

Tools & Databases of Short Linear Motifs

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EMBO Practical Course:

“Computational analysis of protein-protein interactions in
cell function and disease”

Bangalore, 04. 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.

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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			

ELM Class

Condensed information about a motif. Regular Expressions used to annotate the motif (eg. $[KR] \cdot L \cdot \{0, 1\} [FYLVMP]$ 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:	R00C_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 (R00MOD_CDK_1). Also used by cyclin/cdk inhibitors.
Pattern:	$[SR] \cdot L \cdot [0, 1] [FYLVMP]$
Pattern Probability:	0.0053239
Present in taxon:	Eukaryota
Interaction Domain:	R00CYclin_N (PF00134) Cyclin, N-terminal domain (Stoichiometry: 1:1)

PDB Structure: [1H24](#)

ELM Class

Condensed information about a motif. Regular Expressions used to annotate the motif (eg. $[KR] \cdot L \cdot \{0,1\} [FYLI VMP]$ for Cyclin motif)

■ 24 instances for DOC_CYCLIN_1
(click table headers for sorting. Notes column: Δ =Number of Switches, $\#$ =Number of Interactions)

Protein Name	Gene Name	Start	End	Subsequence	Logic	#Ev.	Organism	Notes
RE_HUMAN	RE1	873	877	GGPPPPYQGLAFYIDQSSBA	TP	3	Human sapiens (Human)	1H25
QBLWJB_CHECK	CDK1-A	394	398	ELDPPPPYQGLAFYIDQSSBA	FP	1	Calus gallus (Chicken)	1A
PMYTT1_HUMAN	PKMYT1	486	489	GGPPPPYQGLAFYIDQSSBA	TP	1	Human sapiens (Human)	
E2F1_HUMAN	E2F1	90	94	GGPPPPYQGLAFYIDQSSBA	TP	3	Human sapiens (Human)	1H24
CDK1C_HUMAN	CDK1C	31	34	YLPPTTAQGLAFYIDQSSBA	TP	1	Human sapiens (Human)	
RLUX_DROME	rlux	248	251	PPAAACVYQGLAFYIDQSSBA	TP	1	Drosophila melanogaster (Fruit fly)	
E2F2_HUMAN	E2F2	87	91	AAELPAPQGLAFYIDQSSBA	TP	1	Human sapiens (Human)	
E2F3_HUMAN	E2F3	134	138	GGPPPPYQGLAFYIDQSSBA	TP	1	Human sapiens (Human)	
AKA12_MOUSE	Akap12	501	504	TPDPPPPYQGLAFYIDQSSBA	TP	1	Mus musculus (House mouse)	1A
CDC5_HUMAN	CDC5	94	98	AAELPAPQGLAFYIDQSSBA	TP	2	Human sapiens (Human)	2CCH
CDKN1A_HUMAN	CDKN1A	19	22	PPDPPPPYQGLAFYIDQSSBA	TP	4	Human sapiens (Human)	1B, 1A
CDKN1A_HUMAN	CDKN1A	155	159	TPDPPPPYQGLAFYIDQSSBA	TP	1	Human sapiens (Human)	
ORC5_YEAST	ORC5	178	182	PPDPPPPYQGLAFYIDQSSBA	TP	1	Saccharomyces cerevisiae (Baker's yeast)	
TP53_HUMAN	TP53	381	385	QDPPPPYQGLAFYIDQSSBA	TP	5	Human sapiens (Human)	1H26
RB1_HUMAN	RB1	658	661	PPDPPPPYQGLAFYIDQSSBA	TP	3	Human sapiens (Human)	1H28
RB2_HUMAN	RB2	680	684	PPDPPPPYQGLAFYIDQSSBA	TP	1	Human sapiens (Human)	
HIRA_HUMAN	HIRA	629	633	KAEELPAPQGLAFYIDQSSBA	TP	1	Human 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 ([#KMOD_CDK_1](#)). Also used by cyclin/CDK inhibitors.

Pattern: $[KR] \cdot L \cdot \{0,1\} [FYLI VMP]$

Pattern Probability: 0.0032239

Present in taxon: Eukaryota

Interaction Domain: [#Cyclin_N \(PF00134\)](#) Cyclin, N-terminal domain (Stoichiometry: 1:1)

PDB Structure: [1H24](#)



ELM Instance

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

ELM Class

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Instance

Sequence	Start	End	Subsequence	Logic	PDB	Organism	Length
... (Q99741) CDC8_HUMAN	94	98	ISSTSLAGSGLQQLTQSG	TP		% Homo sapiens (human)	560

Instance evidence

Evidence class	PSM	Method	BioSource	PubMed	Logic	Reliability	Notes
experimental	M0114	x-ray crystallography	in vitro	Chang, 2008	support	certain	InteractionDetection FeatureDetection
experimental	M0096	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:

SWT000339:

CCNA2

CCNA2



CDC8V18

CDC8

DOC_CYCLIN_1

Functional site class: Cyclin recognition site

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ELM with this motif: [MDOC_CYCLIN_1](#)

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- Methods
- References
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Pattern Probability: 0.0033239

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SEARCH the ELM Database

The ELM relational database is curated from the literature. ELM site contains one to many ELM validated motif instances matched to proteins according to the following criteria:

- 239 annotated ELM classes
- 2,675 experimentally validated ELM instances
- 100 ELM methods described
- 358 solved PDB structures
- 118 globular ELM binding domains
- 1,031 interactions mediated by ELM motifs
- 836 regulatory switches mediated by curated ELM instances (from ELM DB)
- 784 pathways from KEGG involving linear motifs annotated in 832 Sequences
- 219 viral instances interfering with host cellular processes
- 11 ELM related diseases annotated as being caused by aberrant motif function
- 2 examples where pathogens abuse motifs to deregulate host cells

Search ELM Instances and Classes

ELM classes

ELM instances

ELM pdb structures

ELM binding domains

ELM switches

ELM pathways

ELM related diseases

ELM viral instances

ELM pathogenic abuse

ELM experiments

ELM GO Terms

kelch

ELM CLASS: DEG_Kelch_actinfilin_1

ELM CLASS: DEG_Kelch_Keap1_1

ELM CLASS: DEG_Kelch_Keap1_2

ELM CLASS: DEG_Kelch_KLHL3_1

INSTANCE: P42260 GRIK2_RAT [881:885] DEG_Kelch_actinfilin_1

INSTANCE: Q14494 NF2L1_HUMAN [231:236] DEG_Kelch_Keap1_1

INSTANCE: Q16236 NF2L2_HUMAN [77:82] DEG_Kelch_Keap1_1

INSTANCE: P20482 CNC_DROME [458:463] DEG_Kelch_Keap1_1

INSTANCE: Q13501 SQSTM_HUMAN [347:352] DEG_Kelch_Keap1_1

INSTANCE: Q96HS1-1 PGAM5_HUMAN [77:82] DEG_Kelch_Keap1_1

INSTANCE: O14920 IKKB_HUMAN [34:39] DEG_Kelch_Keap1_1

INSTANCE: Q5JTC6 AMER1_HUMAN [286:291] DEG_Kelch_Keap1_1

INSTANCE: Q86YC2 PALB2_HUMAN [89:94] DEG_Kelch_Keap1_1

INSTANCE: Q13402 MYO7A_HUMAN [1636:1641] DEG_Kelch_Keap1_1

INSTANCE: Q12830 BPTF_HUMAN [729:734] DEG_Kelch_Keap1_1

- DEG_SPOP_SBC_1
- DOC_GSK3_Axin_1
- LIG_CID_NIM_1
- LIG_GBD_WASP_1
- LIG_Mtr4_Air2_1
- LIG_Mtr4_Trif4_1
- LIG_Mtr4_Trif4_2
- LIG_Pex14_3
- LIG_Pex14_4
- LIG_RPA_C_Funai
- LIG_RPA_C_Insects
- LIG_RPA_C_Plants
- LIG_RPA_C_Vert
- MOD_SUMO_rev_2



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[Help](#)
[«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 (Stoichiometry: 1 : 1)

PDB Structure: [2G30](#)





The Eukaryotic Linear Motif resource for
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Search ELM Instances

Full-Text Search (to show all instances, enter 'all' or '')

Filter by instance Logic: true positive | Filter by organism: Homo sapiens

submit

Reset

■ 58 Instances for search term 'ap2':

export 58 instances as: [fasta](#) [tsv](#)

(click table headers for sorting)

ELM identifier	Sequence	Start	End	Subsequence	Instance Logic	#Evidence	PDB	Organism
TRG_LysEnd_APsAcLL_1	OPRD_HUMAN	241	246	GLMLLR RSVRL LGSKED	true positive	8	---	Homo sapiens (Human)
TRG_AP2beta_CARGO_1	ARRB1_HUMAN	385	395	TND DDIVFDFARQL LKGMK	true positive	5	2IV8	Homo sapiens (Human)
TRG_LysEnd_APsAcLL_1	HG2A_HUMAN	19	24	DQKPVMD QDRDL SNNEQLP	true positive	5	---	Homo sapiens (Human)
LIG_AP2alpha_2	EPS15_HUMAN	672	674	DPFATSS DPF SAANNSSIT	true positive	4	---	Homo sapiens (Human)
LIG_AP2alpha_2	EPS15_HUMAN	692	694	SVETLKHN DPF APGGTVAA	true positive	4	---	Homo sapiens (Human)
LIG_AP2alpha_2	EPS15_HUMAN	709	711	VAASDSAT DPF ASVFGNESF	true positive	4	---	Homo sapiens (Human)
LIG_AP2alpha_2	EPS15_HUMAN	737	739	TLKVN NDPF RSATSSSVS	true positive	4	---	Homo sapiens (Human)
TRG_AP2beta_CARGO_1	EPN1_HUMAN	377	386	FDTEP DEFSDFRL LTALPT	true positive	4	---	Homo sapiens (Human)
TRG_LysEnd_APsAcLL_1	ATP7A_HUMAN	1483	1488	SVTSE PDKHSLL VGDFRED	true positive	4	---	Homo sapiens (Human)
LIG_SxIP_EBH_1	CLAP2_HUMAN	492	502	ASAQ KRSKIPRSQGC SREAS	true positive	3	---	Homo sapiens (Human)
LIG_SxIP_EBH_1	CLAP2_HUMAN	515	525	LSVA RSSIRPRSVSQC SR	true positive	3	---	Homo sapiens (Human)
TRG_LysEnd_APsAcLL_1	BCAM_HUMAN	604	609	HSGSEQ ETGL LGGASGG	true positive	3	---	Homo sapiens (Human)
TRG_LysEnd_APsAcLL_1	NPC1_HUMAN	1271	1276	KSCATEERYKGT ERERLL NF	true positive	3	---	Homo sapiens (Human)
LIG_APCC_KENbox_2	CKAP2_HUMAN	80	84	KLTKMA DKEN MKRPAESKN	true positive	2	---	Homo sapiens (Human)
LIG_MAPK_1	MP2K1_HUMAN	3	11	HP KKKPTPIQL NPAPDGSAV	true positive	2	---	Homo sapiens (Human)
LIG_MAPK_1	MP2K4_HUMAN	40	48	SSMQ KRKALKLN FANPPFK	true positive	2	---	Homo sapiens (Human)
TRG_AP2beta_CARGO_1	ARH_HUMAN	256	266	DDGL DEAFSRLAQS RTPNOV	true positive	2	2G30	Homo sapiens (Human)
TRG_LysEnd_APsAcLL_1	CD44_HUMAN	708	713	GEASKS QEMVHL NKESSET	true positive	2	---	Homo sapiens (Human)
LIG_AP2alpha_1	AMPH_HUMAN	324	328	QENIS FDNF VPETSVTT	true positive	1	1KY7	Homo sapiens (Human)
LIG_AP2alpha_2	EP15R_HUMAN	599	601	RGSFGAMD DPF KNKALLFSN	true positive	1	---	Homo sapiens (Human)
LIG_AP2alpha_2	EP15R_HUMAN	618	620	NNTQELH DPF QTEDPFKSD	true positive	1	---	Homo sapiens (Human)



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 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

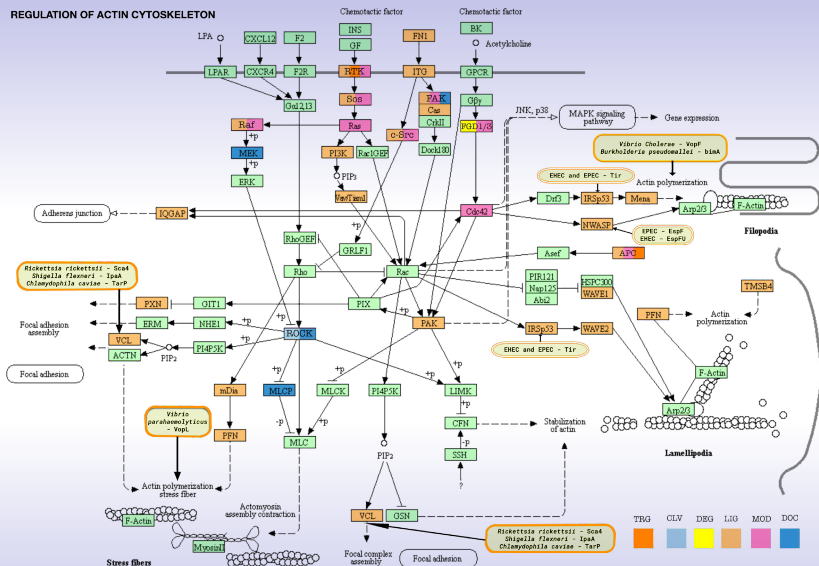
A S->G mutation at position 2 creates a novel **MOD_NMyristoyl** site (irreversible modification) resulting in aberrant targeting of SHOC2 to the plasma membrane and impaired translocation to the nucleus upon growth factor stimulation [[Cordedu et al., 2007](#)].

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





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Functional site prediction

Protein sequence

Enter Uniprot identifier or accession number: (auto-completion)

e.g. [EPN1_HUMAN](#), [P04637](#), [TAU_HUMAN](#), [\[RANDOM\]](#)

EPN1

CARP_CRYPA [P11838] Cryphonectria parasitica
 EPD1_CARAU [P13506] Carassius auratus
[EPN1_ARATH](#) [Q8VY07] Arabidopsis thaliana
[EPN1_HUMAN](#) [Q9Y6I3] Homo sapiens
[EPN1_MOUSE](#) [Q80VP1] Mus musculus
[EPN1_RAT](#) [O88339] Rattus norvegicus
 F2QLC2_PICP7 [F2QLC2] Komagataella pastoris
 K0KY34_WICCF [K0KY34] Wickerhamomyces ciferrii
 A0A024R4S1_HUMAN [A0A024R4S1] Homo sapiens
 K7EMP4_HUMAN [K7EMP4] Homo sapiens
 W8B7F4_CERCA [W8B7F4] Ceratitidis capitata
 A8X4H2_CAEBR [A8X4H2] Caenorhabditis briggsae
 Q9BI71_CAEL [Q9BI71] Caenorhabditis elegans

cytosol
 peroxisome
 glycosome
 glyoxisome

ASTA format):

```
SEIMSHIWKRLNDHGKKNWRHVYKAMTL
LRDEDRLREERHALKTKKLAQTATA
QLALSLSREEDKKEIRRGDDLRQM
IDFWGGPPVFPADPWGGPAPTASGDP
AFSDPWGSGPAKPTSTNGTTAAGGDT
SPPPAATPTPTTPFRKTPESLGPNAA
RLSPVPPVPGAPPTTISPLGGGFLPP
```

Taxonomic Context

Type in species name (auto-completion):

Homo sapiens

Motif Probability Cutoff:

ELM database update

The following elm classes have been added to the database:

- [DEG Kelch actinfilin 1](#)
- [DEG Kelch Keap1 1](#)
- [DEG Kelch Keap1 2](#)
- [DEG Kelch KLHL3 1](#)
- [DEG Nend Nbox 1](#)
- [DEG Nend UBRbox 1](#)
- [DEG Nend UBRbox 2](#)
- [DEG Nend UBRbox 3](#)
- [DEG Nend UBRbox 4](#)
- [DEG SPOD SBC 1](#)
- [DOC GSK3 Axin 1](#)
- [LIG CID NIM 1](#)
- [LIG GBD WASP 1](#)
- [LIG Mtr4 Air2 1](#)
- [LIG Mtr4 Trf4 1](#)
- [LIG Mtr4 Trf4 2](#)
- [LIG Pex14 3](#)
- [LIG Pex14 4](#)
- [LIG RPA C Fungj](#)
- [LIG RPA C Insects](#)
- [LIG RPA C Plants](#)
- [LIG RPA C Vert](#)
- [MOD SUMO rev 2](#)

Many new instances of

DOMAINS: Smart/Pfam domain Signal peptide (pred.) Low-complexity region Coiled-coil (pred.) TM helix (pred.)

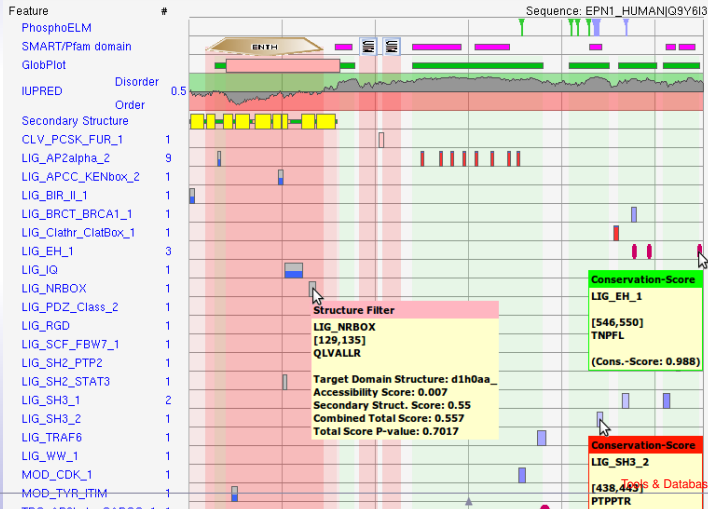
GLOBPLOT: GlobDom Disorder

2D STRUCT: Strand Helix Loop 3/10 Helix

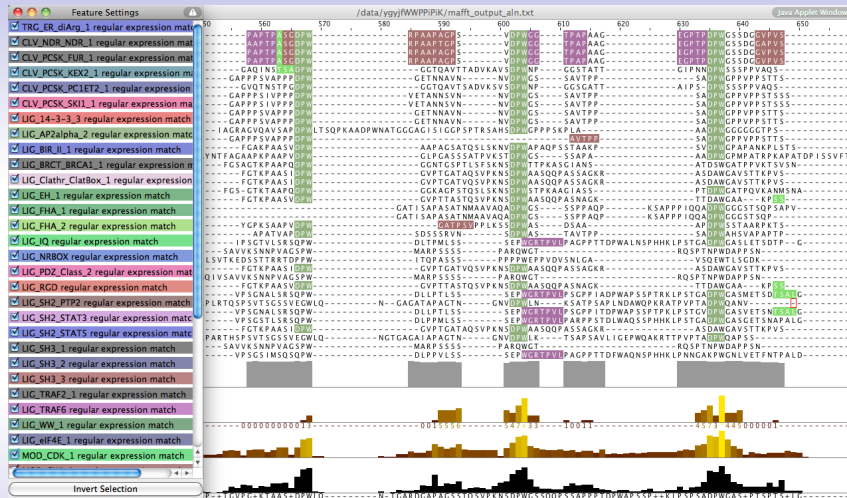
MOTIFS: Favourable Context Sparse/Smart filtered Neutral Annotated: TP FP TN FN < < Assigned by homology

CONSCORE: low Conservation medium Conservation high Conservation

(Mouseover the matches for more details)



VIEW CONSERVATION IN JALVIEW



Questions?



CURIOSITY

Do you really want to know?

fakeposters.com

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.

PROTEIN VISUALIZATION (ProViz)



"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)



"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)

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

SAMPLES

5,161

PATIENTS

4,877

DIAGNOSES

23

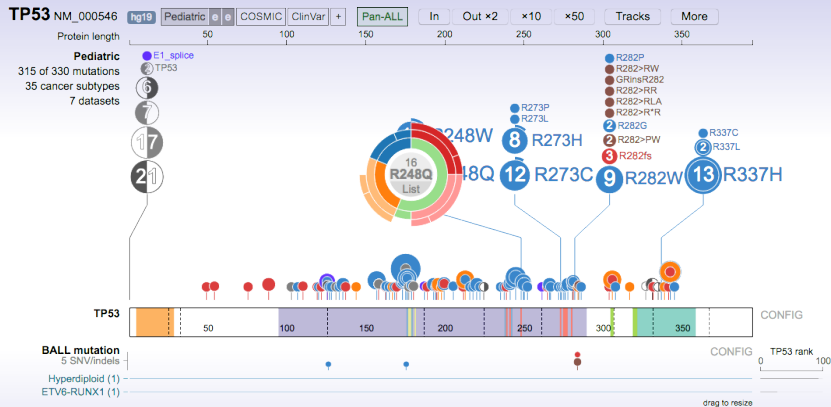
GENES

18,395

MUTATIONS

88,032

PEcAN / PROTEINPAINT – VISUALIZATION OF PEDIATRIC CANCER MUTATIONS



Questions?



CURIOSITY KILLED THE CAT

Good boy curiosity.....
Good boy!!!

motifake.com