Integrative genomic analyses on Ikaros and its expression related to solid cancer prognosis

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Introduction

Abstract. Ikaros is a member of the Kruppel family of zinc finger DNA-binding proteins. The Ikaros protein contains two separate regions of zinc-finger domains: 4 DNA-binding zinc fingers near the N-terminus and 2 zinc fingers for proteinprotein interactions near the C-terminus. Here, we identified the Ikaros gene from 14 vertebrate genomes and found Ikaros existed in all kinds of vertebrate including fish, amphibians, birds and mammals. Moreover, except rat and Xenopus tropicalis Ikaros proteins, which lack the first C2H2-type 1 Zinc finger region, all identified Ikaros proteins contain six C2H2-type 1 Zinc finger regions. We found human Ikaros gene showed a predominant expression in the liver, lymph node, thymus, intestine, lung, mammary gland, bone marrow, brain, heart, placenta and prostate. Moreover, four available SNPs disrupted an existing exonic splicing enhancer were identified in Ikaros. Besides the reported acute lymphoblastic leukemia (ALL), the expression of Ikaros was related to the prognosis of 13 cases of cancers including blood cancers, breast, lung, ovarian and skin cancer. Moreover, the relationship between the expression of Ikaros and prognosis varied in different cancers, even in the same cancer from different database. Two tumor-related transcriptional factor (c-Fos and Elk-1) binding sites were identified within the 1.5-kb regions upstream of the transcriptional start site of human Ikaros, which may be involved in the effect of Ikaros in tumors.

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Key words: Ikaros, comparative genomics, comparative proteomics, cancer, prognosis, meta-analysis The Ikaros (IKZF1, Lyf-1) is a member of the Kruppel family of zinc finger DNA-binding proteins 1 (1). The Ikaros protein contains two separate regions of zinc-finger domains: 4 DNA-binding zinc fingers near the N-terminus and 2 zinc fingers for protein-protein interactions near the C-terminus. The human Ikaros gene, located at 7p12, contains seven exons and gives rise to at least eight isoforms by alternative splicing (2). All isoforms share a common C-terminal domain that contains a transcriptional activation domain and two zinc finger motifs required for hetero- or homodimerization and for interactions with other proteins, but these isoforms differ in the number of N-terminal zinc finger motifs. Long isoforms (Ik1 to 3) have at least three zinc fingers which are capable of binding DNA and considered to be functional. Short isoforms (Ik4 to 8) lack two or more zinc-finger domains, so they cannot bind DNA and impair the function of Ikaros proteins in a dominant-negative manner (3-6).

Ikaros is a transcription factor, which plays an important role in controlling hematopoietic, particularly lymphoid cell differentiation, proliferation and function by binding upstream regulatory regions of target genes and aiding in their recruitment to pericentromeric heterochromatin (PC-HC) (7). This process leads to either activation or repression of transcription of these target genes by elaborate splicing regulation of Ikaros transcripts (3-6). Accordingly, abnormalities in splicing regulation of Ikaros would lead to significant pathological manifestations (3,4,8,9). Mice that are heterozygous for a germline mutation that results in a loss of critical DNA-binding zinc fingers of Ikaros develop a very aggressive form of lymphoblastic leukemia, suggesting that Ikaros has an important tumor suppressor function (10,11). Approximately 30% of pediatric B-cell acute lymphoblastic leukemia (ALL) cases showed genetic inactivation of Ikaros due to deletion or mutations (12-14). High-level expression of dominant-negative isoforms of Ikaros with abnormal subcellular compartmentalization patterns were also found in T-cell ALL (15) and pituitary tumors (16). However, whether Ikaros is involved in other tumors formations, especially solid tumors, is still unknown.

In the present study, we identified Ikaros genes from human, chimpanzee, macaque, orangutan, dog, cow, horse, mouse, rat, opossum, chicken, *Xenopus tropicalis*, zebrafish,

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and fugu by comparative genomic analyses. Conserved transcription factor-binding sites within promoter regions of human Ikaros genes were then searched. The expression data, functional relevant single nucleotide polymorphisms (SNPs) and comparative proteomic analyses were conducted. Furthermore, meta-analysis of the prognostic value of Ikaros genes in various cancers was also performed.

Materials and methods

Identification of novel Ikaros genes in vertebrate genomes and integrative genomic analyses. Ikaros genes were searched for in the genome sequences of human (Homo sapiens), chimpanzee (Pan troglodytes), macaque (Macaca mulatta), orangutan (Pongo pygmaeus), dog (Canis familiaris), cow (Bos taurus), horse (Equus caballus), mouse (Mus musculus), rat (Rattus norvegicus), opossum (Monodelphis domestica), chicken (Gallus gallus), Xenopus tropicalis, zebrafish (Danio rerio), and fugu (Takifugu rubripes) by the method described before using human Ikaros gene (NM_006060) as queries. The assemblies used were human NCBI 36, chimpanzee CHIMP2.1, macaque MMUL 1.0, orangutan PPYG2, dog Canfam 2.0, cow Btau_4.0, horse Equ Cab 2, mouse NCBI m37, rat RGSC 3.4, opossum monDom5, chicken WASHUC2, X. tropicalis JGI 4.1, zebrafish Zv8 and fugu FUGU 4.0. The identified putative Ikaros genes were BLASTed against the database number of GenBank to confirm that the best hits were Ikaros genes. Conserved transcription factor-binding sites within promoter region of human Ikaros gene were then searched for based on the Patch program (http://www.gene-regulation.com) as well as manual inspection as previously described (17-28).

Comparative proteomic analyses of Ikaros proteins. The amino acid sequences of Ikaros were deduced from the identified Ikaros genes and aligned using Clustal X 1.8 software (29). The phylogenetic tree of Ikaros was obtained by using ML (maximum likelihood) (PHYML v2.4.4) (30 and NJ (neighbor-joining) (MEGA 3.0) (31) methods, and the reliability of the tree was evaluated by the bootstrap method with 1,000 replications. The program Codeml implemented in the PAML 3.14 b software package was used to investigate whether Ikaros proteins are under positive selection (32). Six models of codon substitution, M0 (one-ratio), M1a (NearlyNeutral), M2a (PositiveSelection), M3 (discrete), M7 (β), and M8 (β and ω) were used in the analysis (33).

Functional relevant SNP evaluation of human Ikaros gene. Functional relevant SNPs (single nucleotide polymorphisms) of human Ikaros gene were identified as previously described (34,35). The SNPs were extracted from Ensembl (http://www.ensembl.org) and NCBI's SNPdb (http://www.ncbi. nlm.nih.gov). The SNPs that could disrupt ESE/ESS (exonic splicing enhancer/exonic splicing silencer) motifs and cause missense mutation were also identified.

In silico expression analyses of human Ikaros gene. Expressed sequence tags (ESTs) derived from human Ikaros were searched for using the BLAST programs as previously described (15-19). Human Ikaros gene (NM_006060) was used as query sequences for the BLAST programs. The expression profiles for normal human tissues were obtained from GeneAnnot (36) and ArrayExpress (37). Northern analysis of NCBI's uniGene dataset was also extracted (34,35).

Meta-analysis of the prognostic value of Ikaros gene in cancer. A database named 'PrognoScan' has been developed (36). This is: i) a large collection of publicly available cancer microarray datasets with clinical annotation, as well as ii) a tool for assessing the biological relationship between gene expression and prognosis. PrognoScan employs the minimum P-value approach for grouping patients for survival analysis, and it provides a powerful platform for evaluating potential tumor markers and therapeutic targets and is publicly accessible at http://gibk21.bse.kyutech.ac.jp/PrognoScan/ index.html. Human Ikaros (IKZF1) gene was inputted as queries and the data were collected for analysis.

Results

Comparative proteomics of Ikaros proteins identified in vertebrate genomes. Ikaros genes were identified in the genome sequences of human, chimpanzee, macaque, orangutan, dog, cow, horse, mouse, rat, opossum, chicken, Xenopus tropicalis, zebrafish and fugu. Their amino acid sequences are shown in alignment format in Fig. 1. Except rat and Xenopus tropicalis Ikaros proteins, which lack the first C2H2-type 1 Zinc finger region, all identified Ikaros proteins containing six C2H2-type 1 Zinc finger regions (Fig. 1). Refined phylogenetic trees using the identified Ikaros amino acid sequences by ML and NJ methods were almost the same (Fig. 2). It seemed that primate Ikaros proteins clustered into one group, different from other Ikaros proteins. We were unable to identify any site under positive selection with any of the six models in Ikaros proteins. Instead, the Ikaros proteins were under purifying selection (data not shown).

Expression profile of human Ikaros gene. By EST sequence search, human Ikaros gene was expressed in parathyroid, liver, lymph node, stomach, uterus, vascular, thymus, muscle, pharynx, intestine, ovary, thyroid, lung, mammary gland, blood, bone, bone marrow, brain, spleen, heart, placenta, tonsil, prostate, and connective tissue. The investigation of available microarray experiments and 'virtual northern blot' showed a predominant expression of Ikaros in the liver, lymph node, thymus, intestine, lung, mammary gland, bone marrow, brain, heart, placenta, and prostate tissue. When searched in PrognoScan database, human Ikaros was also found expressed in bladde, blood, breast cancer, gliomas, colorectal, head and neck, ovarian, lung and skin cancer tissues.

Comparative genomics on the human Ikaros gene. Transcription factor-binding sites within the 5'-region of Ikaros gene were identified (Fig. 3). The c-Fos, E-26-like protein 1 (Elk-1), GATA-1 and Nk6 homeobox gene-B (NKX6-B) binding sites were identified within the 1.5-kb regions upstream of the transcriptional start site of human Ikaros gene. Functional relevant SNP evaluation showed that 130

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Orangutan	DADEGQDMSQVSGKESPPVSD-TPDEGDEPMP1PEDLSTTSGGQQSSKSDRVVASNVKVETQSDEENGRACEMNGEE-	
Dog	DADEGQDMSRVSGKESPPVSD-TPDDGDEPMPVPEDLSTTSGGQQTSKNERGVASNVKVEAQSDEENARACELNGEE-	
Cow	CRCEQDAQSGKESPPVSD-TPDDSDEPMPVPEDLSTTSGGQQSSKSERGLAGNVKVETQSDEENGRACEVNGEE-	-
Horse	DADEGQDMSQVSGKESPPVSD-TPDDGDEPMPVPEDLSTTSGGQQNSKSERGVASNVKVETQSDEENGRACEMNGEE-	-
Opossum	ETDEAQDMSQVSGKESPSGSD-VPDDSDEPMPVPEDLSTTSGGQQNSKNERVLASNVKIETQSDEENGRACEMNGEE-	
Mouse	DVDEGQDMSQVSGKESPPVSD-TPDEGDEPMPVPEDLSTTSGAQQNSKSDRGMAS	<u>kos</u>
Rat	DVDEGQDMSQVSGKESPPVSD-TPDEGDEPMPVPEDLS-TSGAQQNSKSDRGMG	
Chicken	ETDEAQDMSQVSGKESPP1SD-VPDDADEPMPVPEDLSTTTGGQQSVKNERVLAGNIKIETQSDEENGRACEMNGEE-	
Xenopus	ETDEADD1T0MSGNQSPAMSD-GLDDPDEPMPVPEDLSTNAASQQNSKNEKS1AGN1KMENHSDEENGRACEMNGEE-	
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Chimpanzee	CAEDLRMLDASGEKMNGSHRDQGSSALSGVGGIRLPNGKLKCDICGIICIGPNVLMVHKRSHTGERPFQCNQCGASFTQKGNLLRHIKLHSGEKP	FKC
Macaque	CAEDLRMLDASGEKMNGSHRDQGSSALSGVGGIRLPNGKLKCDICGIICIGPNVLMVHKRSHTGERPFQCNQCGASFTQKGNLLRHIKLHSGEKP	FKC
Orangutan	CAEDLRMLDASGEKMNGSHRDQGSSALSGVGGIRLPNGKLKCDICGIICIGPNVLMVHKRSHTGERPFQCNQCGASFTQKGNLLRHIKLHSGEKP	FKC
Dog	CAEDLRVLDAAGEKMNGSHGGQGGRALSGAGGIRLPNGKLKCDVCGIICIGPNVLMVHKRSHTGERPFQCNQCGASFTQKGNLLRHIKLHSGEKP	FKC
Cow	CAEDLRMLDASGEKMNGSHSVQGSKALSGAGGTRLPNGKLKCDVCGTTCTGPNVLMVHKRSHT-ERPFQCNQCGASFTQKGNLLRHTKLMSGEKP	FKC
Horse	CAEDLRMIDASGEKMNGSHSGQGNKTLSGAGGIRLPNGKLKCDVCGIICIGPNVLMVHKRSHTGERPFQCNQCGASFTQKGNLLRHIKLHSGEKP	FKC
Opossum	CAEDLRMLDTSGEKMNGSHNGQGSKALSGVGGTRLPNGKLKCDTCGTTCTGPNVLMVHKRSHTGERPFQCNQCGASFTQKGNLLRHTKLHSGEKP	FKC
Mouse	CAEDLRMLDASGEKMNGSHRDQGSSALSGVGGIRLPNGKLKCDICGIVCIGPNVLMVHKRSHTGERPFQCNQCGASFTQKGNLLRHIKLHSGEKPF	FKC
Rat	ERPFQCNQCGASFTQKGNLLRHIKLHSGEKPI	FKC
Chicken	CAEDLRMLDASGDKMNGSHNGPGSKAMSGVGGTRLPNGKLKCDTCGTTCTGPNVLMVHKRSHTGERPFOCNOCGASFTOKGNLLRHTKLHSGEKPI	FKC
Xenonus	CAEDLRMLDSAGEK INGSLNGQGTKALTGVGG	FKC
Zehrafieb	AAEDLR1LDCSGAKVNCSHAGPDSKPAAYPTAGGTPLPNCKLKCD1CG1VC1GPNVLWVBKPSHTCEDDE0CNVCCASET0VCNLLDHTVLUSCEPDE	FKC
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Chimpanzee	HLCNYACRRRDALTGHLRTHSVGKPHKCGYCGRSYKQRSSLEEHKERCHNYLESMGLPGTLYPVIKEETNHSEMAEDLCKIGSERSLVLDRLASNVAKJ	RK
Macaque	HLCNYACRRRDALTGHLRTHSVGKPHKCGYCGRSYKQRSSLEEHKERCHNYLESMGLPGTLYPVIKEETNHSEMAEDLCKIGSERSLVLDRLASNVAKH	RK
Orangutan	HLCNYACRRRDALTGHLRTHSVGKPHKCGYCGRSYKQRSSLEEHKERCHNYLESMGLPGTLYPV1KEETNHGEMAEDLCK1GSERSLVLDRLASNVAKH	RK
Dog	HLCNYACRRRDALTGHLRTHSVGKPHKCGYCGRSYKQRSSLEEHKERCHNYLQSMGLPGTMYPVIKEEANHSEMGEDLCKIGSERSLVLDRIASNVAK	RK
Cow	HLCNYACRRDALTGHLRTHSVGKPHKCGYCGRSYKQRSSLEEHKERCHNYLQSMGLPGTLYPVIKEETNHSEMAEDLCKMGSDRSLVLDRLASNVAKH	RK
Horse	HLCNYACRRDALTGHLRTHSVGKPHKCGYCGRSYKQRSSLEEHKERCHNYLQSMGLPGTLYPVIKEEANHSEMAEDLCKIGSERSLVLDRLASNVAKH	RK
Opossum	HLCNYACRRRDALTGHLRTHSVGKPHKCGYCGRSYKQRSSLEEHKERCHNYLQSMGLPATLYPVIKEETNHSEMAEDLCKIGSERSLVLDRLASNVAKH	RK
Mouse	HLCNYACRRRDALTGHLRTHSVGKPHKCGYCGRSYKQRSSLEEHKERCHNYLESMGLPG-MYPV1KEETNHNEMAEDLCKIGAERSLVLDRLASNVAKH	RK
Rat	HLCNYACRRRDALTGHLRTHSVGKPHKCGYCGRSYKQRSSLEEHKERCHNYLESMGLPG-MYPV1KEETNHSEMAEDLCK1GAERSLVLDRLASNVAKH	RK
Chicken	HLCNYACRRDALTGHLRTHSVGKPHKCGYCGRSYKQRSSLEEHKERCHNYLQTMSISSNLYSVIKEETNQSEMAEDLCKIGSERSLVLDRLASNVAKH	RK
Xenopus	HMCNYACRRRDALTGHLRTHSVGKPHKCGYCGRSYKORSSLEEHKERCHNYLOSMGLQSHLYAVKEESN-QNDMAEDLSK IGSERSLVLDRLASNVAKH	RK
Zehrafish	HI CNYACRREDALTCHI RTHSVCKPHKCAVCCRSYKORSSI FFHKERCHNYI OCWCI ONSTYTYKEFNS-ONFOREDMPASFRALVI DRTANNVAKI	RK
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Chimpanzee	SSMPQKFLGDKGLSDTPYDSSASYEKENEMMKSHVMDQA1NNA1NYLGAESLRPLVQTPPGGSEVVPV1SPMYQLHKPLAEGTPRSNHSAQDSAVENLI	LL
Macaque	SSMPQKFLGDKGLSDTPYDSSASYEKENEMMKSHVMDQAINNAINYLGAESLRPLVQTPPGGSEVVPVISPMYQLHKPLAEGTPRSNHSAQDSAVENLI	LL
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Orangutan Dog Cow Horse	SSMPQRFVGDAULSDIPTUSSTSTERESDINGSTUNIAATIONALTUSALETUSTIPTUSEEVIPTUSPALQUEDTESSEVIPTUSST SSMPQRFVGDAULSDMPYDSSASYEKENEMINQTHVMQATINNATSYLGAESLRPLVQTPPGSSEVVPYTSPANQLHKPHAEGPPRSNISAQDSAVENLI SSMPQRFVGDAULSELPYDGSASYEKENEMINQTHVMQATINNATSYLGAESLRPLVQTPPGSSEVVPYTSPANQLHKPHGEGPARSNISAQDSAVENLI SSMPQRFVGDAULSELPYDGSASYEKENEMINQTHVMQATINNATSYLGAESLRPLVQTPPGSSEVVPYTSPANQLHKPHGEGPARSNISAQDSAVENLI	
Orangutan Dog Cow Horse Opossum	SSMPQRFVGDWLSDIPTUSSTSTERESDMIRSHYDMAALINN IATLAARESLAPTVYTPYGSEVYPYTSTAN QGHPFAGD FRSNISANDAAVENL SSMPQRFVGDWLSDMPYDSSASYEKENEDMQTHYMDQATINNATSYLGAESLRPLVQTPPGSSEVVPYTSPHNQLHKPHAEGPPRSNISAQDSAVENL SSMPQRFVGDWLSELPLYDGSASYEKENEDMQTHYMDQATINNATSYLGAESLRPLVQTPPGSSEVVPYTSPTQLHKPHEGEPARSNISAQDSAVENL SSMPQRFVGDWLSDMPYDGSASYEKENEDMQTHYMDQATINNATSYLGAESLRPLVQTPPGSSEVVPYTSPTQLHKPHEGEPARSNISAQDSAVENL	
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Orangutan Dog Cow Horse Opossum Mouse Rat Chicken	SSHPQKFVGDKLISDMP1DSASYEKENEBMQTHVMDQA1NNA1SYLGAESLRPLVQTPYGSEVVPV1SPMQLHKPHAGGPPRSNISAD0AVEAL SSMPQKFVGDKLISDMP1DSASYEKENEBMQTHVMDQA1NNA1SYLGAESLRPLVQTPPGSSEVVPV1SPMQLHKPHAGGPRSNISAD0AVEAL SSMPQKFVGDKLISDMP1DSASYEKENEBMQTHVMDQA1NNA1SYLGAESLRPLVQTPPGSSEVVPV1SPMQLHKPHAGGHPRSNISAD0AVEAL SSMPQKFVGDKLISDMP1DSASYEKENEBMQTHVMDQA1NNA1SYLGAESLRPLVQTPPGSSEVVPV1SSMQLHKPHAGGHPRSNISAD0AVEAL SSMPQKFVGDKLISDMP1DSANYEKENEBMQTHVMDQA1NNA1SYLGAESLRPLVQTPPGSSEVVPV1SSMQLHKPHAGGHPRSNISAD0AVEAL SSMPQKFVGEKLISDMP1DSANYEKENEBMQTHVMDQA1NNA1SYLGAESLRPLVQTPPGSSEVVPV1SSMQLHKPHAGGHPRSNISAD0AVEAL SSMPQKFVGEKLISDMP1DSANYEKENEBMGTHVMDQA1NNA1SYLGAESLRPLVQTPPGSSEVVPV1SSMQLHKPPSDGPPRSNISAD0AVEAL SSMPQKFLGDKCLSDMP1DSANYEKENEBMGTHVMDQA1NNA1SYLGAESLRPLVQTPPGSSEVVPV1SSMQLHKPPSDGPPRSNISAD0AVEAL	
Orangutan Dog Cow Horse Opossum Mouse Rat Chicken Xenopus	SSHPQKFVGDKLISDMP1DSASTERENSIMIKSHNIMA/I NIMA I STUGAESLAPLVQTPYGSEVVPY I SPNQLHKPHAEGIPRSNISAD0AVEAL SSMPQKFVGDKLISDMP1DSASTERENSIMIKSHNIMA/I NIMA I SYLGAESLAPLVQTPYGSSEVVPY I SPNQLHKPHAEGIPRSNISAD0AVEAL SSMPQKFVGDKLISDLPYDGSASTERENEMQTHVMDQA I NIM I SYLGAESLAPLVQTPPGSSEVVPY I SPNQLHKPHAEGIPRSNISAD0AVEAL SSMPQKFVGDKLISDMP1DSASTERENEMQTHVMDQA I NIM I SYLGAESLAPLVQTPPGSSEVVPY I SPNQLHKPHAEGIPRPNIT AQDSAVEAL SSMPQKFVGDKLISDMP1DSANYEKENEMQTHVMDQA I NIM I SYLGAESLAPLVQTPPGSSEVVPY I SSMQLHKPHAEGIPRPNIT AQDSAVEAL SSMPQKFVGDKLISDMP1DSANYEKENEMQTHVMDQA I NIM I NYLGAESLAPLVQTPPGSSEVVPY I SSMQLHKPHAEGIPRPNIT AQDSAVEAL SSMPQKFLGDKLISDMP1DSANYEKENEMQTHVMDQA I NIM I NYLGAESLAPLVQTPPGSSEVVPY I SSMQLHKPHSGCPRSNISADOAVEAL SSMPQKFLGDKLISDMP1DSANYEKENEMQTHVMDQA I NIM I NYLGAESLAPLVQTPPGSSEVVPY I SSMQLHKPHSGCPRSNISAQDAVEAL SSMPQKFLGDKLISDMP1DSANYEKENEMQTHVMDQA I NIM I NYLGAESLAPLVQTPPGSSEVVPY I SSMQLHKPPSGCPRSNISAQDAVEAL SSMPQKFVGEKLISDLPYDMATNYEKENEMQTHVMDQA I NIM I NYLGAESLAPLVQTPPGSSEVVPY I SSMQLHKPPSGCPRSNISAQDFAXEAL	
Orangutan Dog Cow Horse Opossum Mouse Rat Chicken Xenopus Zebra fish	SMPQKFVGDKCLSDIPTDSSTSTERESEMIGNTMUQATINALISULGAESLRPLVQTPYGSEVVPTJSMQLHRPHAGDPPSSISAQDSAVEAL SSMPQKFVGDKCLSDIPTDSSTSTERESEMIQTHVIDQATINALISULGAESLRPLVQTPPGSSEVVPTJSPNQLHRPHAGDPPSSISAQDSAVEAL SSMPQKFVGDKCLSDIPTDSSASYERESEMIQTHVIDQATINALISULGAESLRPLVQTPPGSSEVVPTJSPNQLHRPHAGDPRSNISAQDSAVEAL SSMPQKFVGEKCLSDIPTDSSASYERESEMIQTHVIDQATINALISULGAESLRPLVQTPPGSSEVVPTJSSNQLHRPHAGDIPRSNISAQDSAVEAL SSMPQKFVGEKCLSDIPTDS-ASYERESEMIQTHVIDQATINALISULGAESLRPLVQTPPGSSEVVPTJSSNQLHRPHAGDIPRSNISAQDSAVEAL SSMPQKFVGEKCLSDIPTDS-ASYERESEMIQTHVIDQATINALISULGAESLRPLVQTPPGSSEVVPTJSSNQLHRPHSGPPRSNISAQDSAVEAL SSMPQKFLGBKCLSDMPYDS-ASYERESEMIQTHVIDQATINALISULGAESLRPLVQTPPGSSEVVPTJSSNQLHRPPSGPRSNISAQDSAVEAL SSMPQKFLGBKCLSDMPYDS-ASYERESEMIQTHVIDQATINALISULGAESLRPLVQTPPGSSEVVPTJSSNQLHRPPSGPRSNISAQDSAVEAL SSMPQKFVGERCLSDLPYDATTNYERESEMIQTHVIDQATINALISULGAESLRPLVQTPPGSEEVVPTJSSNQLHRPPSGPRSNISAQDSAVEAL SSMPQKFVGERCLSDLPYDATTNYERESEMIQTHVIDQATINALISULGAESLRPLVQTPPGSEEVVPTJSSNQLHRPPSGCPRSNISAQDSAVEAL SSMPQKFVGERKLSDLPYDATTNYERENEMIQTHVIDQATINALISULGAESLRPLVQTPPGSEEVVPTJSSNQLHRPSGCPVCVQCNAFGAARH	
Orangutan Dog Cow Horse Opossum Mouse Rat Chicken Xenopus Zebrafish	SMPQKFVGDKCLSDPPDSASYEKENEMIQTHVMDQATINATSYLGAESLRPLVQTPPGSEVVPTSMPQLHRPHAGPPRSASHKADAVEAL SSMPQKFVGDKCLSDPPDSASYEKENEMIQTHVMDQATINATSYLGAESLRPLVQTPPGSSEVVPTSMPQLHRPHAGPPRSASHKADQAVEAL SSMPQKFVGDKCLSDPPDSASYEKENEMIQTHVMDQATINATSYLGAESLRPLVQTPPGSSEVVPTSMPQLHRPHGEGPARSNISAQDSAVEAL SSMPQKFVGDKCLSDMPYDSASYEKENEMIQTHVMDQATINATSYLGAESLRPLVQTPPGSSEVVPTSSMPQLHRPHGEGPARSNISAQDSAVEAL SSMPQKFVGDKCLSDMPYDSANYEKENEMIQTHVMDQATINATSYLGAESLRPLVQTPPGSSEVVPTYTSSMPQLHRPHGEGPARSNISAQDSAVEAL SSMPQKFVGDKCLSDMPYDSANYEKENEMIQTHVMDQATINATSYLGAESLRPLVQTPPGSSEVVPTYTSSMPQLHRPHSGPPRNISAQDAVEAL SSMPQKFLGDKCLSDMPYDSANYEKENEMIQTHVMDQATINATINYLGAESLRPLVQTPPGSSEVVPTYTSSMPQLHRPHSGPRSNISAQDSAVEAL SSMPQKFLGDKCLSDMPYDSANYEKENEMIQTHVMDQATINATINYLGAESLRPLVQTPPGSSEVVPTYTSSMPQLHRPPSDGPPRSNISAQDSAVEAL SSMPQKFVGEKCLSDLPYDATNYEKENEMIQTHVMDQATINATINYLGAESLRPLVQTPPGSSEVVPTYTSSMPQLHRPPSDGPPRSNISAQDSAVEAL SSMPQKFVGEKCLSDLPYDATNYEKENEMIQTHVMDQATINATIYLGAESLRPLVQTPPGSSEVVPTYTSSMPQLHRPPSDGPRSNISAQDSAVEAL SSMPQKFVGEKLSDLPYDATNYEKENEMIQTHVMDQATINATIYLGAESLRPLVQTPPGSEVVPTSSMPQLHRPHADTTNTSQSAHESAVEAL SSMPQKFVGEKLSDLPYDHNANYEKENEMIQTHVMDQATINATIYLGAESLRPLVQTPPGSEVVPTSSMPQLHRPHADTTNTSQSAHESAVEAL SSMPQKFVGEKLSDLPYDHNAMYEKENEMIQTHVMDQATINATIYLGAESLRPLVQTPPGSEVVPTSSMPQLHRPHADTTNTSQSAHESAVEAL SSMPQKFVGEKLSDLPYDHNAMYEKENEMIQTHVMDQATINATIYLGAESLRPLVQTPPGSEVVPTSSMPGTAE-CONVSANDAAAEHL	
Orangutan Dog Cow Horse Opossum Mouse Rat Chicken Xenopus Zebrafish Fugu Consensus	SSIPQKFVGDKL.SDMPYDSASYEKENEMINGTHVMDQA1INA1SYLGAESLRPLVQTPYGSEVVPY1SPNQLIKPHAGFPRSNISAD0AVEAL SSIPQKFVGDKL.SDMPYDSASYEKENEMINGTHVMDQA1INA1SYLGAESLRPLVQTPPGSSEVVPY1SPNQLIKPHQEGPARSNISAD0AVEAL SSIPQKFVGDKL.SDMPYDSASYEKENEMINGTHVMDQA1INA1SYLGAESLRPLVQTPPGSSEVVPY1SPNQLIKPHQEGPARSNISAD0AVEAL SSIPQKFVGDKL.SDMPYDSASYEKENEMINGTHVMDQA1INA1SYLGAESLRPLVQTPPGSSEVVPY1SSINQLIKPHQEGPARSNISAD0AVEAL SSIPQKFVGDKL.SDMPYDSASYEKENEMINGTHVMDQA1INA1SYLGAESLRPLVQTPPGSSEVVPY1SSINQLIKPHQEGPARSNISAD0AVEAL SSIPQKFVGDKL.SDMPYDS-ANYEKENEMINGTHVMDQA1INA1SYLGAESLRPLVQTPPGSSEVVPY1SSINQLIKPHQEGPARSNISAD0AVEAL SSIPQKFVGEKLSDLPDATNYEKENEMINGTHVMDQA1INA1INYLGAESLRPLVQTPPGSSEVVPY1SSINQLIKPHQEGPRSNISAD0AVEAL SSIPQKFVGEKLSDLPYDG-ANYEKE-DMITSHVMDQA1INA1INYLGAESLRPLVQTPPGSSEVVPY1SSINQLIKPHQEGPRSNISAD0AVEAL SSIPQKFVGEKLSDLPYDG-ANYEKE-DMITSHVMDQA1INA1INYLGAESLRPLVQTPPGSSEVVPY1SSINQLIKPHADTTNTSQSAHESAVEAL SSIPQKFVGEKLSDLPYDATNYEKENEMINGTHVIDQA1INA1IYLGAESLRPLVQTPPGSSEVVPY1SSINQLIKPHADTTNTSQSAHESAVEAL SSIPQKFVGEKLSDLPYDATNYEKENEMIQTHVIDQA1INA1IYLGAESLRPLVQTPPGSSEVVP1SSNTQLIKPHADTTNTSQSAHESAVEAL SSIPQKFVGEKLSDLPYDATNYEKENEMIQTHVIDQA1INA1IYLGAESLRPLVQTPPGSEVP1SSNTGADSAVEAL SSIPQKFVGEKLSDLPYDATNYEKENEMIQTHVIDQA1INA1IYLGAESLRPLVQTPPGSSEVVP1SSNTGLIKPAAVEAL SSIPQKFVGEKLSDLPYDATNYEKENEMIQTHVIDQA1INA1IYLGAESLRPLVQTPPGSEVP1SSNTGADSAVEAL SSIPQKFVGEKLSDLPYDATNYEKENEMIQTHVIDQA1INA1IYLGAESLRPLVQTPPGSEVP1SSNTGADSAVEAL SSIPQKFVGEKLSDLPYDATNYEKENEMIQTHVIDQA1INA1IYLGAESLRPLVQTPPGSEVP1NS-MYALHKPIADTTNTSQSAHESAVEAL SSIPQKFVGEKLSDLPYDATNYEKENEMIQHTINDQA1INA1IYLGAESLRPLVQTPPGSEVP1NS-MYALHKPIADTTNTSQSAHESAVEAL SSIPQKFVGEKLSDLPYDATNYEKENEMIQHTINDQA1INA1IYLGAESLRPLVQTPPGSEVP1NS-MYALHKPIADTTNTSQSAHESAVEANA	
Orangutan Dog Cow Horse Opossum Mouse Rat Chicken Xenopus Zebrafish Fugu Consensus	SMPQKFVGKCLSDMP105S3YEKENEMQTHVMQQA1NA1TYLGAESLRPLVQTPPGSEVTV11SMPQLHPPHAGEPPRSNEAQDAVEAL SSMPQKFVGKCLSDMP105SAYEKENEMQTHVMQA1NA1SYLGAESLRPLVQTPPGSSEVTV11SMPQLHPHAGEPPRSNEAQDAVEAL SSMPQKFVGKCLSDMP105SAYEKENEMQTHVMQA1NA1SYLGAESLRPLVQTPPGSSEVTV11SMPQLHPHAGPRSNEAQDAVEAL SSMPQKFVGKCLSDMP105-AVFEKENEMQTHVMQA1NA1SYLGAESLRPLVQTPPGSSEVTV11SMPQLHPHAGPRSNEAQDAVEAL SSMPQKFVGKCLSDMP105-AVFEKENEMQTHVMQA1NA1SYLGAESLRPLVQTPPGSSEVTV11SSMPQLHPPSDGPPSNISAQDAVEAL SSMPQKFVGKCLSDMP105-AVFEKENEMQTHVMQA1NA1SYLGAESLRPLVQTPPGSSEVTV11SSMPQLHRPHAGHPRSNTAQDSAVEAL SSMPQKFVGKCLSDMP105-AVFEKENEMMQTHVMQA1NA1SYLGAESLRPLVQTPPGSSEVTV11SSMPQLHRPPSDGPPSNISAQDSAVEAL SSMPQKFVGKCLSDLP10TMTYKEKENEMQTHVMQA1NA1SYLGAESLRPLVQTPPGSSEVTV11SSMPQLHRPPSDGPRSNISAQDSAVEAL SSMPQKFVGKCLSDLP10TMTYKEKENEMQTHVMQA1NA1SYLGAESLRPLVQTPPGSSEVTV11SSMPQLHRPPSDGPRSNISAQDSAVEAL SSMPQKFVGKLSDLP10TMTYKEKENEMQTHVMQA1NA1SYLGAESLRPLVQTPPGSSEVTV11SSMPQLHRPSDGPRSNISAQDSAVEAL SSMPQKFVGKLSDL97DMTMYEKENEMQTHVMQA1NA1TYLGAESLRPLVQTPPGSSEVTV11SSMPQLHRPSDGPRSNISAQDSAVEAL SSMPQKFVGKLSDL97DMTMYEKENEMQTHVMQA1NA1TYLGAESLRPLVQTPPGSSEVTV11SSMPQLHRPADATTHX5QSAESAVEAL SSMPQKFVGKRLSDL97DMTMTKECMQTHVMQA1NA1TYLGAESLRPLVQTPPGSSEVTV11SSMPQLHRPADATTHX5QSAESAMESAVEAL SSMPQKFVGKRLSDL97DG	
Orangutan Dog Cow Horse Opossum Mouse Rat Chicken Xenopus Zebrafish Fugu Consensus Human	SSHPAKFVGDKCLSDHPTOSSSYEKEXEMMQTHVMQQATNNATSYLGAESLRPLVQTPYGSEVVPTJSPMQLHRPHAGCPPRSNEAQD6AVEXL SSMPQKFVGDKCLSDHPTOSSSYEKEXEMQTHVMQQATNNATSYLGAESLRPLVQTPYGSSEVVPTJSPMQLHRPHAGCPRSNEAQD6AVEXL SSMPQKFVGDKCLSDHPTOSASYEKEXEMQTHVMQQATNNATSYLGAESLRPLVQTPPGSSEVVPTJSPMQLHRPHAGCPRSNEAQD6AVEXL SSMPQKFVGEKCLPDIPYDGSASYEKEXEMQTHVMQQATNNATSYLGAESLRPLVQTPPGSSEVVPTJSSMQLHRPHAGGIPRSNIFAQD6AVEXL SSMPQKFVGEKCLDDIPYDGSASYEKEXEMQTHVMQQATNNATSYLGAESLRPLVQTPPGSSEVVPTJSSMQLHRPHAGGIPRSNIFAQD6AVEXL SSMPQKFVGEKCLDDIPYDGSASYEKEXEMQTHVMQQATNNATSYLGAESLRPLVQTPPGSSEVVPTJSSMQLHRPPSDGPPRSNIFAQD6AVEXL SSMPQKFVGEKCLDDIPYDGSASYEKEXEMMQTHVMQQATNNATSYLGAESLRPLVQTPPGSSEVVPTJSSMQLHRPPSDGPPRSNIFAQD6AVEXL SSMPQKFVGEKLSDLPYDGSASYEKEXEMMQTHVMQQATNNATSYLGAESLRPLVQTPPGSEVVPTJSSMQLHRPSDGPPRSNIFAQD6AVEXL SSMPQKFVGEKLSDLPYDGSASYEKENEMQTHVMQQATNNATSYLGAESLRPLVQTPPGSEVVPTJSSMQLHRPSDGPRSNIFAQD6AVEXL SSMPQKFVGEKLSDLPYDGSASYEKENEMQTHVMQQATNNATSYLGAESLRPLVQTPPGSEVVPTJSSMQLHRPSDGPRSNIFAQD6AVEXL SSMPQKFVGEKLSDLPYDGTGSASYEKENMQTHVMQQATNNATSYLGAESLRPLVQTPPGSEVVPTJSSMQLHRPSDGPRSNIFAQD5AVEXL SSMPQKFVGEKLSDLPYDGTGSASYEKENMQTHVMQQATNNATSYLGAESLRPLVQTPPGSEVVPTJSSMQLHRPSDGPRSNIFAQD5AVEXL SSMPQKFVGDKRLSDLSDGCGSGELMQPHTDQATISATSYLGAESLRPLVQTPPGSSEVVPTJSSMQLHRPSDGPRSNIFAQD5AVEXL SSMPQKFVGDKRLSDLSDGCGSGELMQPHTQQGTQTTISSATSYLGAESLRPLVQTSPSSS-SDVALSSMPSLHRTASDGGCTVMAXDSAAESLARL SSMPQKFVGDKRLSDLSDGCGGELMQPHTDQATISATSYLGAESLRPLVQTSPSSSSVPVTJSMVQHRP AEG PRSNHSADD5AVEXLL SSMPQKFVGDKRLSDLSDGCGTUPTISMAXYEKENEMQGHVMQATINATSYLGAESLRPLVQTSPSSSSVPVTJSMVQHRP AEG PRSNHSADD5AVEXLL SSMPQKFVGDKRLSDLSTDGCGGELMQPGTDQGTQATISATSYLGAESLRPLVQTSPSSSSVPVTJSMVQHRP AEG PRSNHSADD5AVEXLL SSMPQKFVGDKRLSDLSTDGCGTUPTISMAXYEKENEMQGSHVMQATINATSYLGAESLRPLVQTSPSSSSVPVTJSMVTJHAASCGCTVMSADD5AVEXLL SSMPQKFVGDKRLSDLSDLSTDG	
Orangutan Dog Cow Horse Opossum Mouse Rat Chicken Xenopus Zebrafish Fugu Consensus Human Chimpanzee	SSHPQKFVGDKCLSDHPTDSSSYEKENEMMGTHVMQQATINATISYLGAESLRPLVQTPPGSSEVVPTISMPQLHPPHAEGPPRSNISAQDSAVEAL SSHPQKFVGDKCLSDHPYDSSSYEKENEMMQTHVMQQATINATISYLGAESLRPLVQTPPGSSEVVPTISMPQLHPPHAEGPPRSNISAQDSAVEAL SSHPQKFVGDKCLSDHPYDSSASYEKENEMMQTHVMQQATINATISYLGAESLRPLVQTPPGSSEVVPTISMPQLHPPHAEGPPRSNISAQDSAVEAL SSHPQKFVGDKCLSDHPYDSSASYEKENEMMQTHVMQQATINATISYLGAESLRPLVQTPPGSSEVVPTISSNPQLHPPHAEGPPRSNISAQDSAVEAL SSHPQKFVGKLDSDHPYDS-ANYEKENEMMQTHVMQATINATISYLGAESLRPLVQTPPGSSEVVPTISSNPQLHPPHAEGPPRSNISAQDSAVEAL SSHPQKFVGKLDSDHPYDS-ANYEKENEMMQTHVMQATINATISYLGAESLRPLVQTPPGSSEVVPTISSNPQLHPPHAEGPPRSNISAQDSAVEAL SSHPQKFVGKLDSDHPYDS-ANYEKENEMMQTHVMQATINATISYLGAESLRPLVQTPPGSSEVVPTISSNPQLHRPPBGPRSNISAQDSAVEAL SSHPQKFVGKRLSDLPYDG-ANYEKE-DMMTSHVMQATINATISYLGAESLRPLVQTPPGSSEVVPTISSNPQLHRPPBGPRSNISAQDSAVEAL SSHPQKFVGKRLSDLPYDG-ANYEKE-DMMTSHVMQATINATISYLGAESLRPLVQTPPGSSEVVPTISSNPQLHRPPBGPRSNISAQDSAVEAL SSHPQKFVGKRLSDLPYDG-ANYEKE-DMMTSHVMQATINATISYLGAESLRPLVQTPPGSSEVVPTISSNPQLHRPHADTTHTSQSAHESAVEAL SSHPQKFVGKRLSDLPYDG-MGCGCUQPHYTDQATINATISYLGAESLRPLVQTPPGSSEVVPTISSNPQLHRPHADTTHTSQSAHESAVEAL SSHPQKFVGKRLSDLPYDG-GSGELMQPHYTDQATINATISYLGAESLRPLVQTPPGSSEVVPTISSNPQLHRPHADTTHTSQSAHESAVEAL SSHPQKFVGKRLSDLPYDG-GGGELMQPHYTDQATINATISYLGAESLRPLVQTPPGSSEVVPTISSNPQLHRPHADTTHTSQGAHESAVEAL SSHPQKFVGKRLSDLSPDG-GGGELMQPHYTDQATINATISYLGAESLRPLVQTPPGSSEVVPTISPNYQLHRPASDGEAVEAL SSHPQKFVGRRLSDLSPSG-GSGELMQPHYTDQATINATISYLGAESLRPLVQTPPGSSEVVPTISPNYQLHRPASDGEGRESAVEAL SSHPQKFVGRRLSDLSPSG-GGGETIDTISTSTVEAGASLARLUVSTSGEQ SSHPQKFVGRRLSDLSPSG-GSGELMQPHYTDQATINATISYLGAESLRPLVQTPPGSSEVVPTISPNYQLHRPASDGEGRESAVEAL SSHPQKFVGRRLSDLSPSG-GSGETDESNEEGRS-GFGGTIDTINATISYLGAESLRPLVGTSPASS-SDVLSMSHIRTASDGGGGTVASADSAAEHL SSHPQKFVGRRLSDLSPSG-GSGESVPTISSNELHTASDGGGTDTISTSTVEAGASLRPLVGTSPASS-SDVLSMSHIRTASDGGSAVEALL SSHPQKFVGBRLSDLSSSQGSTDTESNEEGRS-GFGGTGGTTISTSTVEAGASLRPLVGTSPASS-SDVLARASSMESHKTASDGGSAVEAL LISKAKLVPSERASPSNSCQDSTDTESNEEGRS-GGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGG	
Orangutan Dog Cow Horse Opossum Mouse Rat Chicken Xenopus Zebrafish Fugu Consensus Human Chimpanzee Macaque	SSHPQKFVGDKCLSDHPDGSASYEKENEMMQTHVMQQATNNATSYLGAESLRPLVQTPPGSEVVPYTSPALQHEPHAGEQPPSSHSAQDAVEAL SSMPQKFVGDKCLSDHPDGSASYEKENEMMQTHVMQQATNNATSYLGAESLRPLVQTPPGSSEVVPYTSPALQHEPHAGEQPPSSHSAQDAVEAL SSMPQKFVGDKCLSDHPDGSASYEKENEMMQTHVMQQATNNATSYLGAESLRPLVQTPPGSSEVVPYTSPLQHKPHEGEQARSNISAQDAVEAL SSMPQKFVGDKCLSDMPYDSSASYEKENEMMQTHVMQQATNNATSYLGAESLRPLVQTPPGSSEVVPYTSSNQLHKPHEGEQARSNISAQDAVEAL SSMPQKFVGDKCLSDMPYDSSASYEKENEMMQTHVMQQATNNATSYLGAESLRPLVQTPPGSSEVVPYTSSNQLHKPHEGEQARSNISAQDAVEAL SSMPQKFVGEKCLPDTPDASANYEKENEMMQTHVMQQATNNATSYLGAESLRPLVQTPPGSSEVVPYTSSNQLHKPPSGCPPRSNISAQDAVEAL SSMPQKFLGBKCLSDMPYDSSANYEKENEMMQTHVMQQATNNATSYLGAESLRPLVQTPPGSSEVVPYTSSNQLHKPPSGCPPRSNISAQDAVEAL SSMPQKFLGBKCLSDMPYDSSANYEKENEMMQTHVMQQATNNATSYLGAESLRPLVQTPPGSSEVVPYTSSNQLHKPPSGCPRSNISAQDAVEAL SSMPQKFVGEKCLSDLPYDATTNYEKENEIMQTHVMQQATNNATSYLGAESLRPLVQTPPGSSEVVPTSSNQLHKPPSGCPRSNISAQDAVEAL SSMPQKFVGEKLSDLPYDATTNYEKENEIMQTHVMQQATNNATSYLGAESLRPLVQTPPGSSEVVPTSSNQLHKPPSGCPRSNISAQDAVEAL SSMPQKFVGEKLSDLPYDATTNYEKENEIMQTHVMQATNNATYLGAESLRPLVQTPPGSEVPTVSSNQLHKPFADTTTTSQSAHESAVEAL SSMPQKFVGEKLSDLSPSSSSATEKENEMMQTHVMQATNNATSYLGAESLRPLVQTPPGSSEVVPTSSNJAGSCASVEAL SSMPQKFVGEKLSDLSPSSSSQDSTDTESNNEEQRSSSSSSSSATALSSANGSAVEAL LSKAKLVPSEREASPSNSCQDSTDTESNNEEQRSSSSSSSCQDSTDTESNNEAQSAVEALL LSKAKLVPSEREASPSNSCQDSTDTESNNEEQRSSSSSSCQDSTDTESNNEAQSAVEALL LSKAKLVPSEREASPSNSCQDSTDTESNNEEQRSSSSSSSCQDSTDTESNNEAQSAVEALL LSKAKLVPSEREASPSNSCQDSTDTESNNEEQRSSSSSSSSSSCQDSTDTESNNEAQSAVEALL LSKAKLVPSEREASPSNSCQDSTDTESNNEEQRSSSSSSCQDSTDTESNNEAQSAVEALL LSKAKLVPSEREASPSNSCQDSTDTESNNEEQRSSSSSSCQDSTDTESNNEAQSAVEALL LSKAKLVPSEREASPSNSCQDSTDTESNNEEQRSSSSSSSCQDSTDTESNNEAQSAVEALL LSKAKLVPSEREASPSNSCQDSTDTESNNEEQRSSSSSSCQDSTDTESNNEEQRSSSSSCDLSLEHENATSDLARASSSSSCQDSTDTESNNEAQSAVEALL	
Orangutan Dog Cow Horse Opossum Mouse Rat Chicken Xenopus Zebrafish Fugu Consensus Human Chiepanzee Macaque Orangutan	SSHPAKFVGKCLSDNPTOSASYEKENDMQTHVMQQATNALTSYLGAESLRPLVQTPPGSEVVPTISMPQLHPPHAGEPPRSNEAQDAVEAL SSHPQKFVGKCLSDNPTOSASYEKENDMQTHVMQQATNALTSYLGAESLRPLVQTPPGSSEVVPTISMPQLHPPHAGEPPRSNEAQDAVEAL SSHPQKFVGKCLSDNPTOSASYEKENDMQTHVMQQATNALTSYLGAESLRPLVQTPPGSSEVVPTISMPQLHPPHAGEPPRSNEAQDAVEAL SSHPQKFVGKCLSDNPTOSASYEKENDMQTHVMQQATNALTSYLGAESLRPLVQTPPGSSEVVPTISSMPQLHKPHAGIPRNTAQDAVEAL SSHPQKFVGKCLSDNPTOSANYEKENDMQTHVMQQATNALTSYLGAESLRPLVQTPPGSSEVVPTISSMPQLHKPHAGPRSNEAQDAVEAL SSHPQKFVGKCLSDNPTOS-ANYEKENDMQTHVMQQATNALTSYLGAESLRPLVQTPPGSSEVVPTISSMPQLHKPHAGPRSNEAQDAVEAL SSHPQKFVGKCLSDLPTDF-MYKEKENDMQTHVMQQATNALTSYLGAESLRPLVQTPPGSSEVVPTISSMPQLHKPPSDGPPRSNEAQDAVEAL SSHPQKFVGKCLSDLPTDT-MYKEKENEMQTHVMQQATNALTSYLGAESLRPLVQTPPGSSEVVPTISSMPQLHKPPSDGPPRSNEAQDAVEAL SSHPQKFVGKCLSDLPTDT-TNYEKENEN MQTHVMQQATNALTSYLGAESLRPLVQTPPGSSEVVPTISSMPQLHKPPSDGPPRSNEAQDAVEAL SSHPQKFVGKCLSDLPTDTTNYEKENEN MQTHVMQQATNALTSYLGAESLRPLVQTPPGSSEVVPTISSMPQLHKPSDGPPRSNEAQDAVEAL SSHPQKFVGKCLSDLSTDGGGELUQPPIDQATINALTSYLGAESLRPLVQTPPGSSEVVPTISSMPQLHKPHADTTNTSSGAHESAVEAL SSHPQKFVGKCLSDLSTDGGGELUQPPIDQATINALTSYLGAESLRPLVQTPPGSSEVVPTISSMPQLHKPHADTTNTSSGAHESAVEAL SSHPQKFVGKRLSDLSYDGGGELUQPQIDQTTNSATSYLGAESLRPLVQTPPGSSEVVPTISMPQLHKPLAGF SSHPQKFVGKRLSDLSYDGGGELUQPQIDQTTNSATSYLGAESLRPLVQTPPGSSEVVPTISMPQLHKPAGF SSHPQKFVGKRLSDLSYDG	LL LL LL LL LL LL LL LL LL LL LL LL LL
Orangutan Dog Cow Horse Opossum Mouse Rat Chicken Xenopus Zebrafish Fugu Consensus Human Chinganzee Macaque Orangutan Dog	SSHPQKFVGDKCLSDHPTDSSSVEREXENDMINNADIA INVLOESLRPLVQTPYGSSEVVPT I SNIQ GHEPHAGEOPPSNISADOAVEAL SSHPQKFVGDKCLSDHPTDSSASVEREXENDMINNADIA INVLGAESLRPLVQTPPGSSEVVPT I SNIQ GHEPHAGEOPPSNISADOSAVEAL SSHPQKFVGDKCLSDHPTDSSASVEREXENDMIQTHVNDQA INVA I SYLGAESLRPLVQTPPGSSEVVPT I SNIQ GHEPHAGEOPPSNISADOSAVEAL SSHPQKFVGEKCLPDI PYDASANYEKENEMMQTHVNDQA INVA I SYLGAESLRPLVQTPPGSSEVVPT I SSNIQ HEPHAGEOPPSNISADOSAVEAL SSHPQKFVGEKCLPDI PYDASANYEKENEMMQTHVNDQA INVA I SYLGAESLRPLVQTPPGSSEVVPT I SSNIQ HEPHAGEOPPSNISADOSAVEAL SSHPQKFVGEKCLPDI PYDASANYEKENEMMQTHVNDQA INVA I SYLGAESLRPLVQTPPGSSEVVPT I SSNIQ HEPPSGOPPSNISADOSAVEAL SSHPQKFVGEKLSDLPYDGS - ANYEKENEMMQTHVNDQA INVA I SYLGAESLRPLVQTPPGSSEVVPT I SSNIQ HEPPSGOPPSNISADOSAVEAL SSHPQKFVGEKLSDLPYDGS - ANYEKENEMMQTHVNDQA INVA I SYLGAESLRPLVQTPPGSSEVVPT I SSNIQ HEPPSGOPPSNISADOSAVEAL SSHPQKFVGEKLSDLPYDG - MYEKENE MQTHVI DQA INVA I SYLGAESLRPLVQTPPGSSEVVPT I SSNIQ HEPPSGOPPSNISADOSAVEAL SSHPQKFVGEKLSDLPYDATTNYEKENEMMQTHVDQA INVA I SYLGAESLRPLVQTPPGSESEVVPT I SSNIQ HEPPSGOPPSNISADOSAVEAL SSHPQKFVGEKLSDLPYDATTNYEKENEMMQTHVDQA INVA I SYLGAESLRPLVQTPPGSESEVVPT I SSNIQ HEPPSGOPSNISADOSAVEAL SSHPQKFVGEKLSDLPYDGSASYEKENMQTHVDQA INVA I SYLGAESLRPLVQTPPGSESEVVPT I SSNIQ HEPPSGOPSNISADOSAVEAL SSHPQKFVGEKLSDLSYDG	LL LL LL LL LL LL LL LL LL LL LL LL LL
Orangutan Dog Cow Horse Opossum Mouse Rat Chicken Xenopus Zebrafish Fugu Consensus Human Chimpanzee Macaque Orangutan Dog Cow	SSHPQKFVGDKCLSDHPTDSSSYEREXEMONTHVMDQA INNA ISYLGAESLRPLVQTPYGSSEVVPT ISMIQLHPPHAEGPPRSNISAQDSAVEAL SSHPQKFVGDKCLSDHPTDSSSYEREXEMONTHVMDQA INNA ISYLGAESLRPLVQTPPGSSEVVPT ISMIQLHPPHAEGPPRSNISAQDSAVEAL SSHPQKFVGDKCLSDHPTDSSSYEREXEMONTHVMDQA INNA ISYLGAESLRPLVQTPPGSSEVVPT ISMIQLHRPHEGPARSMISAQDSAVEAL SSHPQKFVGDKCLSDMPYDS-ASYEKENEMNQTHVMDQA INNA ISYLGAESLRPLVQTPPGSSEVVPT ISSNIQLHRPHEGPARSMISAQDSAVEAL SSHPQKFVGEKLDDIPTDASANYEKENEMNQTHVMDQA INNA ISYLGAESLRPLVQTPPGSSEVVPT ISSNIQLHRPHEGPARSMISAQDSAVEAL SSHPQKFVGEKLDDIPTDASANYEKENEMNQTHVMDQA INNA ISYLGAESLRPLVQTPPGSSEVVPT ISSNIQLHRPPSDGPPRSNISAQDSAVEAL SSHPQKFVGEKLDSDHPTDS-ANYEKE-DMITSHVMDQA INNA ISYLGAESLRPLVQTPPGSSEVVPT ISSNIQLHRPPSDGPPRSNISAQDSAVEAL SSHPQKFVGEKLSDHPTDS-ANYEKE-DMITSHVMDQA INNA ISYLGAESLRPLVQTPPGSSEVVPT ISSNIQLHRPPSDGPPRSNISAQDSAVEAL SSHPQKFVGEKLSDLPYDA-NNYEKE-DMITSHVMDQA INNA ISYLGAESLRPLVQTPPGSEVVPT ISSNIQLHRPPSDGPPRSNISAQDSAVEAL SSHPQKFVGEKLSDLPYDATNYEKEEDMQTHVIDQA INNA ISYLGAESLRPLVQTPPGSEVVPT ISSNIQLHRPHAD ITTNTSQSAHESAVEAL SSHPQKFVGEKLSDLPYDATNYEKEEDMQTHVIDQA INNA ISYLGAESLRPLVQTPPGSEVVPT ISSNIQLHRPHAD ITTNTSQSAHESAVEAL SSHPQKFVGEKLSDLPYDATNYEKEEDMQTHVIDQA INNA ISYLGAESLRPLVQTPPGSESEVVPT ISSNIQLHRPHAD ITTNTSQSAHESAVEAL SSHPQKFVGEKLSDLPYDGT-GAGELTQPQTGDTITNSI ISYLGAESLRPLVQTPPGSSEVVPT ISPNQLHRPABOE-CAVSAKDAAEHL SSHPQKFVGEKLSDLSPDCGAGELMQPHVIDQA INNA ISYLGAESLRPLVQTSPSS-SDVLSMS-HINTASDGGGTVABADAAEHL SSHPQKFVGEKLSDLSPDC	LL LL LL LL LL LL LL LL LL LL QM QM QM QM AL
Orangutan Dog Cow Horse Opossum Mouse Rat Chicken Xenopus Zebrafish Fugu Consensus Human Chimpanzee Macaque Orangutan Dog Cow Horse	SSHPQKFVGKCLSDNPTOSSAYEKENEMQTHYMDQA INALISYLGAESLRPLVQTPPGSSEVVPT ISPNQLHPPHAGCPPSSHSAQDAVEAL SSHPQKFVGKCLSDNPTOSSAYEKENEMQTHYMDQA INALISYLGAESLRPLVQTPPGSSEVVPT ISPNQLHPPHAGCPPSSHSAQDAVEAL SSHPQKFVGKCLSDNPTOSSAYEKENEMQTHYMDQA INALISYLGAESLRPLVQTPPGSSEVVPT ISPNQLHRPHAGCPRSHSAQDAVEAL SSHPQKFVGKCLSDNPTOSSAYEKENEMQTHYMDQA INALISYLGAESLRPLVQTPPGSSEVVPT ISSNQLHKPHAGDIPRSHSAQDAVEAL SSHPQKFVGKCLSDNPTOS-ANYEKENEMMQTHYMDQA INALISYLGAESLRPLVQTPPGSSEVVPT ISSNQLHKPHAGDIPRSHSAQDAVEAL SSHPQKFVGKCLSDNPTOS-ANYEKENEMMQTHYMDQA INALISYLGAESLRPLVQTPPGSSEVVPT ISSNQLHKPHAGDIPRSHSAQDAVEAL SSHPQKFVGKCLSDNPTOS-ANYEKENEMMQTHYMDQA INALISYLGAESLRPLVQTPPGSSEVVPT ISSNQLHKPHSDGPPSSHSAQDAVEAL SSHPQKFVGKCLSDNPTOS-ANYEKENEMMQTHYMDQA INALISYLGAESLRPLVQTPPGSSEVVPT ISSNQLHKPHSDGPPSSHSAQDAVEAL SSHPQKFVGKCLSDLPTDFANYEKENEMQTHYMDQA INALISYLGAESLRPLVQTPPGSSEVVPT ISSNQLHKPHSDGPPSSHSAQDAVEAL SSHPQKFVGKCLSDLPTDHANYEKENEMQTHYMDQA INALISYLGAESLRPLVQTPPGSSEVVPT ISSNQLHKPHSDGPPSSHSAQDAVEAL SSHPQKFVGKCLSDLSDG-CGGELQQQGIDQTISSAISYLGAESLRPLVQTPPGSSEVVPT ISSNQLHKPHADITHYSGAEHSAVEAL SSHPQKFVGKRLSDLSYDGGGELQQPGIDQTISSAISYLGAESLRPLVQTPPGSSEVVPT ISSNQLHKPHADITHYSGAEHSAVEAL SSHPQKFVGKKLSDLSYDG	LL LL LL LL LL LL LL LL LL LL LL LL LL
Orangutan Dog Cow Horse Opossum Mouse Rat Chicken Xenopus Zebrafish Fugu Consensus Human Chimpanzee Macaque Orangutan Dog Cow Horse Opossum	SSHPAKFVGKCLSDNPTOSASYEKENDINGTHVIDQA TINA TSYLGAESLRPLVQTPYGSSEVVPT I SPINQLHPPHAGCPPSSISAQOSAVEAL SSHPAKFVGKCLSDNPTOSASYEKENDINQTHVIDQA TINA TSYLGAESLRPLVQTPPGSSEVVPT I SPINQLHPPHAGCPPSSISAQOSAVEAL SSHPAKFVGKCLSDNPTOSASYEKENDINQTHVIDQA TINA TSYLGAESLRPLVQTPPGSSEVVPT I SSINQLHKPHAGGIPRSHSAQOSAVEAL SSHPAKFVGKCLSDNPTOSASYEKENDINQTHVIDQA TINA TSYLGAESLRPLVQTPPGSSEVVPT I SSINQLHKPHAGGIPRSHSAQOSAVEAL SSHPAKFVGKCLSDNPTOSANYEKENDINQTHVIDQA TINA TSYLGAESLRPLVQTPPGSSEVVPT I SSINQLHKPHAGGIPRSHSAQOSAVEAL SSHPAKFVGKCLSDNPTOS-ANYEKENDINQTHVIDQA TINA TSYLGAESLRPLVQTPPGSSEVVPT I SSINQLHKPPSGPRSHSAQOSAVEAL SSHPAKFVGKCLSDNPTOS-ANYEKENDINGTHVIDQA TINA TINLGAESLRPLVQTPPGSSEVVPT I SSINQLHKPPSGPRSHSAQOSAVEAL SSHPAKFVGKCLSDNPTOS-ANYEKENDINGTHVIDQA TINA TINLGAESLRPLVQTPPGSSEVVPT I SSINQLHKPPSGCPRSHSAQOSAVEAL SSHPAKFVGKCLSDLPTOT-TNYEKENE INQTHVI DQA TINA TSYLGAESLRPLVQTPPGSEEVVPT I SSINQLHKPPSGCPRSHSAQOSAVEAL SSHPAKFVGKCLSDLPTOTTNYEKENE INQTHVI DQA TINA TSYLGAESLRPLVQTPPGSEEVVPT I SSINQLHKPSGCPGVSVISAGDAAVEAL SSHPAKFVGKCLSDLPYDATTNYEKENE INQTHVIDQA TINA TSYLGAESLRPLVQTSPGS-ADWYSPLTVNHKSQTAE-GONGXABDSAARELI STIPPKFVGKRLSLSFES-GGSGELMQPHY TDQA TINA TSYLGAESLRPLVQTSPGS-SDVALSSINSLHKTASDGAGGTVISAKDSAAKDAVEAL SSHPAKFVGDKCLSDLYDGSASYEKENBMQGHVIDQA TINA TSYLGAESLRPLVQTSPGS-SDVALSSINSLHKTASDGAGGTVISAKDSAAKDAVEAL SSHPAKFVGDKCLSDLYDGSASYEKENBMQGHVIDQA TINA TSYLGAESLRPLVQTSPGS-SDVALSSINSLHKTASDGAGGTVISAKDSAKDENL SSKAKLYSSEREASPSNSCQDSTDTESNNEEQRS-GLIVLTINHTAPHARG-LSLKEEHRAYDLLRAAS-ENSQALRVVSTSGEQ LSKAKLYPSEREASPSNSCQDSTDTESNNEEQRS-GLIVLTINHTAPHARG-LSLKEEHRAYDLLRAAS-ENSQALRVVSTSGEQ LSKAKLYPSEREASPSNSCQDSTDTESNNEEQRS-GLIVLTINHTAPHARG-LSLKEEHRAYDLLRAAS-ENSQALRVVSTSGEQ LSKAKKYSSEREASPSNSCQDSTDTESNNEEQRS-GLIVLTINHTAPHARG-LSLKEEHRAYDLLRAAS-ENDAAFVETIGTSGEP LSKAKSYSSEREASPSNSCQDSTDTESNNEEQRS-GLIVLTINHTAPHARG-LSLKEEHRAYDLLRAAS-ENSQALRVVSTSGEQ LSKAKSYSSEREASPSNSCQDSTDTESNNEEQRS-GLIVLTINHTAPHARG-LSLKEEHRAYDLLRAAS-ESQALRVVSTSGEQ LSKAKSYSSEREASPSNSCQDSTDTESNNEEQRS-GLIVLTINHTAPHARG-LSLKEEHRAYDLLRAAS-ESQALRVSTSGEQ LSKAKSYSSEREASPSNSCQDSTDTESNNEEQRS-GLIVLTINH	LL LL LL LL LL LL LL LL LL LL LL LL LL
Orangutan Dog Cow Horse Opossum Mouse Rat Chicken Xenopus Zebrafish Fugu Consensus Human Chiganzee Macaque Orangutan Dog Cow Horse Opossum	SSHPQKFVGDKCLSDHPTDSSSVEREENDMQTHVMDQA INNA ISYLGAESLRPLVQTPPGSSEVVPTISPNQLHRPHAGEPPRSVISAQDAVEAL SSMPQKFVGDKCLSDHPTDSSSVEREENDMQTHVMDQA INNA ISYLGAESLRPLVQTPPGSSEVVPTISPNQLHRPHAGEPPRSVISAQDAVEAL SSMPQKFVGDKCLSDMPTDSSASYEREENDMQTHVMDQA INNA ISYLGAESLRPLVQTPPGSSEVVPTISPNQLHRPHGEGPARSNISAQDSAVEAL SSMPQKFVGDKCLSDMPTDSSASYEREENDMQTHVMDQA INNA ISYLGAESLRPLVQTPPGSSEVVPTISSNQLHRPPSGCPPRSNISAQDSAVEAL SSMPQKFVGDKCLSDMPTDSSASYEREENDMQTHVMDQA INNA ISYLGAESLRPLVQTPPGSSEVVPTISSNQLHRPPSGCPPRSNISAQDSAVEAL SSMPQKFLGDKCLSDMPTDSSASYEREENDMQTHVMDQA INNA ISYLGAESLRPLVQTPPGSSEVVPTISSNQLHRPPSGCPPRSNISAQDSAVEAL SSMPQKFLGDKCLSDMPTDSSASYEREENDMQTHVMDQA INNA ISYLGAESLRPLVQTPPGSSEVVPTISSNQLHRPPSGCPPRSNISAQDSAVEAL SSMPQKFUGKRLSDLPYDSSASYEREENDMQTHVMDQA INNA ISYLGAESLRPLVQTPPGSSEVVPTISSNQLHRPPSGCPPSNISAQDSAVEAL SSMPQKFVGEKLSDLPYDSSASYEREENDMQTHVIDQA INNA ISYLGAESLRPLVQTPPGSSEVVPTISSNQLHRPPSGCPPSNISAQDSAVEAL SSMPQKFVGEKLSDLPYDATTNYEREENDMQTHVMDQA INNA ISYLGAESLRPLVQTPPGSSEVVPTISSNQLHRPSGCPRSNISAQDSAVEAL SSMPQKFVGEKLSDLPYDGSASYEREENDMQTHVMDQA INNA ISYLGAESLRPLVQTPPGSSEVVPTISSNQLHRPSGCPRSNISAQDSAVEAL SSMPQKFVGEKLSDLPYDGSASYEREENDMQTHVMDQA INNA ISYLGAESLRPLVQTPPGSSEVVPTISSNQLHRVSTASQGSAVEAL SSMPQKFVGEKLSDLSPDGSSCOGSTDTESNREEQBS GLIVLTNIHAPHARGSSCOGSTDTESNREEQBS GLIVLTNIHAPHARGSSEVFTISSRVEXSLEEHRANDLRAAS LSKAKLVPSEREASPSNSCQDSTDTESNREEQBS GLIVLTNIHAPHARGSSSEVFTISSRVEXSLEEHRANDLRAAS ENSQDALRVYSTSGEQ LSKAKLVPSEREASPSNSCQDSTDTESNREEQBS SLIVLTNIHAPHARGSSSEVFTISSREEHRANDLRAAS ENSQDALRVYSTSGEQ LSKAKSSEREASPSNSCQDSTDTESNREEQBS SLIVLTNIHAPHARGSSSEVFTISSREEHRANDLRAAS ENSQDALRVYSTSGEQ LSKAKSSSEREASPSNSCQDSTDTESNREEQBS SLIVLTNIHAPHARGSSSEVFTISSREEHRANDLRAAS ENSQDALRVYSTSGEQ LSKAKSSSEREASPSNSCQDSTDTESNREEQBS SLIVLTNIHAPHARNGSSSEVFTISSREEHRANDLRAAS ENSQDALRVYSTSGEQ LSKAKSSSEREASPSNSCQDSTDTESNREEQRS SLIVLTNIHAPHARNGSSSEVFTILSRAEEHRANDLRAAS ENSQDALRVYSTSGEQ LSKAKSSEREASPSNSCQDSTDTESNREEQRS SLIVLTNIHAPHARNGSSCQDSTDTESNREEQRS SLIVLTNIHAPHARNGSSSEVFTILSRAEEHRANDLRAAS ENSQDALRVSTSGEQ LSKAKSSSERASPSNSCQDSTDTESNREEQRS SLIVLTNIH	LL LL LL LL LL LL LL LL LL LL LL QM QM QM QM QM QM QM QM QM QM QM QM QM
Orangutan Dog Cow Horse Opossum Mouse Rat Chicken Xenopus Zebrafish Fugu Consensus Human Chimpanzee Macaque Orangutan Dog Cow Horse Opossum Mouse Rat	SSHPQKFVGDKCLSDHPTOSSSVEREXEMONTHWOQA INNA ISTLGAESLAPLVQTPYGSSEVVPTI SPNYQLHEPHAGCPPPSSISAQDSAVEAL SSMPQKFVGDKCLSDHPYGSASYEKEXEMONTHWOQA INNA ISTLGAESLAPLVQTPPGSSEVVPTI SPNYQLHEPHAGCPPPSSISAQDSAVEAL SSMPQKFVGDKCLSDMPYDSASYEKEXEMONTHWOQA INNA ISTLGAESLAPLVQTPPGSSEVVPTI SPNYQLHEPHAGCPPPSNISAQDSAVEAL SSMPQKFVGDKCLSDMPYDS-ASYEKEXEMONTHWOQA INNA ISTLGAESLAPLVQTPPGSSEVVPTI SSNYQLHEPHAGCPPPSNISAQDSAVEAL SSMPQKFVGKCLPD IPYDASANYEKEXEMONTHWOQA INNA ISTLGAESLAPLVQTPPGSSEVVPTI SSNYQLHEPHAGCPPRSNISAQDSAVEAL SSMPQKFVGKCLDDI PYDASANYEKEXEMONTHWOQA INNA ISTLGAESLAPLVQTPPGSSEVVPTI SSNYQLHEPHSGPPRSNISAQDSAVEAL SSMPQKFLGKCLSDMPYDS-ANYEKE-DMOTSHWOQA INNA INTLGAESLAPLVQTPPGSSEVVPTI SSNYQLHEPPSDGPPRSNISAQDSAVEAL SSMPQKFLGKCLSDMPYDS-ANYEKE-DMOTSHWOQA INNA INTLGAESLAPLVQTPPGSSEVVPTI SSNYQLHEPPSDGPPRSNISAQDSAVEAL SSMPQKFVGEKLSDLPYDASANYEKENEMQTHWIQQA INNA ISTLGAESLAPLVQTPPGSSEVVPTI SSNYQLHEPPSDGPPRSNISAQDSAVEAL SSMPQKFVGEKLSDLPYDATNYEKEEDMQTHWIQQA INNA ISTLGAESLAPLVQTPPGSEVVPTI SSNYQLHEPPSDGPPSNISAQDSAVEAL SSMPQKFVGEKLSDLPYDATNYEKEEDMQTHWIQQA INNA ISTLGAESLAPLVQTPPGSEVVPTI SSNYQLHEPADOTTHX5QSAHESAVEAL SSMPQKFVGEKLSDLPYDATNYEKEEDMQTHWIQQA INNA ISTLGAESLAPLVQTPPGSESEVVPTI SSNYQLHKPLGDNQTRSNITAQDSAVEAL SSMPQKFVGEKLSDLPYDATNYEKEEDMQTHWIQQA INNA ISTLGAESLAPLVQTPPGSESEVVPTI SSNYLHKTASDGGGTAE-GNVSAKDAAEHL SSMPQKFVGEKLSDLPYDSASYEKEEDMQTHWIQQAINNA ISTLGAESLAPLVQTSPSS-SDVLSMSHIRTASDGGGTAE-GNVSAKDAAEHL SSMPQKFVGEKLSDLPYDSSASYEKEEMQSHVMQQAINNA ISTLGAESLAPLVQTSPSS-SDVLSMSHIRTASDGGCATAE-GNVSAKDAAEHL SSMPQKFVGDKLSDLPYDSSASYEKEEMQSHVMQQAINNA ISTLGAESLAPLVQTSPSS-SDVLSMSHIRTASDGGCATAE-GNSQALARVSTSGEQ LSKAKLVPSEREASPSNSCQDSTDTESNNEEQRS-GLIVITINIHPHANG-LSLKEEHRAYDLLRAAS-ENSQALRVVSTSGEQ LSKAKLVPSEREASPSNSCQDSTDTESNNEEQRS-GLIVITINIHAPHANG-LSIKEEHRAYDLLRAAS-ENSQALRVVSTSGEQ LSKAKVPSEREASPSNSCQDSTDTESNNEEQRS-SLIVITINIHPHARNG-LSIKEEHRAYDLLRAAS-ESQADAFRVIGTSGEL LSKAKSVSEREASPSNSCQDSTDTESNNEEQRS-GLIVITINIHINPHARNG-LSIKEEHRAYDULRAAS-ESQAAFRVIGTSGEL LSKAKSVSEREASPSNSCQDSTDTESNNEEQRS-GLIVITINIHPHARNG-LSIKEEHRAYDULRAAS-ESQAAFRVIGTSGEL LSKAKSVSEREASPSNSCQDSTDTESNNEE	LL
Orangutan Dog Cow Horse Opossum Mouse Rat Chicken Xenopus Zebrafish Fugu Consensus Human Chimpanzee Macaque Orangutan Dog Cow Horse Opossum Mouse Rat Chicken	SSHPAKFVGKCLSDNPTOSASYEKENEMAQTHVMQQATINATISYLCAESLAPLVQTPPGSEVIVYTSPHQLHPPHAGPPPSNISAQDAVELL SSMPQKFVGKCLSDNPTOSASYEKENEMAQTHVMQQATINATISYLCAESLAPLVQTPPGSSEVIVYTSPHQLHRPHAGPPSNISAQDAVELL SSMPQKFVGKCLSDNPTOSASYEKENEMAQTHVMQQATINATISYLCAESLAPLVQTPPGSSEVVPTISPHQLHRPHAGPPSNISAQDAVELL SSMPQKFVGKCLSDNPTOSASYEKENEMAQTHVMQQATINATISYLCAESLAPLVQTPPGSSEVVPTISSMQLHRPHAGPARSNISAQDAVELL SSMPQKFVGKCLSDNPTOSANYEKENEMAQTHVMQQATINATISYLCAESLAPLVQTPPGSSEVVPTISSMQLHRPHAGPARSNISAQDAVELL SSMPQKFVGKCLSDNPTOSANYEKENEMAQTHVMQQATINATISYLCAESLAPLVQTPPGSSEVVPTISSMQLHRPHAGPARSNISAQDAVELL SSMPQKFVGKCLSDNPTOS-ANYEKENEMAQTHVMQQATINATISYLCAESLAPLVQTPPGSSEVVPTISSMQLHRPHSGPPRSNISAQDSAVELL SSMPQKFVGKCLSDNPTOS-ANYEKENEMQTHVMQQATINATISYLCAESLAPLVQTPPGSSEVVPTISSMQLHRPHSGPPRSNISAQDSAVELL SSMPQKFVGKCLSDLPYDATTNYEKENEMQTHVMQQATINATISYLCAESLAPLVQTPPGSSEVVPTISSMQLHRPHSGCPRPSNISAQDSAVELL SSMPQKFVGKCLSDLPYDATTNYEKENEMQTHVMQQATINATISYLCAESLAPLVQTPPGSSEVVPTISSMQLHRPHSGCPRPSNISAQDSAVELL SSMPQKFVGKCLSDLSTGGGELUQPQTQQTDQTISNATISYLCAESLAPLVQTPPGSSEVVPTISSMQLHRPHSGTAF-ROXXSADSAAELL SSMPQKFVGKRLSDLSYDGGGELUQPQTQTDQTISNATISYLCAESLAPLVQTPPGSSEVVPTISMPQLHRPHSGTAF-ROXXSADSAAELL SSMPQKFVGKRLSDLSYDGGGELUQPQTDQTINSATISYLCAESLAPLVQTSPGSDADVVSPLTNHKSQTAF-COXXSADSAAELL SSMPQKFVGKRLSDLSYDG	LL 200 PM
Orangutan Dog Cow Horse Opossum Mouse Rat Chicken Xenopus Zebrafish Fugu Consensus Human Chimpanzee Macaque Orangutan Dog Cow Horse Opossum Mouse Rat Chicken Xenopus	SSHPQKFVGDKCLSDUPUDSASYEKENEMQTHVMDQA INNA ISYLGAESLRPLVQTPYGSEVVPLSPMQLHPPHAGCPPSSISAQOSAVEAL SSMPQKFVGDKCLSDUPUDSASYEKENEMQTHVMDQA INNA ISYLGAESLRPLVQTPYGSSEVVPLSPMQLHRPHAGCPRSNISAQDSAVEAL SSMPQKFVGDKCLSDUPUDSASYEKENEMQTHVMDQA INNA ISYLGAESLRPLVQTPPGSSEVVPLSPMQLHRPHAGCPRSNISAQDSAVEAL SSMPQKFVGKCLSDUPUDS-ANYEKE-DMRTHVMDQA INNA ISYLGAESLRPLVQTPPGSSEVVPLSSMQLHRPHAGGIPRSNISAQDSAVEAL SSMPQKFVGKCLSDUPUDS-ANYEKE-DMRTHVMDQA INNA ISYLGAESLRPLVQTPPGSSEVVPLSSMQLHRPHAGGIPRSNISAQDSAVEAL SSMPQKFVGKCLSDUPUDS-ANYEKE-DMRTHVMDQA INNA ISYLGAESLRPLVQTPPGSSEVVPLSSMQLHRPHSGOPPRSNISAQDSAVEAL SSMPQKFVGKCLSDUPUDS-ANYEKE-DMRTHVMDQA INNA ISYLGAESLRPLVQTPPGSSEVVPLSSMQLHRPHSGOPPRSNISAQDSAVEAL SSMPQKFVGKRLSDUPUDS-ANYEKE-DMRTHVMDQA INNA ISYLGAESLRPLVQTPPGSSEVVPLSSMQLHRPHSGOPPRSNISAQDSAVEAL SSMPQKFVGKRLSDUPUDS-ANYEKE-DMRTHVIDQA INNA ISYLGAESLRPLVQTPPGSEVVPLSSMQLHRPHSGOPPRSNISAQDSAVEAL SSMPQKFVGKRLSDLYDDG-ANYEKE-DMRTHVIDQA INNA ISYLGAESLRPLVQTPPGSEVVPLSPMQLHRPLGDNQTESMHTADDSAVEAL SSMPQKFVGKRLSDLYDG-GGELMQPHVIDQA INNA ISYLGAESLRPLVQTPPGSSEVVPU ISSMQLHRPPSGCPRSNISAQDSAVEAL SSMPQKFVGKRLSDLYDG-GGELMQPHVIDQA INNA ISYLGAESLRPLVQTPPGSSEVVPU ISSMQLHRPSGCPG-SADMVSPCLMLHRSQTAE-GNGVSAKDSAAEHL ISSMLVPSEREASPSNSCQDSTDTESNNEEQRS-GLIVLITNHIAPHARG-LSLKEEHRAYDLLRAAS-ENGQALRVVSTSGQL LSKAKLVPSEREASPSNSCQDSTDTESNNEEQRS-GLIVLITNHIAPHARG-LSLKEEHRAYDLLRAAS-ENSQALRVVSTSGQL LSKAKLVPSEREASPSNSCQDSTDTESNNEEQRS-GLIVLITNHIAPHARG-LSLKEEHRAYDLLRAAS-ENSQALRVVSTSGQL LSKAKLVPSEREASPSNSCQDSTDTESNNEEQRS-GLIVLITNHIAPHARG-LSLKEEHRAYDLLRAAS-ENSQALRVVSTSGQL LSKAKLVPSEREASPSNSCQDSTDTESNNEEQRS-GLIVLITNHIAPHARG-LSLKEEHRAYDLLRAAS-ESQALRVVSTSGQL LSKAKSSEREASPSNSCQDSTDTESNNEEQRS-GLIVLITNHIAPHARG-LSLKEEHRAYDLLRAAS-ESQALRVVSTSGQL LSKAKSVSSERASPSNSQDSTDTESNNEEQRS-GLIVLITNHIAPHARG-LSLKEEHRAYDLLRAAS-ESQALRVVSTSGQL LSKAKSVSSERASPSNSQDSTDTESNNEEQRS-GLIVLITNHINPHARNG-LSLKEEHRAYDLLRAAS-ESQALRVVSTSGQL LSKAKSVSSERASPSNSQDSTDTESNNEEQRS-GLIVLITNHINPHARNG-LSLKEEHRAYDLLRAAS-ESQALRVVSTSGQL LSKAKSVSSERASPSNSQDSTDTESNNEEQRS-GLIVLININIPHARNG-LSLKEEHRAYDLLRAAS-ESQALRVVSTSGQL LSKAKSVSSERASPSNSQDSTDTESNNEEQR	LL LL LL LL LL LL LL LL AM
Orangutan Dog Cow Horse Opossum Mouse Rat Chicken Xenopus Zebrafish Fugu Consensus Human Chimpanzee Macaque Orangutan Dog Cow Horse Opossum Mouse Rat Chicken Xenopus Zebrafish	SSHPQKFVGDKL.SDHP105SX5FEREXBINGTHWDQA INNA ISTLGAESLAPLVQTPPGSEVVPT I SPINQLHPPHAGEPPPSKISAQDSAVEAL SSHPQKFVGDKCLSDHP105SX5FEREXBINQTHWDQA INNA ISTLGAESLAPLVQTPPGSSEVVPT I SPINQLHKPHGEGPARSNISAQDSAVEAL SSHPQKFVGDKCLSDHP105SX5FEREXBINQTHWDQA INNA ISTLGAESLAPLVQTPPGSSEVVPT I SSINQLHKPHGEGPARSNISAQDSAVEAL SSHPQKFVGDKCLSDMP105-ANYEKE-DBMTSHVDQA INNA ISTLGAESLAPLVQTPPGSSEVVPT I SSINQLHKPHGEGPARSNISAQDSAVEAL SSHPQKFVGDKCLSDMP105-ANYEKE-DBMTSHVDQA INNA ISTLGAESLAPLVQTPPGSSEVVPT I SSINQLHKPHGEGPARSNISAQDSAVEAL SSHPQKFVGEKCLSDLP105-ANYEKE-DBMTSHVDQA INNA ISTLGAESLAPLVQTPPGSSEVVPT I SSINQLHKPHSGGPPRSNISAQDSAVEAL SSMPQKFVGEKLSDLP105-ANYEKE-DBMTSHVDQA INNA ISTLGAESLAPLVQTPPGSSEVVPT I SSINQLHKPPSGGPPRSNISAQDSAVEAL SSMPQKFVGEKLSDLP105-ANYEKE-DBMTSHVDQA INNA ISTLGAESLAPLVQTPPGSSEVVPT I SSINQLHKPPSGGPPRSNISAQDSAVEAL SSMPQKFVGEKLSDLP105-ANYEKE-DBMTSHVDQA INNA ISTLGAESLAPLVQTPPGSEVPTVI SSINQLHKPPSGGPPRSNISAQDSAVEAL SSMPQKFVGEKLSDLP105-ANYEKE-DBMTSHVDQA INNA ISTLGAESLAPLVQTPPGSEVPTVI SSINQLHKPSGGPRSNISAQDSAVEAL SSMPQKFVGEKLSDLP105-ANYEKE-DBMTSHVDQA INNA ISTLGAESLAPLVQTPPGSEVTPVI SSINQLHKPIGDNQTESNIFAQDSAVEAL SSMPQKFVGEKLSDLP105ASYEKENBMQTHVDQA INNA ISTLGAESLAPLVQTPPGSEVTPVI SSINQLHKPAGDCGTVGSAKDSAADHL SSMPQKFVGEKLSDLP105ASYEKENBMQTHVDQA INNA ISTLGAESLAPLVQTPPGSEVTPVI SSINQLHKP3ADCGTVGSAKDSAADHL SSMPQKFVGDKCLSDLP105ASYEKENBMQSHVDQA INNA ISTLGAESLAPLVQTPPGSSEVVPVI SPMYQLHKP AEG PRSNHSAQDSAVEALL SSMPQKFVGDKCLSDLP105ASYEKENBMQSHVDQA INNA ISTLGAESLAPLVQTPPGSSEVVPVI SPMYQLHKP AEG PRSNHSAQDSAVEALL SSMPQKFVGDKCLSDLP105SASYEKENBMQSHVDQA INNA ISTLGAESLAPLVQTPPGSSEVVPVI SPMYQLHKP AEG PRSNHSAQDSAVEALL SKAKLVPSEREASPSNSCQ0STDTESNNEEQRS-GLIVLTNI HPHARCG-LSLKEEHRAYDLLRAAS-ENSQDALRVYSTSGEQ LSKAKLVPSEREASPSNSCQ0STDTESNNEEQRS-GLIVLTNI HPHARMG-LSLKEEHRAYDLLRAAS-ENSQDALRVYSTSGEQ LSKAKLVPSEREASPSNSCQ0STDTESNNEEQRS-GLIVLTNI HPHARMG-LSIKEEHRAYDLLRAAS-ENSQDALRVYSTSGEQ LSKAKSVSSEREASPSNSCQ0STDTESNNEEQRS-GLIVLTNI HPHARMG-LSIKEEHRAYDLLRAAS-ENSQDALRVYSTSGEQ LSKAKSVSSEREASPSNSCQ0STDTESNNEEQRS-GLIVLTNI HPHARMG-LSIKEEHRAYDLLRAAS-ESQDALRVYSTSGEQ LSKAKSVSSEREAS	LL
Orangutan Dog Cow Horse Opossum Mouse Rat Chicken Xenopus Zebrafish Fugu Consensus Human Chimpanzee Macaque Orangutan Dog Cow Horse Opossum Mouse Rat Chicken Xenopus Zebrafish Fugu	SSHPQKFVGKCLSDNPTOSASYEKENEMQTHVMQQATNNATSYLGAESLRPLVQTPPGSSEVVPTISPMQLHPPHAGCPPSSHSAQDAVEAL SSMPQKFVGKCLSDNPTOSASYEKENEMQTHVMQQATNNATSYLGAESLRPLVQTPPGSSEVVPTISPMQLHPPHAGCPPSSHSAQDAVEAL SSMPQKFVGKCLSDNPTOSASYEKENEMQTHVMQQATNNATSYLGAESLRPLVQTPPGSSEVVPTISPMQLHPPHAGCPPSSHSAQDAVEAL SSMPQKFVGKCLSDNPTOSASYEKENEMQTHVMQQATNNATSYLGAESLRPLVQTPPGSSEVVPTISSMQLHKPHAGDIPRSNHSAQDAVEAL SSMPQKFVGKCLSDNPTOSASYEKENEMQTHVMQQATNNATSYLGAESLRPLVQTPPGSSEVVPTISSMQLHKPHAGDIPRSNHSAQDAVEAL SSMPQKFVGKCLSDNPTOSANYEKENEMMQTHVMQQATNNATSYLGAESLRPLVQTPPGSSEVVPTISSMQLHKPHAGDIPRSNHSAQDAVEAL SSMPQKFVGKCLSDNPTOS-ANYEKENEMMQTHVMQQATNNATSYLGAESLRPLVQTPPGSSEVVPTISSMQLHKPHSQGPPRSNHSAQDSAVEAL SSMPQKFVGKCLSDLPTDATTNYEKENEMQTHVMQQATNNATSYLGAESLRPLVQTPPGSSEVVPTISSMQLHKPHSQGPPRSNHSAQDSAVEAL SSMPQKFVGKCLSDLPTDATTNYEKENEMQTHVMQQATNNATSYLGAESLRPLVQTPPGSSEVVPTISSMQLHKPHSQGAPTKSHSAQDSAVEAL SSMPQKFVGKCLSDLPTDATTNYEKENEMQTHVMQQATNNATSYLGAESLRPLVQTPPGSSEVVPTISSMQLHKPHSQGAPTKSHSAQDSAVEAL SSMPQKFVGKGKLSDLSYDGGGELIQQPGTQTTISSATSYLGAESLRPLVQTSPGS-ADMVYSPLNALHKPHADTTTSSGAEMSAVEAL SSMPQKFVGKRLSDLSYDG	LL
Orangutan Dog Cow Horse Opossum Mouse Rat Chicken Xenopus Zebrafish Fugu Orangutan Dog Comensus Human Chimpanzee Macaque Orangutan Dog Cow Horse Opossum Mouse Rat Chicken Xenopus Zebrafish Fugu Human	SSIPPOKFOGKCI.SDIPPOSSYEREXEMONGTINVIDQA TINA TSYLGAESLIPI.VGTPOSSEVIVY TSYINQLIHEPHAGEPPSSISAQOSAVELI SSIPPOKFOGKCI.SDIPPOSASYEREXEMONGTINVIDQA TINA TSYLGAESLIPI.VGTPOSSEVIVY TSYINQLIHEPHAGEPASNISAQDAVELI SSIPPOKFOGKCI.SDIPPOSASYEREXEMONGTINVIDQA TINA TSYLGAESLIPI.VGTPOSSEVIVY TSYINQLIHEPHAGEPASNISAQDAVELI SSIPPOKFOGKCI.SDIPPOSASYEREXEMONGTINVIDQA TINA TSYLGAESLIPI.VGTPOSSEVIVY TSYNQLIHEPHAGEPASNISAQDAVELI SSIPPOKFOGKCI.SDIPPOSASYEREXEMONGTINVIDQA TINA TSYLGAESLIPI.VGTPOSSEVIVY TSSINQLIHEPHAGEPASNISAQDAVELI SSIPPOKFOGKCI.SDIPPOSANYEREXEMIQTINVIDQA TINA TSYLGAESLIPI.VGTPOSSEVIVY TSSINQLIHEPHAGEPASNISAQDAVELI SSIPPOKFOGKCI.SDIPPOSANYEREXEMIQTINVIDQA TINA TSYLGAESLIPI.VGTPOSSEVIVY TSSINQLIHEPHAGEPASNISAQDAVELI SSIPPOKFOGKCI.SDIPPOSANYEREXEMIQTINVIDQA TINA TSYLGAESLIPI.VGTPPOSSEVIVY TSSINQLIHEPHAGEPASNISAQDAVELI SSIPPOKFOGKCI.SDIPYDS-ANYEKEXEMIQTINVIDQA TINA TSYLGAESLIPI.VGTPPOSSEVIVY TSSINQLIHEPHAGTITTSSGAHEBAVELI SSIPPOKFOGKLI.SDI.SPTOHANYEKENEMIQTINVIDQA TINA TSYLGAESLIPI.VGTPPOSSEVIVY TSSINQLIHEPHAGTITTSSGAHEBAVELI SSIPPOKFOGKLI.SDI.SYDGGGELIAPPOKTIDQA TINA TSYLGAESLIPI.VGTPPOSSEVIVY TSMIQLIHEPHAGTITTSSGAHEBAVELI SSIPPOKFOGKILSDI.SYDG	LL
Orangutan Dog Cow Horse Opossum Mouse Rat Chicken Xenopus Zebrafish Fugu Orangutan Dog Cow Human Opossum Mouse Rat Chicken Xenopus Zebrafish Fugu Human	SSIPQKFVGDKCLSDIPPOSASYEKENDINGALINALISULGAESLIPLVQTPOSSEVVPTISPIQLIPPIAGEOPPSNISAQDAVELL SSIPQKFVGDKCLSDIPPOSASYEKENDINGTHVINDQA INNA ISYLGAESLIPLVQTPOSSEVVPTISPIQLIPPIAGEOPPSNISAQDAVELL SSIPQKFVGDKCLSDIPPOSASYEKENDINGTHVINDQA INNA ISYLGAESLIPLVQTPOSSEVVPTISPIQLIPPIAGEOPPSNISAQDSAVELL SSIPQKFVGEKCLPDIPDISASYEKENDINGTHVINDQA INNA ISYLGAESLIPLVQTPOSSEVVPTISSINQLIHKPHGEGARSNISAQDSAVELL SSIPQKFVGEKCLPDIPDISASYEKENDINGTHVINDQA INNA ISYLGAESLIPLVQTPOSSEVVPTISSINQLIHKPHGEGARSNISAQDSAVELL SSIPQKFVGEKCLPDIPDISASYEKENDINGTHVINDQA INNA ISYLGAESLIPLVQTPOSSEVVPTISSINQLIHKPHGEGARSNISAQDSAVELL SSIPQKFVGEKCLPDIPDISASYEKENDINGTHVINDQA INNA ISYLGAESLRPLVQTPPOSSEVVPTISSINQLIHKPPSGGPPSNISAQDSAVELL SSIPQKFVGEKLSDIPYDG-ANYEKE-DINTSHVINDQA INNA ISYLGAESLRPLVQTPPOSSEVVPTISSINQLIHKPPSGGPPSNISAQDSAVELL SSIPQKFVGEKLSDLPYDATNYEKENDINQTHVIDQA INNA ISYLGAESLRPLVQTPPOSSEVVPTISSINQLIHKPSGGPPSNISAQDSAVELL SSIPQKFVGEKLSDLPYDATNYEKENDINQTHVIDQA INNA ISYLGAESLRPLVQTPPOSSEVVPTISSINQLIHKPSGGPSNISAQDSAVELL SSIPQKFVGEKLSDLPYDATNYEKENDINQTHVIDQA INNA ISYLGAESLRPLVQTPPOSSEVVPTISSINQLIHKPLGDXGTESMITAQDSAVELL SSIPQKFVGEKLSDLSYDG	LL
Orangutan Dog Cow Horse Opossum Mouse Rat Chicken Xenopus Zebrafish Fugu Consensus Human Chimpanzee Macaque Orangutan Dog Cow Horse Opossum Mouse Rat Chicken Xenopus Zebrafish Fugu Human Chimpanzee	SSIPPQKFVGDKLSDIPPOSSYEREENDMQTHVMQQATINATISULGAESLRPLVQTPPQSSEVVPTISPNQLHPPHAGEPPPSNISAQDAVELU SSIPQKFVGDKCLSDIPPOSASYEREENDMQTHVMQQATINATISULGAESLRPLVQTPPQSSEVVPTISPNQLHRPHAGEPPPSNISAQDAVELU SSIPQKFVGDKCLSDIPPOSASYEREENDMQTHVMQQATINATISULGAESLRPLVQTPPQSSEVVPTISSNQLHKPHGEGPARSNISAQDAVELU SSIPQKFVGDKCLSDIPPOSASYEREENDMQTHVMQQATINATISULGAESLRPLVQTPPQSSEVVPTISSNQLHKPPGGPARSNISAQDAVELU SSIPQKFVGKCLSDIPPOSASYEREENDMQTHVMQQATINATISULGAESLRPLVQTPPQSSEVVPTISSNQLHKPPSGCPPRSNISAQDAVENL SSIPQKFVGKCLSDIPPOS-ANYERE-DMMTSHVMQQATINATISULGAESLRPLVQTPPQSSEVVPTISSNQLHKPPSGCPPRSNISAQDAVENL SSIPQKFVGKCLSDIPPOS-ANYERE-DMMTSHVMQQATINATISULGAESLRPLVQTPPQSSEVVPTISSNQLHKPPSGCPPRSNISAQDAVENL SSIPQKFVGKLSDLPYDS-ANYERE-DMMTSHVMQQATINATISULGAESLRPLVQTPPQSSEVVPTISSNQLHKPPSGCPPRSNISAQDAVENL SSIPQKFVGKRLSDLPYDATTNYEKEEDMQTHVIDQATINATISULGAESLRPLVQTPPQSSEVVPTISSNQLHKPPSGCPPRSNISAQDAVENL SSIPQKFVGKRLSDLPYDG-ANYERE-DMMTSHVMQQATINATISULGAESLRPLVQTPPQSEVVPTISSNQLHKPHADITISTSQAHEAXDEXAUEXL SSIPQKFVGKRLSDLPYDATTNYEKENEMQTHVMQQATINATISULGAESLRPLVQTPPGSEVVPTISSNQLHKPHADITISTSQAHEAXDEXAUEXL SSIPQKFVGKRLSDLSPDG	LL
Orangutan Dog Cow Horse Opossum Mouse Rat Chicken Xenopus Zebrafish Fugu Consensus Human Chinganzee Macaque Orangutan Dog Cow Horse Qpossum Mouse Rat Chicken Xenopus Zebrafish Fugu Human Chicken Nose Rat Chicken Xenopus Zebrafish Fugu	SSIPPORFORK.ISDNP105SASYEREENING/THVIDQA I INA I SYLGAESLAPI.VUT PPOSSEVPV1 SPINQLIHPHAGOPPSNISAQDAVELL SSIPPORFORK.ISDNP105SASYEREENING/THVIDQA I INA I SYLGAESLAPI.VUT PPOSSEVVP1 SPINQLIHPHAGOPPSNISAQDAVELL SSIPPORFORK.ISDNP105SASYEREENING/THVIDQA I INA I SYLGAESLAPI.VUT PPOSSEVVP1 SPINQLIHPHAGOPPSNISAQDAVELL SSIPPORFORK.ISDNP105SASYEREENING/THVIDQA I INA I SYLGAESLAPI.VUT PPOSSEVVP1 SSINQLIHPHAGOPPSNISAQDAVELL SSIPPORFORK.ISDNP105SASYEREENING/THVIDQA I INA I SYLGAESLAPI.VUT PPOSSEVVP1 SSINQLIHPHAGOPPSNISAQDAVELL SSIPPORFORK.ISDNP105SASYEREENING/THVIDQA I INA I SYLGAESLAPI.VUT PPOSSEVVP1 SSINQLIHPHAGOPPSNISAQDAVELL SSIPPORFORK.ISDNP105SANYEREENING/THVIDQA I INA I SYLGAESLAPI.VUT PPOSSEVVP1 SSINQLIHPPSDGPPSNISAQDAVELL SSIPPORFORK.ISDNP105SANYEREENING/THVIDQA I INA I SYLGAESLAPI.VUT PPOSSEVVP1 SSINQLIHPPSDGPPSNISAQDAVELL SSIPPORFORK.ISDI PYDATNYEREENING/THVIDQA I INA I SYLGAESLAPI.VUT PPOSSEVVP1 SSINQLIHR/PSDGPPSNISAQDAVELL SSIPPORFORKI.SDI PYDHNANYEKENING/THVIDQA I INA I SYLGAESLAPI.VUT PPOSSEVVP1 I SSINQLIHR/PSDGPPSNISAQDAVELL SSIPPORFORKI.SDI SYDGGGELIQPOGI DQI I ISA I SYLGAESLAPI.VUT SPOS-ADUVYSLIVI.HIKSQTAECONCYASIDAAAELL SSIPPORFORKI.SDI SYDGGGELIQPOGI DQI I ISA I SYLGAESLAPI.VUT SPOS-ADUVYSLIVI.HIKSQTAECONCYASIDAAAELL SSIPPORFORKI.SDI SYDG	LL
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Figure 1. Alignments of amino acid sequences of identified Ikaros. Ikaros genes were identified in the genome sequences of human, chimpanzee, macaque, orangutan, dog, cow, horse, mouse, rat, opossum, chicken, *Xenopus tropicalis*, zebrafish, and fugu. Except rat and *Xenopus tropicalis* Ikaros proteins, which lack the first C2H2-type 1 Zinc finger region, all identified Ikaros proteins containing six C2H2-type 1 Zinc finger regions. The C2H2-type 1 Zinc finger regions of identified Ikaros proteins are underlined.



Figure 2. Phylogenetic analysis of Ikaros genes. The phylogenetic tree of Ikaros genes was obtained by using ML and NJ methods. The primate Ikaros clustered into one group, different from other Ikaros.

Elk-1

GTTATTATGCAGTAGGAAATTAACAATAAATAACAAATTTGGTCCTCCTGTGCTTGTAATGATATTTTTATAAATCTTTGTAA TGCTGTTTTTAAAAGGATCAAGGTCTGTGCCAGTCTGATACTCCAGCAAGTATGTGAGGAGGAAAATGCATTATTCTTGCTAG ATAACCTTGTT<u>GTTAAATA</u>GCATAGGGGTTCT<u>TTATCTCTC</u>TCTCTTTTCTCATATCTTATTAGTATTTTTGCTTTAAACTAAA NKX6 GATA-1 ATCCCTTCCTCTCTTTTCTCAGATAACCTGAGGACCATG

Figure 3. The identification of transcription factor-binding sites within the 5'-region of the human Ikaros gene. The transcription factor-binding sites are underlined. The transcriptional start sites (ATG) of human Ikaros is indicated in bold.

available SNPs were identified in human Ikaros gene. Among these, 5 SNPs were functionally relevant, including four available alleles disrupted an existing exonic splicing enhancer (rs11980379, rs11978363, rs6980115, rs11552047) and one SNP causing missense mutation (rs61731359). For rs61731359, an amino acid change from Asn to Asp in site 319 was reported. Moreover, two identical amino acid changes were also found for rs61731356 (site 391, Asn) and rs61731355 (site 333, Pro) (Table I). *Meta-analysis of the prognostic value of human Ikaros gene in cancer*. When given the gene, PrognoScan displays a summary in table format of tests for the gene with columns for dataset, cancer type, subtype, endpoint, cohort, contributor, array type, probe ID, number of patient, optimal cut-point, Pmin and Pcor. Among the database detected expression of Ikaros, 14 out of 46 tests showed an association between microarray expression in Ikaros and cancer prognosis (bladder cancer 0/2, blood cancer 4/9, breast cancer 6/16,

SNP ID	Chr 7 position	Sequence	Туре	
rs11980379	50437475(+)	GAAATTGTACATAAGT/CACCTCAGCATTTAAT	ESE	
rs11978363	50437793(+)	TATTCCCAATATTCCC/TGGTCAGCAGTATCAA	ESE	
rs6980115	50436016(+)	AGATTTTTATTTTTAG/CAGGCAGGGCTGCATT	ESE	
rs11552047	50437045(+)	TCACCTGTTTGAAACC/TAAGCTTTCAAACATG	ESE	
rs61731359	50435217(+)	ATCAACAACGCCATCA/GACTACCTGGGGGGCC	Missense	
rs61731356	50435435(+)	GGCGTCCCCGAGCAAC/TAGCTGCCAAGACTC	Synonymous	
rs61731355	50435261(+)	GCTGGTGCAGACGCCA/CCCGGGCGGTTCCG	Synonymous	

Table I. Functional relevant SNP evaluation of the human Ikaros gene.

Four available alleles disrupted an existing exonic splicing enhancer (ESE), one SNP causing missense mutation (rs61731359), two SNPs (rs61731356 and rs61731355) causing two identical amino acid changes were identified.

Table II. Dataset content from PrognoScan showed an association between microarray expression in Ikaros and cancer prognosis.

Database	Case type cancer	Subsyte	Patients no.	End-point	Cut-point	P-value	Prognosis	Refs.
GSE12417-GPL96	Blood	AML	163	Overall survival	0.69	0.0209	1	42
E-TABM-346	Blood	DLBCL	53	Event free survival	0.34	0.0231	2	43
GSE16131-GPL97	Blood	Follicular lymphoma	180	Overall survival	0.22	0.0111	1	44
GSE2658	Blood	Multiple myeloma	559	Cause specific survival	0.31	0.0453	2	45
GSE6532-GPL570	Breast		87	Recurrence free survival	0.13	0.0276	1	46
GSE9195	Breast		77	Distant metastasis free survival	0.83	0.0297	1	47
GSE1379	Breast		60	Recurrence free survival	0.47	0.0024	1	48
GSE2034	Breast		286	Distant metastasis free survival	0.5	0.0138	1	49
E-TABM-158	Breast		129	Distant metastasis free survival	0.74	0.0375	2	50
GSE3494-GPL96	Breast		236	Disease specific survival	0.17	0.0016	1	51
GSE13213-2	Lung	Adenocarcinoma	30	Overall survival	0.87	0.0036	2	52
GSE4573	Lung	Squamous cell carcinoma	129	Overall survival	0.47	0.0237	1	53
DUKE-OC	Ovarian		134	Overall survival	0.64	0.0246	2	54
GSE19234	Skin	Melanoma	38	Overall survival	0.55	0.0268	1	55

Fourteen tests showed an association between microarray expression in Ikaros and cancer prognosis (blood cancer 4/9, breast cancer 6/16, lung cancer 2/10, ovarian cancer 1/2, skin cancer 1/1) with 5% significance level. AML, acute myelocytic leukemia; DLBCL, diffuse large B-cell lymphoma; 1 represents poorer expression of Ikaros associated with poor survival; 2 represents higher expression of Ikaros associated with poor survival.

colorectal cancer 0/1, gliomas 0/3, head and neck cancer 0/1, lung cancer 2/10, ovarian cancer 1/2, skin cancer 1/1) with 5% significance level (Table II). Among the four blood cancers, we found a higher expression of Ikaros associated

with poor survival in the case of diffuse large B-cell lymphoma (DLBCL) and multiple myeloma. However, a lower expression of Ikaros was related to poor survival in the case of diffuse large acute myeloid leukemia (AML) and follicular lymphoma. Among the six breast cancers, the higher expression of Ikaros was related to poor survival was found in only one case (E-TABM-158). Among the lung cases, we found a higher expression of Ikaros associated with poor survival in the case of adenocarcinoma and a lower expression of Ikaros associated with poor survival in the case of squamous cell carcinoma. Moreover, a higher expression of Ikaros associated with poor survival was found in the case of ovarian cancer, and a lower expression of Ikaros associated with poor survival in the case of skin cancer.

Discussion

Ikaros is a member of the Kruppel family of zinc finger DNA-binding proteins, which locates at 7p12 in human genome. In the present study, we identified other Ikaros genes from other 13 vertebrate genomes and found Ikaros existed in all kinds of vertebrate including fish, amphibians, birds and mammals. Moreover, except rat and Xenopus tropicalis Ikaros proteins, which lack the first C2H2-type 1 Zinc finger region, all identified Ikaros proteins containing six C2H2-type 1 Zinc finger regions (Fig. 1). The phylogenetic tree shows that Ikaros is separated with the order fish, amphibians, birds and mammals, and primate Ikaros are almost the same and clustered together. From the alignment and phylogenetic tree, mammalian Ikaros are conversed among vertebrate genomes, suggesting that the function of Ikaros is essential for all the vertebrates in the long evolution process. Moreover, this process was under purifying selection.

Though Ikaros expression is essential for normal hematopoiesis in the lymphoid, myeloid, and erythroid lineages, it is not limited to the hematopoietic system. We found human Ikaros gene was expressed in many tissues and organs. It shows a predominant expression in the liver, lymph node, thymus, intestine, lung, mammary gland, bone marrow, brain, heart, placenta, and prostate. It implied Ikaros may be involved in the physiological functions of these tissues. Alternative splicing of Ikaros gene results in a number of mRNA and protein isoforms (Ik1-8) with distinct activity and capability of DNA binding regulating the role in controlling hematopoietic, particularly lymphoid cell differentiation, proliferation and function (3-6). Abnormalities in splicing regulation of Ikaros would lead to significant pathological manifestations (3,4,8,9). We identified four available SNPs disrupting an existing exonic splicing enhancer, which may affect the alternative splicing of Ikaros. The effects of these SNPs on Ikaros physiological and pathological function need further investigation.

Ikaros is involved in apoptosis and cell cycle regulation in lymphocytes and thought as a hematological and pituitary tumor suppressor (15,16). In the present study, we found Ikaros was widely expressed in solid tumors including bladder, blood, breast, colorectal cancer, gliomas, head and neck, lung, ovarian and skin cancer. Prognostic analysis of Ikaros has been reported only in AML (15). We also found a lower expression of Ikaros was related to poor survival in AML, this was confirmed by PrognoScan analysis. However, the PrognoScan analysis depicted statistical significance in other 13 tests (blood cancer 3/9, breast cancer 6/16, lung cancer 2/10, ovarian cancer 1/2, skin cancer 1/1), which were not previously reported. It suggested that the expression of Ikaros was related to the prognosis of many cancers including hematological and solid cancers. The mechanism of Ikaros involved in the process of these tumors needed further investigation. It is important to note that relationship between the expression of Ikaros and prognosis varied in different cancers, even in the same cancer from different database. It implied that the function of Ikaros in these tumors may be multidimensional (Table II), not just as a tumor suppressor. The c-Fos, Elk-1, GATA-1 and NKX6-B binding sites were identified within the upstream of the transcriptional start site of human Ikaros gene. c-Fos is a cellular proto-oncogene belonging to the immediate early gene family of transcription factors. Members of the Fos family dimerise with C-Jun to form the AP-1 transcription factor, which has been implicated in transformation and progression of many cancers (39). ELK1, is a member of the Ets family of transcription factors, originally identified as a key regulator of immediate-early genes, such as FOS, which are rapidly and transiently induced following exposure to extracellular ligands that activate the MAP kinase pathways. ELK1 is also an oncogene implicated in transformation and progression of many cancers (40,41). These two tumorrelated transcriptional factors (c-Fos and Elk-1) may be involved in the effect of Ikaros in tumors.

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