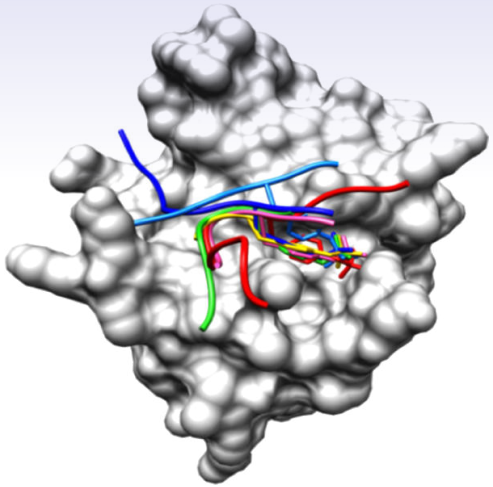

Tools & Databases of Short Linear Motifs

Holger Dinkel

EMBO Practical Course:
"Computational analysis of protein-protein interactions in cell function and disease"
Bangalore, 05. 12. 2019

The Eukaryotic Linear Motif resource for

Functional Sites in Proteins

The ELM resource

is a collection of 289 thoroughly annotated motif classes with over 3500 annotated instances.

It is also a prediction tool to detect these motifs in protein sequences employing different filters to distinguish between **functional** and **non-functional** motif instances.

"ELM-the eukaryotic linear motif resource in 2020."; KUMAR M, GOUW M, MICHAEL S, SMANO-SNCHEZ H, PANCSA R, GLAVINA J, DIAKOGIANNI A, VALVERDE JA, BUKIROVA D, ALYEVA J, PALOPOLI N, DAVEY NE, CHEMES LB, GIBSON TJ.; (NUCLEIC ACIDS RES. 2019)

The Eukaryotic Linear Motif resource for *Functional Sites in Proteins*

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Functional sites		ELM classes		ELM instances		GO terms		PDB structures	ELM instances with affinity values	PubMed Links
Total	176		289		3523		791	516	265	3467
By category		LIG	163	Human	2090	Biological process	430			
		MOD	37	Mouse	341					
		DOC	31	Rat	150	Cellular component	163			
		DEG	25	Yeast	110					
		TRG	22	Fly	98	Molecular function	198			
		CLV	11	Others	734					

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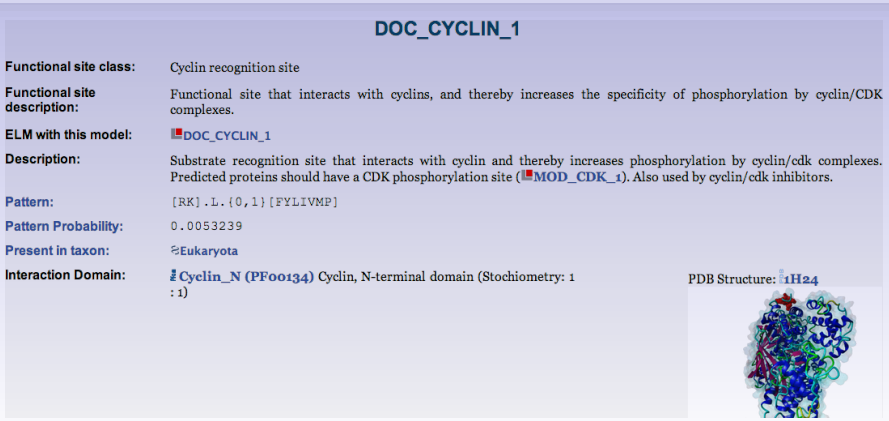
ELM Class

Condensed information about a motif. Regular Expressions used to annotate the motif (eg. `[KR].L.{0,1}[FYLIVMP]` for Cyclin motif)



DOC_CYCLIN_1

Functional site class:	Cyclin recognition site
Functional site description:	Functional site that interacts with cyclins, and thereby increases the specificity of phosphorylation by cyclin/CDK complexes.
ELM with this model:	DOC_CYCLIN_1
Description:	Substrate recognition site that interacts with cyclin and thereby increases phosphorylation by cyclin/cdk complexes. Predicted proteins should have a CDK phosphorylation site (MOD_CDK_1). Also used by cyclin/cdk inhibitors.
Pattern:	[RK].L.{0,1}[FYLIVMP]
Pattern Probability:	0.0053239
Present in taxon:	Eukaryota
Interaction Domain:	Cyclin_N (PF00134) Cyclin, N-terminal domain (Stochiometry: 1 : 1)

PDB Structure: 1H24

ELM Class

Condensed information about a motif. Regular Expressions used to annotate the motif (eg. `[KR].L.{0,1}[FYLIVMP]` for Cyclin motif)

24 Instances for DOC_CYCLIN_1
(click table headers for sorting; Notes column: =Number of Switches, =Number of Interactions)

Protein Name	Gene Name	Start	End	Subsequence	Logic	#Ev.	Organism	Notes
RB_HUMAN	RB1	873	877	SNPPKPLKKLRFDIEGSDEA	TP	3	Homo sapiens (Human)	1H25 1
Q8UWJ8_CHICK	CDH1-A	394	398	KLTGHSYRVLYLAMSPDGEA	FP	1	Gallus gallus (Chicken)	
PMYT1_HUMAN	PKMYT1	486	489	GSFPSFEPRNLLSLFEDTLD	TP	1	Homo sapiens (Human)	
E2F1_HUMAN	E2F1	90	94	LGRPPVKRRLDLETDHQYLA	TP	3	Homo sapiens (Human)	1H24
CDN1C_HUMAN	CDKN1C	31	34	VLVRTSACRSLFGPVDHEEL	TP	1	Homo sapiens (Human)	
RUX_DROME	rux	248	251	PTARRCVRRTLFTEENTQKE	TP	1	Drosophila melanogaster (Fruit fly)	
E2F2_HUMAN	E2F2	87	91	AGRLPAKRKLDLEGIGRPVV	TP	1	Homo sapiens (Human)	
E2F3_HUMAN	E2F3	134	138	GGGPPAKRRLELGESGHQYL	TP	1	Homo sapiens (Human)	
AKA12_MOUSE	Akap12	501	504	IKVQGSPLKKLFSSSGLKKL	TP	1	Mus musculus (House mouse)	1
CDC6_HUMAN	CDC6	94	98	HSHTLKGRRLVFDNQLTIKS	TP	2	Homo sapiens (Human)	2CCH 1
CDN1A_HUMAN	CDKN1A	19	22	NPCGSKACRRLFGPVDSEQL	TP	4	Homo sapiens (Human)	1 1
CDN1A_HUMAN	CDKN1A	155	159	TSMTDFYHSKRRLIFSKRKP	TN	1	Homo sapiens (Human)	
ORC6_YEAST	ORC6	178	182	ESPSITRRKLAFEEDEDEDE	TP	1	Saccharomyces cerevisiae (Baker's yeast)	
P53_HUMAN	TP53	381	385	GQSTSRHKKLMFKTEGPDSD	TP	5	Homo sapiens (Human)	1H26
RBL1_HUMAN	RBL1	658	661	SPTAGSAKRRLFGEDPPKEM	TP	3	Homo sapiens (Human)	1H28
RBL2_HUMAN	RBL2	680	684	PPASTTRRRLFVENDSPSDG	TP	1	Homo sapiens (Human)	
HIRA_HUMAN	HIRA	629	633	KASSLSKRKLELEVETVEKK	TP	1	Homo sapiens (Human)	

DOC_CYCLIN_1

Functional site class: Cyclin recognition site

Functional site description: Functional site that interacts with cyclins, and thereby increases the specificity of phosphorylation by cyclin/CDK complexes.

ELM with this model: DOC_CYCLIN_1

Description: Substrate recognition site that interacts with cyclin and thereby increases phosphorylation by cyclin/cdk complexes. Predicted proteins should have a CDK phosphorylation site (MOD_CDK_1). Also used by cyclin/cdk inhibitors.

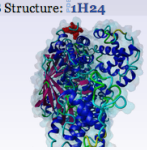
Pattern: `[RK].L.{0,1}[FYLIVMP]`

Pattern Probability: 0.0053239

Present in taxon: Eukaryota

Interaction Domain: Cyclin_N (PF00134) Cyclin, N-terminal domain (Stochiometry: 1 : 1)

PDB Structure: 1H24



ELM Instance

An experimentally verified instance of an ELM class in a particular sequence.

ELM Class

Condensed information about a motif. Regular Expressions used to annotate the motif (eg. `[KR].L.{0,1}[FYLIVMP]` for Cyclin motif)

DOC_CYCLIN_1

Functional site class:	Cyclin recognition site
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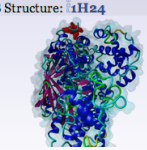


Instance

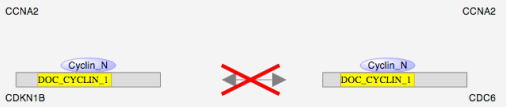
Sequence	Start	End	Subsequence	Logic	PDB	Organism	Length
(Q99741) CDC6_HUMAN	94	98	HSHTLKGRRLVFDNQLTIKS	TP	2CCH	Homo sapiens (Human)	560

Instance evidence

Evidence class	PSMI	Method	BioSource	PubMed	Logic	Reliability	Notes
experimental	MI:0114	x-ray crystallography	in vitro	Cheng,2006	support	certain	InteractionDetection FeatureDetection
experimental	MI:0096	pull down	in vivo/in vitro	Petersen,1999	support	certain	InteractionDetection

This ELM instance is part of the following switching mechanism(s) annotated at the switches.ELM resource:

SWTI000330:



ELM Instance

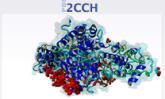
An experimentally verified instance of an ELM class in a particular sequence.

- Experimental Evidences
- Methods
- References
- Interactions

ELM Class

Condensed information about a motif. Regular Expressions used to annotate the motif (eg. `[KR].L.{0,1}[FYLIVMP]` for Cyclin motif)

Instance

Sequence	Start	End	Subsequence	Logic	PDB	Organism	Length
(Q99741) CDC6_HUMAN	94	98	HSHTLKGRRLVFDNQLTIKS	TP	2CCH 	Homo sapiens (Human)	560

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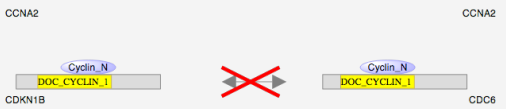

DOC_CYCLIN_1

Functional site class:	Cyclin recognition site
Functional site description:	Functional site that interacts with cyclins, and thereby increases the specificity of phosphorylation by cyclin/CDK complexes.
ELM with this model:	DOC_CYCLIN_1
Description:	Substrate recognition site that interacts with cyclin and thereby increases phosphorylation by cyclin/cdk complexes. Predicted proteins should have a CDK phosphorylation site (MOD_CDK_1). Also used by cyclin/cdk inhibitors.
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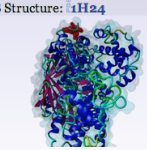
Pattern Probability:	0.0053239
Present in taxon:	Eukaryota
Interaction Domain:	Cyclin_N (PF00134) Cyclin, N-terminal domain (Stochiometry: 1 : 1)

PDB Structure: 1H24 

ELM Instance

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Condensed information about a motif. Regular Expressions used to annotate the motif (eg. `[KR].L.{0,1}[FYLIVMP]` for Cyclin motif)

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Sequence	Start	End	Subsequence	Logic	PDB	Organism	Length
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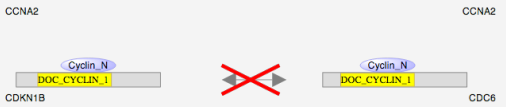

DOC_CYCLIN_1

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Functional site description:	Functional site that interacts with cyclins, and thereby increases the specificity of phosphorylation by cyclin/CDK complexes.
ELM with this model:	DOC_CYCLIN_1
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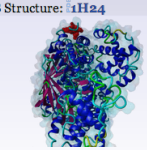
Pattern:	[RK].L.{0,1}[FYLIVMP]
Pattern Probability:	0.0053239
Present in taxon:	Eukaryota
Interaction Domain:	Cyclin_N (PF00134) Cyclin, N-terminal domain (Stochiometry: 1 : 1)

PDB Structure: 1H24



ELM Instance

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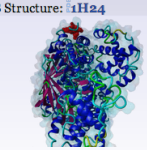
Pattern Probability:	0.0053239
Present in taxon:	Eukaryota
Interaction Domain:	Cyclin_N (PF00134) Cyclin, N-terminal domain (Stochiometry: 1 : 1)

PDB Structure: 1H24



ELM Instance

An experimentally verified instance of an ELM class in a particular sequence.

- Experimental Evidences
- Methods
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- Interactions

ELM Class

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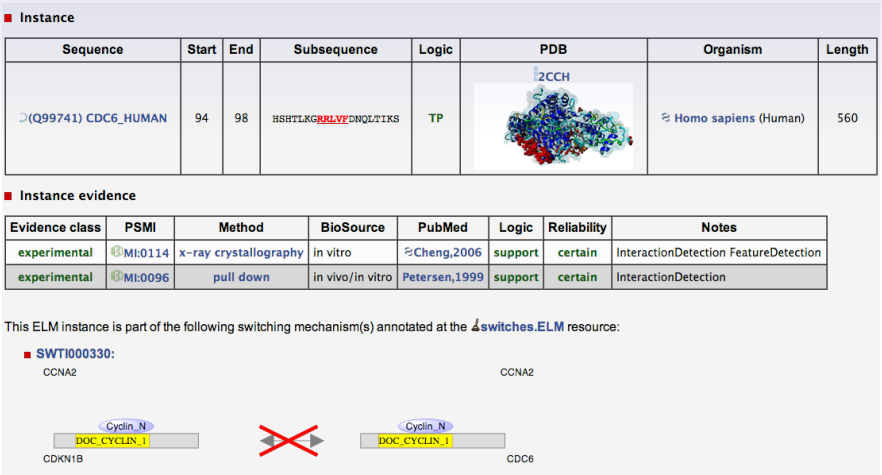

Instance

Sequence	Start	End	Subsequence	Logic	PDB	Organism	Length
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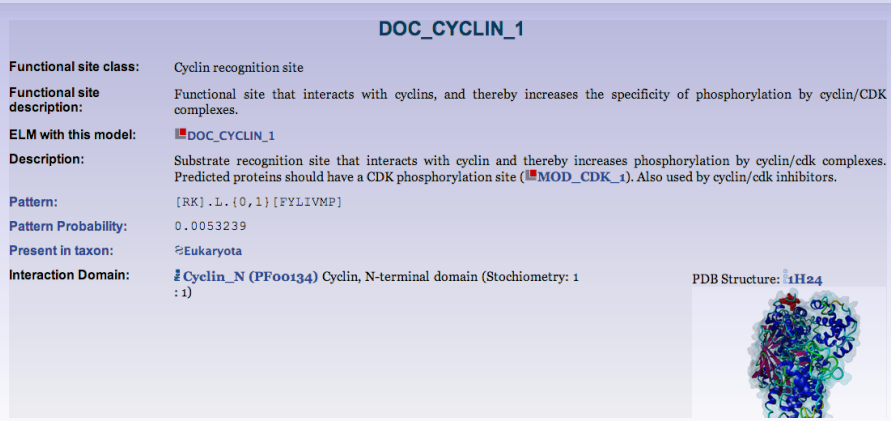

DOC_CYCLIN_1

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Present in taxon:	Eukaryota
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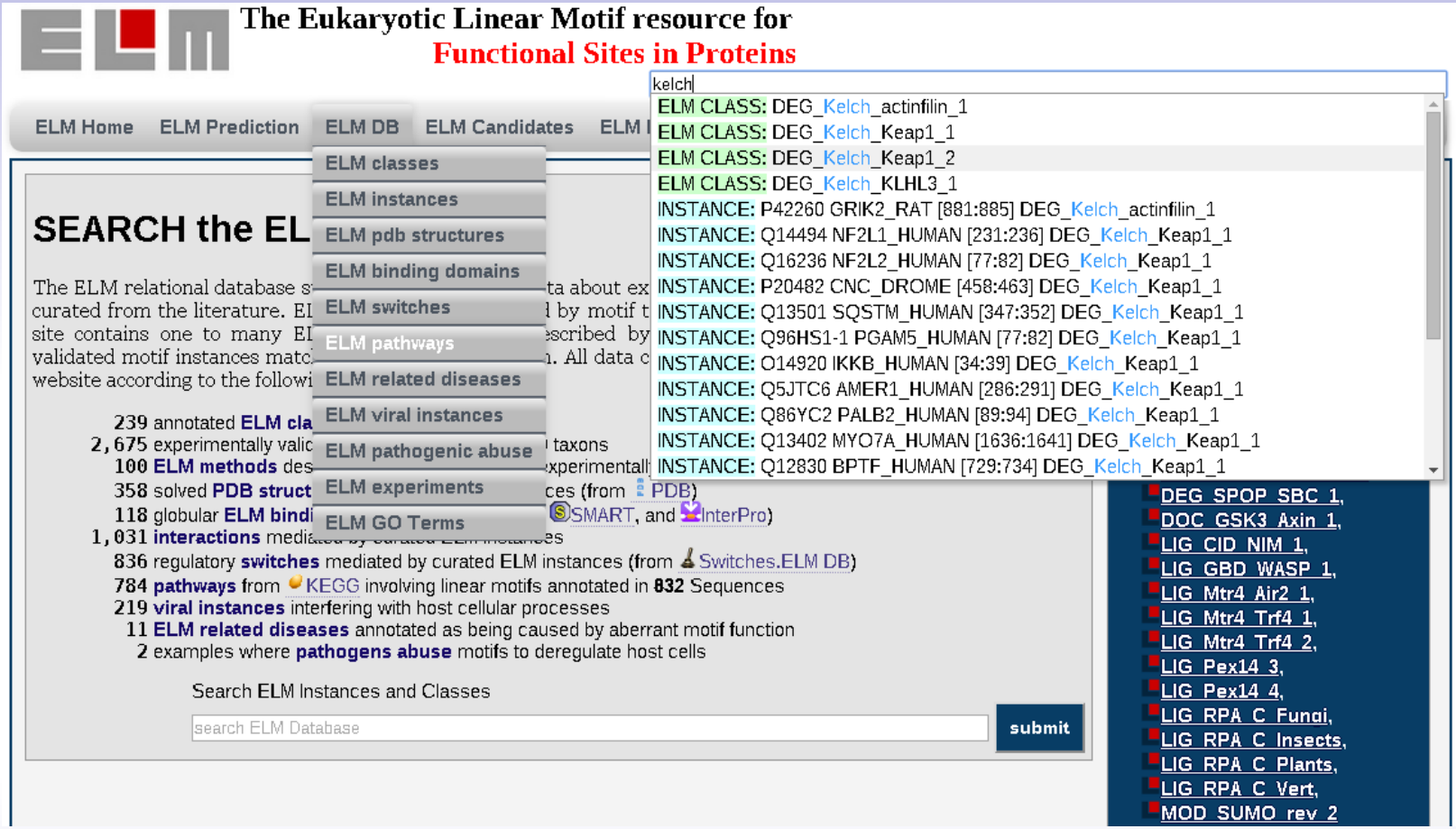
ELM Instance

An experimentally verified instance of an ELM class in a particular sequence.

- Experimental Evidences
- Methods
- References
- Interactions

"iELM – a web server to explore short linear motif-mediated interactions."; WEATHERITT, JEHL, DINKEL & GIBSON ; (NUCLEIC ACIDS RES. 2012)

ELM DATABASE



The Eukaryotic Linear Motif resource for
Functional Sites in Proteins

search ELM Database

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«MOD_WntLipid« »TRG_Cilium_Arf4_1»

TRG_AP2beta_CARGO_1

Accession: ELME000247

Functional site class: AP-2 beta2 appendage CCV component motifs

Functional site description: Several motifs are responsible for the binding of accessory endocytic proteins to the beta2-subunit appendage of the adaptor protein complex AP-2 as part of their recruitment to the site of clathrin coated vesicle (CCV) formation. Proteins binding the platform subdomain have been found to be cargo family specific (for example can load all GPCRs, or all LDL receptor family members) clathrin adaptors. Accessory proteins which help in CCV formation bind the sandwich subdomain site or the alpha ear domain.

ELM Description: Motif binding as a helix in a depression on the top surface of the AP-2 beta appendage platform subdomain. The pattern [ED]x(1,2)Fxx[FL]xxxR is conserved in beta Arrestins, ARH and Epsin-1, -2 of vertebrates. It is also found in homologues of other metazoans, but the pattern is sometimes not matched exactly, meaning that the ELM regular expression will not provide a match. In other lineages, if there is an equivalent motif, the pattern is likely to have diverged.

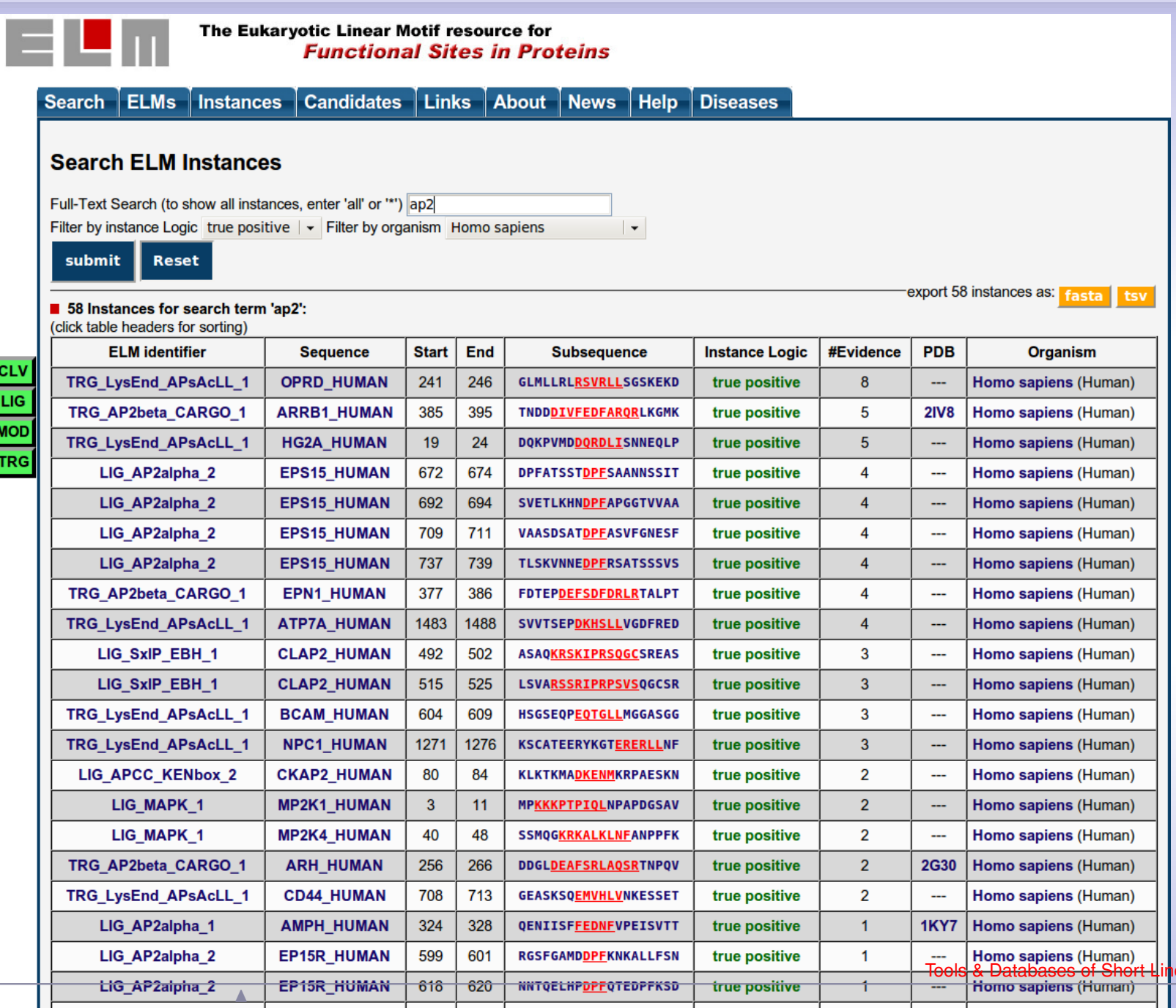
Pattern: `[DE].{1,2}F[^P][^P][FL][^P][^P][^P]R`

Pattern Probability: 0.0000182

Present in taxon: Metazoa

Interaction Domain: B2-adapt-app_C (PF09066) Beta2-adaptin appendage, C-terminal sub-domain (Stochiometry: 1 : 1)

PDB Structure: 2G30



The Eukaryotic Linear Motif resource for
Functional Sites in Proteins

Search | ELMs | Instances | Candidates | Links | About | News | Help | Diseases

CLV
LIG
MOD
TRG

Search ELM Instances

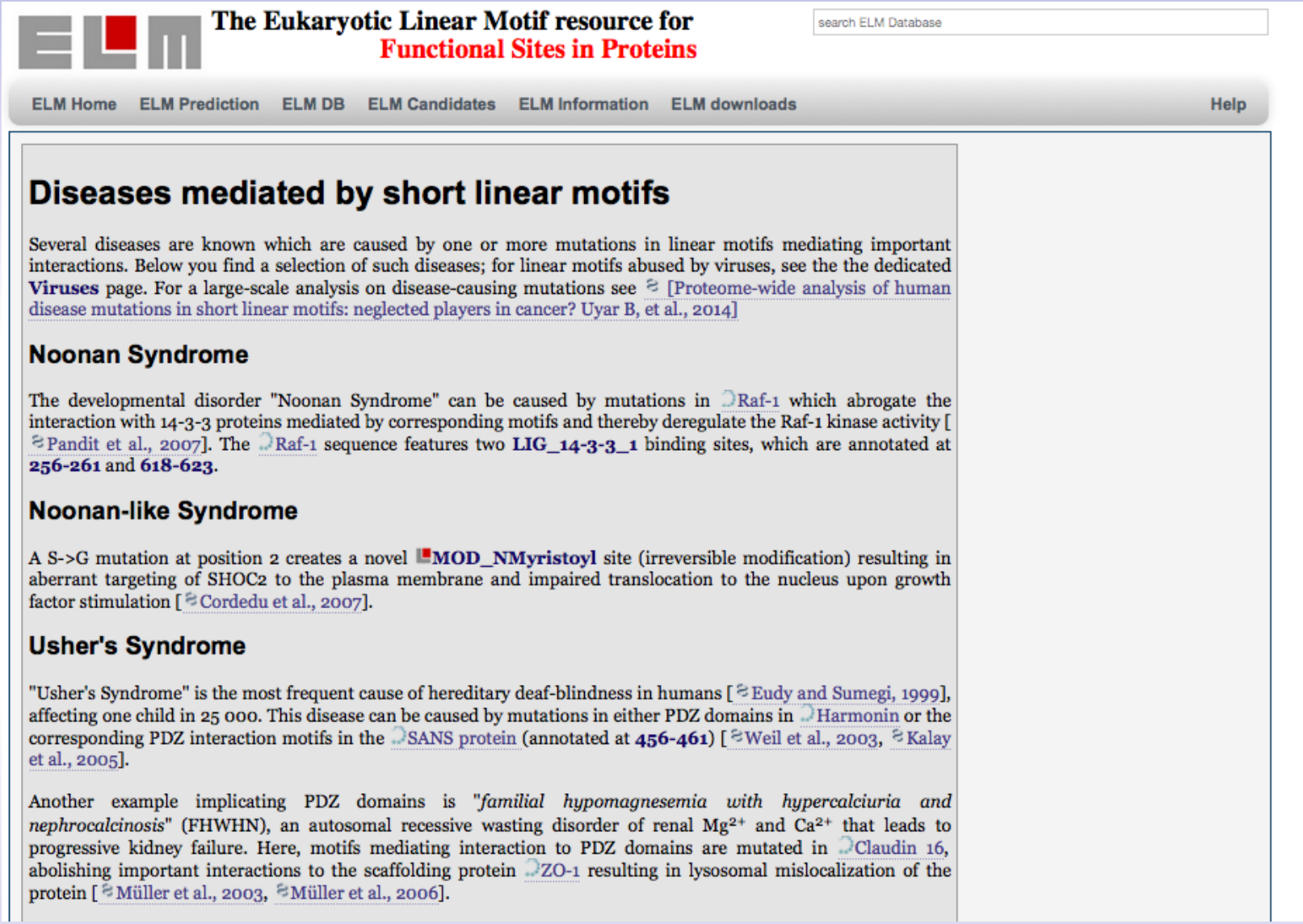
Full-Text Search (to show all instances, enter 'all' or '*') ap2
Filter by instance Logic true positive | Filter by organism Homo sapiens

submit Reset

export 58 instances as: fasta tsv

58 Instances for search term 'ap2':
(click table headers for sorting)

ELM identifier	Sequence	Start	End	Subsequence	Instance Logic	#Evidence	PDB	Organism
TRG_LysEnd_APsAcLL_1	OPRD_HUMAN	241	246	GLMLLRLRSVRLLSGSKEKD	true positive	8	---	Homo sapiens (Human)
TRG_AP2beta_CARGO_1	ARRB1_HUMAN	385	395	TNDDDIVFEDFARQRLKGMK	true positive	5	2IV8	Homo sapiens (Human)
TRG_LysEnd_APsAcLL_1	HG2A_HUMAN	19	24	DQKPVMDDQRDLISNNEQLP	true positive	5	---	Homo sapiens (Human)
LIG_AP2alpha_2	EPS15_HUMAN	672	674	DPFATSSTDPFSAANNSSIT	true positive	4	---	Homo sapiens (Human)
LIG_AP2alpha_2	EPS15_HUMAN	692	694	SVETLKHNDPFAPGGTVVAA	true positive	4	---	Homo sapiens (Human)
LIG_AP2alpha_2	EPS15_HUMAN	709	711	VAASDSATDPFASVFGNESF	true positive	4	---	Homo sapiens (Human)
LIG_AP2alpha_2	EPS15_HUMAN	737	739	TLSKVNNEDPFRSATSSSVS	true positive	4	---	Homo sapiens (Human)
TRG_AP2beta_CARGO_1	EPN1_HUMAN	377	386	FDTEPDEFSDFDRLRTALPT	true positive	4	---	Homo sapiens (Human)
TRG_LysEnd_APsAcLL_1	ATP7A_HUMAN	1483	1488	SVVTSEPDKHSLLVGDFRED	true positive	4	---	Homo sapiens (Human)
LIG_SxIP_EBH_1	CLAP2_HUMAN	492	502	ASAQKRSKIPRSQGCSREAS	true positive	3	---	Homo sapiens (Human)
LIG_SxIP_EBH_1	CLAP2_HUMAN	515	525	LSVARSSRIPRPSVSQGCSR	true positive	3	---	Homo sapiens (Human)
TRG_LysEnd_APsAcLL_1	BCAM_HUMAN	604	609	HSGSEQPEQTGLLMGGASGG	true positive	3	---	Homo sapiens (Human)
TRG_LysEnd_APsAcLL_1	NPC1_HUMAN	1271	1276	KSCATEERYKGTERERLLNF	true positive	3	---	Homo sapiens (Human)
LIG_APCC_KENbox_2	CKAP2_HUMAN	80	84	KLKTKMADKENMKRPAESKN	true positive	2	---	Homo sapiens (Human)
LIG_MAPK_1	MP2K1_HUMAN	3	11	MPKKKPTPIQLNPAPDGSAV	true positive	2	---	Homo sapiens (Human)
LIG_MAPK_1	MP2K4_HUMAN	40	48	SSMQGKRKALKLNFANPPFK	true positive	2	---	Homo sapiens (Human)
TRG_AP2beta_CARGO_1	ARH_HUMAN	256	266	DDGLDEAFSRLAQSRTNPQV	true positive	2	2G30	Homo sapiens (Human)
TRG_LysEnd_APsAcLL_1	CD44_HUMAN	708	713	GEASKSQEMVHLVNKESSET	true positive	2	---	Homo sapiens (Human)
LIG_AP2alpha_1	AMPH_HUMAN	324	328	QENIISFFEDNFVPEISVTT	true positive	1	1KY7	Homo sapiens (Human)
LIG_AP2alpha_2	EP15R_HUMAN	599	601	RGSFGAMDDPFKNKALLFSN	true positive	1	---	Homo sapiens (Human)
LIG_AP2alpha_2	EP15R_HUMAN	618	620	NNTQELHPDPFQTEDPFKSD	true positive	1	---	Homo sapiens (Human)



The Eukaryotic Linear Motif resource for
Functional Sites in Proteins

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Diseases mediated by short linear motifs

Several diseases are known which are caused by one or more mutations in linear motifs mediating important interactions. Below you find a selection of such diseases; for linear motifs abused by viruses, see the the dedicated **Viruses** page. For a large-scale analysis on disease-causing mutations see [Proteome-wide analysis of human disease mutations in short linear motifs: neglected players in cancer? Uyar B, et al., 2014]

Noonan Syndrome

The developmental disorder "Noonan Syndrome" can be caused by mutations in Raf-1 which abrogate the interaction with 14-3-3 proteins mediated by corresponding motifs and thereby deregulate the Raf-1 kinase activity [Pandit et al., 2007]. The Raf-1 sequence features two **LIG_14-3-3_1** binding sites, which are annotated at **256-261** and **618-623**.

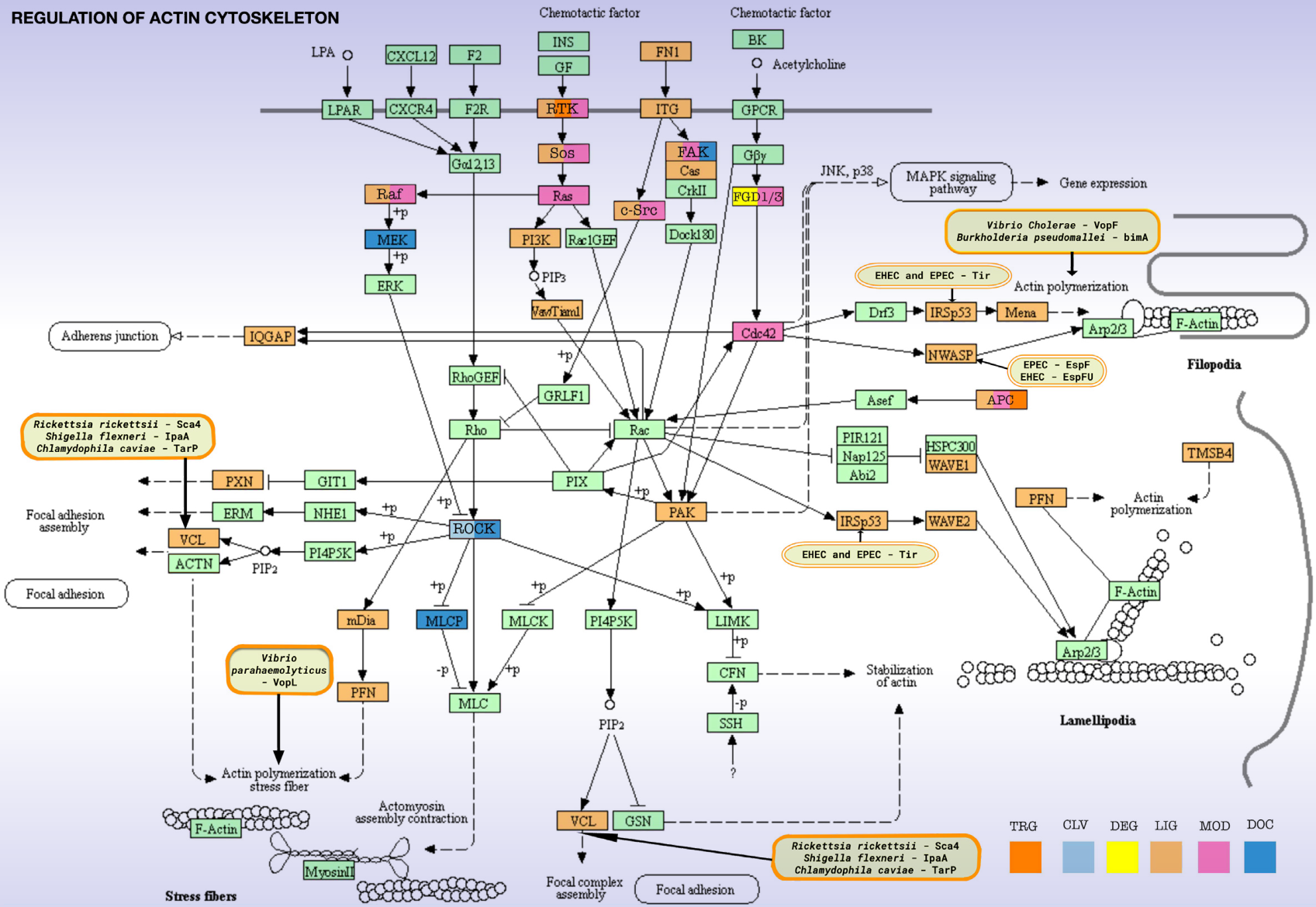
Noonan-like Syndrome

A S->G mutation at position 2 creates a novel **MOD_NMyristoyl** site (irreversible modification) resulting in aberrant targeting of SHOC2 to the plasma membrane and impaired translocation to the nucleus upon growth factor stimulation [Cordedu et al., 2007].

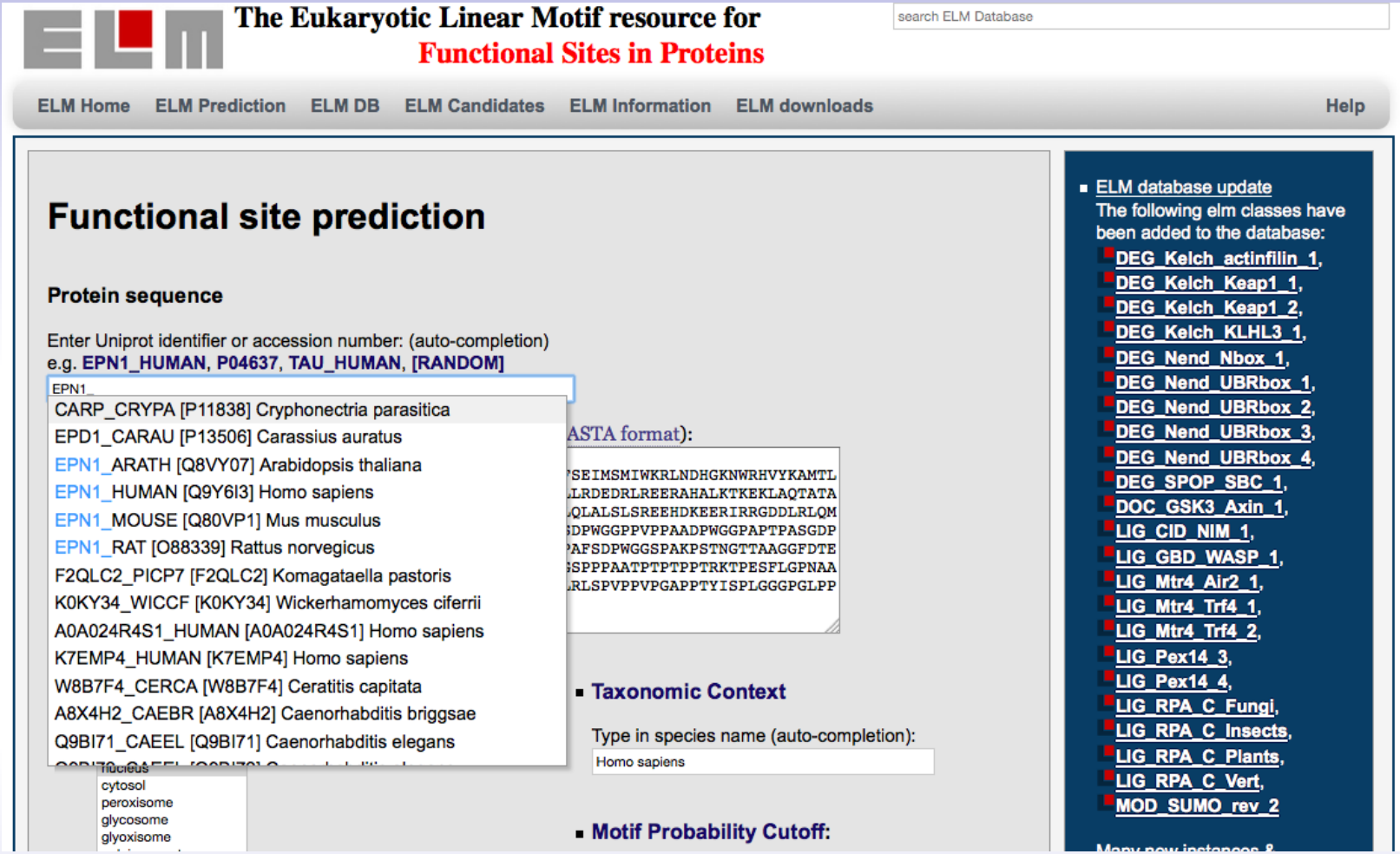
Usher's Syndrome

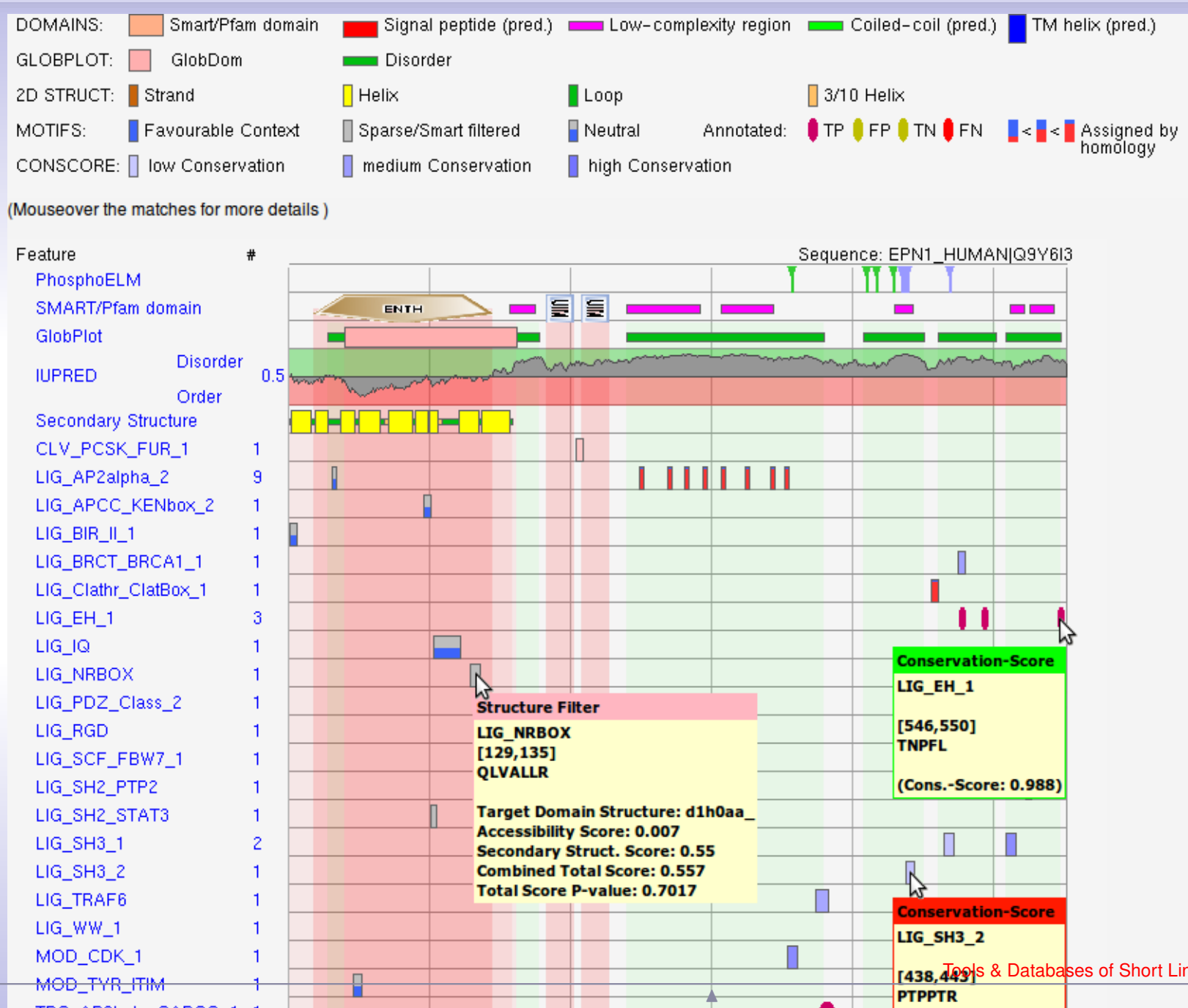
"Usher's Syndrome" is the most frequent cause of hereditary deaf-blindness in humans [Eudy and Sumegi, 1999], affecting one child in 25 000. This disease can be caused by mutations in either PDZ domains in Harmonin or the corresponding PDZ interaction motifs in the SANS protein (annotated at **456-461**) [Weil et al., 2003, Kalay et al., 2005].

Another example implicating PDZ domains is "*familial hypomagnesemia with hypercalciuria and nephrocalcinosis*" (FHWHN), an autosomal recessive wasting disorder of renal Mg^{2+} and Ca^{2+} that leads to progressive kidney failure. Here, motifs mediating interaction to PDZ domains are mutated in Claudin 16, abolishing important interactions to the scaffolding protein ZO-1 resulting in lysosomal mislocalization of the protein [Müller et al., 2003, Müller et al., 2006].

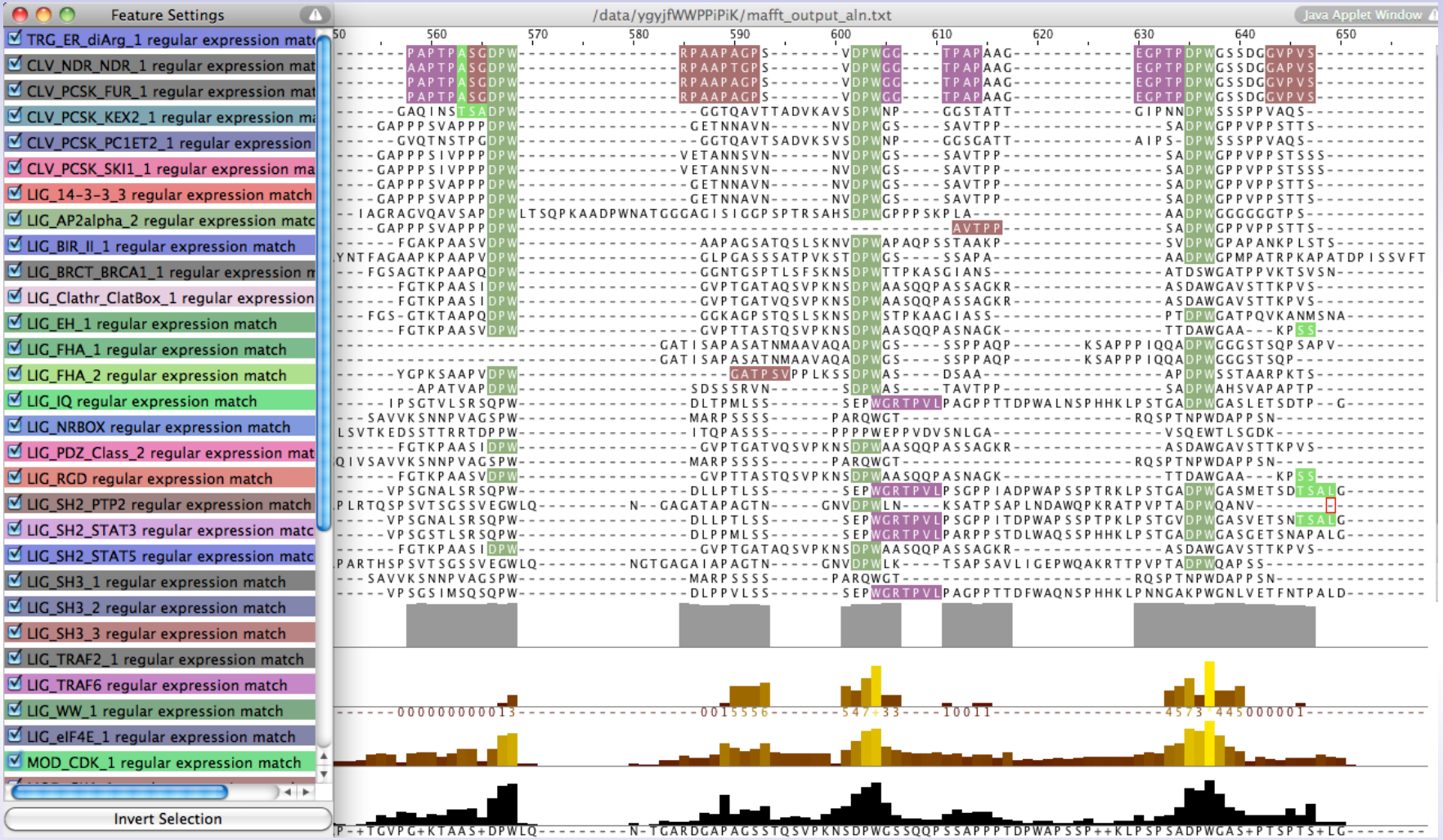

REGULATION OF ACTIN CYTOSKELETON
Chemotactic factor
Chemotactic factor
LPA
CXCL12
F2
INS
GF
FN1
BK
Acetylcholine
LPAR
CXCR4
F2R
RTK
ITG
GPCR
Gα12,13
Sos
FAK
Cas
CrkII
Gβγ
FGD1/3
JNK, p38
MAPK signaling pathway
Gene expression
Raf
MEK
ERK
Ras
PI3K
Rac1GEF
PIP3
Vav/Tiam1
c-Src
Dock180
Vibrio Cholerae - VopF
Burkholderia pseudomallei - bimA
EHEC and EPEC - Tir
Actin polymerization
Drf3
IRSp53
Mena
Arp2/3
F-Actin
Adherens junction
IQGAP
Cdc42
NWASP
EPEC - EspF
EHEC - EspFU
Filopodia
RhoGEF
GRLF1
Asef
APC
Rickettsia rickettsii - Sca4
Shigella flexneri - IpaA
Chlamydophila caviae - TarP
Rho
Rac
PIR121
Nap125
Abi2
HSPC300
WAVE1
TMSB4
PXN
GIT1
PIX
PFN
Actin polymerization
Focal adhesion assembly
ERM
NHE1
PAK
VCL
ACTN
PIP2
PI4P5K
ROCK
IRSp53
WAVE2
EHEC and EPEC - Tir
Focal adhesion
F-Actin
mDia
MLCP
MLCK
PI4P5K
LIMK
Arp2/3
Vibrio parahaemolyticus - VopL
PFN
MLC
CFN
Stabilization of actin
Lamellipodia
PIP2
SSH
Actin polymerization stress fiber
Actomyosin assembly contraction
F-Actin
MyosinII
Stress fibers
VCL
GSN
Rickettsia rickettsii - Sca4
Shigella flexneri - IpaA
Chlamydophila caviae - TarP
Focal complex assembly
Focal adhesion
TRG
CLV
DEG
LIG
MOD
DOC

ELM PREDICTION TOOL

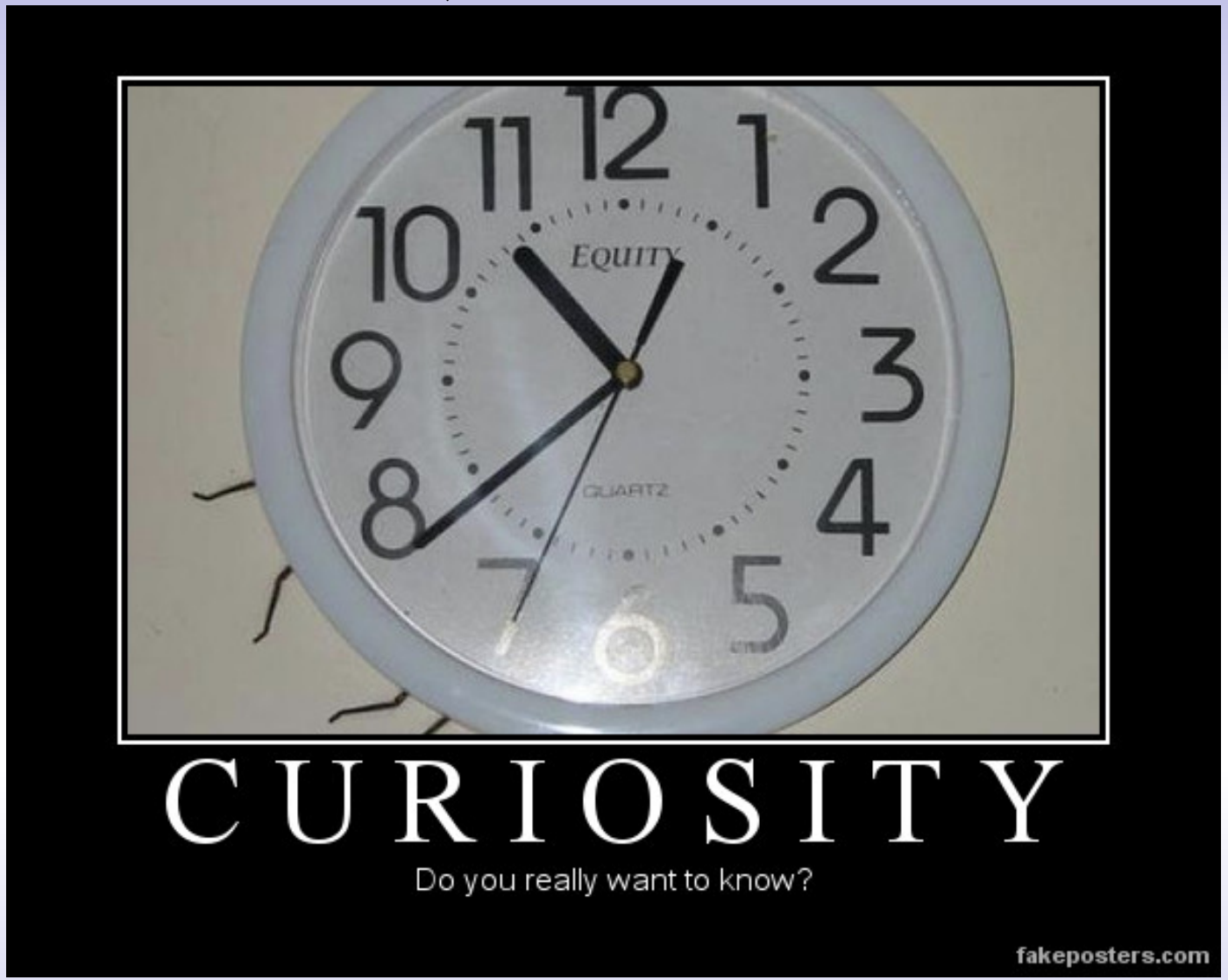



DOMAINS: Smart/Pfam domain
Signal peptide (pred.)
Low-complexity region
Coiled-coil (pred.)
TM helix (pred.)
GLOBPLOT: GlobDom
Disorder
2D STRUCT: Strand
Helix
Loop
3/10 Helix
MOTIFS: Favourable Context
Sparse/Smart filtered
Neutral
Annotated: TP FP TN FN
Assigned by homology
CONSCORE: low Conservation
medium Conservation
high Conservation
(Mouseover the matches for more details)
Feature
#
Sequence: EPN1_HUMAN|Q9Y6I3
PhosphoELM
SMART/Pfam domain
ENTH
UIM
UIM
GlobPlot
IUPRED
Disorder
Order
0.5
Secondary Structure
CLV_PCSK_FUR_1 1
LIG_AP2alpha_2 9
LIG_APCC_KENbox_2 1
LIG_BIR_II_1 1
LIG_BRCT_BRCA1_1 1
LIG_Clathr_ClatBox_1 1
LIG_EH_1 3
LIG_IQ 1
LIG_NRBOX 1
LIG_PDZ_Class_2 1
LIG_RGD 1
LIG_SCF_FBW7_1 1
LIG_SH2_PTP2 1
LIG_SH2_STAT3 1
LIG_SH3_1 2
LIG_SH3_2 1
LIG_TRAF6 1
LIG_WW_1 1
MOD_CDK_1 1
MOD_TYR_ITIM 1
Structure Filter
LIG_NRBOX
[129,135]
QLVALLR
Target Domain Structure: d1h0aa_
Accessibility Score: 0.007
Secondary Struct. Score: 0.55
Combined Total Score: 0.557
Total Score P-value: 0.7017
Conservation-Score
LIG_EH_1
[546,550]
TNPFL
(Cons.-Score: 0.988)
Conservation-Score
LIG_SH3_2
[438,443]
PTPPTR

View Conservation in Jalview



Questions?


EQUITY
QUARTZ
CURIOSITY
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Protein Visualization (ProViz)

ProViz `http://proviz.ucd.ie/` is a tool to visualize biological data allowing the investigation of functional and evolutionary protein features. The tool is designed to be an intuitive and accessible resource to allow users with limited bioinformatic skills to rapidly access and visualise data pertinent to their research.

"ProViz-a web-based visualization tool to investigate the functional and evolutionary features of protein sequences."; Jehl P, Manguy J, Shields DC, Higgins DG, Davey NE.; (Nucleic Acids Res. 2016 Apr 16)

Protein Visualization (ProViz)

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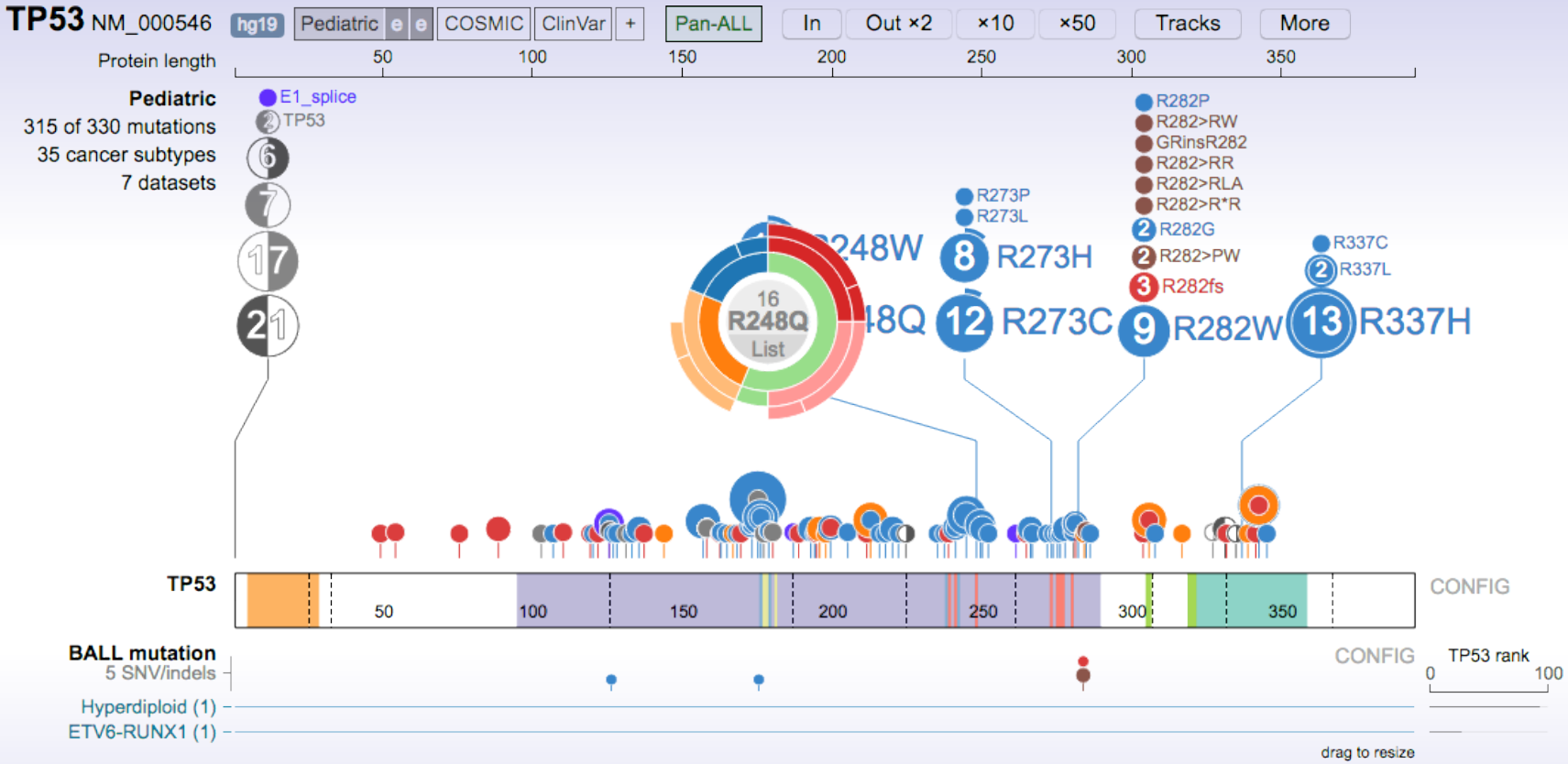
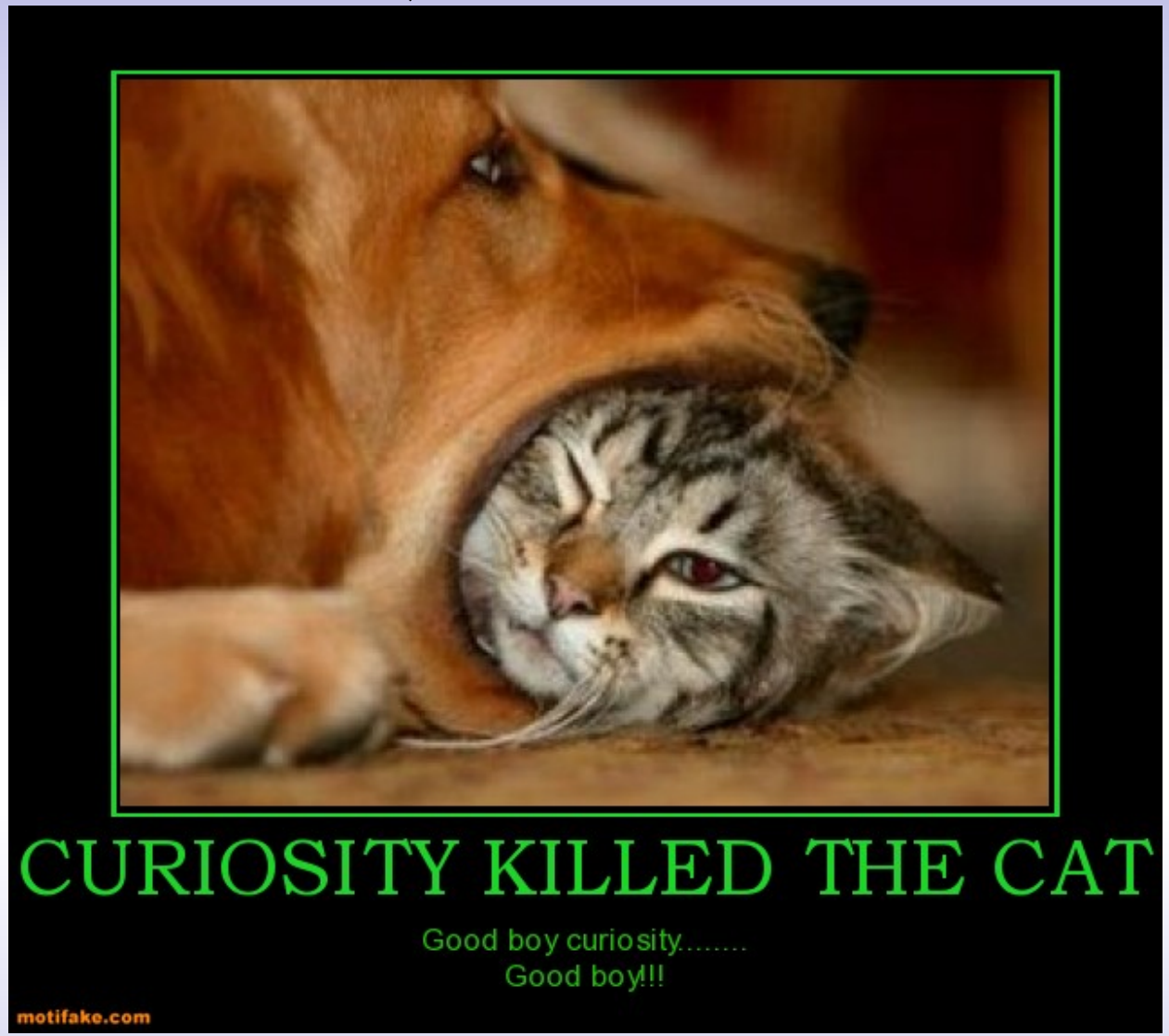
PeCan `https://pecan.stjude.cloud/` provides interactive visualizations of pediatric cancer mutations across various projects at St. Jude Children's Research Hospital and its collaborators.

Data Summary

PeCan / ProteinPaint – visualization of PEdiatric CANcer mutations



Questions?


CURIOSITY KILLED THE CAT
Good boy curiosity.....
Good boy!!!
motifake.com