQVNQSVQVVLLPASVHAAHALPNYSISSRLSPKVWV HEGLVPLPRANSPLLGKVQSVLHQVNQSVQVVLLPASVRAAHALPSYSISSRLSPKVWV HEGLVPLPRANSPLGKVQSULAQVNQSVQVVLLPASARAHAHEPSYSISSKLSRKVWV HEGLVPLPRANSPLGKVQSULAQVNQSVQVVLPASARAHAHEPSYSISSKLSRKVWV HEGLVPLPRANSPLGKVQSULAQVNQSVQVVLPASARAHAHEPSYSISSKLSRKVWV HEGLVPLPRANSPLGKVQSULAQVNQSVQVVLPASARAHHTPSHIISSRLSPKVWV HEGLVPLPRANSPLGKVQSULAQVNQSVQVVLPASARAHHTPSHIISSKLSRKVWV ZSGLMPLPRAGGTRLGSVQSLLAQVNQSVQVVVLPSSAQATYSLFSYSIITGKLSPKVWV HEGLVPLPRAGGTRLGSVQSLLAQVNQSVQVVVLPASARATFLSYSIITGKLSPKVWV HEGLVPQHDTSGQQLGKVVDVLRQVNQSKVQVVVLPASARATFLSYSIIHGLSPKVWV ASEAWLTSDLVMGLPQMAQMGTVLGFLQRAQLHSPPQVVKTHLALADPAPCSALGBRE ASEAWLTSDLVMGLPQMAQMGTVLGFLQRAQLHSPPQVVKTHLALADPAPCSALGBRE ASEAWLTSDLVMGLPQMAQMGTVLGFLQRAQLHSPPQVVKTHLALADPAPCSALGBRE ASEAWLTSDLVMGLPQMAQMGTVLGFLQRAQLHSPPQVVKTHLALADPAPCSALGBRE ASEAWLTSDLVMGLPQMAQMGTVLGFLQRAQLHSPPQVVKTHLALADPAPCSALGBRE ASEAWLTSDLVMGLPQMAQMGTVLGFLQRAQLHSPPQVVKTHLALADPAPCALGBRE ASEAWLTSDLVMGLPQMAQMGTVLGFLQRAQLHSPPSQVVKTHLALADPAPCALGBRE ASEAWLTSDLVMGLPQMAQMGTVLGFLQRAQLHSPPQVVKTHLALADPAPCALGBRE ASEAWLTSDLVMGLPQMAQMGTVLGFLQRAQLHSPPQVVKTHLALADPAPCALGBRE ASEAWLTSDLVMGLPQMAQMGTVLGFLQRAQLHSPPQVVKTHLALAPAPRCALGBRE ASEAWLTSDLVMGLPQMAQMGTVLGFLQRAQLHSPQVVKTHLALAPAPRCALGBRE ASEAWLTSDLVMGLPQMAQMGTVLGFLQRAQLHSPQVVKTHLALAPAPRCALGBRE ASEAWLTSDLVMGLPQMAQMGTVLGFLQRAQLHSPQVVKTHLALAPAPRCALGBRE ASEAWLTSDLVMGLPQMAQMGTVLGFLQRAQLHSPQVVKTHLALAPAPRCALGBRE ASEAWLTSDLVMGLPQMAQMGTVLGFLQRAQLBFPQVVKTHLALAPAPRCALGBRE ASEAWLTSDLVMGLPQMAQMGTVLGFLQRAQLBFPQVVKTHLALAPAPRCALGBRE ASEAWLTSDLVMGLPQMAQMGTVLGFLQRAQLBFPQVVKTHLALAPAPRCALGBRE ASEAWLTSDLVMGLPQMAQMGTVLGFLQRAQLBFPQVVKTHLALAPAPRCALGBRE ASEAWLTSDLVMGLPQMAQMGTVLGFLQRAQLBFPQVKTHLALAPAPRCALGBRE	298 298 298 298 298 298 298 298 298 298
human chimpanzee gorilla orangutan baboon <u>rhesus monkey</u> marmoset cow dog rat mouse human chimpanzee gorilla orangutan baboon <u>rhesus monkey</u> <u>squirrel</u> monkey marmoset cow dog rat	HBGLVPLPRADDSRLGKVQDVLHQVNQSSVQVVLLFASVHAAHALFNYSISSRLSPKVWV HBGLVPLPRADDSRLGKVQDVLHQVNQSSVQVVLLFASVHAAHALFNYSISSRLSPKVWV HBGLVPLPRADDSRLGKVQDVLHQVNQSVQVVLLFASVHAAHALFNYSISSRLSPKVWV HBGLVPLPRADDSRLGKVQDVLHQVNQSVQVVLLFASVHAAHALFNYSISSRLSPKVWV HBGLVPLPRANSPLLGKVQSVLHQVNQSVQVVLFASVHAAHALFNYSISSRLSPKVWV HBGLVPLPRANSPLLGKVQSVLHQVNQSVQVVLFASARAHALFYSSISSKLSRKVWV HBGLVPLPRANSPLGKVQSVLHQVNQSSVQVVLFASARAHALFYSSISSKLSRKVWV HBGLVPLPRANSPLGKVQSVLHQVNQSSVQVVLFASARAHALFYSSISSKLSRKVWV HBGLVPLPRANSPUGKVQSULHQVNQSSVQVVLFASARAHAFTFSHISSKLSRKVWV HBGLVPLPRANSPUGKVQSULHQVNQSSVQVVLFASARAHTFFSHISSKLSRKVWV HBGLVPLPRTSSQLGKVVDLFQNQSSVQVVVFSATAAHTFFSHISTUGLSPKVWV HBGLVPLPTSSQLGKVVDLFQNQSGVVVVFSATAAFTFFSHISTUGLSPKVWV HBGLVPLPTSSQLGKVDVLFQVNQSSQVVVFSATAAFTFSYSIIGJLSPKVWV HBGLVPLPTSSQLGKVDVLFQVNQSGVVVVFSATAAFTFSYSIIGJLSFKVWV HBGLVPLPTSSQLGKVVUFLQVNQSKQVVVFSATAAFTFSYSIIGJLSFKVWV HBGLVPLPTSSQLGKVUVFLQVNQSKVQVVFSATAAFTFSYSIIGJLSFKVWV HBGLVPQHDTSGQQLGKVLDVLFQVRGAGLHSFPQVVKTHLALAAPAFCSALGBRE ASBAWLTSDLVMGLPQNQGVTVLGFLQRAQLHSFPQVVKTHLALAAPAFCSALGBRE ASBAWLTSDLVMGLPQNQGVTVLGFLQRAQLHSFPQVVKTHLALAAPAFCSALGBRE ASBAWLTSDLVMSLFQNQVQTVTLGFLQRAQLHSFPQVVKTHLALAAPAFCSALGBRE ASBAWLTSDLVMSLFQNQVQTVLGFLQRAQLHSFPQVVKTHLALAAPAFCSALGBRE ASBAWLTSDLVMSLFQNQVQTVLGFLQRAQLHSFPQVVKTHLALAAPAFCSALGBRE ASBAWLTSDLVMSLFQNQVQTVLGFLQRAQLHSFPQVVTCHLALAAPAFCSALGBRE ASBAWLTSDLVMSLFQNQVQTVLGFLQRAQLHSFPQVVTCHLALAAPAFCSALGBRE ASBAWLTSDLVMSLFQNQVQTVLGFLQRAQLFFPQVVTCHLALAAPAFCSALGBRE ASBAWLTSDLVMSLFQNQVQTVLGFLQRAQLFFPQVVTCHLALAAPAFCSLGBRE ASBAWLTSDLVMSLFQNQVQTVLGFLQRAQLFFPQVVTCHLALAAPAFCSLGBRE ASBAWLTSDLVMSLFQNQVQTVLGFLQRAQLFFPQVVTCHLALAAPAFCSLGBRE ASBAWLTSDLVMSLFQNQVQTVLGFLQRAQLFFPQVVCTHLALAAPAFCSLGBRE ASBAWLTSDLVMSLFQNQVQTVLGFLQRAQLFFPQVVCTHLALAAPAFCSLGBRE ASBAWLTSDLVMSLFQNQVQTVLGFLQRAQLFFPQVVCTHLALAAPAFCTSLGBRE ASBAWLTSDLVMSLFQNQVQTVLGFLQRAQLFFPQVVCTHLALAAPAFCTSLGBRE ASBAWLTSDLVMSLFQNQVQTVLGFLQRAQLBFFFPYQTCTLALAAPAFCTSLGBRE ASBAWLTSDLVMTLFQNRQVTVLGFLQRAGABAPEFFSLZVQTLAAPAFCTALAAPAFCTALGBRE ASBAWLTSDLVMTLFQNRQVTVLGFLQRAGALFFFPQVVCTHLALAAPAFCTALGBRE	298 298 298 298 298 298 298 298 298 298
human chimpanzee gorilla orangutan baboon <u>rhesus</u> monkey marmoset cow dog rat mouse human chimpanzee gorilla orangutan baboon <u>rhesus</u> monkey <u>squirre1</u> monkey marmoset cow dog rat monkey marmoset cow dog rhesus monkey marmoset cow dog rat monkey marmoset cow dog rat monkey marmoset cow dog rat monkey marmoset cow dog rhesus monkey marmoset cow dog rhesus monkey rat monkey rat monkey rat monkey rat monkey rat rat monkey rat monkey rat monkey marmoset cow dog rhesus monkey marmoset cow marmoset cow marmoset cow	HBGLVPLPRADDSRLGKVQDVLHQVNQSSVQVVLLPASVHAAHALPNYSISSRLSPKVWV HBGLVPLPRADDSRLGKVQDVLHQVNQSSVQVVLLPASVHAAHALPNYSISSRLSPKVWV HBGLVPLPRADDSRLGKVQDVLHQVNQSVQVVLLPASVHAAHALPNYSISSRLSPKVWV HBGLVPLPRADDSRLGKVQDVLHQVNQSVQVVLLPASVHAAHALPNYSISSRLSPKVWV HBGLVPLPRANSPLLGKVQSVLHQVNQSVQVVLLPASVHAAHALPSYSISSRLSPKVWV HBGLVPLPRANSPLLGKVQSVLHQVNQSVQVVLPASAHAHALPSYSISSKLSRKVWV HBGLVPLPRANSPLGKVQSVLHQVNQSSVQVVLPASAHAHALPSYSISSKLSRKVWV HBGLVPLPRANSPUGKVQSULHQVNQSSVQVVLPASAHAHALPSYSISSKLSRKVWV HBGLVPLPRANSPUGKVQSULHQVNQSSVQVVLPASAHAHALPSYSISSKLSRKVWV HBGLVPLPRANSPUGKVQSULHQVNQSSVQVVLPASAHAHTFSHISTUBSLSFKVWV HBGLVPLPRAGTRLGVVGLLQVNQSSVQVVVLPASAHATFFSHISTUBSLSFKVWV HBGLVPLPRTSSQLGKVVDLQVNQSVQVVVLPASAHTFSHISTUBJLSFKVWV HBGLVPLPRTSGQLGKVDULQVNQSVQVVVLPSTHAAHTFSYSILGLSFKVWV HBGLVPLPRTSGQLGKVDUFLQVNQSSVQVVVLPSTHAAHTFSYSILGLSFKVWV HBGLVPLPRTSGQLGKVDVLFQVRGSLQVVVVLPSTHAAHTFSYSILGLSFKVWV HBGLVPQHDTSGQQLGKVDVLPQNGSCQVVVLPSTHAAHTFSYSILGLSFKVWV HBGLVQCHVTSGQLGKVDVLPQNGSCQVVVVFSTHAAHTFSYSILGLSFKVWV HBGLVPQHDTSGQQLGKVDVLPQNGSCQVVVVFSTHAAHTFSYSSILGLSFKVWV HBGLVSQLGKVDVLPQNGSCQUVVVFFSTHAATFFSYSILGLSSFKVWV HBGLVPQHDTSGQQLGKVDVLPQNGSCQVVVVFFSTHAATFFSYSILGLSSFKVWV HBGLVPQHDTSGQQLGKVDVLPQNGSCQQVVVVFFSTHAAFTFSYSILGLSSFKVWV HBGLVPQHDTSGQQLGKVDVLPQNGSCQVVVVFFSTHAAFTFSYSSILGSLSSKVFS ASEAWLTSDLVMSLDQNAQVGTVLGFLQRGAQLHFSQVVVTHLALAAPPAFCSALGBRE ASEAWLTSDLVMSLDQNAQVGTVLGFLQRGAQLHFSQVVVTHLALAAPPAFCSALGBRE ASEAWLTSDLVMSLDQNAQVGTVLGFLQRGAQLFFSQVVTCHLALAAPPAFCSALGBRE ASEAWLTSDLVMSLDQNAQVGTVLGFLQRGAQLFFSQVVCTHLALAAPPAFCSLGSRE ASEAWLTSDLVMSLDQNAQVGTVLGFLQRGAQLFFSQVVCTHLALAAPPAFCSLGSRE ASEAWLTSDLVMSLDQNAQVGTVLGFLQRGAQLFFSQVVCTHLALAAPPAFCSLGSRE ASEAWLTSDLVMSLDQNAQVGTVLGFLQRGAQLFFSQVVCTHLALAAPPAFCSLGSRE ASEAWLTSDLVMTLDNNLGVTVLGFLQRGAQLFFSQVVCTHLAAPPAFCSLGSRE ASEAWLTSDLVMTLDNAGVGTVLGFLQRGAQLFFSQVVCTHLAAAPPAFCSLGSRE ASEAWLTSDLVMTLDNAGVGTVLGFLQRGAQLFFSQVVCTHLAAAPPAFCSLGARA ASEAWLTSDLVMTLDNAGVGTVLGFLQRGAQLFFSQVVCTHLAAAPPAFCSLGARA ASEAWLTSDLVMTLDNAGVGTVLGFLQRGAQLFFSQVVCTHLAAAPPAFCSLGARA ASEAWLTSDLVMTLDNAGVGTVLGFLQRGAQLFFSQVVCTHLAAAPPAFCSLGARA ASEAWLTSDLVMTLDNAGVGTVLGFLQRGAQA	298 298 298 298 298 298 298 298 298 298
human chimpanzee gorilla orangutan baboon <u>rhesus monkey</u> marmoset cow dog rat mouse human chimpanzee gorilla orangutan baboon <u>rhesus monkey</u> marmoset cow dog grat	HBGLVPLPRADDSRLGKVQDVLHQVNQSSVQVVLLPASVHAAHALPNYSISSRLSPKVWV HBGLVPLPRADDSRLGKVQDVLHQVNQSSVQVVLLPASVHAAHALPNYSISSRLSPKVWV HBGLVPLPRADDSRLGKVQDVLHQVNQSVQVVLLPASVHAAHALPNYSISSRLSPKVWV HBGLVPLPRADDSRLGKVQDVLHQVNQSVQVVLLPASVHAAYALPNYSISSRLSPKVWV HBGLVPLPRANSPLLGKVQSVLHQVNQSVQVVLLPASVHAAYALPNYSISSRLSPKVWV HBGLVPLPRANSPLGKVQSVLHQVNQSVQVVLPASAHAHALPSYSISSKLSRKVWV HBGLVPLPRANSPLGKVQSVLHQVNQSSVQVVLPASAHAHALPSYSISSKLSRKVWV HBGLVPLPRANSPUGKVQSULQVNQSSVQVVLPASAHAHALPSYSISSKLSRKVWV HBGLVPLPRANSPUGKVQSULQVNQSSVQVVLPASAHAHTPSHISTRELPSVFW HBGLVPLPRAGTRLGSVQSLLQVNNQSSVQVVLPASAHAHTPSHISTRELPSVFW HBGLVPLPHTSSRLGTVQGLLQVNQSSVQVVVLPASAHTPSHISTRELPSVFW HBGLVPLPHTSSRLGTVQGLLQVNQSSVQVVVLPSSTHAAFLPSYSILGRLSBRVWV ASEAWLTSDLVMGLPQNQMGTVLGPLQRAQLEPPQVVKTHLALATDPAPCSALGERE ASEAWLTSDLVMGLPQNQMGTVLGPLQRAQLEPPQVVKTHLALATDPAPCSALGERE ASEAWLTSDLVMGLPQNQMGTVLGPLQRAQLEPPQVVKTHLALAAPPAPCALGERE ASEAWLTSDLVMGLPQNQVTVLFQLQRAQLEPPQVVKTHLALAAPPAPCALGERE ASEAWLTSDLVMGLPQNQVTVLFQLQRAQLEPPQVVKTHLALAAPPAPCALGERE ASEAWLTSDLVMGLPQNQVTVLFQLQRAQLEPPQVVKTHLALAAPPAPCALGERE ASEAWLTSDLVMGLPQNQVTVLFQLQRAQLEPPQVVKTHLALAAPPAPCALGERE ASEAWLTSDLVMGLPQNQVTVLFQLQRAQLEPPQVVKTHLALAAPPAPCALGERE ASEAWLTSDLVMGLPQNQVTVLFQLQRAQLEPPQVVKTHLALAAPPAPCALGERE ASEAWLTSDLVMGLPQNQVTVLFQLQRAQLEPPQVVKTHLALAAPPAPCALGERE ASEAWLTSDLVMGLPQNQVTVLFQLQRAQLEPPQVVKTHLALAAPPAPCALGERE ASEAWLTSDLVMGLPQNQVTVLFQLQRAQLEPPQVVKTHLALAAPPAPCALGERE ASEAWLTSDLVMGLPQNAQVTVLFQLQRAQLEPPQVVKTHLALAAPPAPCALGERE ASEAWLTSDLVMGLPQNAQVTVLFQLQRAQLEPPQVVKTHLALAAPPAPCALGERE ASEAWLTSDLVMTLPNIARVGTVLGPLQRAQLEPPQVVKTHLALAAPPAPCALGERE ASEAWLTSDLVMTLPNIARVGTVLGPLQRAQLEPPQVVKTHLALAAPPAPCALGERE ASEAWLTSDLVMTLPNIARVGTVLGPLQRAQLEPPQVVTHLALAAPPAPCALGERE ASEAWLTSDLVMTLPNIARVGTVLGPLQRAQLEPPQVVTHLALAAPPAPCALGERE ASEAWLTSDLVMTLPNIARVGTVLGPLQRAQLEPPQVVTHLAAAPPAPCALGERE ASEAWLTSDLVMTLPNIARVGTVLGPLQRAQLEPPSVVQTCLAAAPPAPCALGERE ASEAWLTSDLVMTLPNIARVGTVLGPLQRAALPPEPSVVGTCLAAAPPAPCALGERA	298 298 298 298 298 298 298 298 298 298
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human chimpanzee gorilla orangutan baboon rhesus monkey marmoset cow dog rat mouse human chimpanzee gorilla orangutan baboon rhesus monkey squirre1_monkey marmoset cow dog rat mouse human chimpanzee gorilla orangutan baboon rhesus monkey squirre1_monkey marmoset cow dog rat mouse human chimpanzee gorilla orangutan baboon rhesus monkey squirre1_monkey marmoset cow dog rat mouse human chimpanzee gorilla orangutan baboon rhesus monkey squirre1_monkey marmoset com dog rat mouse	HBGLVPLPRADDSRLGKVQDVLHQVNQSSVQVVLLPASVHAAHALPNYSISSRLSPKVWV HBGLVPLPRADDSRLGKVQDVLHQVNQSVQVVLLPASVHAAHALPNYSISSRLSPKVWV HBGLVPLPRADDSRLGKVQDVLHQVNQSVQVVLLPASVHAAHALPNYSISSRLSPKVWV HBGLVPLPRADDSRLGKVQDVLHQVNQSVQVVLLPASVHAAHALPNYSISSRLSPKVWV HBGLVPLPRADDSRLGKVQDVLHQVNQSVQVVLLPASVHAAHALPNYSISSRLSPKVWV HBGLVPLPRANSPLLGKVQSVLHQVNQSVQVVLLPASVHAAHALPSYSISSKLSRKVWV HBGLVPLPRANSPLGKVQSVLHQVNQSVQVVLPASAHAHALPSYSISSKLSRKVWV HBGLVPLPRANSPLGKVQSVLHQVNQSVQVVLPASAHAHALPSYSISSKLSRKVWV HBGLVPLPRANSPUGKVQSULLQVNQSSVQVVLPASAHAHALPSYSISSKLSRKVWV HBGLVPLPRANSPUGKVQSULLQVNQSSVQVVLPSSTRAHTPSHISTRJBLSPKVWV HBGLVPLPTSSQLGKVVDLQVNQSVQVVVPSAAHATPSPHISTRJBLSPKVWV HBGLVPLPTSSQLGKVVDLQVNQSVQVVVPSAAHATPSPHISTRJBLSFKVWV HBGLVPLPTSSQLGKVVDLQVNQSSVQVVVLPSSTRAHTPSYSIJGLSPKVWV HBGLVPLPTSSQLGKVDVLPQNQSVQVVVFSAAHATYSEYSIJGLSPKVWV HBGLVPQHDTSGQQLGKVDVLPQNGSCVQVVVFSAAHATYSEYSIJGLSSFKVWV HBGLVPQHDTSGQQLGKVDVLPQNGSCVQVVVFSAAHATYSEFYSIJGLSSFKVW HBGLVPQHDTSGQQLGKVDVLPQNGSCVQVVVFSAAHATYSEFYSIJGLSSFKVW HBGLVPQHDTSGQQLGKVDVLPQNGSCVQVVFSAAHATYSEFYSIJGLSSFKVW HBGLVPQHDTSGQQLGKVDVLPQNGSCVQVVFSAAHATYSEFYSIJSSIJGLSSFKVW HBGLVPQHDTSGQQLGKVDVLPQNGSCVQVVFSAAHATYSEFYSIJGLSSFKVW HBGLVPQHDTSGQQLGKVDVLPQNGSCVQVVFSAAHATYSEFYSIJSJLSSF ASSAWLTSDLVMSLPANAQVGTVLGFLQRGAQLHSPQVVTTHLALAAPPAFCSALGBRE ASSAWLTSDLVMSLPANAQVGTVLGFLQRGAQLHSPQVVTTHLALAAPPAFCSALGBRE ASSAWLTSDLVMSLPANAQVGTVLGFLQRGAQLEFPQVVTTHLALAAPPAFCSALGBRE ASSAWLTSDLVMSLPANAQVGTVLGFLQRGAQLEFPQVVTTHLALAAPPAFCSLGBRE ASSAWLTSDLVMSLPANAQVGTVLGFLQRGAQLEFPQVVTTHLALAAPPAFCSLGBRE ASSAWLTSDLVMTLPNIXAVXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX	298 298 298 298 298 298 298 298 298 350 358 358 358 358 358 358 358 358 358 358
human chimpanzee gorilla orangutan baboon <u>rhesus</u> monkey marmoset cow dog rat mouse human chimpanzee gorilla orangutan baboon <u>rhesus</u> monkey marmoset cow dog rat mouse human chimpanzee gorilla orangutan baboon rhesusmonkey squirrel_m	HBGLVPLPRADDSRLGKVQDVLHQVNQSSVQVVLLPASVHAAHALPNYSISSRLSPKVWV           HBGLVPLPRADDSRLGKVQDVLHQVNQSSVQVVLLPASVHAAHALPNYSISSRLSPKVWV           HBGLVPLPRADDSRLGKVQDVLHQVNQSVQVVLLPASVHAAHALPNYSISSRLSPKVWV           HBGLVPLPRADDSRLGKVQDVLHQVNQSVQVVLLPASVHAAHALPNYSISSRLSPKVWV           HBGLVPLPRADDSRLGKVQDVLHQVNQSVQVVLLPASVHAAHALPNYSISSRLSPKVWV           HBGLVPLPRADDSRLGKVQDVLHQVNQSVQVVLLPASVHAAYALPNYSISSRLSPKVWV           HBGLVPLPRANSPLLGKVQSVLHQVNQSVQVVLLPASARAHALPSYSISSKLSKKVWV           HBGLVPLPRANSPLGKVQSVLLQVNQSSVQVVLPASARAHALPSYSISSKLSKKVWV           HBGLVPLPRANSPUCKVQSLLQVNQSSVQVVLPASARAHALPSYSISSKLSKKVWV           HBGLVPLPRADGLMVGKVQELLQVNQSSVQVVVLPASARAHTFSHITISSRLSPKVWV           HBGLVPLPRADGLMVGKVQELLQVNQSSVQVVVLPSARAHTFSHITISSKLSKKVWV           HBGLVPLPRADGLMVGKVQLLQVNQSKVQVVVLPSARAHTSSYSIIHIGLSPKVWV           ASEAWLTSDLVMGLPQNAQMGTVLGPLQRGAQLHESPQVKTHLALADPPCSLGBRE           ASEAWLTSDLVMGLPQNAQMGTVLGPLQRGAQLHESPQVKTHLALADPPCSLGBRE           ASEAWLTSDLVMGLPQNAQWGTVLGPLQRGAQLHESPQVKTHLALADPPCCLGBRE           ASEAWLTSDLVMGLPQNAQWGTVLGPLQRGAQLHESPQVKTHLALADPPCCLGBRE           ASEAWLTSDLVMGLPQNAQWGTVLGPLQRGAQLHESPQVKTHLALADPPCCLGBRE           ASEAWLTSDLVMGLPQNAQWGTVLGPLQRGAQLESPSQVVCTRLALADPPCCLGBRE           ASEAWLTSDLVMGLPQNAQWGTVLGPLQRGAQLESPSQVVCTRLALADPPCCLGBRE           ASEAWLTSDLVMTLPNNLTHQUTTLQRAQUGTVLGPLQRGAQLESPSQVVCTRLALADPAPCALADPPCCALGBRE           ASEAWLTSDLVMTLPNNLTHQUTTLQRAQUGTVLGPLQRGAQLESPSQVVCTRLALADPAPCALADPPCCALGBRE           AS	298 298 298 298 298 298 298 298 298 358 358 358 358 358 358 358 358 358 35

human	VGRFNGSLRTERLKIRWHTSDNQKPVSRCSRQCQEGQVRRVKGFHSCCYDCVDCEAGSYR	530
chimpanzee	VGRFNGSLRTERLKIRWHTSDNQKPVSRCSRQCQEGQVRRVKGFHSCCYDCVDCEAGSYR	530
gorilla	VGRFNGSLRTERLKIRWHTSDNQKPVSRCSRQCQEGQVRRVKGFHSCCYDCVDCEAGSYR	530
orangutan	VGGFNGSLWTERLKIRWHTPDNQKPVSQCSRQCQEGQVRRVKGFHSCCYDCVDCKAGSYR	530
baboon	VGRFNGSLRTERLKIRWHTSDNQKPVSRCSRRCQEGQVRRVKGFHSCCYDCVDCEAGSYR	530
rhesus monkey	XXXXXXSLWIDSPKIRWHTSNNQKPVSQCSRQCQEGQVRRVKGFHSCCYDCVDCKAGSYR	529
squirrel_monkey	VGIFNGSLWPERLKMRWHTPDNQEPVSQCSRQCQEGQVRRVKGFHSCCYDCVDCEAGSYR	530
marmoset	***************************************	
COW	VGSFNGSLELQFSSMIWHTPGNQEPVSQCSRQCREGQVRRVKGFHSCCYDCVDCKAGSYQ	532
dog	VGAFNGRLKVWHSOMSWHTPGNORPVSOCSROCGEGOVRRVKGFHSCCYDCVDCKAGTYO	528
rat	VGTFNGTLOLOHSKMYWPGNOVPVSOCSROCKDGOVRRVKGFHSCCYDCVDCKAGSYR	535
mouse	VGTFNGTLOLOOSKMYWPGNOVPVSOCSROCKDGOVRRVKGFHSCCYDCVDCKAGSYR	535
human	QNPDDIACTFCGQDEWSPERSTRCFRRSRFLAWGEPAVLLLLLLSLALGLVLAALGLF	590
chimpanzee	ONPDDIACTFCGQDEWSPERSTRCFRRRSRFLAWGEPAVLLLLLLLSLALGLVLAALGLF	590
gorilla	QNPDDVTCTSCGQDEWSPERSTRCFHRRSRFLAWGEPAVLLLLLLLSLALGLVLAALGLF	590
orangutan	HSPDDLACTFCRODEWSPERSTRCFRRRSRFLAWGEPAVLLLLLLLSLALGLVLAALGLF	590
baboon	ONPDDIACPFCGODEWSPERSTRCFRRRSRFLAWGEPAVLLLLLLLSLALGLVLAALGLF	590
rhesus monkey	KSPDDLACTFCGQEEWSPERSTRCFRRRLRFLAWGESAVLLLLLLFGLALGLVLAALGLF	589
squirrel monkey	RNPDDPTCTPCRHDQWSPKRSTRCFHRRPRFLTWGEPAVLLLLLLLGLALGLVLATLGLF	590
marmoset	*****	
COW	RHPDDALCSKCDODOWSPDGSTRCFPRRPRFLAWGEPAVLGLLLLLGIVLGLVLVALGLF	592
dog	RSPDDLLCTQCDQNQWSPDRSTRCFPRRLTFLAWGQPAVLVLLILLALALGLVLVALGLF	588
rat	KHPDDFTCTPCGKDOWSPEKSTTCLPRRPKFLAWGEPAVLSLLLLCLVLGLTLAALGLF	595
mouse	KHPDDFTCTPCNQDQWSPEKSTACLPRRPKFLAWGEPVVLSLLLLLCLVLGLALAALGLS	595
human	VHHRDSPLVQASGGPLACFGLVCLGLVCLSVLLFPGQPSPARCLAQQPLSHLPLTGCLST 650	
chimpanzee	IHHRDSPLVQASGGPLACFGLVCLGLVCLSVLLFPGQPSPARCLAQQPLSHLPLTGCLST 650	
gorilla	VHHRDSPLVQASGGPLACFGLVCLGLVCLSVLLFPGQPSPAQCLAQQPLSHLPLTGCLST 650	
orangutan	IRHRDSPLVRASGGPLACFGLVCLGLVCLSVLLFPGRPGTARCLAQQPLSHLPLTGCLST 650	
baboon	VHHRDSPLVQASGGPLACFGLVCLGLVCLSVLLFPGQPSPARCLAQQPLSHLPLTGCLST 650	
rhesus monkey	IRHRDSPLVQASGGPLACFGLVCLGLVCISVLLFPGQPSPARCLAQQPSSHLPLTGCLST 649	
squirrel_monkey	IRHRDSPLVQASGGALACFGLVCLGLVCLSVLLFPGQPSPARCLAQQPLSHLPLTGCLST 650	
marmoset	***************************************	
COW	TWHRDSPLVQAAGGPRACFGLACLGLVCLSVLLFPGRPSTASCMGQQLLLHLPLTGCLST 652	
dog	IRHRDSPLVQASGGPRACFGLACLGLVCLSVLLFPGQPGPASCLAQQPLLHLPLTGCLST 648	
rat	VHYWDSPLVQASGGSLFCFGLICLGLFCLSVLLFPGRPRSASCLAQQPMAHLPLTGCLST 655	
mouse	VHHWDSPLVQASGGSQFCFGLICLGLFCLSVLLFPGRPSSASCLAQQPMAHLPLTGCLST 655	
human	LFLQAAEIFVESELPLSWADRLSGCLRGPWAWLVVLLAMLVEVALCTWYLVAFPPEVVTD 710	
chimpanzee	LFLQAAEIFVESELPLSWADRLSGCLRGPWAWLVVLLAMLVEVALCTWYLVAFPPEVVTD 710	
gorilla	LFLQAABIFVESELPLSWADRLSGCLRGPWAWLVVLLAMLVEVALCTWYLVAFPPEVVTD 710	
orangutan	LFLQAAEIFVESELPLSWADRLSGCLRGPWAWLVVLLAMLVEVALCTWYLVAFPPEVVTD 710	
baboon	LFLQAAEIFVESELPLSWADRLSGCLRGPWAWLVVLLAMLVEVALCTWYLVAFPPEVVTD 710	
rhesus_monkey	FILQAAEIFAESELPLSWADRLSGCLRGPWAWLVVLLAMLVEAALCAWYLVAFPPEVVTD 709	
squirrel_monkey	LFLQAAETFVESELPPSWADRLWGCLRGPRAWLAVLLAMLVEAALCAWYLLTFPPEVVTD 710	
marmoset	***************************************	
COW	LFLLAAEIFVGSELPPSWTDWLHSCLRGPWAWLVVLLAMLAEAALCSWYLAVFPPVVVTN 712	
dog	LFLQAAQIFVGSELPSSWADQLRCLQGPWAWLLVLLALLAEAALCAWYLVAFPPEVVTD 708	
rat	LFLQAAEIFVESELPLSWANWLCSYLRGPWAWLVVLLATLVEAALCAWYLMAFPPEVVTD 715	
mouse	LFLQAAETFVESELPLSWANWLCSYLRGLWAWLVVLLATFVEAALCAWYLIAFPPEVVTD 715	
	,	
human	WHMLPTEALVHCRTRSWVSFGLAHATNATLAFLCFLGTFLVRSQPGRYNRARGLTFAMLA 770	
chimpanzee	WHMLPTEALVHCRTRSWVSFGLAHATNATLAFLCFLGTFLVRSQPGRYNRARGLTFAMLA 770	
chimpanzee gorilla	WHMLPTEALVHCRTRSWVSFGLAHATNATLAFLCFLGTFLVRSQPGRYNRARGLTFAMLA 770 WHMLPTEALVHCRTRSWVSFGLAHATNATLAFLCFLGTFLVRSQPGRYNRARGLTFAMLA 770	
chimpanzee gorilla orangutan	WHMLPTERALVHCETRSWVSFGLAHATNATLAFLCFLGFELVRSQPGRYNRARGLFFAMLA 770 WHMLPTEALVHCETRSWVSFGLAHATNATLAFLCFLGFELVRSQPGRYNRARGLFFAMLA 770 WHILPTERALVHCETRSWVSFGLAHATNATLAFLCFLGFELVQSRPGRYNRARGLFFAMLA 770	
chimpanzee gorilla orangutan baboon	WHILPTEALVHCRTRSWUSFGLAHATNATLAFLCFLGTFLVRSOPGRYNRARGLFFAMLA 770 WHILPTEALVHCRTRSWUSFGLAHATNATLAFLCFLGTFLVRSOPGRYNRARGLFFAMLA 770 WHILPTEALVHCRTRSWUSFGLAHATNATLAFLCFLGTFLVQSFPGRYNRARGLFFAMLA 770	
chimpanzee gorilla orangutan baboon rhesus monkey	WHILPTEALVHCRTRSWVSFGLAHATNATLAFLCFLOTFLVRSOPGRYNRARGLFFAMLA 770 WHILPTEALVHCRTSSWVSFGLAHATNATLAFLCFLOTFLVRSOPGRYNRARGLFFAMLA 770 WHILPTEALVHCRTSSWVSFGLAHATNATLAFLCFLOTFLVOSRPGRYNRARGLFFAMLA 770 WHILPTEALVHCRTSSWVSFGLVHATNATLAFLCFLOTFLVOSRPGRYNRARGLFFAMLA 770 WHILPTEALVHCRTSSWVSFGLVHATNATLAFLCFLOTFLXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX	
chimpanzee gorilla orangutan baboon rhesus monkey squirrel_monkey	WHLIPTEALVHCRTRSWSFGLAHATNATLAFLCFLOTFLVRSOPGRYNRARGLFFAMLA 770 WHLIPTEALVHCRTRSWSFGLAHATNATLAFLCFLOTFLVSSOPGRYNRARGLFFAMLA 770 WHLIPTEALVHCRTRSWSFGLAHATNATLAFLCFLOTFLVQSRPGRYNRARGLFFAMLA 770 WHLIPTEALVHCRTRSWSFGLVHATNATLAFLCFLOTFLVQSRPGRYNRARGLFFAMLA 770 WHLIPTEALVHCRTRSWSFGLVHATNATLAFLCFLOTFLVQSRPGRYNRARGLFFAMLA 770 WHLIPTEALVHCRTRSWSFGLVHATNATLAFLCFLOTFLVQSRPGRYNRARGLFFAMLA 770	
chimpanzee gorilla orangutan baboon <u>rhesus monkey</u> squirrel_monkey marmoset	WHILPTEALVHCRTRSWSPGLAHATNATLAFLCFLGTFLVFSQPGRYNRARGLFPANLA 770 WHILPTEALVHCRTSWSPGLAHATNATLAFLCFLGTFLVSSQPGRYNRARGLFPANLA 770 WHILPTEALVHCRTSWSPGLAHATNATLAFLCFLGTFLVQSPGRYNRARGLFPANLA 770 WHILPTEALVHCRTSWSPGLVHATNATLAFLCFLGTFLVQSPGRYNRARGLFPANLA 770 WHILPTEALVHCRTSWSPGLVHATNATLAFLCFLGTFLVQSPGRYNRARGLFPANLA 770 XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX	
chimpanzee gorilla orangutan baboon <u>rhesus monkey</u> squirrel_monkey marmoset cow	WHMLPTEALVHCRTRSWSFGLAHATNATLAFLCFLOTFLVFSOGGRYNRARGLFFAMLA 770 WHMLPTEALVHCRTSWSFGLAHATNATLAFLCFLOTFLVFSOGGRYNRARGLFFAMLA 770 WHILPTEALVHCRTRSWSFGLAHATNATLAFLCFLOTFLVQSPGRYNRARGLFFAMLA 770 WHMLPTEALVHCRTSSWSFGLVHATNATLAFLCFLOTFLVQSPGRYNRARGLFFAMLA 770 WRMLPTEALVHCRTSSWSFGLVHTNATLAFLCFLOTFLVQSPGRYNRARGLFFAMLA 770 XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX	
chimpanzee gorilla orangutan baboon rhesus monkey squirrel_monkey marmoset cow dog	WHELPTEALVHCRTRSWVSFGLAHATNATLAFLCFLGFUVFSQGGRYNRARGLFFAMLA 770 WHELPTEALVHCRTRSWVSFGLAHATNATLAFLCFLGFUFVNSSGGRYNRARGLFFAMLA 770 WHELPTEALVHCRTSSWVSFGLAHATNATLAFLCFLGFUVGSFGRYNRARGLFFAMLA 770 WHELPTEALVHCRTSSWVSFGLWATNATLAFLCFLGFUVGSFGRYNRARGLFFAMLA 770 WRELPTEALVHCRTSSWVSFGLWATNATLAFLCFLGFUVGSFGRYNRARGLFFAMLA 770 XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX	
chimpanzee gorilla orangutan baboon rhesus monkey squirrel_monkey marmoset cow dog rat	WHELPTEALVHCRTFSWVSFGLAHATNATLAFLCFLGTFLVFSOPGRYNRARGLFFAMLA 770 WHELPTEALVHCRTFSWVSFGLAHATNATLAFLCFLGTFLVSSOPGRYNRARGLFFAMLA 770 WHELPTEALVHCRTFSWVSFGLAHATNATLAFLCFLGTFLVOSSPGRYNRARGLFFAMLA 770 WHELPTEALVHCRTFSWVSFGLVHATNATLAFLCFLGTFLVOSSPGRYNRARGLFFAMLA 770 WRELPTEALVHCRTFSWVSFGLVHATNATLAFLCFLGTFLVOSSPGRYNRARGLFFAMLA 770 XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX	
chimpanzee gorilla orangutan baboon rheaus monkey squirrel_monkey marmoset cow dog rat mouse	WHELPTEALVHCRTRSWVSPGLAHATNATLAFLCFLGTFLVFSQPGRYNRARGLFFAMLA 770 WHELPTEALVHCRTRSWVSPGLAHATNATLAFLCFLGTFLVFSQPGRYNRARGLFFAMLA 770 WHELPTEALVHCRTSSWVSPGLAHATNATLAFLCFLGTFLVQSSPGRYNRARGLFFAMLA 770 WHELPTEALVHCRTSSWVSPGLWHATNATLAFLCFLGTFLVQSSPGRYNRARGLFFAMLA 770 WRELPTEALVHCRTSSWVSPGLWHATNATLAFLCFLGTFLVQSSPGRYNRARGLFFAMLA 770 XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX	
chimpanzee gorilla orangutan baboon rhesus monkey squirrel monkey marmoset cow dog rat mouse	WHELPTEALVHCRTRSWVSFGLAHATNATLAFLCFLGFLVFSQGGRYNRARGLFFAMLA 770 WHELPTEALVHCRTRSWVSFGLAHATNATLAFLCFLGFLVFNSGGGRYNRARGLFFAMLA 770 WHELPTEALVHCRTSSWVSFGLAHATNATLAFLCFLGFLVQSFGRYNRARGLFFAMLA 770 WHELPTEALVHCRTSSWVSFGLWATNATLAFLCFLGFLVQSFGRYNRARGLFFAMLA 770 WHELPTEALVHCRTSSWVSFGLWHATNATLAFLCFLGFFLVQSFGRYNRARGLFFAMLA 770 XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX	
chimpanzee gorilla orangutan baboon <u>rhesus monkey</u> squirrel_monkey marmoset cow dog rat mouse human	WHELPTEALVHCRTRSWVSPGLAHATNATLAFLCFLGTFLVFSQPGRYNRARGLFFAMLA 770 WHELPTEALVHCRTRSWVSPGLAHATNATLAFLCFLGTFLVFSQPGRYNRARGLFFAMLA 770 WHELPTEALVHCRTRSWVSPGLAHATNATLAFLCFLGTFLVQSRPGRYNRARGLFFAMLA 770 WRELPTEALVHCRTRSWVSPGLWHATNATLAFLCFLGTFLVQSRPGRYNRARGLFFAMLA 770 WRELPTEALVHCRTRSWVSPGLWHATNATLAFLCFLGTFLVQSRPGRYNRARGLFFAMLA 770 XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX	
chimpanzee gorilla orangutan baboon <u>rheaus monkey</u> squirrel_monkey marmoset cow dog rat dog rat mouse human chimpanzee	WHELPTEALVHCKTRSWVSFGLAHATNATLAFLCFLGTFLVFSQGGKNNRARGLFFAMLA 770 WHELPTEALVHCKTRSWVSFGLAHATNATLAFLCFLGTFLVVSSGGRKNNRARGLFFAMLA 770 WHELPTEALVHCKTSSWVSFGLAHATNATLAFLCFLGTFLVVSSFGRKNRARGLFFAMLA 770 WHELPTEALVHCKTSSWVSFGLWATNATLAFLCFLGTFLVVSSFGRKNRARGLFFAMLA 770 WHELPTEALVHCKTSSWVSFGLWATNATLAFLCFLGTFLVVSSFGRKNRARGLFFAMLA 770 XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX	
chimpanzee gorilla orangutan baboon <u>rhesus monkey</u> squirrel_monkey marmoset cow dog rat mouse human chimpanzee gorilla	WHELPTEALVHCRTRSWVSFGLAHATNATLAFLCFLGTFLVRSQPGRYNRARGLTFAMLA 770 WHELPTEALVHCRTRSWVSFGLAHATNATLAFLCFLGTFLVRSQPGRYNRARGLTFAMLA 770 WHELPTEALVHCRTSSWVSFGLAHATNATLAFLCFLGTFLVQSRPGRYNRARGLTFAMLA 770 WHELPTEALVHCRTSSWVSFGLVHATNATLAFLCFLGTFLVQSRPGRYNRARGLTFAMLA 770 WHELPTEALVHCRTSSWVSFGLVHATNATLAFLCFLGTFLVQSRPGRYNRARGLTFAMLA 770 XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX	
chimpanzee gorilla rrangutan baboon rhesus monkey squirrel_monkey marmoset cow dog rat dog rat mouse human chimpanzee gorilla orangutan	WHELPTEALVHCRTRSWVSFGLAHATNATLAFLCFLGTFLVRSQPGRYNRARGLFFAMLA 770 WHELPTEALVHCRTRSWVSFGLAHATNATLAFLCFLGTFLVRSQPGRYNRARGLFFAMLA 770 WHELPTEALVHCRTSSWVSFGLAHATNATLAFLCFLGTFLVQSFPGRYNRARGLFFAMLA 770 WHELPTEALVHCRTSSWVSFGLWATNATLAFLCFLGTFLVQSFPGRYNRARGLFFAMLA 770 WRELPTEALVHCRTSSWVSFGLWATNATLAFLCFLGTFLVQSFPGRYNRARGLFFAMLA 770 XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX	
chimpanzee gorilla orangutan baboon rhesus monkey squirrel_monkey marmoset cow dog rat mouse human chimpanzee gorilla orangutan baboon	WHELPTEALVHCRTRSWVSFGLAHATNATLAFLCFLGTFLVRSQPGRYNRARGLFFAMLA 770 WHELPTEALVHCRTRSWVSFGLAHATNATLAFLCFLGTFLVRSQPGRYNRARGLFFAMLA 770 WHELPTEALVHCRTSSWVSFGLAHATNATLAFLCFLGTFLVQSFPGRYNRARGLFFAMLA 770 WHELPTEALVHCRTSSWVSFGLWATNATLAFLCFLGTFLVQSFPGRYNRARGLFFAMLA 770 WHELPTEALVHCRTSSWVSFGLWATNATLAFLCFLGTFLVQSFPGRYNRARGLFFAMLA 770 WHELPTEALVHCRTSSWVSFGLWATNATLAFLCFLGTFLVQSFPGRYNRARGLFFAMLA 770 WHELPTEALVHCRTSSWVSFGLWATNATLAFLCFLGTFLVQSFPGRYNRARGLFFAMLA 770 WHELPTEALVHCRTSSWVSFGLWATNATLAFLCFLGTFLVQSFPGRYNRARGLFFAMLA 775 WHELPTEALVHCRTSSWVSFGLWATNATLAFLCFLGTFLVQSFPGRYNRARGLFFAMLA 775 WHELPTQLUHCRTSSWVSFGLWATNATLAFLCFLGTFLVQSFPGRYNRARGLFFAMLA 775 WSTLFTQUHCRTSSVVSFGLWATNATLAFLCFLGTFLVQSSPGRYNRARGLFFAMLA 775 WSTLFTQUHCRTSSVVSFGLWATNATLAFLCFLGTFLVQSSPGRYNRARGLFFAMLA 775 WSTLFTEVLENCOVLREAVQMGALLLCVLGILAAFHLFRCYLLERQGLNTFEFFL 830 YFITWVSFVFLLANVQVVLRPAVQMGALLLCVLGILAAFHLFRCYLLERQGGLNTFEFFL 830 YFITWVSFVFLLANVQVVLRPAVQMGALLLCVLGILAAFHLFRCYLLERQGGLNTFEFFL 830 YFITWVSFVFLLANVQVVLRPAVQMGALLLCVLGILAAFHLFRCYLLERQGENTFEFFL 830 YFITWVSFVFLLANVQVVLRPAVQMGALLLCVLGILAAFHLFRCYLLERQGENTFEFFL 830 YFITWVSFVFLLANVQVVLRPAVQMGALLLCVLGILAAFHLFRCYLLERQGENTFEFFL 830 YFITWVSFVFLLANVQVVLRPAVQMGALLLCVLGILAAFHLFRCYLLERQGENTFEFFL 830 YFITWVSFVFLLANVQVVLRPAVQMGALLCVLGILAAFHLFRCYLLERQGENTFEFFL 830	
chimpanzee gorilla rangutan baboon rheaus monkey squirrel_monkey cow dog rat dog rat mouse human chimpanzee gorilla orangutan baboon rheaus monkey	WHELPTEALVHCRTRSWVSPGLAHATNATLAFLCFLGTFLVFSQPGRYNRARGLFFAMLA 770 WHELPTEALVHCRTRSWVSPGLAHATNATLAFLCFLGTFLVFSQPGRYNRARGLFFAMLA 770 WHELPTEALVHCRTSSWVSPGLAHATNATLAFLCFLGTFLVQSSPGRYNRARGLFFAMLA 770 WHELPTEALVHCRTSSWVSPGLWHATNATLAFLCFLGTFLVQSSPGRYNRARGLFFAMLA 770 WRULPTEALVHCRTSSWVSPGLWHATNATLAFLCFLGTFLVQSSPGRYNRARGLFFAMLA 770 XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX	
chimpanzee gorilla orangutan baboon rhesus monkey squirrel monkey marmoset cow dog rat mouse human chimpanzee gorilla orangutan baboon rhesus monkey squirrel monkey	WHELPTEALVHCRTRSWVSFGLAHATNATLAFLCFLGTFLVRSQPGRYNRARGLFFAMLA 770 WHELPTEALVHCRTRSWVSFGLAHATNATLAFLCFLGTFLVRSQPGRYNRARGLFFAMLA 770 WHELPTEALVHCRTSSWVSFGLAHATNATLAFLCFLGTFLVQSFPGRYNRARGLFFAMLA 770 WHELPTEALVHCRTSSWVSFGLWATNATLAFLCFLGTFLVQSFPGRYNRARGLFFAMLA 770 WRELPTEALVHCRTSSWVSFGLWATNATLAFLCFLGTFLVQSFPGRYNRARGLFFAMLA 770 WRELPTEALVHCRTSSWVSFGLWATNATLAFLCFLGTFLVQSFPGRYNRARGLFFAMLA 770 WRELPTEALVHCRTSSWVSFGLWATNATLAFLCFLGTFLVQSFPGRYNRARGLFFAMLA 770 WRELPTEALVHCRTSSWVSFGLWATNATLAFLCFLGTFLVQSGPGRYNRARGLFFAMLA 775 WRELPTEALVHCRTSSWVSIGLWATNATLAFLCFLGTFLVQSGPGRYNRARGLFFAMLA 775 WRELPTEALVHCRTSSWVSIGLWATNATLAFLCFLGTFLVQSGPGRYNRARGLFFAMLA 775 WRELPTEVLEHCHWSSWVSIGLWATNATLAFLCFLGTFLVQSGPGRYNRARGLFFAMLA 775 WRELPTEVLEHCHWSSWVSIGLWATNATLAFLCFLGTFLVQSGPGRYNRARGLFFAMLA 775 WRELPTEVLEHCHWSSWVSIGLWATNATLAFLCFLGTFLVQSGPGRYNRARGLFFAMLA 775 WRELPTEVLEHCHWSSWVSIGLWATNATLAFLCFLGTFLVQSGPGRYNRARGLFFAMLA 768 WRENTERVENTERSWVSIGLWATNATLAFLCFLGTFLVQSGPGRYNRARGLFFAMLA 768 WRENTERVENTERSWVSIGLWATNATLAFLCFLGTFLVQSGPGRYNRARGLFFAMLA 768 WRENTERVENTERSWVSIGLWATNATLAFLCFLGTFLVQSGPGRYNRARGLFFAMLA 768 WRENTERVENTERSWVSIGLWATNATLAFLCFLGTFLVQSGPGRYNRARGLFFAMLA 768 WRENTERVENTERSWVSIGLWATNATLAFLCFLGTFLVQSGPGRYNRARGLFFAMLA 768 WRENTERVENTERSWVSIGLWATNATATATATATATATATATATATATATATATATATAT	
chimpanzee gorilla orangutan baboon rheaus monkey squirrel_monkey marmoset cow dog rat mouse human chimpanzee gorilla orangutan baboon rheaus monkey squirrel_monkey marmoset	WHELPTEALVHCRTRSWVSPGLAHATNATLAFLCFLGTFLVRSOPGRYNRARGLFFAMLA 770 WHELPTEALVHCRTRSWVSPGLAHATNATLAFLCFLGTFLVRSOPGRYNRARGLFFAMLA 770 WHELPTEALVHCRTSSWVSPGLAHATNATLAFLCFLGTFLVQSSPGRYNRARGLFFAMLA 770 WHELPTEALVHCRTSSWVSPGLWATNATLAFLCFLGTFLVQSSPGRYNRARGLFFAMLA 770 WRELPTEALVHCRTSSWVSPGLWATNATLAFLCFLGTFLVQSSPGRYNRARGLFFAMLA 770 XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX	
chimpanzee gorilla orangutan baboon rheaus monkey squirrel_monkey marmoset cow dog rat mouse human chimpanzee gorilla orangutan baboon rheaus monkey squirrel_monkey marmoset cow	<pre>WHILPTEALVHCRTRSWVSPGLAHATNATLAFLCFLGTFLVFSQPGRYNRARGLFFAMLA 770 WHILPTEALVHCRTRSWVSPGLAHATNATLAFLCFLGTFLVQSPGRYNRARGLFFAMLA 770 WHILPTEALVHCRTSWVSPGLAHATNATLAFLCFLGTFLVQSPGRYNRARGLFFAMLA 770 WHILPTEALVHCRTSWVSPGLWATNATLAFLCFLGTFLVQSPGRYNRARGLFFAMLA 770 WHILPTEALVHCRTSWVSPGLWATNATLAFLCFLGTFLVQSPGRYNRARGLFFAMLA 770 WHILPTEALVHCRTSWVSFGLWATNATLAFLCFLGTFLVQSPGRYNRARGLFFAMLA 770 WHILPTEALVHCRTSWVSFGLWATNATLAFLCFLGTFLVQSPGRYNRARGLFFAMLA 770 WHILPTEALVHCRTSWVSFGLWATNATLAFLCFLGTFLVQSPGRYNRARGLFFAMLA 770 WHILPTEALVHCRTSWVSIGLWATNATLAFLCFLGTFLVQSPGRYNRARGLFFAMLA 770 WHILPTEALVHCRTSWVSIGLWATNATLAFLCFLGTFLVQSPGRYNRARGLFFAMLA 775 WHILPTEALVHCRTSWVSIGLWATNATLAFLCFLGTFLVQSPGRYNRARGLFFAMLA 775 WHILPTEALVHCRTSWVSIGLWATNATLAFLCFLGTFLVQSPGRYNRARGLFFAMLA 775 WJIPTEVLEHCHWSSWVSIGLWATNATLAFLCFLGTFLVQSPGRYNRARGLFFAMLA 775 WJIPTEVLEHCHWSSWVSIGLWATNATLAFLCFLGTFLVQSPGRYNRARGLFFAMLA 775 WJIPTEVLEHCHWSSWVSIGLWATNATLAFLCFLGTFLVQSPGRYNRARGLFFAMLA 775 WJIPTEVLEHCHWSSWVSIGLUCUGILAFHLFRCYLLINGOGINTPEFFL 830 YFTWWSFVFLLANVQVVLRPAVQMGALLLCVLGILAAFHLPRCYLLINGOGINTPEFFL 830 YFTWWSFVFLLANVQVVLRPAVQMGALLLCVLGILAAFHLPRCYLLINGOGINTPEFFL 830 YFTWWSFVFLLANVQVVLRPAVQMGALLCVLGILAAFHLPRCYLLINGOGINTPEFFL 830 YXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX</pre>	
chimpanzee gorilla orangutan baboon rheaus monkey marmoset cow dog rat mouse human chimpanzee gorilla orangutan baboon rheaus monkey squirrel_monkey marmoset cow dog	<pre>WHELPTEALVHCRTRSWVSPGLAHATNATLAFLCFLGTFLVFSQPGRYNRARGLFFAMLA 770 WHELPTEALVHCRTRSWVSPGLAHATNATLAFLCFLGTFLVFSQPGRYNRARGLFFAMLA 770 WHELPTEALVHCRTRSWVSPGLAHATNATLAFLCFLGTFLVQSSPGRYNRARGLFFAMLA 770 WHELPTEALVHCRTSSWVSPGLWATNATLAFLCFLGTFLVQSSPGRYNRARGLFFAMLA 770 WREUPTEALVHCRTSSWVSPGLWATNATLAFLCFLGTFLVQSSPGRYNRARGLFFAMLA 770 WREUPTEALVHCRTSSWVSPGLWATNATLAFLCFLGTFLVQSSPGRYNRARGLFFAMLA 770 WREUPTEALVHCRTSSWVSIGLWATNATLAFLCFLGTFLVQSSPGRYNRARGLFFAMLA 770 WREUPTEALVHCRTSSWVSIGLWATNATLAFLCFLGTFLVQSSPGRYNRARGLFFAMLA 770 WREUPTEALVHCRTSSWVSIGLWATNATLAFLCFLGTFLVQSSPGRYNRARGLFFAMLA 770 WREUPTEUHRCNSSWVSIGLWATNATLAFLCFLGTFLVQSSPGRYNRARGLFFAMLA 770 WREUPTEUHRCRNSSWVSIGLWATNATLAFLCFLGTFLVQSSPGRYNRARGLFFAMLA 775 WSUPTEVLEHRCMSSWVSIGLWATNATLAFLCFLGTFLVQSSPGRYNRARGLFFAMLA 775 WSUPTEVLEHRCMSSWVSIGLWATNATLAFLCFLGTFLVQSSPGRYNRARGLFFAMLA 775 WSUPTEVLEHRCMSSWVSIGLWATNATLAFLCFLGTFLVQSSPGRYNRARGLFFAMLA 775 WSUPTEVLEHRCMSSWXIGLWATNATUAFLCFLGTFLVQSSPGRYNRARGLFFAMLA 775 WSUPTEVLEHRCMSSWXIGLWATNATUAFLCYLGTLAFFLDFCYLLENGSGLATFEFEL 330 YFTTWVSFVELLANVQVLEPAVQMGALLLCVLGTLAFHLPRCYLLENGSGLATFEFEL 330 YFTTWVSFVELLANVQVLEPAVQMGALLLCVLGTLAFHLPRCYLLENGSGLATFEFEL 330 YFTTWVSFVELLANVQVLEPAVQMGALLCVLGTLAFHLPRCYLLENGSGLATFEFEL 330 YFTTWVSFVELLANVQVLEPAVQMGALLCVLGTLAFHLPRCYLLENGSGLATFEFEL 330 YFTTWVSFVELLANVQVLEPAVQMGALLCVLGTLAFHLPRCYLLENGSGLATFEFEL 330 YFTTWVSFVELLANVQVLEPAVQMGALLCVLGTLAFHLPRCYLLENGSGLATFEFEL 330 YFTTWVSFVELLANVQVLEPAVQMGALLCVLGTLAFHLPRCYLLENGSGLATFEFEL 330 YFTTWVSFVELLANVQVLEPAVQMGALLCVLGTLAFHLPRCYLLENGSLATFEFEL 330 YFTTWVSFVELLANVQVLEPAVQMGALLCVLGTLAFHLPRCYLLENGSLATFEFEL 330 YFTTWVSFVELLANVQVLEPAVQMGALLCVLGTLAFHLPRCYLLENGSLATFEFEL 330 YFTTWVSFVELLANVQVLEPAVQMGALLCVLGTLAFHLPRCYLLENGSLATFEFEL 330 YFTTWVSFVELLANVQVVLEPAVQMGALLCVLGTLAFFELPRCYLLENGSLATFEFEL 330 YFTTWVSFVELLANVQVVLEPAVQMGALLCVLGTLAFFELPRCYLLENGSLATFEFEL 330 YFTTWVSFVELLANVQVVLEPAVQMGALLCVLGTLAFFELPRCYLLENGSLATFEFEL 330 YFTTWVSFVELANVQVVVQVQVLGTLGVQLGTLFFELDGCLLENGEFEFEL 330 YFTTWVGFFELFAVHVVGHPQVQMGALLCVLGTLGTLFFELPRCYLLENGSLATFEFEL 331 YFTTNFFVELFAVHVVGHPQVQMGALLCVLGTL</pre>	
chimpanzee gorilla orangutan baboon rheaus monkey squirrel_monkey marmoset cow dog rat mouse human chimpanzee gorilla orangutan baboon rheaus monkey squirrel_monkey marmoset cow dog	<pre>WHILPTEALVHCRTRSWVSPGLAHATNATLAFLCFLGTFLVFSQPGRYNRARGLFFAMLA 770 WHILPTEALVHCRTRSWVSPGLAHATNATLAFLCFLGTFLVVSSQPGRYNRARGLFFAMLA 770 WHILPTEALVHCRTSWVSPGLAHATNATLAFLCFLGTFLVVSSPGRYNRARGLFFAMLA 770 WHILPTEALVHCRTSWVSPGLWATNATLAFLCFLGTFLVVSSPGRYNRARGLFFAMLA 770 WRILPTEALVHCRTSWVSPGLWATNATLAFLCFLGTFLVVSSPGRYNRARGLFFAMLA 770 WRILPTEALVHCRTSWVSPGLWATNATLAFLCFLGTFLVVSSPGRYNRARGLFFAMLA 770 WRILPTEALVHCRTSWVSPGLWATNATLAFLCFLGTFLVVSSPGRYNRARGLFFAMLA 770 WRILPTEALVHCRTSWVSUGLWATNATLAFLCFLGTFLVVSSPGRYNRARGLFFAMLA 770 WRILPTEALVHCRTSWVSUGLWATNATLAFLCFLGTFLVVSSPGRYNRARGLFFAMLA 775 WRILPTEVLBHCRWSWSUGLWATNATLAFLCFLGTFLVVSSPGRYNRARGLFFAMLA 775 WRILPTEVLBHCRWSWVSUGLWATNATLAFLCFLGTFLVVSSPGRYNRARGLFFAMLA 775 WRILPTEVLBHCRWSWVSUGLWATNATLAFLCFLGTFLVVSSPGRYNRARGLFFAMLA 775 WRILPTEVLBHCRWSWVSUGLWATNATLAFLCFLGTFLVVSSPGRYNRARGLFFAMLA 775 WRILPTEVLBHCRWSWVSUGLWATNATLAFLCFLGTFLVVSSPGRYNRARGLFFAMLA 775 WRILPTEVLBHCRWSWVSUGLWATNATLAFLCLGTFLVVSSPGRYNRARGLFFAMLA 775 WRILPTEVLBHCRWSWVSUGLWATNATLAFLCLUNGTLAFHLBRCYLLINGVGRNRARGLFFAMLA 775 WRILPTEVLBHCRWSWVSUGLWATNATURAFUCFUGTFLFUVGSPGRYNRARGLFFAMLA 775 WRILPTEVLBHCRWSVVSUGLWATNATURAFUCFUGTLAFHLBRCYLLINGVGRNRARGLFFAMLA 775 WRITTEVVSVVLLANVVVVLRPAVQMGALLLCVLGTLAAFHLBRCYLLINGVGRNRARGLFFAMLA 775 WRITTEVSVVLLANVVVVLRPAVQMGALLLCVLGTLAAFHLBRCYLLINGVGRNRARGLFFAMLA 775 WRITTEVSVVLLANVVVVLRPAVQMGALLLCVLGTLAAFHLBRCYLLINGVGRNRARGLFFAMLA 775 WRITTEVSVVLLANVVVVLRPAVQMGALLLCVLGTLAAFHLBRCYLLINGVGLNTPEFFL 330 YFTWSVVLLANVVVVVRRAVVVXXXXXXXXXXXXXXXXXXXXXXXXXXX</pre>	
chimpanzee gorilla orangutan baboon rhesus monkey squirrel_monkey marmoset cow dog rat mouse human chimpanzee gorilla orangutan baboon rhesus monkey squirrel_monkey marmoset cow dog rat mouse	<pre>WHILLPTEALVHCRTRSWVSPGLAHATNATLAFLCFLGTFLVFSQPGRYNRARGLFFAMLA 770 WHILLPTEALVHCRTRSWVSPGLAHATNATLAFLCFLGTFLVFSQPGRYNRARGLFFAMLA 770 WHILLPTEALVHCRTRSWVSPGLAHATNATLAFLCFLGTFLVQSRPGRYNRARGLFFAMLA 770 WHILLPTEALVHCRTRSWVSPGLWATNATLAFLCFLGTFLVQSRPGRYNRARGLFFAMLA 770 WRILPTEALVHCRTSSWVSPGLWATNATLAFLCFLGTFLVQSRPGRYNRARGLFFAMLA 770 WRILPTEALVHCRTSSWVSPGLWATNATLAFLCFLGTFLVQSRPGRYNRARGLFFAMLA 770 WRILPTEALVHCRTSSWVSPGLWATNATLAFLCFLGTFLVQSRPGRYNRARGLFFAMLA 770 WRILPTEALVHCRTSSWVSIGLWATNATLAFLCFLGTFLVQSRPGRYNRARGLFFAMLA 770 WRILPTEALVHCRTSSWVSIGLWATNATLAFLCFLGTFLVQSRPGRYNRARGLFFAMLA 770 WRILPTEALVHCRTSSWVSIGLWATNATLAFLCFLGTFLVQSRPGRYNRARGLFFAMLA 770 WRILPTEALVHCRTSSWVSIGLWATNATLAFLCFLGTFLVQSRPGRYNRARGLFFAMLA 775 WSILPTEVLEHCHVFSWVSIGLWATNATLAFLCFLGTFLVQSRPGRYNRARGLFFAMLA 775 WSILPTEVLEHCNMSSWISIGLWATNATLAFLCFLGTFLVQSRPGRYNRARGLFFAMLA 775 YFTWYSFVFLLANVQVVLRPAVQMGALLLCVLGILAAFHLPRCYLLINQSGRGRYNFRARGLFFAMLA 775 YFTWYSFVFLLANVQVVLRPAVQMGALLCVLGILAAFHLPRCYLLINQSGRGRYNFRARGLFFAMLA 775 YFTWYSFVFLLANVQVVLRPAVQMGALLCVLGILAAFHLPRCYLLINQSGRATHFEFL 330 YFTTWYSFVFLLANVQVVLRPAVQMGALLCVLGILAAFHLPRCYLLINQSGLNTPEFFL 330 XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX</pre>	
chimpanzee gorilla rangutan baboon rheaus monkey squirrel_monkey cow dog rat mouse human chimpanzee gorilla orangutan baboon rheaus monkey squirrel_monkey marmoset cow dog rat mouse	WHELPTEALVHCRTRSWVSPGLAHATNATLAFLCFLGTFLVFSQPGRYNRARGLFFAMLA 770 WHELPTEALVHCRTSSWVSPGLAHATNATLAFLCFLGTFLVFSQPGRYNRARGLFFAMLA 770 WHELPTEALVHCRTSSWVSPGLAHATNATLAFLCFLGTFLVQSSPGRYNRARGLFFAMLA 770 WHELPTEALVHCRTSSWVSPGLWATNATLAFLCFLGTFLVQSSPGRYNRARGLFFAMLA 770 WRELPTEALVHCRTSSWVSPGLWATNATLAFLCFLGTFLVQSSPGRYNRARGLFFAMLA 770 XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX	
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Model	Active si	Active site				Allosteric site				
	Mean Standard error Standard of mean deviation		Nonbinder/binder Mean threshold		Standard error of mean	Standard deviation	Nonbinder/binder threshold			
Active-close										
hT1R3	-26	1	9	-44	-26	1	6	-38		
hT1R2	-27	2	13	-53	-53 -23		7	-37		
mT1R2	-19	1	5	-29	-28	1	9	-46		
Active-open										
hT1R3	-23	1	7	-37	-21	1	8	-37		
hT1R2	-17	1	8	-33	-16	1	8	-32		
mT1R2	-25	1	7	-39	-24	1	8	-40		

 Table 2
 Statistical analysis of calculated binding energies (kcal/mol) obtained by molecular docking and force field scoring of 100 decoy ligands to the T1R 3D models

These ligands are not expected to have significant binding affinity for the target proteins and, hence, their calculated binding energies represent nonspecific binding interactions. Nonbinder/binder thresholds were calculated as the mean plus 2 times the standard deviation. Calculated binding affinities at or below these thresholds are reasonably expected to represent specific intermolecular interactions. Ligands below these thresholds are expected to bind to the target sites, albeit not necessarily causing biological response.

sites found among taster species were present in any nontaster species. This strategy was adopted because we did not know whether there is a single variant site that determines binding to aspartame or multiple interacting sites in the receptor, and whether acquisition of aspartame sensitivity was a single event in a common ancestor (and thus all sensitive species would have the same variant site), or there were multiple events (and then aspartame sensitivity can be due to different variants at the same site or variants at different sites). We allowed for both possibilities when assessing the amino acid variation in the receptors and therefore did not exclude locations in which one aspartame tasting species differed from another aspartame tasting species, as long as they did not share amino acids in common at that location with nontaster species. Using these criteria, we found 9 variant sites in T1R2 (Table 7) and 32 variant sites in T1R3 (Table 8).

T1R3 is not more variable at the amino acid sequence level than T1R2 among all species assessed here (sequence identities range from 69% to 99% for T1R3 and from 69% to 98% for T1R2), but it makes a lopsided contribution to the variation that parses aspartame tasters from nontasters, with an approximately a 3-fold increase in the variation that separates tasters from nontasters in the T1R3 protein compared with the T1R2 protein. This observation may be an artifact from having only 2 nontaster primate species for the T1R3 protein (squirrel monkey and marmoset), whereas 4 nontaster primate species were used for comparative purposes for the T1R2 protein (patas and tamarin as well as squirrel monkey and marmoset).

Variation in the T1R3 protein is found evenly distributed across its sequence. The most common type of sequence variants associated with aspartame taster status were amino acid substitutions, but a 5 amino acid deletion at human amino acid positions 348–352 of the T1R2 protein was observed in some nontasters. The amino acids were deleted only in the nontasters but not taster primates. The other nontasters, mouse, rat, cow, and dog, did not have the deletion but do instead have amino acid substitutions that distinguish them from tasters at 2 of these 5 positions (349 and 351).

#### Molecular modeling

Molecular modeling and docking were used to gain insights into the role of the variant sites identified by sequence alignment which are associated with T1R2/T1R3 dimerization and aspartame binding. The goal was to identify structural difference associated to the variant sites that may correlate to taster/ nontaster status. We analyzed the distribution of the variant sites throughout the predicted dimer structure (Figure 4), the calculated binding energies for aspartame and natural sugars bound to the various 3D models (Table 3; additional data not shown), and receptor-tastant interactions for the complex structures obtained from molecular docking (Tables 9 and 10; Figure 5, additional data not shown).

#### Determining nonbinder/binder thresholds

In order to determine threshold values of binding energies for discriminating nonbinding compounds (referred as "nonbinders") from binding compounds (referred as "binders") based on calculated binding energies, we examined the mean values of calculated binding energies for the set of 100 decoy ligands. The rationale is that the calculated binding energies for nonbinder decoys reflect the nonspecific nature of the intermolecular interactions between target receptor and these ligands, whereas binding energies calculated for binders reflect specific protein–ligand interactions. Therefore, it is reasonable to expect that calculated

Table 3         Calculated binding energies <sup>a</sup> (kcal/mol) for aspartame and
natural sugars bound to 3D models of the VFT domain of the human T1R2,
mouse T1R2, and human T1R3 receptors in the active-close and
active-open conformations

Ligand	Active-close	b	Active-open <sup>b</sup>		
	Active site	Allosteric site	Active site	Allosteric sit	
hT1R2					
Aspartame	- <u>90</u>	- <u>72</u>	-12	- <u>60</u>	
Sucrose	- <u>75</u>	- <u>53</u>	32	- <u>73</u>	
Fructose	- <u>67</u>	- <u>38</u>	-26	- <u>63</u>	
Dextrose	- <u>74</u>	- <u>49</u>	- <u>43</u>	- <u>46</u>	
Lactose	- <u>77</u>	- <u>58</u>	17	- <u>73</u>	
mT1R2					
Aspartame	- <u>70</u>	- <u>70</u>	- <u>48</u>	<u> </u>	
Sucrose		- <u>49</u>		- <u>58</u>	
Fructose	- <u>35</u>	- <u>55</u>	-25	-37	
Dextrose	- <u>34</u>	-44	-32	<u> </u>	
Lactose	- <u>50</u>	- <u>50</u>	- <u>39</u>		
hT1R3					
Aspartame	- <u>86</u>	-32	- <u>74</u>	13	
Sucrose	- <u>68</u>			- <u>56</u>	
Fructose	- <u>55</u>	- <u>40</u>	- <u>44</u>	- <u>56</u>	
Dextrose	- <u>61</u>	- <u>41</u>	-33	- <u>40</u>	
Lactose	- <u>50</u>		- <u>66</u>	- <u>70</u>	

<sup>a</sup>Values below the nonbinder/binder threshold (see Table 2) are underlined. Calculated binding energies above the threshold reflect nonspecific intermolecular interactions and are not expected to be biologically meaningful. Calculated binding energies below the threshold are due to specific intermolecular interactions. Missing binding energies are the result of unfavorable intermolecular interactions (binding energies above 100 kcal/mol) or shallowly bound ligands (buried surfaces below 70%). <sup>b</sup>Two binding sites are analyzed. The active site is located at the center of the VFT and corresponds to the site where glutamate is found to bind in the experimentally determined structure of rMGR1. The allosteric site is consistent with variant sites identified by DNA analysis and with a mutation site experimentally found to interfere with aspartame response T1R2 (E63K; see Table 4). Based on the calculated energies (more negative is better; positive values indicate unfavorable binding), aspartame binding is more favorable at the allosteric site when the receptor is in an active-open conformation. For an active-close receptor, however, agonist binding is more favorable at the putative active site.

binding energies for binders will have lower values than the mean of binding energies for decoys. Assuming that most (95%) decoy ligands are nonspecific to the target, calculated binding affinities that are better than the decoy mean by 2 standard deviations (Crocker and Algina 1986) can be considered to reflect specific binding. The mean of calculated binding affinities for a set of decoy nonbinders can be used to set threshold values to identify binders. These

threshold values (mean plus 2 times the standard deviation) are shown in Table 2. Ligands with calculated binding affinity at or below (more negative) these thresholds present specific binding interactions to the site and are, thus, expected to bind to the target receptor. Supporting this rationale, the calculated binding energies for natural sugars (Table 3), sucrose and dextrose, believed to bind to the VFT domain of hT1R2 and hT1R3 (Xu et al. 2004; Jiang, Cui, Zhao, et al. 2005; Nie et al. 2005; Zhang et al. 2010) are consistently below the nonbinder/binder thresholds for that site. These thresholds were used to assess whether the binding energies for aspartame bound to the putative active and allosteric sites were indicative of specific intermolecular interactions and not the result of nonspecific binding. Values below the threshold for each site/model are underlined in Table 3.

#### Comparative analysis of calculated binding affinities

Many studies have compared calculated binding energies across multiple protein models representing closely related proteins (Wang and Wade 2001; Murcia et al. 2006; Henrich et al. 2010) or the same protein in different species (Fratev and Benfenati 2008; Tamamis et al. 2010). However, there is no consensus at the present on how one can determine when comparative analysis of calculated binding energies can be performed with reasonable confidence. In our analysis, we compare calculated binding affinities for the same ligand bound with different sites within the same target protein in different structural conformations. It is reasonable to assume that these energies can be compared since they are calculated for equivalent systems (same atoms, different coordinates). Moreover, the means of binding energies for the decoy ligands across multiple binding sites and multiple conformations of the receptors are within standard deviation of each other (Figure 3), consistent with the nonspecific nature of the intermolecular interactions that generated them. The means of binding energies for natural sugars are consistently lower than for decoys, which reflect the higher specificity of these ligands for the receptors (Table 3, Figure 3). These observations increase confidence in the validity of the comparative analysis of binding energies we present below. A caveat, however, is that although force-field-based binding energies can be used to rank ligands according to their affinity for the target protein, their absolute values are not expected to correspond to experimental binding constants (Ferrari et al. 2007; Grigoriev et al. 2007). This is mostly due to intrinsic exclusion of entropic contributions (Gilson and Zhou 2007; Hnizdo et al. 2008; Irudayam and Henchman 2009), which vary with the nature of the ligand.

We used the nonbinder/binder thresholds to infer which values of calculated binding energies should be taken as meaningful (i.e., representing specific intermolecular interactions between ligand and receptor). The analysis of binding energies and bound structures (Table 3 and Figure 5, additional

Table 4         T1R binding sites for aspartame and other sweeteners from in vitro studies	
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Compounds	Interact receptors	Results	References
Aspartame	hT1R2	VTFD of hT1R2 is required for aspartame binding	Xu et al. (2004)
Neotame	hT1R3	S144A and E302A of hT1R2 abolish aspartame sensitivity	
Cyclamate	rT1R2		
	rT1R3		
Aspartame	hT1R2	hT1R2 + hT1R3 but not rT1R2 + rT1R3 responses to aspartame	Li et al. (2002)
Neotame	hT1R3		
Cyclamate	rT1R2		
37 other compounds	rT1R3		
Aspartame	hT1R2	Response to brazzein requires hT1R3 residues 536-545 (cysteine-rich region; hT1R2 + mT1R3 but not mT1R2 + hT1R3 responds to aspartame	Jiang et al. (2004)
Brazzein	mT1R2		
Other compounds	hT1R3		
	mT1R3		
Aspartame	hT1R3	A733 in hT1R3 is required for lactisol sensitivity	Jiang, Cui, Zhao, et al. (2005)
Lactisol	hT1R2, mT1R2, mT1R3		
Cyclamate	hT1R3	TMD of hT1R3 determines responsiveness of cyclamate.	Jiang, Cui, Zhao, Snyder, et al. (2005)
Aspartame	hT1R2	E63K of hT1R2 showed reduced activity for D-Tryp and aspartame.	Jiang, Cui, Ji, et al. (2005)
D-tryptophan, brazzein, sucrose, monellin	hT1R3	D307A and D307N reduce or abolish responses of D-Tryp and aspartame.	Walters et al. (2009)
Trehalose	hT1R3	mT1R3 responses to trehalose	Ariyasu et al. (2003)
Aspartame	mT1R1	rT1R2 + rT1R3 does not respond to aspartame	Nelson et al. (2001)
Other compounds	mT1R2		
	mT1R3		
Aspartame D and	mT1R1	hT1R2 + mT1R3 but not mT1R2 + hT1R3 responds	Nelson et al. (2002)
L amino acids	mT1R2	to aspartame	
	mT1R3		
Aspartame	hT1R2	V738A and L735F of the rT1R3 mediate insensitivity to lactisole	Winnig et al. (2005)
Lactisol	hT1R3		
	rT1R2		
	rT1R3		
Aspartame	hT1R2	hT1R2 rescues the mouse's response to aspartame	Zhao et al. (2003)
	mT1R1		
	mT1R2		
	mT1R3		

#### Table 4 Continued

Compounds	Interact receptors	Results	References
Sucrose	hT1R2	R383A, E302A, D278A, D142A, Y103A, and S40A abolish response; P277A and D307A significantly reduce response; K65A reduces response to sucralose but not to sucrose	Zhang et al. (2010)
Sucralose			

The prefix h, r, or m before the receptor protein designation refers to the human, rat, or mouse receptor sequence, respectively. All compounds listed taste sweet to humans or are sweet-blockers (lactisole). All studies used one of several lines of human embryonic kidney cells. Amino acid changes are denoted by their single letter codes followed by the species-appropriate position. The cysteine-rich region links the VFT domain (VFTD) on the N-terminus to the transmembrane domains (TMDs) and C-terminus of the protein. When receptors are linked by a + sign, this indicates that coexpression and presumably dimerization is required for function.

 Table 5
 Percent of sequence identity among pairs of species for the T1R2 gene and protein

Species	Human	Chimpanzee	Gorilla	Orangutan	Baboon	Rhesus monkey	Squirrel monkey	Marmoset	Cow	Dog	Rat	Mouse
Human		98	98	95	92	91	89	86	70	76	71	69
Chimpanzee	99		99	96	92	91	88	86	70	76	71	70
Gorilla	99	99		96	92	92	88	87	70	76	71	69
Orangutan	96	96	96		93	92	89	87	71	76	71	70
Baboon	94	94	94	94		99	89	87	71	76	72	71
Rhesus monkey	94	94	94	94	99		89	87	71	76	72	71
Squirrel monkey	92	92	92	92	92	92		92	70	75	71	70
Marmoset	90	90	91	90	90	90	94		70	74	70	69
Cow	77	77	77	77	76	76	77	76		72	65	66
Dog	83	83	83	83	83	83	83	81	79		71	71
Rat	78	78	78	78	79	79	79	78	72	79		91
Mouse	78	78	77	78	78	78	79	77	73	79	91	

Upper right-hand cells (italics) contain deduced amino acid identity; lower left cells (bold) contain nucleotide identity. Patas monkey and tamarin, for which extended areas of the gene were refractory to sequencing, were excluded from this analysis.

Table 6	Percent of sec	nuence identity	among nairs	of species	for the T1R3	gene and	protein
lable 0	Tercent Of Sec	juence identity	amony pairs	o o species		yene anu	protein

Species	Human	Chimpanzee	Gorilla	Orangutan	Baboon	Squirrel monkey	Marmoset	Cow	Dog	Rat	Mouse
Human		99	98	95	95	84	84	69	75	73	72
Chimpanzee	98		98	95	95	84	85	69	75	73	73
Gorilla	98	98		94	94	84	85	69	75	73	73
Orangutan	95	95	95		93	84	84	70	76	73	73
Baboon	96	96	95	94		84	84	69	75	73	73
Squirrel monkey	88	88	88	88	88		92	68	74	72	72
Marmoset	88	88	88	87	88	93		65	75	70	71
Cow	77	77	76	76	76	76	72		75	68	67
Dog	78	79	79	77	77	78	78	80		73	73
Rat	75	75	75	75	75	75	73	72	75		92
Mouse	73	73	73	73	74	75	74	72	74	93	

Upper right cells (italics) contain deduced amino acid identity; lower left cells (bold) contain nucleotide identity. See the caption of Table 5 for other details.

Table 7 T1R2 variant sites associated with aspartame taster/nontaster status

Position <sup>a</sup>	Specie	pecies name												
	Tasters						Nontasters							
	Hu	Ch	Go	Or	Ра	Ва	Re	Sq	Ma	Та	Co	Do	Ra	Mo
67	I	Ι	Ι	I	I	I	I	S	S	S	L	L	L	L
175	V	V	V	V	Х	V	V	Q	Q	Х	Х	Q	R	R
228	R	R	R	R	R	R	R	G	G	G	Н	Т	Т	Т
248	Ν	Ν	Ν	Ν	Ν	Ν	Ν	D	D	D	Т	V	V	А
259	Т	Т	Т	Т	Т	Т	Т	S	S	S	А	А	Ν	Ν
286	Ν	Ν	Ν	Ν	Ν	Ν	Ν	R	R	R	R	R	Н	R
348	Р	Р	Р	Р	Р	Р	Р	_	_	_	Р	Р	Р	Р
349	Р	Р	Р	Р	Р	Р	Р	_	_	_	А	Е	V	Μ
350	L	L	L	L	L	L	L	_	_	_	L	Р	Р	Р
351	S	S	S	G	S	S	S	_	_	_	Ν	Ν	Ν	Ν
352	R	R	R	К	R	R	R	_	_	_	R	R	Т	E
512	V	V	V	V	I	I	I	Т	Т	Т	Р	S	Р	Р
682	М	М	М	М	Μ	Μ	М	V	V	V	V	V	V	V

<sup>a</sup>Position based on human sequences. Hu, human; Ch, chimpanzee; Go, gorilla; Or, orangutan; Pa, palas monkey; Ba, baboon; Re, rhesus monkey; Sq, squirrel monkey; Ma, common marmoset; Ta, tamarin; Co, cow; Do, dog; Ra, rat; Mo, mouse. Missing sequence data are shown by "X." Deletions are shown by "-." The aa 348–352 deletion is considered a single variant site. Thus there are 9 variant sites in T1R2.

data not shown) suggests that, for aspartame and for other natural and artificial sweeteners, the most favorable conformation of T1R2 bound to an agonist is active-close, equivalent to the chain A conformation of the rMGR1 homodimer structure. A secondary energetically favorable site exists for agonist binding in the VFT domain of human and mouse T1R2, in both active-close and active-open conformations. This secondary site is equally or more energetically favorable than the putative active site for all bound sweet tastants in the active-open conformation. This secondary site may be important in the transition from active-open to active-close state. Because changes in conformation upon binding are consistent with allosteric regulation, we will refer to this secondary site as "putative allosteric site" throughout the text. As discussed later, this putative allosteric site is consistent with mutation data (Jiang, Cui, Zhao, et al. 2005; Zhang et al. 2010). Aspartame prefers to bind to the site of human T1R3 corresponding to the glutamate-binding site in rMGR1 over all other potential sites identified in the 3D models. Both active-open and active-close conformations of hT1R3 are favorable for aspartame-bound complexes.

## Molecular docking to the active site in the active-close conformation of T1R2

Natural sugars (sucrose, fructose, dextrose, and lactose) and aspartame bind more favorably to the active site of the

hT1R2 than to any other available pocket in active-close conformation (Table 3 and additional data not shown). There are 22 residues directly (within 4.5 Å from bound ligand) involved in binding in the active site of hT1R2 model. These are: Y103, D142, N143, S144, S165, A166, I167, S168, Y215, R270, V272, V274, F275, S301, E302, S303, A305, T326, R378, L379, S380, and R383 (position numbers relative to human sequence; Table 9). For ligands docked to the mouse T1R2 in the active-close conformation, the active site residues involved in direct binding did not include S144, S168, A305, T326, and L379. All the other residues found in the human aspartame-hT1R2 complex were also found in the mouse complex. These 22 positions are all very well conserved among the species represented here. Tasters have identical amino acids in all these positions, except for S168, which is a G in Chimpanzee. Among nontasters, some conserved variations are observed in positions 142, 165, 168, 274, and 275. Notably, the most variability in the active site is observed at position 378, which is an R in human and other species, M in dog and mouse, I in rat, and T in cow. The high degree of conservation of these 22 positions is consistent with a role in agonist binding. Variations in these positions may explain differences in sensitivity or preference for different natural sugars observed among species. However, it is unlikely to fully account for aspartame taster/nontaster status. Based on the predicted binding mode for aspartame (Figure 5), the positions most likely to alter affinity for this

Position <sup>a</sup>	Species	Species name													
	Tasters						Nontas	Nontasters							
	Hu	Ch	Go	Or	Ва	Re	Sq	Ma	Co	Do	Ra	Mo			
4	Р	Р	Р	Р	Р	Р	S	S	L	L	L	L			
60	Р	Р	Р	Р	Р	Р	L	L	Т	Т	L	I			
172	Е	E	E	E	E	E	D	D	D	D	D	D			
176	А	А	А	А	А	А	Т	Т	Ν	Ν	D	D			
197	А	А	А	А	А	А	Т	Т	М	М	V	V			
198	А	А	А	А	А	А	V	V	V	V	V	V			
228	А	А	А	А	А	А	G	G	S	S	G	S			
290	S	S	S	S	S	S	R	R	Y	С	Н	Н			
317	Q	Q	Q	Q	Q	Q	E	E	R	E	R	R			
332	Н	Н	Н	Н	Н	R	Р	Р	Р	Р	Р	Р			
353	А	А	А	А	Т	А	S	S	S	S	S	S			
364	D	D	D	D	D	D	Н	Н	Н	Н	R	Н			
386	Ν	Ν	Ν	Ν	Ν	Ν	Q	Q	L	L	М	L			
438	G	G	G	G	G	Х	А	А	Y	R	R	R			
464	S	S	S	S	S	_	Р	Х	R	L	Р	Р			
467	R	R	R	К	R	_	E	_	М	E	V	V			
473	R	R	R	G	R	_	I	_	S	А	Т	Т			
480	Т	Т	Т	Т	Т	I	Р	_	L	V	L	L			
485	I	I	I	I	I	I	М	_	М	М	М	М			
494	К	К	К	К	К	К	E	_	E	R	V	V			
540	F	F	S	F	F	F	Р	_	К	Q	Р	Р			
545	E	Е	E	E	E	E	Q	_	Q	Q	Q	Q			
673	S	S	S	S	S	S	W	_	Н	R	С	С			
713	М	М	М	I	М	М	V	_	А	V	V	V			
739	Т	Т	Т	Т	Т	Т	I	_	М	М	V	Μ			
798	L	L	L	L	L	_	F	_	I	I	I	T			
818	М	М	I	М	V	_	L	_	L	L	L	L			
835	G	G	G	G	G	_	I	_	S	D	К	К			
842	D	D	D	D	D	_	V	_	G	S	S	S			
844	Ν	D	D	D	D	_	Т	_	G	G	S	G			
845	Т	Т	Т	Т	Т	_	E	_	Н	S	S	G			
847	Ν	Ν	Ν	Ν	Ν	_	А	_	E	G	А	А			

Table 8 T1R3 variant sites associated with aspartame taster/nontaster status

<sup>a</sup>Position based on human sequences. See caption for Table 7 for other details.

sweetener are R378 (anchors aspartame's carboxyl group) and E302 (charge–charge interaction to aspartame's amine group). This is consistent with experimental results showing that the mutation of E302 to A abolishes response to

aspartame (Xu et al. 2004). S144 was also found to abolish aspartame response experimentally when mutated to A (Xu et al. 2004). Another position of interest is D142, which is the only difference in the putative active site between tasters



**Figure 3** Calculated binding energies (kcal/mol) for 100 decoy ligands and 4 natural sugars docked to the active-close and active-open conformations of the human T1R2, mouse T1R2, and human T1R3 receptors. Decoy ligands are not expected to bind, whereas natural sugars are expected to bind to these receptors. The mean values of binding energies are marked as horizontal lines within the cluster of points corresponding to a particular site/conformer/ receptor. Positive values of binding energies are nonfavorable and, hence, were omitted. Ligands with a percentage of buried surface above 70% were eliminated. The lowest mean of the binding energies for the decoy ligands is marked as dashed line in both the decoys and natural sugar graphs, for reference. As expected, the mean binding energies for sugars are consistently lower than for decoys.

and primate nontasters squirrel monkey, marmoset, and tamarin. A more recent study (Zhang et al. 2010) mapping the binding of sweet taste enhancers onto the VFT domain of T1R2 found that mutations Y103A, D142A, E302, and R383 abolish response to sucrose. These positions are all present in our predicted active-close active site for hT1R2, which increases confidence in the docked models.

## Aspartame binding to the putative allosteric site in the active-close conformation of T1R2

According to the molecular modeling results, a secondary energetically favorable site exists for aspartame binding in the VFT domain of human and mouse T1R2 in both active-close and active-open conformations. For human, aspartame binding in the putative allosteric site is less favorable than binding to the active site in the active-close conformation. In contrast, this site in mouse T1R2 in the active-close conformation is as favorable for binding as the active site (Table 3). The residues comprising this allosteric site are: F27, L41, H42, K60, E61, Y62, E63, Y69, E340, W341, R352, T353, S354, Q355, and S356 (positions relative to human sequence; Table 10). The same residues are found to be involved in binding in independent analysis of mT1R2ligand complex structures. The positions comprising the putative allosteric site are well conserved among aspartame tasters, except for E340, which is V for palas monkey, baboon, and rhesus monkey, and W341, which is an R for half of the tasters. Interestingly, sequence variability is observed among nontasters for most of these positions. Mutation of E63 to K in human T1R2 was found experimentally to reduce aspartame response (Jiang, Cui, Ji, et al. 2005), which supports the idea that binding to this putative allosteric site is critical for response. Three key replacements (E63N, R352E, and S356R) between human and mouse T1R2 change the orientation and geometry (binding mode) of aspartame bound to the putative allosteric site in human compared with

Position <sup>a</sup>	Species name													
	Tasters	5						Non-tasters						
	Hu	Ch	Go	Or	Ра	Ва	Re	Sq	Ma	Ta	Co	Do	Ra	Мо
103	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
142	D	D	D	D	D	D	D	<u>E</u>	<u>E</u>	<u>E</u>	D	D	D	D
143	Ν	Ν	Ν	Ν	Ν	Ν	Ν	Ν	Ν	Ν	Ν	Ν	Ν	Ν
144	S	S	S	S	S	S	S	S	S	S	S	S	S	S
165	S	S	S	S	Х	S	S	S	S	S	S	S	S	S
166	А	А	А	А	Х	А	А	А	А	А	А	А	А	А
167	Ι	I	I	I	Х	Ι	Ι	I	I	I	<u>F</u>	Ι	I	T
168	S	G	S	S	Х	S	S	S	S	S	<u>N</u>	S	S	T
215	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
270	R	R	R	R	R	R	R	R	R	R	R	R	R	R
272	V	V	V	V	V	V	V	V	V	V	V	V	V	V
274	V	V	V	V	V	V	V	V	V	V	V	L	V	Ι
275	F	F	F	F	F	F	F	F	F	F	F	F	F	F
301	S	S	S	S	S	S	S	S	S	S	S	S	S	S
302	Е	Е	Е	Е	Е	Е	Е	Е	Е	Е	Е	Е	Е	Е
303	S	S	S	S	S	S	S	S	S	S	S	S	S	S
305	А	А	А	А	А	А	А	А	А	А	А	А	А	А
326	Т	Т	Т	Т	Т	Т	Т	Т	Т	Т	Т	Т	Т	Т
378	R	R	R	R	R	R	R	R	R	R	<u>T</u>	M	<u> </u>	M
379	L	L	L	L	L	L	L	L	L	L	L	L	L	L
380	S	S	S	S	S	S	S	S	S	S	S	S	S	S
383	R	R	R	R	R	R	R	R	R	R	R	R	R	R

 Table 9
 Residues within 4.5 Å of bound aspartame in the active site of modeled T1R2 (active-close conformation)

<sup>a</sup>Position numbers based on human sequence. Undetermined residues are labeled "X." Species abbreviations as in Table 7. Amino acids different from human residues at corresponding position are underlined.

mouse (Figure 5). For example, the carboxyl group of aspartame points toward R352 in hT1R2 but flips toward W341 (which is replaced with R) in the mouse T1R2. These differences in binding mode may confer extra stability to aspartame binding in the mouse T1R2 compared with human. This stronger binding to the allosteric site may compete with binding to the active site which would explain, at least in part, mouse nontaster/taster status.

#### Positioning of the variant sites in the 3D models and with respect to bound aspartame

The mapping of the taster/nontaster variant positions identified by sequence analysis onto the T1R 3D models (Figure 4) suggests that the positions likely to be responsible for species differences in taste response to aspartame are located within segment P348-R352 (hT1R2) (pictured as

a green ribbon in Figure 4) and I67 (hT1R2) at the entry of the active site in the VFT. The segment P348-R352 (hT1R2) is a deletion in some aspartame nontasters (squirrel monkey, marmoset, and tamarin), variable among the other nontasters (PMPNE in mouse, PALNR in cow, PEPNR in dog, and PVPNT in rat, compared with PPLSR in human), and well conserved among all primate tasters. This segment is likely involved in allosteric binding, as discussed later. I67 (hT1R2) is replaced by L in nontasters mouse, rat, cow, and dog and by S in all other nontaster in Figure 2. The conserved replacement I-L is not expected to significantly impact the nature of interactions between ligand and receptor, whereas nonpolar polar I for S replacement may change the dynamics of access to the center of the VFT. Positions most likely involved in dimerization are V175 (hT1R2) and A176 (hT1R3) because of their location and orientation at the dimer interface. These 2 amino acids

Position <sup>a</sup>	Species name													
	Tasters	;					Nontasters							
	Hu	Ch	Go	Or	Ра	Ва	Re	Sq	Ma	Та	Co	Do	Ra	Мо
27	F	F	F	F	F	F	F	F	F	F	F	F	F	F
41	L	L	L	L	L	L	L	L	L	L	L	L	L	L
42	Н	Н	Н	Н	Н	Н	Н	Н	Н	Н	Н	Н	Н	Н
60	K	К	К	К	Х	К	К	К	К	К	К	К	N	N
61	E	E	E	Е	Х	Е	Е	Е	E	Е	Е	<u>K</u>	Е	Е
62	Y	Y	Y	Y	Х	Y	Y	Y	Y	Y	Y	Y	<u>F</u>	Υ
63	Е	Е	Е	Е	Е	Е	Е	Е	E	Е	Е	Е	<u>T</u>	N
69	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
340	E	E	E	Е	V	V	V	V	V	V	V	<u> </u>	V	V
341	W	W	W	<u>R</u>	<u>R</u>	<u>R</u>	<u>R</u>	<u>R</u>	<u>R</u>	<u>R</u>	<u>R</u>	<u>R</u>	<u>R</u>	<u>R</u>
352	R	R	R	<u>K</u>	R	R	R	_	_	_	R	R	<u>T</u>	<u>E</u>
353	Т	Т	Т	Т	Т	Т	Т	Т	Т	Т	S	Т	Т	Т
354	S	S	S	S	S	S	S	N	<u>N</u>	N	-	<u>S</u>	N	<u>S</u>
355	Q	Q	Q	Q	Q	Q	Q	Q	Q	Q	-	L	L	L
356	S	S	S	<u>R</u>	<u>R</u>	<u>R</u>	<u>R</u>	<u>R</u>	<u>R</u>	<u>R</u>	S	<u>E</u>	<u>R</u>	<u>R</u>

Table 10 Residues within 4.5 Å of bound aspartame in the putative allosteric site of modeled T1R2 (active-close conformation)

<sup>a</sup>Position numbers based on human sequence. Deletion in the sequences are marked as "-." Undetermined residues are labeled "X." Species abbreviations as in Table 7. Amino acids different from human residues at corresponding position are underlined.

are replaced with R and D, respectively, in the mouse receptor, forming a salt bridge between mT1R2 and mT1R3. This replacement may affect dimerization and/ or activation after dimerization. Other nontaster species also display complementary replacements, with V175 (hT1R2) replaced by Q and A176 (hT1R3) replaced by T or N. Both Q-T and Q-N pairs may form hydrogen bonds in the dimer. None of the taster/nontaster variant sites were found to be within 4.5 Å of the best (most energetically favorable) active site-bound aspartame in either T1R2 or T1R3 (Table 9 and Figure 4). However, I67 (hT1R2) at the entry of the active site was found to interact with aspartame in some of the higher energy conformations during molecular docking. Overall, the modeling data suggest that the putative allosteric site competes for binding of aspartame with the active site in mouse T1R2 (similar binding affinities) but not in human (much better binding affinity in the active site) (Table 3). The fact that positions E302 in the active site and E63 in the allosteric site predicted in our molecular docking analyses were found to abolish or reduce aspartame response experimentally (Jiang et al. 2004; Xu et al. 2004) supports the idea that both sites play a role in aspartameinduced activation of the receptor. The other taster/nontaster variants are not involved in receptor-ligand or receptorreceptor interactions, and their role in aspartame response,

if any, cannot be assessed from the models without performing further calculations to probe structural stability.

#### Discussion

#### Nucleotide and amino acid sequence similarity

We found that the nucleotide homology was consistently higher between any 2 pairs of species for the Tas1r2 gene compared with the Tas1r3 gene, but these differences in nucleotides did not lead to the same degree of difference in amino acid similarity (Tables 5 and 6). In other words, Tas1r3 varies more among species at the nucleotide level but these differences are not translated into a more variable T1R3 protein. This observation is consistent with other types of analysis which suggests that the Tas1r3 gene has been subject to more purifying selection than the Tas1r2 gene (Shi and Zhang 2006), which should result in *de novo* mutations in the Tas1r3 gene to be more often eliminated by natural selection than for the Tas1r2 gene. T1R3 may be under pressure of purifying selection because it has at least 2 roles: it combines with the T1R1 protein to make the umami or savory receptor, and it combines with the T1R2 protein to make the sweet receptor. It may also combine with other GPCRs to form receptors for minerals (Tordoff et al. 2008). As a consequence, its structure and,



Figure 4 Taster/nontaster variant sites (shown as space-filled representation) and centers of binding regions (shown as green or black spheres) displayed onto the VFT domain of the hT1R2 (active-close)-hT1R3 (active-open) heterodimer. The binding regions at the center of the VFT are referred to as active site (the centers of these regions are shown as green spheres labeled AC), whereas the binding regions near the P348-R352 (hT1R2) segment are referred to as allosteric site (the centers of these regions are shown as black spheres labeled AL). The C-alpha trace for hT1R2 is shown as blue ribbon, whereas hT1R3 is shown in purple. The segment P348-R352 (hT1R2) (shown in green ribbon), which is a deletion in most aspartame nontasters and it is replaced with PMPNE in mouse from PPLSR in human T1R2, is key to the spatial arrangement of the putative allosteric site (its center is shown as a black sphere). Taster/nontaster variant sites V175 (hT1R2) and A176 (hT1R3) are found at the interaction interface between hT1R2 and hT1R3. These amino acids are replaced with R and D, respectively, in the mouse receptors. The introduction of charge interactions and steric effects due to the larger side chains at these positions may affect dimerization and/or activation after dimerization.

therefore, sequence does not tolerate variation, so that it can perform its multiple functions.

## Variant sites likely to be responsible for species differences in taste response to aspartame

This study was designed to resolve whether DNA differences in the sweet receptor account for the ability of some species to perceive aspartame as sweet. We identified 41 variant sites that differed among aspartame tasters and nontasters within the 2 sweet receptor genes, any one of which could potentially account for differential response to aspartame. Based upon the modeling work, however, the 5 amino acid segment P348-R352 in T1R2 is the most likely to be responsible for species differences in aspartame taste response. This variation is part of a putative allosteric binding site for aspartame that may compete for binding against the active site in nontaster species that preserve this segment (cow, dog, rat, and mouse). For nontasters with a deletion of this segment, the lack of this allosteric site may prevent the conformational changes which are necessary for dimerization and/or activation of the receptor by aspartame. Our hypothesis is, thus, that binding of aspartame to this allosteric site is a necessary step in receptor activation, but too much affinity for this site will halt the activation process. Other variant sites that may play an important role in aspartame response are I67 (hT1R2) at the entry of the flytrap and the pair V175 (hT1R2)-A176(hT1R3) at the interaction interface of the putative hT1R2/hT1R3 dimer. Their structural positioning suggests that I67 (hT1R2) is involved in the movement of aspartame from the allosteric to the active site, whereas V175 (hT1R2)-A176 (hT1R3) is important for dimer stability.

### An alternative binding site for aspartame explains species differences in taste response

The sweet receptor forms a large protein that is characterized by a long N-terminus, thought to form a VFT domain that contains the ligand binding sites for aspartame. Ligand– receptor interactions for aspartame have been studied using 2 methods: computer-assisted modeling, which is used to predict the shape and binding sites for aspartame (Temussi 2002, 2006, 2007; Walters 2002; Jiang, Cui, Ji, et al. 2005; Jiang, Cui, Zhao, et al. 2005; Jiang, Cui, Zhao, Snyder, et al. 2005; Morini et al. 2005; Cui et al. 2006) and cell-based assay systems (Nelson et al. 2001, 2002; Li et al. 2002; Ariyasu et al. 2003; Zhao et al. 2003; Xu et al. 2004; Jiang, Cui, Zhao, et al. 2005; Jiang, Cui, Zhao, Snyder, et al. 2005; Winnig et al. 2005; Jiang, Cui, Zhao, Snyder, et al. 2005; Winnig et al. 2005; Jiang, Cui, Zhao, Snyder, et al. 2005; Winnig et al. 2005; Jiang, Cui, Zhao, Snyder, et al. 2005; Winnig

Computer methods assume the receptor is similar to the glutamate receptor (chosen because more is known about its exact structure). Previous results using this method are listed in Table 11. None of the variant sites identified in our study map onto key aspartame binding sites suggested by these modeling studies. This observation is also consistent with results of our modeling, where none of the taster/nontaster variant sites was found to be close to the expected active site at the center of the VFT. A possible reason for this lack of agreement is that the response to aspartame is elicited through, or depends upon, a binding site other than that of some natural sugars and sweet proteins.

Cell-based assay results, shown in Table 4, have suggested that T1R2 is more crucial than T1R3 in aspartame sensitivity, and several T1R2 moieties have been identified that are essential for aspartame transduction (S144, E302, E63, and D307). None of the sites identified as essential for aspartame binding in cell-based assays distinguish aspartame tasters and nontasters in the species tested here. All, except E63, are located near the center of the VFT domain, where the closely related MGR1 has the active site for glutamate.

The modeling of the aspartame-T1R2 and aspartame-T1R3 interactions along with the variant sites identified in our work suggests that aspartame may rely on an allosteric site in T1R2 for its activity. According to our 3D models,



**Figure 5** Aspartame (carbon atoms are cyan) bound to the allosteric site of hT1R2 superposed to aspartame (carbon atoms are purple) bound to the allosteric site of mT1R2. Amino acids within 4.5 Å of bound aspartame in hT1R2 are shown in stick representation. The equivalent amino acids in mT1R2 are shown as shadow. Amino acids involved in binding that are identical in mouse and human T1R2 were omitted for clarity. Amino acids E340 and S356 (V and R, respectively, in mouse) are not visible because they are behind the aspartame molecules in this view. Amino acid E63 was found experimentally to reduce aspartame response (see Table 11). E63K (hT1R2) reduces but does not abolish response to aspartame, which is consistent with our proposed model of an allosteric binding site in addition to the active site at the center of the VFT. One of the taster/nontaster variant sites we have identified in hT1R2, R352, is predicted to be directly involved in binding of aspartame into the putative allosteric site. This taster/nontaster variant site corresponds to E356 in mT1R2, which contributes to the difference in geometry and orientation of aspartame into the site, as seen in the picture, and leads to stronger binding of aspartame to the mouse site compared with human.

aspartame binds preferentially and with strong affinity to the active site in human and mouse T1R3. For T1R2, however, a secondary site seems to be energetically favorable for aspartame binding, in addition to the putative active site. For mouse, an aspartame nontaster, the allosteric site is as favorable for binding as the active site in both active-close and active-open conformations. For human T1R2, the allosteric site is preferable in the active-open conformation, whereas the active site is better for binding in the activeclose conformation. The fact that many nontasters have a P348-R352 (hT1R2) deletion within this putative allosteric site further supports its involvement in sweet taste response to aspartame. Although there is no evidence for an activation mechanism that combines both sites, we can speculate that aspartame first binds to the allosteric site, inducing conformational changes that make binding to the active site more favorable. The binding of aspartame to the active site then induces activation and response. Whether aspartame migrates from one site to the other or 2 molecules are required for activation are among the questions that require further investigation into this proposed mechanism.

Regardless of the particular mechanism, our variant analysis combined with modeling studies and supported by experimental mutation data suggests that aspartame may act as an allosteric regulator of taste response mediated by T1R2, in addition to the more traditional role of agonist for both T1R2 and T1R3. Allosteric regulation of GPCRs by physiologically relevant ions and small organic molecules has been observed for many GPCRs (May and Christopoulos 2003; Liu et al. 2005; Pin et al. 2005; Winnig et al. 2006; Springael et al. 2007; Conn et al. 2009; Servant et al. 2010).

#### The curious case of the fruit fly and the lesser panda

One relative of the raccoon, the lesser panda, strongly prefers aspartame (Li et al. 2009) yet does not have the signature sequence of T1R2 of the aspartame tasters species. Similarly, fruit flies have a different types of taste receptors altogether compared with mammals, also strongly prefer aspartame compared with water (Gordesky-Gold et al. 2008). There are at least 2 explanations for these observations: 1) to these species, aspartame may have a pleasant taste which is not sweet, for example, the di-peptide combination may be savory; alternatively, the ability of these species to taste and prefer aspartame may be an example of convergent evolution, in which the phenotype is the same but the mechanism supporting it differs. The motivating force for convergent evolution may be that some foods eaten by these species have compounds with a structural similarity to aspartame.

Compounds	Interact receptors	Tools	Predicted binding site	References
Aspartame	hT1R2	SWISS MODEL	Small molecules like aspartame bind to the active site corresponding to the glutamate active site; sweet proteins binds to an active site that is different from the one for glutamate.	Temussi (2002, 2006, 2007)
Brazzein	hT1R3			
Monellin				
Thaumatin				
Aspartame	hT1R2	SWISS MODEL	Four binding sites could be present on heterodimers: 2 sites for small sweet compounds (one in each VFT), one wedge site for sweet proteins, and one site for allosteric modulators in the 7TMD.	Morini et al. (2005)
15 other sweeteners	hT1R3			
Neotame	hT1R3	Quanta program	Neotame, superaspartame and SC-45647 bind to T1R3, interacts with H163, H407, and E318 of this protein.	Walters (2002)
Superaspartame				
SC-45647				
Aspartame	hT1R2	MODELLER	E63 and D307 of hT1R2 interact with brazzein and small molecules like aspartame.	Jiang, Cui, Zhao, et al. (2005)
D-tryptophan	hT1R3			
Brazzein				
Sucrose				
Monellin				
Aspartame	hT1R2	MODELLER	ATD of hT1R2 interacts with aspartame, CRDs of hT1R3 interacts with brazzein, TMD of hT1R3 binds to cyclamate and lactisole.	Cui et al. (2006)
Cyclamate	hT1R3			
Lactisole				

 Table 11
 T1R binding sites for aspartame and other sweeteners predicted based on computer modeling

Brazzein, monellin, and thaumatin are large proteins that are sweet to humans. Neotame and superaspartame are structurally similar to aspartame and thought to act at the receptor in the same or similar manner. SC-45647 is a high-potency sweetener. "h" as a prefix before the gene symbol denotes the human form of the receptor. The interactions between aspartame and the specific amino acids of the receptor are shown by the one-letter amino acid code, and the position in the human sequence, for example, H407. VFT domain, the extracellular domain. Seven transmembrane (7TMD) domain, the portion of the receptor that transverses in and out of the taste receptor cell. Wedge site refers the ability of the large proteins to "wedge" open the VFT similar to a large object preventing a door from closing. Allosteric modulators are compounds that bind to the receptor and modulate its activation but do not by themselves cause receptor activation. ATD = amino terminal domain.

#### Assessing species-related differences in taste response

The assigning of species into aspartame taster and nontaster groups was sometimes done based on behavioral data alone, and in this case, we can know what an animal does but not why. We assume that animals perceive aspartame as sweet when they prefer it to water but they might perceive it as a different but desirable quality, like salty or savory. Therefore, nerve recordings are useful as objective measures because the pattern of firing to aspartame can be compared with sugars like sucrose, but this type of data is not available for all species. Conditioned taste aversion generalization data are another way to try to understand how animals perceive taste quality (Danilova, Hellekant, Tinti, and Nofre 1998). The combination of different types of data would be a more ideal method to chose aspartame taster species because our reliance upon behavioral data alone could be misleading, as it was in the case of the effect of gymnemic acid in the chimpanzee (Hellekant et al. 1996; Hellekant, Ninomiya, and Danilova 1997, 1998).

#### Evolution of aspartame taste sensitivity

Why humans and closely related primates should find aspartame sweet is puzzling. It is a synthetic di-peptide consisting of aspartic acid and phenylalanine, and it is not known if this small protein exists normally in human food. Thus, it could be by chance that the receptor responds to many chemically diverse compounds. On the other hand, if aspartame or a structurally similar chemical is found in nature, it is possible that the primate T1R receptor evolved to respond to this compound. Primates that could taste this hypothetical, naturally-occurring aspartame-mimetic compound might have a larger food repertoire and therefore an advantage over nontaster primates. Chemicals like aspartame may exist in edible plants.

#### Development of novel sweeteners

There is a demand for new high-potency sweeteners with improved characteristics. Many consumers complain about after-taste characteristics or worry about negative health consequences of aspartame consumption, even though recent studies show no association between aspartame intake and cancer risks (Weihrauch and Diehl 2004; Gallus et al. 2007; Bosetti et al. 2009). Finding alternatives to aspartame with improved temporal profiles of taste activation or increased potency (i.e., achieving the same sweetness with a lesser amount) might allay some consumer concerns. Modifications in the structure of aspartame guided by structure-activity relationship studies successfully led to the discovery of neotame, a more potent analog of aspartame (Nofre and Tinti 2000). Findings of this study could guide design of novel sweeteners by modifying the structure of aspartame to take advantage of unsatisfied intermolecular interactions within the binding pocket. We might also use information about the interaction of aspartame with the primate sweet receptor to find naturally occurring plant or animal compounds that have aspartame-like structural characteristics. The discovery and development of a natural source of aspartame might also reduce consumer health concerns.

#### Concluding remarks/summary

The work undertaken here builds upon the ideas and data of investigators, who demonstrated that humans, Old World monkeys, and apes can perceive aspartame sweetness, whereas New World monkeys and most other mammals cannot (Glaser et al. 1995). Here, we determined that the specific protein variant sites most likely to be responsible for aspartame tasting in mammals are within a putative allosteric binding site. Previous efforts to develop new sweeteners based on aspartames structure have been successful (Nofre and Tinti 2000), and the identification of this allosteric site provides a complementary method for the design of novel sweeteners and sweet taste enhancers.

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