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Survey on the PABC recognition motif PAM2

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Abstract

The PABP-interacting motif PAM2 has been identified in various eukaryotic proteins as an important binding site for the PABC domain. This domain is contained in homologs of the poly(A)-binding protein PABP and the ubiquitin–protein ligase HYD. Despite the importance of the PAM2 motif, a comprehensive analysis of its occurrence in different proteins has been missing. Using iterated sequence profile searches, we obtained an extensive list of proteins carrying the PAM2 motif. We discuss their functional context and domain architecture, which often consists of RNA-binding domains. Our list of PAM2 motif proteins includes eukaryotic homologs of eRF3/GSPT1/2, PAIP1/2, Tob1/2, Ataxin-2, RBP37, RBP1, Blackjack, HELZ, TPRD, USP10, ERD15, C1D4.14, and the viral protease P29. The identification of the PAM2 motif in as yet uncharacterized proteins can give valuable hints with respect to their cellular function and potential interaction partners and suggests further experimentation. It is also striking that the PAM2 motif appears to occur solely outside globular protein domains.

Keywords: PAM2 motif; PABC domain; Protein interaction; Function prediction

The PAM2 motif is the second of two known PABP-interacting motifs (PAM1 and PAM2) and has been identified in various eukaryotic proteins as an important binding site for the PABC domain [1]. This domain is contained at the C-terminus of the poly(A)-binding protein PABP, in yeast also known as PAB1 [2–7]. PABP homologs have an evolutionarily conserved and vital function in RNA metabolism including the biosynthesis, turnover, and export of mRNA [8,9]. PABP also serves as a scaffolding protein for the assembly of the ribonucleic acid protein (RNP) complex around the poly(A) tail at the 3′-end of mRNA. The domain architecture of PABP consists of four N-terminal RNA-recognition motifs (RRMs) and a C-terminal PABC domain.

Generally, the PABC domain appears to mediate essential protein–protein interactions not only for PABP homologs, but it also occurs in the E3 ubiquitin–protein ligase HYD (hyperplastic discs) [10–13]. HYD, which is also named EDD or Rat100 [14], is a member of the HECT (homologous to E6-AP C-terminus) domain family of ubiquitin ligases [15] and interacts with the progesterone receptor and topoisomerase IIβ-binding protein 1 (TopBP1), both implicated in the DNA damage response [16,17].

The structure of the PABC domain has been determined for three PABP homologs [3,4,7] and human HYD [13]. Recently, the solution structure of the human PABC domain has been solved in complex with PAM2 peptides from the PABP-interacting proteins PAIP1 and PAIP2 [5]. The PABC domain structure is composed of a right-handed supercoil of four or five helices and binds a PAM2 peptide that forms a pair of β-turns.

Despite the apparent importance of the PAM2 motif, a comprehensive analysis of its occurrence in different proteins is missing. The motif is not yet included in sequence motif databases either. Therefore, using iterated sequence profile searches, we obtained an extensive list of proteins carrying the PAM2 motif. Some of them have not yet been discussed in the literature with respect to their domain architecture, but the PAM2 motif may give valuable hints on the function of these proteins.

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Here, we detail our results on PAM2 containing proteins and explore their functional context.

Materials and methods

We obtained protein sequences from the Swiss-Prot/TrEMBL (SPTrEMBL) [18] and retrieved domain architectures from the Pfam [19], SMART [20], and NCBI conserved domain databases [21]. The GeneDB database [22] provided additional annotations of yeast proteins. We searched the sequence databases by means of the (PSI-) BLAST [23] and HMMER [24] suites of programs (using the *E*-value cut-offs 0.005 and 0.5, respectively). Multiple sequence alignments were computed using CLUSTAL W [25]. Species names are abbreviated by first letters, see Table 2. The multiple sequence alignment shown in Fig. 2 is deposited with the European Bioinformatics Institute (EBI) under alignment number ALIGN_000664 (ftp://ftp.ebi.ac.uk/pub/databases/embl/align/ALIGN_000664.aln).

Results and discussion

Sequence profile search

In order to analyze the PABP-interacting motif PAM2 in different proteins, we searched the SPTrEMBL database with an HMM (hidden Markov model) built from a small multiple sequence alignment of PAM2 peptides, which are marked in Fig. 1 and provided originally as supplementary online material by Kozlov et al. [3]. We clustered the search results manually into

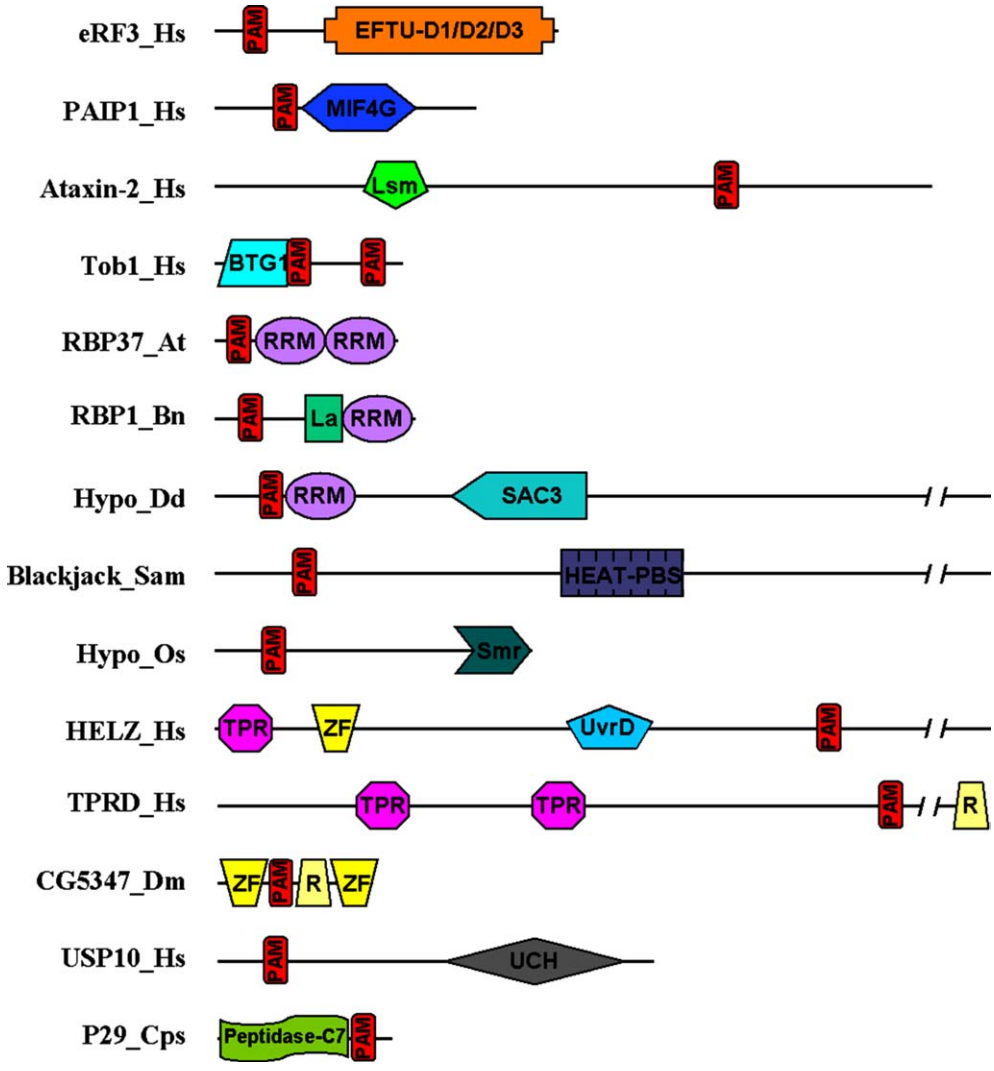

Fig. 1. Domain architecture of selected proteins with a PABC recognition motif PAM2. Pfam domain name abbreviations are as follows: EFTU-D1/2/3, domains homologous to elongation factor Tu; MIF4G, middle domain homologous to eukaryotic initiation factor 4G (eIF4G); Lsm, RNA-binding domain of Sm-like proteins; BTG1, domain shared by APRO family proteins; RRM, RNA-recognition motif; La, domain homologous to the RNA-binding protein La; SAC3, domain homologous to the yeast mRNA-export factor SAC3; HEAT-PBS, phycobilisomes (PBS) lyase HEAT-like repeats; Smr, domain in MutS-related proteins involved in nucleic acid mismatch repair; TPR, tetratricopeptide repeat; ZF, zinc finger; UvrD, REP family helicase domain; RING, zinc finger; UCH, ubiquitin C-terminal hydrolase domain; and Peptidase-C7, peptidase domain of C7 family in hypoviridae.

functionally related groups of proteins sharing similar domain architectures (Figs. 1 and 2, Tables 1 and 2). We numbered the PAM2 peptide according to Kozlov et al. [5], who identified amino acids 3, 10, and 12 of PAIP1 and PAIP2 as specifically important for binding to the PABC domain. Above all, the strictly conserved phenylalanine 10 of PAM2 is involved in essential aromatic stacking interactions with the PABC domain [5]. The conserved leucine residue at position 3 binds in a hydrophobic pocket of the PABC domain. The C-terminal PAM2 region including position 12 also contributes substantially to binding of the peptide into a groove formed by two helices of the PABC domain.

eRF3 and PAIPs

Proteins that have already been reported to interact with PABP in experiment include the translation termination factor eRF3 (eukaryotic release factor 3, homologs are also known as GSPT1/2 for G1 to S phase transition protein 1/2) and the PABP-interacting proteins PAIP1 and PAIP2, which are eIF4G domain homologs [26,27]. While the latter PAIPs contain two distinct binding sites PAM1 and PAM2 for PABP and function as stimulator and repressor of mRNA translation, respectively [1,5,28–30], the N-terminus of eRF3 containing the PAM2 motif binds to the PABC domain

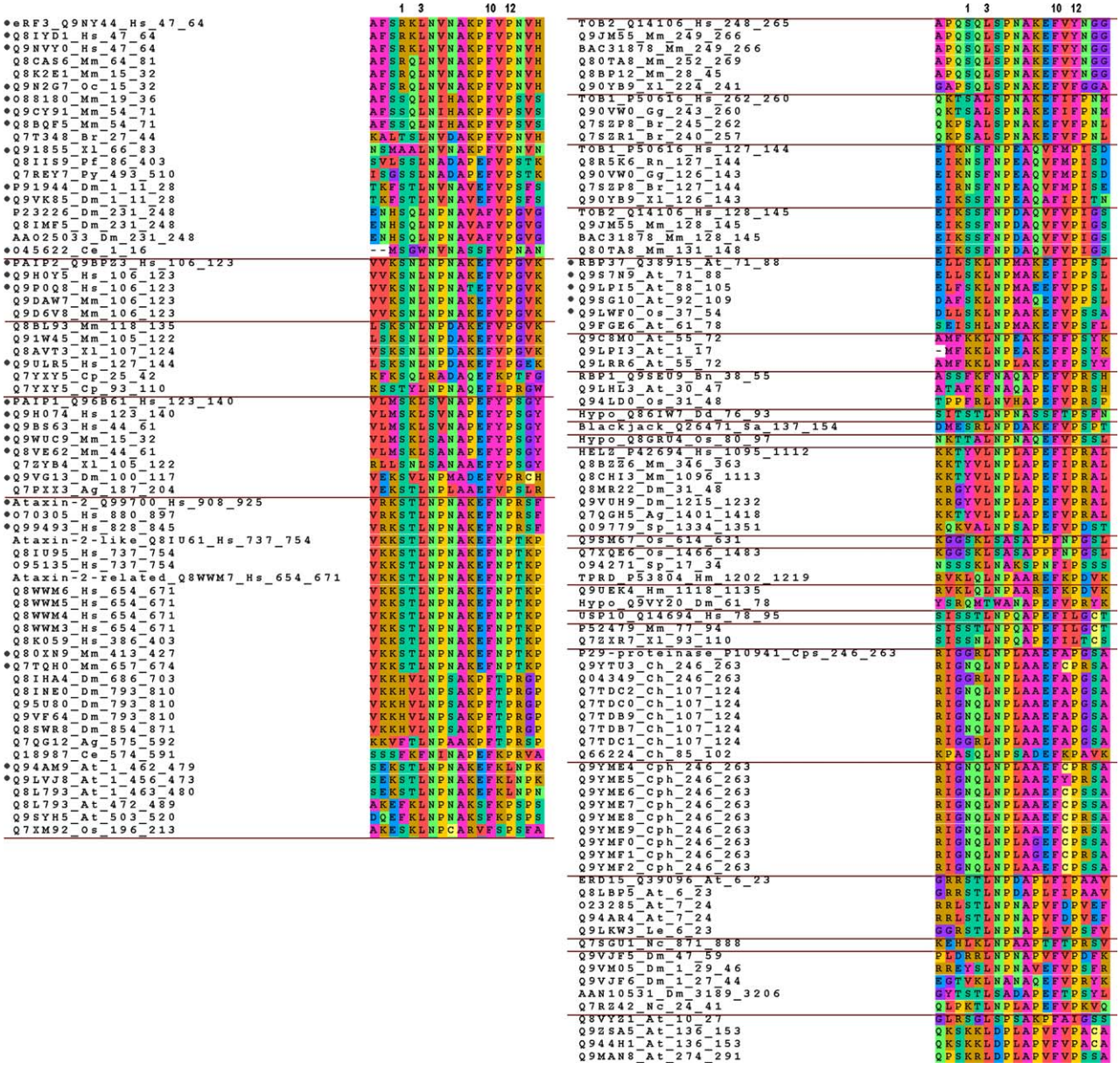

Fig. 2. Multiple sequence alignment of proteins with a PABC recognition motif PAM2. Based on homology and functionally related domain architectures, the proteins are clustered manually into groups separated by horizontal lines. Physico-chemically similar amino acids are colored identically. The PAM2 peptide is numbered at the top of the alignment. Gene and protein names are detailed in Table 1. Sequences forming the initial search profile are marked by solid circles in gray.

Table 1
SPTrEMBL accession numbers and gene and protein names of PAM2 motif containing proteins shown in Fig. 2

SPTrEMBL	Gene	Protein
Q9NY44_Hs	GSPT2	Polypeptide chain release factor 3b
Q8IYD1_Hs	—	G1 to S phase transition 2
Q9NVY0_Hs	—	Hypothetical protein FLJ10441
Q8CAS6_Mm	GSPT1	G1 to phase transition 1
Q8K2E1_Mm	GSPT1	Hypothetical protein
Q9N2G7_Oc	—	Eukaryotic polypeptide chain release factor 3
O88180_Mm	GSPT2	Guanine nucleotide regulatory protein
Q9CY91_Mm	GSPT2	G1 to phase transition 2
Q8BQF5_Mm	GSPT2	G1 to phase transition 2
Q7T348_Br	—	Hypothetical protein
Q91855_Xl	SUP35	SUP35
Q8IIS9_Pf	PF11_0086	Hypothetical protein
Q7REY7_Py	PY04926	Hypothetical protein
P91944_Dm	ELF/DELF/CG6382	Elongation factor 1α-like factor
Q9VK85_Dm	ELF/CG6382	ELF protein/RE07731p
P23226_Dm	MAP205/CG1483	205 kDa microtubule-associated protein
Q8IMF5_Dm	MAP205/CG1483	CG1483-PB
AAO25033_Dm	MAP205	LD12965p
O45622_Ce	H19N07.1	Hypothetical protein H19N07.1
Q9BPZ3_Hs	—	PAIP2
Q9H0Y5_Hs	DKFZP564F163	Hypothetical protein
Q9P0Q8_Hs	—	HSPC218
Q9DAW7_Mm	PAIP2	2310050K10Rik protein
Q9D6V8_Mm	PAIP2	2310050K10Rik protein
Q8BL93_Mm	—	Weakly similar to PAIP2
Q91W45_Mm	—	Hypothetical protein
Q8AVT3_Xl	—	Similar to hypothetical protein MGC27648
Q9ULR5_Hs	KIAA1155	Hypothetical protein KIAA1155
Q7YXY5_Cp	1MB.129	Conserved MIF4G domain protein
Q7YXY5_Cp	1MB.129	Conserved MIF4G domain protein
Q96B61_Hs	—	PAIP1
Q9H074_Hs	PAIP1	PAIP1
Q9BS63_Hs	—	Similar to PAIP1
Q9WUC9_Mm	—	PAIP1
Q8VE62_Mm	PAIP	Similar to PAIP1
Q7ZYB4_Xl	—	Similar to PAIP1
Q9VG13_Dm	PAIP2/CG12358	CG12358 protein/LD15606p
Q7PXX3_Ag	AGCG49365	AgCP12245
Q99700_Hs	SCA2	Ataxin-2
O70305_Hs	SCA2	Ataxin-2
Q99493_Hs	SCA2	Ataxin-2
Q8IU61_Hs	A2RP	Ataxin-2-like protein
Q8IU95_Hs	A2RP	Ataxin-2-like protein
O95135_Hs	A2LG	Ataxin-2-like protein A2LP
Q8WWM7_Hs	A2D-A	Ataxin-2 related domain protein
Q8WWM6_Hs	A2D-B	Ataxin-2 related domain protein
Q8WWM5_Hs	A2D-C	Ataxin-2 related domain protein
Q8WWM4_Hs	A2D-D	Ataxin-2 related domain protein
Q8WWM3_Hs	A2D-E	Ataxin-2 related domain protein
Q8K059_Hs	—	Similar to Ataxin 2 related protein
Q80XN9_Mm	LOC233871	LOC233871 protein
Q7TQH0_Mm	—	Hypothetical protein
Q8IHA4_Dm	ATX2/CG5166	AT22221p
Q8INE0_Dm	CG5166	CG5166-PC
Q95U80_Dm	ATX2/CG5166	GH01409p
Q9VF64_Dm	ATX2/CG5166	CG5166-PA
Q8SWR8_Dm	ATX2/CG5166	GH13857p/CG5166-PB
Q7QG12_Ag	AGCG51770	AgCP13861
Q18987_Ce	D2045.1	D2045.1 protein
Q94AM9_At	MDC16.14/AT3G14010	Hypothetical protein
Q9LVJ8_At	—	MDC16

Table 1 (*continued*)

SPTrEMBL	Gene	Protein
Q8L793_At	AT1G54170	Hypothetical protein
Q8L793_At	AT1G54170	Hypothetical protein
Q9SYH5_At	F15I1.27	F15I1.27
Q7XM92_Os	OSJNBb0060E08.7	OSJNBb0060E08.7 protein
Q14106_Hs	TOB2/TOB4/KIAA1663	Tob2 protein/transducer of erbB-2, 2
Q9JM55_Mm	TOB2	Tob2 protein/transducer of erbB-2, 2
BAC31878_Mm	—	Transducer of ERBB2, 2
Q80TA8_Mm	MKIAA1663	MKIAA1663 protein
Q8BP12_Mm	TOB2	Transducer of ERBB2
Q90YB9_Xl	—	Tob
P50616_Hs	TOB1/TOB	Tob1 protein/transducer of erbB-2, 1
Q90VW0_Gg	TOB	TOB protein/transducer of erbB-2
Q7SZP8_Br	—	Hypothetical protein
Q7SZR1_Br	—	Hypothetical protein
P50616_Hs	TOB1/TOB	Tob1 protein/transducer of erbB-2, 1
Q8R5K6_Rn	—	Tob1
Q90VW0_Gg	TOB	Tob protein/transducer of erbB-2
Q7SZP8_Br	—	Hypothetical protein
Q90YB9_Xl	—	Tob
Q14106_Hs	TOB2/TOB4	Tob2 protein/transducer of erbB-2, 2
Q9JM55_Mm	TOB2	Tob2 protein/transducer of erbB-2, 2
BAC31878_Mm	—	Transducer of ERBB2, 2
Q80TA8_Mm	MKIAA1663	MKIAA1663 protein
Q38915_At	RBP37	RNA-binding protein
Q9S7N9_At	T4F9.70/F3H7.12/RBP37	RNA-binding protein/AT4g10610/T4F9_70
Q9LPI5_At	—	F6N18.17
Q9SG10_At	T1G12.9/F2K15.250	Putative RNA-binding protein
Q9LWF0_Os	OSJNBA0016I09.30	Similar to RNA-binding protein
Q9FGE6_At	—	RNA-binding protein-like
Q9C8M0_At	F22G10.7	Putative RNA-binding protein
Q9LPI3_At	T3F20.1	T3F20.1 protein
Q9LRR6_At	—	Similarity to RNA-binding protein
Q9SEU9_Bn	RBP1	RNA-binding protein homolog
Q9LHL3_At	—	RNA-binding protein-like
Q94LD0_Os	—	Putative RNA-binding protein
Q86IW7_Dd	—	—
Q26471_Sa	—	Blackjack protein
Q8GRU4_Os	OSJNBA0050H14.18	Hypothetical protein
P42694_Hs	HELZ	Potential helicase with zinc-finger domain
Q8BZZ6_Mm	9630002H22RIK	Hypothetical protein
Q8CHI3_Mm	MKIAA0054	MKIAA0054 protein
Q8MR22_Dm	CG9425	LD34142p
Q9VUH9_Dm	CG9425	CG9425 protein
Q7QGH5_Ag	AGCG44750	AgCP13018
Q09779_Sp	SPAC1D4.14/SPAC22	Hypothetical protein C1D4.14
Q9SM67_Os	—	Zhb0018.1
Q7XQE6_Os	OSJNBa0070O11.2	OSJNBa0070O11.2 protein
O94271_Sp	SPBP8B7.23	Zinc finger protein
P53804_Hm	TTC3/TPRD	Tetratricopeptide (TPR) repeat protein 3/D
Q9UEK4_Hm	DCRR1	DCRR1 protein
Q9VY20_Dm	CG5347	CG5347 protein/LP05025p
Q14694_Hs	USP10	Ubiquitin C-terminal hydrolase/thiolesterase/protease 10
P52479_Mm	USP10	Ubiquitin C-terminal hydrolase/thiolesterase/protease 10
Q7ZXR7_Xl	—	Similar to ubiquitin specific protease 10
P10941_Cps	—	P29 proteinase
Q9YTU3_Ch	—	Hypothetical protein

Table 1 (*continued*)

SPTrEMBL	Gene	Protein
Q04349_Ch	—	OrfA
Q7TDC2_Ch	—	OrfA
Q7TDB0_Ch	—	OrfA
Q7TDB9_Ch	—	OrfA
Q7TDC7_Ch	—	OrfA
Q7TDC1_Ch	—	OrfA
Q66224_Ch	—	ORFA and ORFB
Q9YME4_Cph	—	Hypothetical protein
Q9YME5_Cph	—	Hypothetical protein
Q9YME6_Cph	—	Hypothetical protein
Q9YME7_Cph	—	Hypothetical protein
Q9YME8_Cph	—	Hypothetical protein
Q9YME9_Cph	—	Hypothetical protein
Q9YMF0_Cph	—	Hypothetical protein
Q9YMF1_Cph	—	Hypothetical protein
Q9YMF2_Cph	—	Hypothetical protein
Q39096_At	ERD15/T26J13.2	Dehydration-induced protein ERD15/F13H10.2
Q8LBP5_At	—	ERD15 protein
O23285_At	AT4G14270	Hypothetical protein
Q94AR4_At	DL3175W/AT4G14270	Hypothetical protein
Q9LKW3_Le	—	Dehydration-induced protein ERD15
Q7SGU1_Nc	NCU03228.1	Hypothetical protein
Q9VJF5_Dm	CG15136	CG15136 protein
Q9VM05_Dm	CG6441	CG6441 protein
Q9VJF6_Dm	CG6304	CG6304 protein/GH09088p
AAN10531_Dm	CG31916	CG31916-PA
Q7RZ42_Nc	NCU04432.1	Predicted protein
Q8VYZ1_At	AT1G33050	Hypothetical protein
Q9ZSA5_At	F3H7.18/F7L13.50	F3H7.18 protein
Q944H1_At	—	AT4g10470/F7L13_50
Q9MAN8_At	F9L11.20	CDS

[31,32]. The *Saccharomyces cerevisiae* eRF3 homolog (encoded by the SUP35 gene) mediates mRNA decay through deadenylation regulation [33], and the numerous eukaryotic eRF3 homologs with a PAM2 motif play very similar roles in translational processes [34,35]. Recently, it has been discovered that the human eRF3 homolog GSPT1 is proteolytically processed into an isoform for binding inhibitors of apoptosis (IAP) [36].

Tob1/2 homologs

An anti-proliferative (APRO) protein family contains Tob1/2 homologs (previously identified as transducers of ErbB-2, a receptor tyrosine kinase) [37], which have one or even two PAM2 motifs, but have not yet been shown experimentally to bind PABC domain homologs. However, Tob1 is the substrate of the mitogen-activated protein kinases (MAPKs) ERK2 and JNK2 [38] and has already been implicated in the negative regulation of the cell cycle; it associates with Smads to control osteoblast-growth and enhance Smad DNA-binding [39–41]. In addition, Tob2 associates with CAF1 [42], which links the poly(A) deadenylase CCR4 of the exonuclease III family to the evolutionarily conserved CCR4-NOT transcriptional regulatory complex involved in mRNA degradation [43–45]. Generally, the APRO family members Tob1/2 and BTG1/2 are multi-ubiquitinated and degraded by the ubiquitin–proteasome system [46].

Ataxin-2 homologs

Another interesting group of homologous proteins are Ataxin-2 and Ataxin-2 like and related proteins of unknown function [47,48]. A polyglutamine expansion of Ataxin-2 is causative of the inherited neurodegenerative disease spinocerebellar ataxia type 2 (SCA2) [49]. In contrast to Ataxin-2, its yeast homolog PBP1 (PAB1-binding protein) lacks a detectable PAM2 motif in the C-terminal tail [3]. Nevertheless, this C-terminal tail of PBP1 has been shown experimentally to bind to the PABC domain of PABP/PAB1 and to regulate polyadenylation in pre-mRNA splicing [50]. Without PBP1, the 3′-end of pre-mRNA is not properly cleaved and exhibits an incomplete poly(A) tail.

The C-terminal tail of human Ataxin-2, which contains the PAM2 motif, interacts with A2BP1/HRNBP1 (Ataxin-2 binding protein 1/hexaribonucleotide binding protein 1), whose cellular function is unknown and does

Table 2
Abbreviations of species names

Ag	*Anopheles gambiae* str. PEST
At	*Arabidopsis thaliana* (mouse-ear cress)
Bn	*Brassica napus* (rape)
Br	*Brachydanio rerio* (zebrafish) (*Danio rerio*)
Ce	*Caenorhabditis elegans*
Ch	*Cryphonectria hypovirus* 1
Cp	*Cryptosporidium parvum*
Cph	*Cryphonectria parasitica* hypovirulence associated virus
Cps	*Cryphonectria parasitica* (chestnut blight fungus) (*Endothia parasitica*)
Dd	*Dictyostelium discoideum* (slime mold)
Dm	*Drosophila melanogaster* (fruit fly)
Gg	*Gallus gallus* (chicken)
Hs	*Homo sapiens* (human)
Mm	*Mus musculus* (mouse)
Nc	*Neurospora crassa*
Le	*Lycopersicon esculentum* (tomato)
Oc	*Oryctolagus cuniculus* (rabbit)
Os	*Oryza sativa* (rice)
Pf	*Plasmodium falciparum* (isolate 3D7)
Py	*Plasmodium yoelii yoelii*
Rn	*Rattus norvegicus*
Sa	*Schistocerca americana* (American grasshopper)
Sp	*Schizosaccharomyces pombe* (fission yeast)
Xl	*Xenopus laevis* (African clawed frog)
Zr	*Zygosaccharomyces rouxii* (*Candida mogii*)

not seem to carry a PABC domain [51]. However, both A2BP1/HRNBP1 and PABP are evolutionarily related and possess N-terminal RNA recognition motifs (RRMs) [51]. The RNA-binding *Caenorhabditis elegans* homolog FOX-1 of A2BP1 regulates tissue-specific alternative splicing by specific binding to a pentanucleotide [52].

A *Drosophila melanogaster* homolog of Ataxin-2 also carries a PAM2 motif and has been observed to be a dosage-sensitive regulator of cytoskeletal actin filament formation [53]. Another Ataxin-2 homolog in *C. elegans* with a PAM2 motif plays a vital role in early embryonic development [54]. Furthermore, a human homolog named Ataxin-2 domain protein (A2D) with a PAM2 motif has been found in association with the cytokine receptor Mpl and the endogenous erythropoietin receptor EPO-R, suggesting A2D homologs as components of cytokine signaling pathways.

The common Lsm (Like Sm) domain of Ataxin-2 homologs and the yeast homolog PBP1 has already been discovered some time ago [53,55], but its function and structure has not yet been examined experimentally. However, proteins with this RNA-binding Lsm domain are generally involved in important processes of RNA metabolism including RNA modification, splicing, and degradation [56–58].

Other nucleic acid binding proteins

While Ataxin-2 homologs possess a putatively RNA-binding Lsm domain, other PAM2 containing proteins with RNA-binding domains carry one or two RRM domains or a La domain (Fig. 1), for instance, RBP37 (RNA-binding protein 37) from *Arabidopsis thaliana* [59] and RBP1 (RNA-binding protein homolog 1) from *Brassica napus* [60]. Interestingly, Lsm proteins involved in tRNA-processing have been observed recently to associate with the homolog Lhp1 of the La ribonucleoprotein in *S. cerevisiae* [61].

Further, largely uncharacterized, PAM2 containing proteins are the Blackjack protein from *Schistocerca americana* and a hypothetical protein from *Oryza sativa*, the latter of which has a C-terminal Smr domain that can be indicative of proteins involved in DNA-damage repair of mismatches made by the replication machinery [62]. The Blackjack protein is associated with microtubules and is mainly expressed in embryonic neurons [63].

The PAM2 motif is also detected in diverse proteins with zinc fingers and tetratricopeptide repeats (TPRs). While zinc fingers are often involved in nucleic acid binding [64,65], TPRs generally mediate protein–protein interactions without common features of the interaction partners, but some are involved in transcriptional control [66]. Two examples are human proteins, the putative RNA helicase HELZ [67] and the TPR-containing Down syndrome candidate gene product TPRD (TTC3/DCRR1) of unknown function [68].

Further PAM2 containing proteins

Besides proteins putatively involved in nucleic acid binding, other PAM2 motif proteins appear to be associated with different functions. For instance, the mammalian ubiquitin-specific processing protease USP10 includes a PAM2 motif and interacts with the Ras-GAP SH3-binding protein G3BP1 to modulate the enzymatic activity of USP10 [69]. The yeast orthologs UBP3/YER151C and BRE5/YNR051C of USP10 and G3BP1, respectively, also form a protein complex through the NTF2 (nuclear transport factor 2) domain of BRE5 [70,71]. Like USP10 and G3BP1, UBP3 requires BRE5 as cofactor to specifically de-ubiquitinate other proteins such as the COPI and COPII (coat protein complex I and II) subunits Sec27 and Sec23, respectively. Therefore, the human USP10-G3BP1 and yeast UBP3-BRE5 complexes have been proposed to be evolutionarily conserved and to regulate transport between Golgi and endoplasmic reticulum [70].

Furthermore, both orthologs G3BP1 and BRE5 share a C-terminal RRM domain, and UBP3 interacts with SIR4 to control the SIR protein complex [72], which is involved in transcriptional silencing and DNA repair [73]. It has also been observed that the yeast-2-hybrid interaction of UBP3 with the transcriptional adaptor ADA3/NGG1/YDR176W requires the HECT-domain E3 ubiquitin-ligase TOM1, which is assumed to

regulate the ADA histone acetyltransferase complex by ubiquitination [74–76].

Other interesting PAM2 containing proteins are the viral P29 peptidases, whose binding to a PABC domain has not been investigated yet experimentally. However, it is known that the 2A and 3C proteases of coxsackievirus and poliovirus cleave PABP at the N-terminus of the PABC domain to diminish translation initiation [77–80]. Further, PAM2 motif proteins with as yet unidentified functional domains are the dehydration-induced gene product ERD15 from *A. thaliana* [81] and a hypothetical protein named C1D4.14 from *Schizosaccharomyces pombe*. The *S. cerevisiae* ortholog RLR1/THO2/YNL139C of the latter protein does not contain the PAM2 motif, but is part of the conserved transcription elongation and mRNA export complex TREX [82]. Therefore, the discovery of a PAM2 motif in the *S. pombe* protein C1D4.14 makes much sense from a functional point of view. Unfortunately, the PAM2 motif could not be detected in other eukaryotic orthologs of this protein and lies in a less conserved region of the corresponding multiple sequence alignment of orthologs (data not shown).

Conclusions

Our comprehensive analysis of proteins with the PAM2 motif emphasizes its general role as protein interaction site with PABC domain proteins. It is striking that this motif appears to occur solely outside globular protein domains. Presumably, the possible interactions of PAM2 peptides are not restricted to PABP homologs because the PABC domain also precedes the C-terminal ubiquitin ligase HECT domain of HYD homologs, which can interact with PAIP1 in vitro [13]. Interestingly, the PAM2 motif has also been found in the de-ubiquitinating hydrolase USP10 and the APRO family members Tob1/2, the latter of which associate with an mRNA deadenylation complex and are ubiquitinated.

Generally, some caution needs to be applied to assumptions about the functional relevance of the PAM2 motif if orthologs of some PAM2 containing protein do not show this motif to be conserved. However, in contrast to this general cautionary note, Ataxin-2 contains a PAM2 motif, but this motif is not detectable in the PABP-binding homolog PBP1 of Ataxin-2. Therefore, the PABC domain also binds to peptides different from PAM2.

Taken together, it appears indeed to be worthwhile to investigate the binding partners of the remaining proteins that appear to possess a PAM2 motif, but have not been reported yet to interact with PABC domain homologs. Some of the described proteins such as Tob1/2 homologs from different species, a PAIP2 homolog from *Cryptosporidium parvum*, and a distant homolog of Ataxin-2 from *A. thaliana* appear to have even two PAM2 motifs, pointing to multiple interactions.

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