

Gene Section

Review

YEATS4 (YEATS domain containing 4)

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Abstract

This entry reviews the structure, function and clinical significance of YEATS4, a gene originally identified from an amplicon on 12p15 found in a glioblastoma cell line and originally named glioma-amplified sequence (GAS41). The gene is amplified in several other cancers and translocations or rearrangements of chromosome 12 with breakpoints in YEATS4 are noted in such cancers as glioblastoma, lung cancer and soft tissue sarcomas. Several frameshift and one nonsense mutations have also been detected in cancer. As the YEATS4 protein is involved in chromatin modeling, transcriptional regulation and mitotic regulation, such aberrations are likely to deregulate cellular mechanisms

involved in the normal control of cellular proliferation and cell death.

Keywords

YEATS4, glioblastoma, chromatin, centrosome

Identity

Other names

Gas41, NuB11, YAF9

HGNC (Hugo)

YEATS4

Location

12q15; Extends between Chromosome 12: 69,359,703-69,390,796, (according to hg38-Dec 2013)(Fig. 1)

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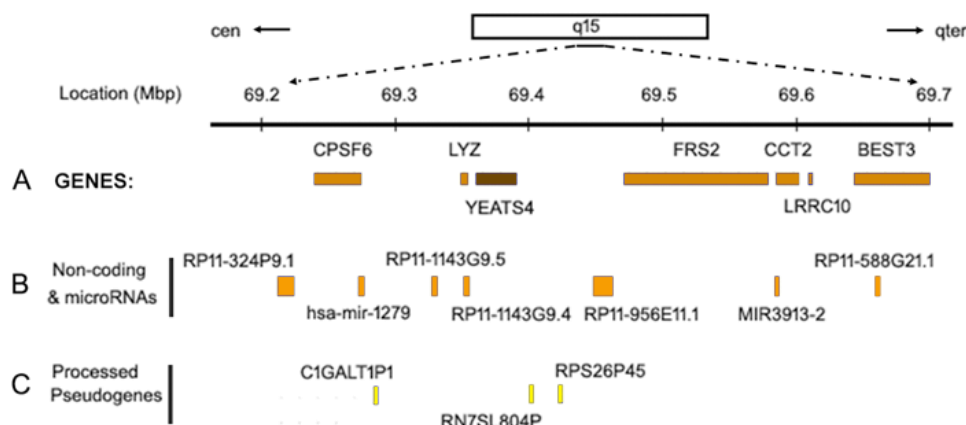


Fig. 1. Location of the YEATS4 gene is shown within a 500kb region of 12p15. A) Protein-coding genes; B) Genes for non-coding and microRNAs; C) Processed pseudogenes.

DNA/RNA

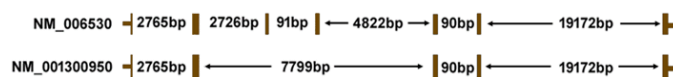


Fig. 2. Genomic structure of YEATS4. The exon distributions for the two alternatively spliced products (RefSeq accessions NM_006530 and NM_001300950) are shown, with the intron sizes given in base pairs (bp). Coding regions are shown in thicker lines; non-coding regions (5' untranslated and 3' untranslated regions) are depicted as thinner lines.

Description

YEATS4 is encoded by 7 exons spread over 31,094bp (Fig. 2). The gene encodes two alternatively spliced products (RefSeq accessions NM_006530 and NM_001300950). Transcript 1 (NM_006530) is 1501 nucleotides in length and

encodes a protein of 227 amino acids. Transcript 2 (NM_001300950) is 1339 nucleotides long and encodes a protein of 173 amino acids.

Protein

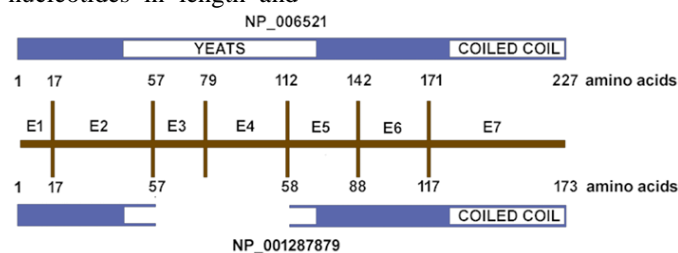


Fig. 3. Structure of the YEATS4 protein. Location of exon boundaries (vertical lines) are shown relative to the protein structure. The YEATS and Coiled domains are involved in the functional interactions of the protein. Alternative splicing removes exon 3 and 4, yielding transcript 2, such that isoform 2 (NP_001287879) misses 55 amino acids of the YEATS domain.

Description

The YEATS4 transcripts produce two proteins; isoform 1 is 227 amino acids long (RefSeq accession: NP_006521) and isoform 2 is 173 amino acids long (RefSeq accession: NP_001287879). Isoform 1 has two defined structural/functional features: the YEATS domain located between amino acid residue 44 and 123, and a coiled coiled domain

(amino acid 168 - ter). The YEATS domain is conserved in YNK7 (Yaf9), MLLT1 (ENL), MLLT3 (AF-9) and the TFIIF small subunit. Yaf9 in *S. cerevisiae* is a subunit of the NuA4 histone acetyltransferase complex (Le Masson et al., 2003). Thus, the YEATS domain is thought to be involved in transcriptional regulation. A C-terminal coiled coil domain interacts with several proteins indicated

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below and is critical for incorporation of YEATS4 into the human TIP60 complex (Park and Roeder 2006). Six chemical modifications have been annotated in the Prosite database on amino acids conserved between human and mouse (Fig. 4), four

of which are ubiquitinylation of lysines located in the coiled coil domain (Hornbeck et al., 2014). Fifty five amino acids of the YEATS domain are missing from isoform 2.

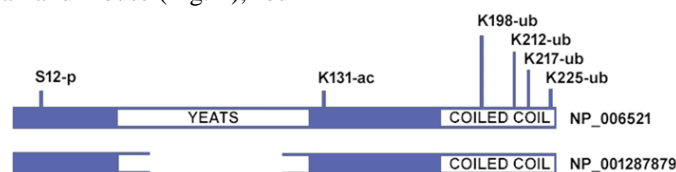


Fig. 4. Location of chemically modified amino acid side chains. Amino acid residues positions are given relative to NP_006521. Key: p- phosphorylation, ac- acetylation, ub- ubiquitination.

Expression

Northern blot analysis detects a ubiquitously expressed transcript of approximately 1.7kb, with high expression in brain, heart and skeletal muscle (Harbroth et al., 2000). In general, RNA-seq analysis consistently indicates highest expression in the testes, tissues of the immune system (bone marrow, lymph node and thymus) and the brain, specifically the cerebellum (Fagerberg et al., 2013; Duff et al., 2015; GTEx Portal 2017).

Localisation

Several articles indicate that YEATS4 is located in punctate structures in the nucleoplasm of the interphase nucleus of the majority of tested cells, including glioblastoma cell lines (Harborth et al., 2000; Munnia et al., 2001; Debernardi et al., 2002; Lauffart et al., 2002). However, YEATS4 is localized to nucleoli in the neuroblastoma cell lines SK-N-SH, Neuro 2a, and NS20 (Munnia et al., 2001), suggesting a possible functional differentiation for YEATS4 in tumors of the peripheral compared to central nervous system.

Function

Based on its homology with Yaf 9 (by what is now called the YEATS domain [Fig. 1]), YEATS4 was predicted to be a subunit of the human homologue of the NuA4 histone acetyltransferase complex, the Tip60 complex. This complex is involved in gene regulation and the repair of double-stranded DNA breaks. This multisubunit complex has histone H4/H2A acetyltransferase activity, is capable of ATP-dependent H2AZ -H2B histone dimer exchange, and has DNA helicase activity (Auger et al., 2008). YEATS4 is also a subunit of the SNP2-related CBP activator protein (SRCAP) complex, which is a distinct complex also involved in the exchange of Histone H2A for H2Z in chromatin, although the complex functions without acetyltransferase activity (Auger et al., 2008). YEATS4 also directly interacts with SWI/SNF component SMARCB1 (BAF47 or INI1) (Debernardi et al., 2002), MLLT10, which is a histone lysine methyltransferase DOT1L cofactor (Debernardi et al., 2002), the KDM1A demethylase

(Piccinni et al., 2011), and the TFIIF component GTF2F2 (RAP30) (Heisel et al., 2010). It has been suggested that the YEATS domain acts as an evolutionarily conserved chromatin modification reader, and possibly directly binds to histones (Schulze et al., 2010).

Further evidence for a function of YEATS4 in transcription has come from direct interactions with transcription factor TFAP2A (AP-2) (Ding et al., 2006), and the C-terminal region of the myc family members MYCN and MYC (Piccinni et al., 2011), identified by affinity capture techniques such as yeast two-hybrid analysis, GST-pull down and coimmunoprecipitation. The β -catenin gene (CTNNB1) is regulated by binding of YEATS4 to its promoter, either via these transcription factors, or in combination with the chromatin modeling complexes discussed above (Ji et al., 2017; Jixiang et al., 2017). Downstream targets of β -catenin such as CCND1 (Cyclin D1), CDK4, CDK6 and c-Myc, and the apoptotic proteins BCL2 and BAX also respond to overexpression and decreased expression of YEATS4 in gastric cancer and pancreatic cancer (Ji et al., 2017; Jixiang et al., 2017).

As noted above, the Tip60 and SCRAP complex play roles in double-stranded DNA repair. However, YEATS4 is involved in the regulation of DNA repair independent of these complexes. YEATS4 overexpression results in destabilization of TP53, with downregulation of YEATS4 leading to stabilization of p53 with concomitant upregulation of p53 target genes such as CDKN1A (p21), and induction of senescence and apoptosis (Llanos et al., 2006; Park et al., 2006; Pikor et al., 2013; Tao et al., 2015). Furthermore, overexpression of YEATS4 increases resistance of normal bronchial epithelial cells to the platinum drug cisplatin and p53- MDM2 interaction inhibitor, nutlin (Pikor et al., 2013). Mechanistically, YEATS4 acts with PP2C β to dephosphorylate ser-366 on p53, and can decrease cell death due to UV-induced DNA damage (Park et al., 2011). Thus, overexpression of YEATS4 may contribute to the cancers described below in part by overcoming the tumor suppressor properties of p53. Additional functions of YEATS4 in nuclear architecture and regulation of mitotic spindle

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assembly were uncovered shortly after its discovery. Harborth et al., (2000) performed yeast two-hybrid analysis to identify proteins that bind to the C-terminus (amino acids 1048-2115) of NUMA1 (NuMA). Further mapping indicated that YEATS4 bound via its coiled coil domain to the C-terminal region of the coiled-coil rod domain of NuMA (amino acids 1048-1700). This interaction was confirmed independently by co-immunoprecipitation, Dot Overlay Assays, Surface Plasmon Resonance, and by a separate study (Munnia et al., 2001). Later studies showed that interaction between NuMA and YEATS4 was cell-cycle regulated with the interaction being low in G1 to S, increasing in S phase and being maximal at G2/M (Schmitt et al., 2012). NuMA is a nuclear matrix protein that relocalizes to and anchors microtubules to the spindle poles (reviewed in Haren et al., 2009). Manipulation of the expression of YEATS4 and NuMA via expression plasmids and siRNA results in an increased rate of spindle defects leading to multipolar spindles and misaligned chromosomes (Schmitt et al., 2012). Additional interactions of YEATS4 with CEP162 (Munnia et al., 2001), and TACC1 - TACC2 - TACC3 (Lauffart et al., 2002; Lauffart et al., 2003), proteins with known roles in centrosomal dynamics during mitosis (Gergley et al., 2000a,b; Leon et al., 2006), have also been identified. However, even these YEATS4-interacting proteins have been implicated in transcriptional regulation. For instance, during interphase NuMA binds to and acts as a transcriptional coregulator of p53 upon DNA-damage (Endo et al., 2013; Ohata et al., 2013); CEP162 associates with predominantly nuclear localized KAT14 lysine acetyltransferase (Gupta et al., 2015; Wang et al., 2008); and the TACC proteins bind to nuclear localized histone acetyltransferases (Gangisetty et al., 2004), nuclear hormone receptors (Vettaikorumakankau et al., 2008; Guyot et al., 2010; Hein et al., 2015; Huttlin et al., 2017) and other transcription factors (Sadek et al., 2000; Simpson et al., 2004); Bargo et al., 2010), and coregulate their transcriptional targets. YEATS4 has been found in complexes with a further 108 proteins by high-throughput analysis via affinity purification-mass spectrometry (Li et al., 2015; Huttlin et al., 2015; Huttlin et al., 2017). Many of these interactions support the proposed functions of YEATS4 in the TIP60 and SCRAP complexes,

transcriptional regulation, and mitotic regulation. For instance, additional transcription factors of relevance to cancer, such as FOS, Fox family members, and the myc partner MAX have been identified as YEATS4-binding factors (Li et al., 2015).

Homology

The YEATS domain is highly conserved within eukaryotes and defines a family of proteins involved in key functions including transcriptional regulation and chromatin structure (see above). Four YEATS family members are found in humans (MLLT1 [ENL], MLLT3 [AF9], YEATS2, and YEATS4). A BLASTp search of the protein database can identify a defined YEATS4 protein in metazoan eukaryotes representing fungi, arthropods, cnidarians, and chordates, but not plants. In *S. cerevisiae*, Yaf9 has been proposed to be the closest functional homolog to YEATS4, containing both the YEATS domain and the C-terminal coiled coil region (Le Masson et al., 2003). The Yaf9 protein shows 33% amino acid identity and 57% homology to human YEATS4. The N-terminal YEATS domain of YEATS4 is able to functionally interchange with that of Yaf9 (Piccinni et al., 2011).

Mutations

Somatic

A total of 39 somatic sequence variations involving the coding region of YEATS4 are recorded in COSMIC v81, released 09-May-17, at <http://cancer.sanger.ac.uk/cosmic> (Bamford et al., 2004; Forbes et al., 2017). Of those, seven are silent, twenty-seven are missense, four are frameshifts, and one is a nonsense mutation. Each sequence variant has been found in a single case, except for G75D which was detected in 3 colon cancer cell lines HCT8, HCT15, DLD1. c.63C>T, c.66T>G, c.333T>C, c.475C>T, c.498T>C, c.680_681insA are noted as single nucleotide polymorphisms in the dSNP database (https://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?locusId=8089).

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Position (AA)	Mutation (CDS)	Mutation (Amino Acid)	Mutation Type	Cancer type
2	c.6C>G	p.F2L	s.m.	Rectal adenocarcinoma

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8	c.22T>C	p.F8L	s.m.	Hepatocellular carcinoma
10	c.28C>T	p.P10S	s.m.	Stomach adenocarcinoma
21	c.63C>T#	p.I21I	s.s	Malignant melanoma
22	c.66T>G#	p.V22V	s.s	Clear cell renal cell carcinoma
35	c.103G>A	p.G35R	s.m.	Thyroid carcinoma
43	c.127C>T	p.H43Y	s.m.	Malignant melanoma
43	c.124delG	p.H43fs*9	d.fs.	Lung adenocarcinoma
52	c.156A>G	p.K52K	s.s.	Stomach adenocarcinoma
58	c.172G>C	p.D58H	s.m.	Lung adenocarcinoma
75	c.224G>A	p.G75D	s.m.	Colon
78	c.234A>G	p.L78L	s.s	Lung carcinoma
93	c.279G>T	p.W93C	s.m.	Primitive neuroectodermal tumour - medulloblastoma
95	c.284A>C	p.E95A	s.m.	Papillary renal cell carcinoma
97	c.289G>A	p.E97K	s.m.	Rectal Adenocarcinoma
100	c.300C>G	p.I100M	s.m.	Pancreatic ductal carcinoma
110	c.328A>G	p.R110G	s.m.	Malignant melanoma
111	c.333T>C#	p.P111P	s.s	Adenocarcinoma of Large intestine
125	c.375C>A	p.T125T	s.s	Malignant melanoma
133	c.398C>G	p.T133R	s.m.	Clear cell renal cell carcinoma
136	c.407C>T	p.S136L	s.m.	Malignant melanoma
141	c.421G>T	p.E141*	s.n.	Endometrioid carcinoma
147	c.438delC	p.P147fs*4	d.fs.	Breast Ductal carcinoma
150	c.449T>C	p.M150T	s.m.	Pancreas Ductal carcinoma
151	c.453G>A	p.M151I	s.m.	Liver neoplasm
154	c.461T>C	p.L154S	s.m.	Head neck Squamous cell carcinoma
159	c.475C>T#	p.R159C	s.m.	Malignant melanoma
162	c.485C>T	p.T162I	s.m.	Papillary renal cell carcinoma
163	c.489A>C	p.L163F	s.m.	Breast Carcinoma

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166	c.498T>C#	p.Y166Y	s.s.	Head neck Squamous cell carcinoma
170	c.509C>G	p.T170R	s.m.	Basal (triple-negative) carcinoma
174	c.521A>C	p.E174A	s.m.	Breast Phyllodes tumour
180	c.539G>C	p.R180T	s.m.	Lung Adenocarcinoma
192	c.575T>C	p.F192S	s.m.	Stomach Intestinal adenocarcinoma
207	c.619A>T	p.T207S	s.m.	Central nervous system Oligodendroglioma
207	c.619delA	p.T207fs*2	d.fs.	Endometrium Serous carcinoma
208	c.624A>G	p.I208M	s.m.	Hepatocellular carcinoma
224	c.671C>T	p.A224V	s.m.	Breast Ductal carcinoma
228	c.680_681insA#	p.*228fs?	i.fs.	Breast Carcinoma

Table 1: Sequence variations tabulated from COSMIC v81 (accessed 7/25/2017). KEY: d.fs. - deletion leading to frameshift; i.fs. - insertion leading to frameshift; s.m. - missense substitutions; s.s. - silent substitution; s.n. - nonsense substitution; # variants recorded as single nucleotide polymorphisms. Cells in green denote variations located in the YEATS domain, and cells in blue denote variations located in the C-terminal coiled coil domain.

Implicated in

The YEATS4 gene is located in a region of Chromosome 12 that is subject to genomic instability and amplification in several different cancers. 117 of 508 human cancer cell lines (23%) exhibited copy number gains of YEATS4 (Pikor et al., 2015). Fusion genes have been identified by RNA-seq analysis of the samples in the Cancer Genome Atlas, as well as in other tumor samples. As many rearrangements resulting in fusions between YEATS4 and other coding genes are found in the same region of the long arm of chromosome 12 that

is also subject to amplification, they may be the result of intrachromosomal inversions or deletions. However, as the mechanism of the rearrangements is unclear, the genomic alterations will be designated as translocations for the purpose of this review.

Bladder urothelial carcinoma

RNA-seq analysis of 414 bladder urothelial carcinomas, detected one rearrangement, t(12;12)(q15;q15), fusing exon 4 of YEATS4 out-of-frame to exon 2 of the human lysozyme (LYZ) gene (Yoshihara et al., 2015). Presumably non-sense mediated decay would prevent significant protein product accumulating.

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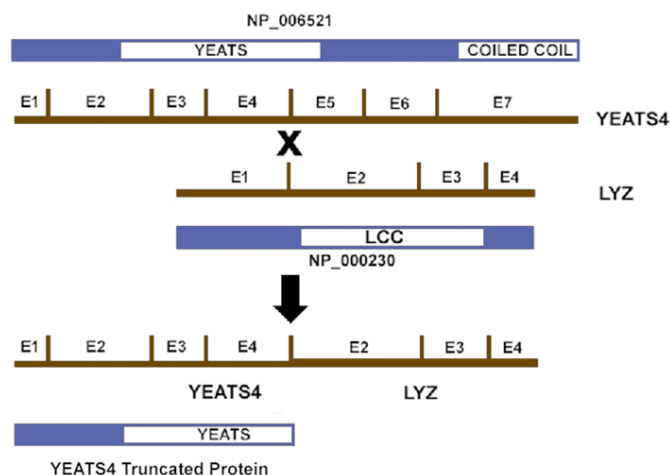


Fig. 5. Hybrid gene and protein produced by t(12;12)(q15;q15). With a breakpoint located in intron 4 of YEATS4 and intron 1 of LYZ, RNA-seq detected an out-of-frame fusion gene that could only produce a significantly truncated YEATS4 protein.

Brain cancer

YEATS4 was identified as an amplified sequence (GAS41) in glioblastoma multiforme (GBM) cell line TX3868, with amplification subsequently noted at higher frequency in lower grade astrocytoma grades I and II. (Fischer et al., 1997). In a larger study by Schmitt et al. (2012) of 258 glioblastoma samples from the Cancer Genome Atlas, 9 glioblastomas had high level of YEATS4 amplification. However, 26.1% of the samples exhibited reduced expression.

Four genomic rearrangements involving YEATS4 have been noted in glioblastoma. Frattini et al. (2013) performed RNA-sequencing of 161 primary

GBM and 24 short-term glioma sphere cultures. These authors detected a single rearrangement t(12;12)(q14.1;q15), resulting in a fusion between YEATS4 and XRCC6BP1 (X-ray repair cross-complementation group 6 binding protein). XRCC6BP1 (AKA ATP23) is involved in double-stranded DNA break repair (Fischer et al., 2013) and, based on homology via its metalloprotease domain, is suggested to be important in the biosynthesis of mitochondrial ATPase (Zeng et al., 2007). The detected transcript indicates that the fusion protein contains the YEATS domain fused to the majority of the peptidase M76 domain of XRCC6BP1 (missing 20 amino acids at the N-terminus) (Fig. 6).

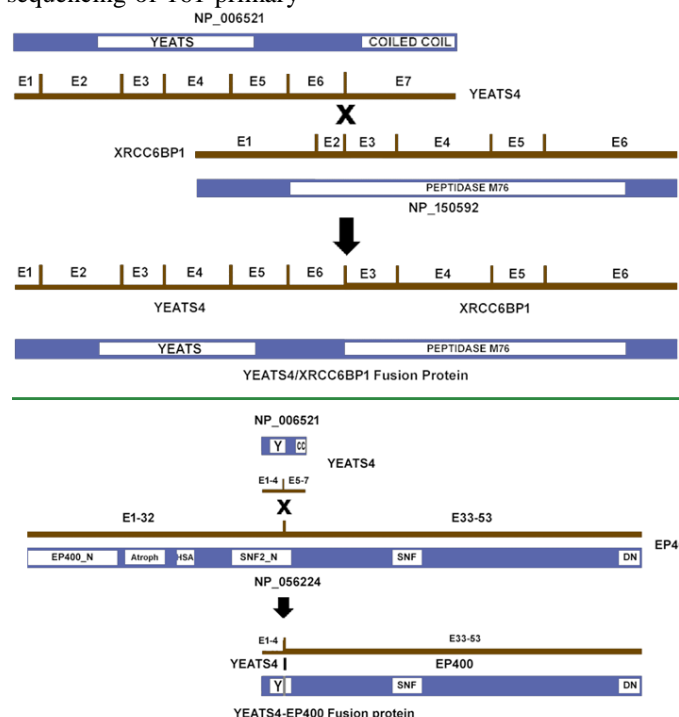


Fig. 6. Hybrid gene and protein produced by t(12;12)(q14.1;q15) that fuses YEATS4 exon 6 to exon 3 of XRCC6BP1. The Mitelman database contains records generated from paired-end whole genome-sequencing of

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42 paired TCGA glioblastoma tumors and matching normal samples (Zheng et al., 2013, Yoshihara et al., 2015).

A translocation t(12;12)(q15;q24) resulting in an in-frame fusion between YEATS4 exon 4 and exon 33 of EP400 (Fig. 7) was reported in the Mitelman database, however this fusion is absent from the TUMOR FUSION GENE DATA PORTAL developed by the same authors (<http://54.84.12.177/PanCanFusV2/>), and may not have survived further validation. The YEATS4-EP400 hybrid protein would contain contains 111 amino acids of YEATS4, containing part of the YEATS domain fused to the C-terminal 1811 amino acids of EP400, containing the SNF2 family domain and DNA_pol3_delta2 super family domain (c126247). Yoshihara et al (2015) detected one case of a t(12;12)(q13.3;q15), generating an out-of-frame fusion of YEATS4 exon 6 to methionyl-tRNA synthetase (MARS) exon 12 (Fig. 8). If the fusion protein is produced from the initiator methionine of YEATS4, the protein would be 187 amino acids long and contain the YEATS domain. However, one might predict that nonsense-mediated decay may reduce the accumulation of the fusion mRNA, and subsequent protein. A larger RNA-seq analysis followed by sequencing of 185 GBM samples from TCGA and Ivy center cohort also detected a fusion between YEATS4 (exon 1) and exon 4 of SLC35E3 located 601kb centromeric (Shah et al., 2013). While the fusion RNA detected would be driven from the YEATS4 promoter, the 106 amino acid fusion protein would only contain part of the triose phosphate transporter domain of SLC35E3 (Fig. 9). While it is possible that the fusion could inhibit the function of any normal YEATS4 or SLC35E3 protein in the tumor cell, it would seem more likely that the reciprocal product, if produced, would be of functional significance. However, the reciprocal SLC35E3-YEATS4 fusion transcript was not recorded.

Fig. 7. Fusion between exon 4 of YEATS4 and exon 33 of EP400 (numbering based on NM_015409 and protein NP_056224). The fusion protein is 1922 amino acids long. Domain Key: Y: YEATS domain; cc: Coiled coil domain; EP400_N: pfam15790, E1A-binding protein p400, N-terminal domain is characterized by low-complexity but its function is unknown; Atroph: Atrophin-1 super family domain, a polyglutamine stretch may interact with histone acetyltransferase CBP; HSA: domain found in helicases and associated with SANT domains; SNF2_N: SNF2 family N-terminal domain; SNF: SNF2 family domain; DN: DNA_pol3_delta2 super family domain (c126247).

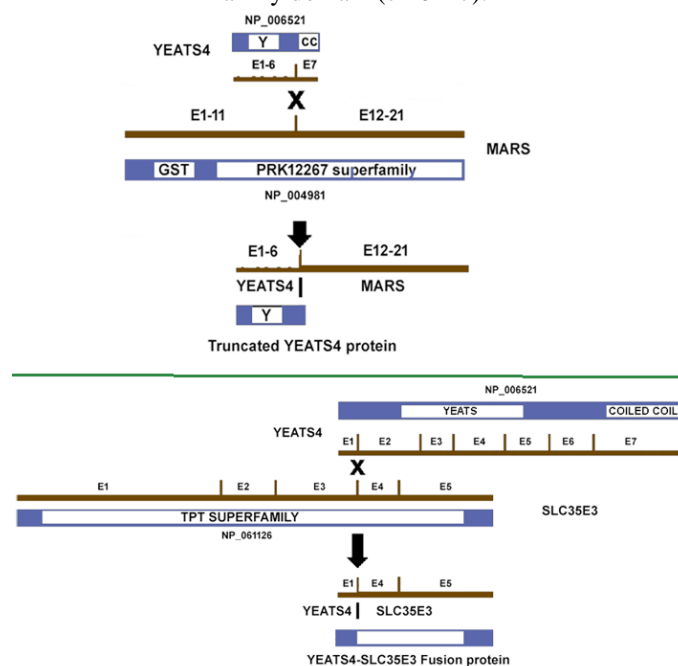


Fig. 8. Out-of-frame fusion between YEATS4 and MARS. The hybrid gene could produce a truncated YEATS4 protein missing the coiled coil domain. Domain Key: Y: YEATS domain; cc: Coiled coil domain; GST: Glutathione S-transferase C-terminal-like, alpha helical domain of Methionyl-tRNA synthetase from higher eukaryotes; PRK12267 super family domain: Methionyl-tRNA synthetase.

Fig. 9. Hybrid gene and protein produced by t(12;12)(q15;q15) that fuses YEATS4 exon 1 to exon 4 of SLC35E3. SLC35E3 encodes a protein of 313 amino acids (NP_061126) and is identified as a member of the triose-phosphate transporter (TPT) family based upon a central 278 amino acid domain.

Colorectal carcinoma

In a study of 86 colorectal carcinoma patients, increased expression (> 4th quartile) of YEATS4 correlated with decreased survival HR = 1.910, 95%

CI: 1.005-3.632, P = 0.048 (Tao et al., 2015).

One rearrangement involving YEATS4 was detected in a study of 95 rectal adenocarcinomas by RNA-seq analysis and recorded in the TUMOR FUSION

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GENE DATA PORTAL. The rearrangement is identical to that observed in hepatocellular adenocarcinoma, fusing YEATS4 exon 6 to the final (noncoding exon) of CPSF6 (Fig. 11). Thus, the predicted fusion protein contains a truncated YEATS4 coding sequence contain the YEATS domain, but lacking the C-terminal coiled coil domain.

Gastric Cancer

Quantitative real time reverse transcriptase PCR analysis of 30 Gastric cancers by Ji et al. (2017) detected increased expression of the YEATS4 transcript compared to normal adjacent tissue. 13% of samples showed decreased expression. Overexpression of YEATS4 mRNA and protein was associated with cancer stage, with highest expression observed in Stage III gastric cancer. Overall survival and disease-free survival was decreased with high expression of YEATS4 (Ji et al., 2017). The authors detected increased occupancy of the beta-catenin promoter by the YEATS4 protein, leading to histone acetylation and increased transcription of the beta catenin gene.

One case of a t(12;12)(q15;q15) fusing exon 6 of YEATS4 to exon 2 of the human lysozyme gene (LYZ) was identified from 414 cases in the Tumor Fusion Gene Data Portal. The resulting fusion protein contains the YEATS domain and the hydrolytic catalytic cleft of lysozyme. This rearrangement is identical to that detected in liver hepatocarcinoma cancer (see Fig. 10).

Hypertension

The SNP rs7297610, located between YEATS4 and FRS2, was associated with antihypertensive response to hydrochlorothiazide. Specifically, the C/C genotypes was associated with significant improvement in blood pressure in treated African Americans. Baseline YEATS4 expression was increased in peripheral blood of C/C genotype individuals, but decreased upon treatment with hydrochlorothiazide (Duarte et al., 2013).

Liposarcoma

Amplification and overexpression of YEATS4 occurs in liposarcomas (Italiano et al., 2008; Barretina et al., 2010; Creytens et al., 2015). In a study of 28 well-differentiated liposarcomas and 10 dedifferentiated liposarcomas, Italiano et al., (2008) subdivided the 12q13-15 amplicon into three independent amplicons. One amplicon, centered on MDM2 in 12q15 often contained YEATS4 with concomitant increased expression of the gene. A larger study of 77 lipomatous soft tissue tumors (including lipomas, well-differentiated liposarcomas (WDLPS), dedifferentiated liposarcomas (DDLPS) and pleomorphic liposarcomas) found that amplification of the YEATS4 gene was more frequent and at a higher level in dedifferentiated liposarcomas than in well-differentiated liposarcomas (Creytens et al., 2015). Knockdown of YEATS4 by shRNA in dedifferentiated liposarcoma independently reduced cell proliferation suggesting that YEATS4 acts as a driver gene within the 12q15 amplicon (Barretina et al., 2010).

Liver hepatocellular carcinoma

Two rearrangements involving YEATS4 have been detected in a study of 374 hepatocellular. carcinomas by RNA-seq analysis and recorded in the TUMOR FUSION GENE DATA PORTAL (2017). One case of a t(12;12)(q15;q15) fusing exon 6 of YEATS4 to exon 2 of the human lysozyme gene (LYZ) was identified. The resulting fusion protein contains the YEATS domain and the hydrolytic catalytic cleft of lysozyme (Fig. 10). This rearrangement is identical to that detected in stomach cancer (see below). The second rearrangement involves CPSF6 (cleavage and polyadenylation specific factor 6), located 101kb centromeric to YEATS4 (Fig. 1), and fuses exon 6 to the final, noncoding, exon of CPSF6 (Fig. 11). Thus, the fusion protein would be a truncated YEATS4 coding sequence containing the YEATS domain, but lacking the C-terminal coiled coil domain. The rearrangement is identical to that detected in rectal adenocarcinoma (see below).

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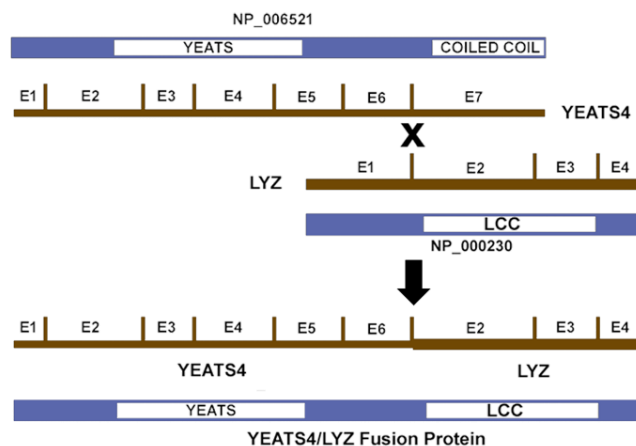


Fig. 10. Fusion between YEATS4 and LYZ, with a breakpoint located in intron 6 of YEATS4 and intron 2 of LYZ. The resulting fusion gene produces a fusion protein containing the YEATS domain and the Lysozyme catalytic cleft (LCC).

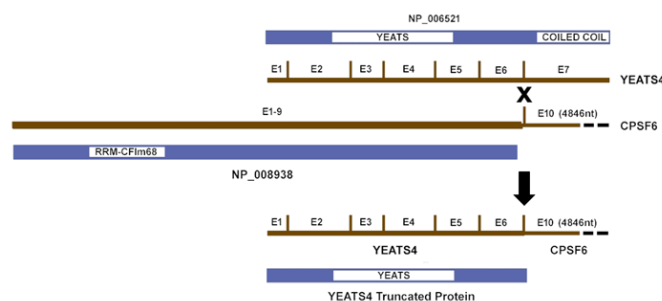


Fig. 11. The CPSF6 protein (NP_0008938) is coded by the first 9 exons of the CPSF6 transcript (NM_007007). CPSF6 has one conserved domain (RRM_CFIm68) defined as a 'RNA recognition motif of pre-mRNA cleavage factor Im 68 kDa subunit (CFIm68 or CPSF6) and similar protein'. The 4846 base pair tenth exon is untranslated, thus the fused hybrid gene produces a truncated YEATS4 protein.

Lung cancer

Pikor et al., (2015) performed gene expression and copy number analysis of 261 non-small cell lung cancers (NSCLC) relative to matched normal tissues. The 432 kb region encompassing LYZ to BEST3 (Fig. 1) (and RAB3IP located telomeric to BEST3) was amplified in 20% of the samples tested. Of the 7 genes within the amplicon, only YEATS4 was both gained/amplified and concomitantly overexpressed in lung tumors with YEATS4 amplified in 18% (47/261) and overexpressed in 31% (15/48) of tumor samples originally tested. YEATS4 copy gain/amplification was detected in an additional 43/128 (33.6%) lung cancer cell lines. YEATS4 was overexpressed in 18% (15/83) of the Early Detection Research Network samples and 33% (14/42) from the Cancer Genome Atlas. 3/83 tumors showed higher amplification of YEATS4 compared to the MDM2 protooncogene, that is the main

suspected driver of 12q15 amplification, suggesting that YEATS4 can provide an independent advantage over MDM2 in some lung cancers. The study validated overexpression of the YEATS4 protein in 15/59 (25.4%) tumors and 8/18 (44.4%) NSCLC cell lines. Knockdown of YEATS4 in cell lines containing YEATS4 amplification induced senescence and apoptosis in a p53/p21 mediated manner. Overexpression of YEATS4 increased resistance of normal bronchial epithelial cells to the platinum drug cisplatin and p53-MDM2 interaction inhibitor, nutlin (Pikor et al., 2015).

The TUMOR FUSION GENE DATA PORTAL (2017) reports one case of a t(12;12)(q15;q15) from 541 Lung adenocarcinomas, involving YEATS4 and SLC35E3. The rearrangement fuses YEATS4 (exon 4) to exon 4 of SLC35E3 resulting in part of the YEATS domain to 65 amino acids of the triose phosphate transporter domain (Fig. 12).

YEATS4 (YEATS domain containing 4)

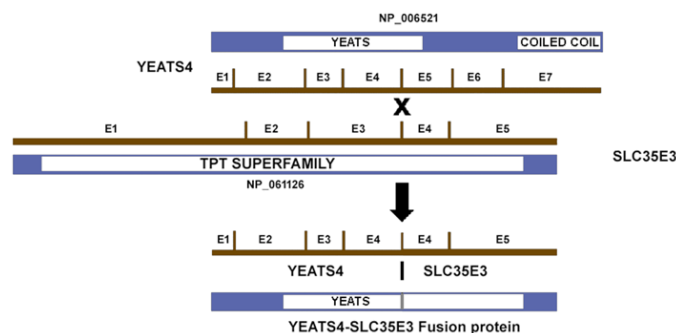


Fig. 12. In-frame fusion between YEATS4 and SLC35E3. SLC35E3 encodes a protein of 313 amino acids (NP_061126) and is identified as a member of the triose-phosphate transporter (TPT) family based upon a central 278 amino acid domain. The YEATS4-SLC35E3 fusion protein contains 111 amino acids of YEATS4 fused to 88 amino acids of the SLC35E3 protein containing the C-terminal 65 amino acids of the triose phosphate transporter domain.

Müllerian adenocarcinomas of the uterus

In an analysis of 15 uterine and one ovarian Müllerian adenocarcinomas, five cases showed amplification of a 900kb region stretching from SLC35E3 to BEST3, and thereby encompassing the YEATS4 locus on 12q15 (Lee et al., 2016).

Pancreatic cancer

YEATS4 transcript overexpression was noted in 31 pancreatic cancer samples relative to adjacent non-cancerous tissues (Jixiang et al., 2017). An expansion of this study to 93 pancreatic samples in the ONCOMINE database (Rhodes et al., 2004) further indicated clinical significance of YEATS4 expression in pancreatic cancer. Introduction of YEATS4 into a normal pancreatic epithelial cell lines promote growth invasion and motility. These effects were mediated, at least in part, by activation of the Wnt pathway and direct interaction with beta catenin (Jixiang et al., 2017).

Soft tissue Sarcomas (unclassified)

Five translocations were identified by Verhaak and colleagues from 263 Sarcomas and reported in the TUMOR FUSION GENE DATA PORTAL (2017). The adult sarcomas are unclassified in the National Cancer Institute Genomic Data Commons Data Portal. Each translocation fuses YEATS4 3' prime to its fusion partner.

One case t(1;12)(q21.3;q15) fuses the exon 4 of KCNN3 (potassium calcium-activated channel subfamily N member 3)(based on transcript NM_002249) in-frame to exon 2 of YEATS4. The fusion protein would be 740 amino acids long and contain the calcium-activated SK potassium channel

domain and part of the ion channel domain (pfam03530 and pfam07885) from KCNN3 and the YEATS4 YEATS domain and coiled coil domain (Fig. 13).

In a different tumor, another in-frame fusion occurs between exon 2 of MARCH9 on 12q14.1 and exon 2 of YEATS4 (Fig. 14). MARCH9 is a member of the MARCH family of membrane-bound E3 ubiquitin ligases. The fusion protein product is 380 amino acids long, containing the C4HC3 zinc-finger like RING domain and the YEATS4 YEATS domain and coiled coil domain.

The other three translocations observed fuse YEATS4 exon 7 out of frame 3-prime to its fusion partner, suggesting that these rearrangements produce a truncated protein lacking any YEATS4 components. One case of t(1;12)(q24.2;q15) fuses exon 16 of a coactivator of ligand-dependent nuclear receptors, DCAF6, to exon 7 of YEATS4 (Fig. 15). A truncated protein would contain the WD40 and c126247 (DNA polymerase III, delta subunit) domains involved in transcriptional regulation, but miss the final 200 amino acids of the coactivator. A single t(12;12)(q21.1;q15) fuses exon 1 of the THAP domain containing, apoptosis associated protein 2 (THAP2) out-of-frame to exon 7 of YEATS4. The "fusion" protein would also be truncated, and only contain the first 24 amino acids of the THAP2 protein, and 5 amino acids encoded out of frame from exon 7 of YEATS4 (Fig. 16). The last case noted was an out of frame fusion between exon 10 of TMTC1 and exon 7 of YEATS4 t(12;12)(p11.22;q15). If the truncated 564 amino acid 'fusion' protein is produced, it would lack the C-terminal tetrapeptide repeats of TMTC1 (Fig. 17).

YEATS4 (YEATS domain containing 4)

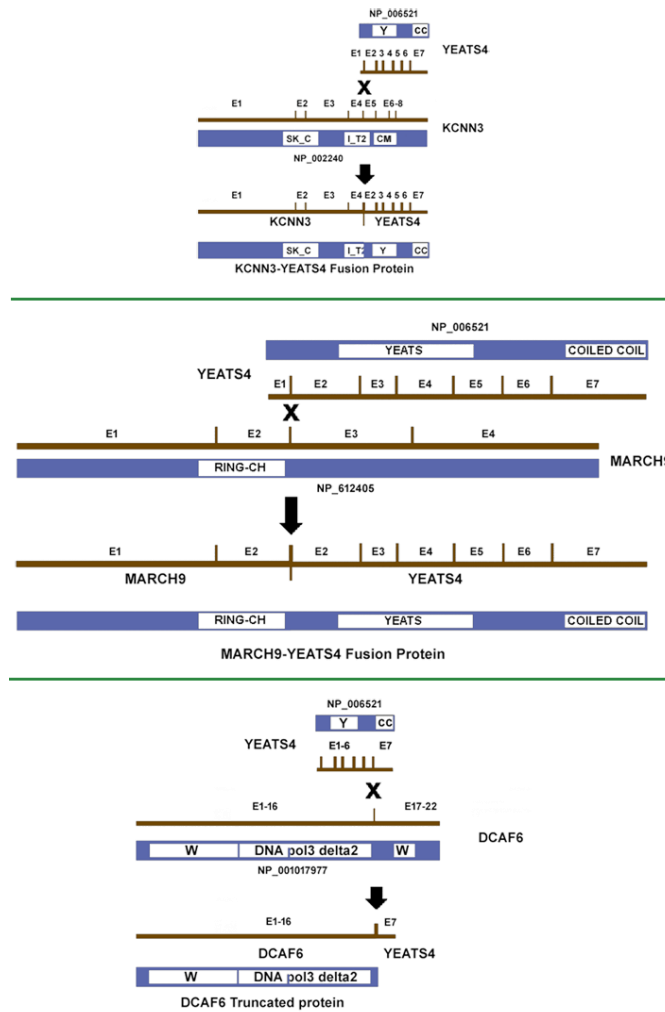


Fig. 13. In-frame fusion between KCNN3 and YEATS4. Exon numbering for KCNN3 is based upon transcript NM_002249 that codes for isoform a (NP_002240). Key: Y: YEATS domain; CC: coiled coil domain; SK_C: calcium-activated SK potassium channel domain; I_T2: Ion Transporter_2 (ion channel) domain; CM: Calmodulin binding domain; Grey box: Prefoldin super family domain structure.

Fig. 14. The MARCH9 gene contains 4 exons and encodes a transcript (NM_138396) of 2985 nucleotides, with a 5' untranslated region of 431 nucleotides and a 3' untranslated region of 1517 nucleotides. The full length MARCH9 protein is 346 amino acids long (NP_612405). The fusion between exon 2 of MARCH9 and exon 2 of YEATS4 could produce a fusion peptide of 380 amino acids.

Fig. 15. The DCAF6 gene contains 22 exons and encodes multiple alternatively splice transcripts. Protein Isoform b (NP_001017977) was selected as the canonical form by UniProtKB, coded by a transcript 2 (NM_001017977) of 3360 nucleotides, with a 5' untranslated region of 353 nucleotides and a 3' untranslated region of 1064 nucleotides. This transcript is missing exon 11, 12, and 17. W: WDR11 repeat region.

YEATS4 (YEATS domain containing 4)

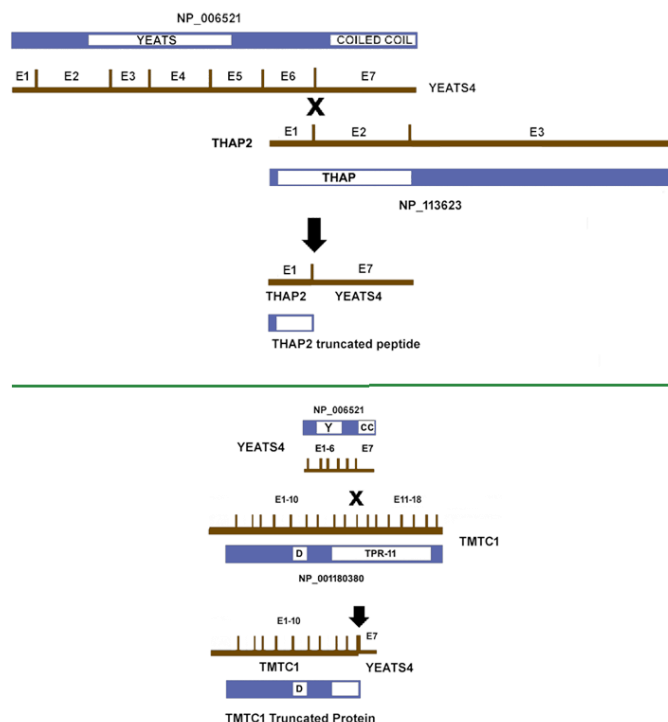


Fig. 16. The THAP2 gene contains 3 exons and encodes a transcript of 4840 nucleotides, with a 5' untranslated region of 613 nucleotides and a 3' untranslated region of 3959 nucleotides. The full length THAP2 protein is 228 amino acids long (NP_113623), containing the DNA binding THAP domain. The fusion between exon 1 of THAP2 and exon 7 of YEATS could produce a fusion peptide of only 29 amino acids in size.

Fig. 17. The TMTC1 mRNA is encoded by 18 exons and is 8.75kb long with a 3' untranslated region of 6.2kb.

The full length TMTC1 protein (NP_001180380) is 882 amino acid long and contains two domains: the DUF1736 (D) and the TPR-11 domain. The TMTC1-YEATS4 fusion gene would produce a 2468 nucleotide mRNA encoding 559 amino acids of TMTC1, missing the C-terminal 323 amino acid region containing most of the tetratricopeptide repeats of the TPR-11 domain.

References

- . GTEx Portal.
<https://gtexportal.org/home/gene/ENSG00000127337.2#geneExpression> accessed on 07/07/2017.
- Auger A, Galarnau L, Altaf M, Nourani A, Doyon Y, Utlej RT, Cronier D, Allard S, Cté J.. Eaf1 is the platform for NuA4 molecular assembly that evolutionarily links chromatin acetylation to ATP-dependent exchange of histone H2A variants. *Mol Cell Biol.* 2008; 28(7): 2257-2270.
- Bamford S, Dawson E, Forbes S, Clements J, Pettett R, Dogan A, Flanagan A, Teague J, Futreal PA, Stratton MR, Wooster R.. The COSMIC (Catalogue of Somatic Mutations in Cancer) database and website. *Br J Cancer.* 2004; 91: 355-358.
- Bargo S, Raafat A, McCurdy D, Amirjazi I, Shu Y, Traicoff J, Plant J, Vonderhaar BK, Callahan R.. Transforming acidic coiled-coil protein-3 (Tacc3) acts as a negative regulator of Notch signaling through binding to CDC10/Ankyrin repeats. *Biochem Biophys Res Commun.* 2010; 400(4): 606-12.
- Barretina J, Taylor BS, Banerji S, Ramos AH, Lagos-Quintana M, Decarolis PL, Shah K, Socci ND, Weir BA, Ho A, Chiang DY, Reva B, Mermel CH, Getz G, Antipin Y, Beroukhi R, Major JE, Hatton C, Nicoletti R, Hanna M, Sharpe T, Fennell TJ, Cibulskis K, Onofrio RC, Saito T, Shukla N, Lau C, Nelander S, Silver SJ, Sognnez C, Viale A, Winckler W, Maki RG, Garraway LA, Lash A, Greulich H, Root DE, Sellers WR, Schwartz GK, Antonescu CR, Lander ES, Varmus HE, Ladanyi M, Sander C, Meyerson M, Singer S.. Subtype-specific genomic alterations define new targets for soft-tissue sarcoma therapy. *Nat Genet.* 2010; 42: 715-721.
- Creytens D, Van Gorp J, Speel EJ, Ferdinande L.. Characterization of the 12q amplicons in lipomatous soft tissue tumors by multiplex ligation-dependent probe amplification-based copy number analysis. *Anticancer Res.* 2015; 35: 1835-1842.
- Debernardi S, Bassini A, Jones LK, Chaplin T, Linder B, de Bruijn DR, Meese E, Young BD.. The MLL fusion partner AF10 binds GAS41, a protein that interacts with the human SWI/SNF complex. *Blood* 2002; 99(1): 275-281.
- Ding X, Fan C, Zhou J, Zhong Y, Liu R, Ren K, Hu X, Luo C, Xiao S, Wang Y, Feng D, Zhang J.. GAS41 interacts with transcription factor AP-2beta and stimulates AP-2beta-mediated transactivation. *Nucleic Acids Res.* 2006; 34(9): 2570-2578.
- Duarte JD, Turner ST, Tran B, Chapman AB, Bailey KR, Gong Y, Gums JG, Langae TY, Beitelshes AL, Cooper-Dehoff RM, Boerwinkle E, Johnson JA.. Association of chromosome 12 locus with antihypertensive response to hydrochlorothiazide may involve differential YEATS4 expression. *Pharmacogenomics J.* 2013; 13(3): 257-263.
- Duff MO, Olson S, Wei X, Garrett SC, Osman A, Bolisetty M, Plocik A, Celniker SE, Graveley BR.. Genome-wide identification of zero nucleotide recursive splicing in *Drosophila*. *Nature* 2015; 521(7552): 376-379.
- Endo A, Moyori A, Kobayashi A, Wong RW.. Nuclear mitotic apparatus protein, NuMA, modulates p53-mediated transcription in cancer cells. *Cell Death Dis.* 2013; 4: e713.

YEATS4 (YEATS domain containing 4)

- Fagerberg L, Hallström BM, Oksvold P, Kampf C, Djureinovic D, Odeberg J, Habuka M, Tahmasebpoor S, Danielsson A, Edlund K, Asplund A, Sjöstedt E, Lundberg E, Szgyarto CA, Skogs M, Takanen JO, Berling H, Tegel H, Mulder J, Nilsson P, Schwenk JM, Lindskog C, Danielsson F, Mardinoglu A, Sivertsson A, von Feilitzen K, Forsberg M, Zwaalen M, Olsson I, Navani S, Huss M, Nielsen J, Ponten F, Uhlén M.. Analysis of the human tissue-specific expression by genome-wide integration of transcriptomics and antibody-based proteomics. *Mol Cell Proteomics* 2013; 13(2): 397-406.
- Fischer U, Heckel D, Michel A, Janka M, Hulsebos T, Meese E.. Cloning of a novel transcription factor-like gene amplified in human glioma including astrocytoma grade I. *Hum. Mol. Genet.* 1997; 6(11): 1817-22.
- Fischer U, Rheinheimer S, Krempler A, Löbrich M, Meese E.. Glioma-amplified sequence KUB3 influences double-strand break repair after ionizing radiation. *Int J Oncol.* 2013; 43: 50-56.
- Forbes SA, Beare D, Boutselakis H, Bamford S, Bindal N, Tate J, Cole CG, Ward S, Dawson E, Ponting L, Stefancsik R, Harsha B, Kok CY, Jia M, Jubb H, Sondka Z, Thompson S, De T, Campbell PJ.. COSMIC: somatic cancer genetics at high-resolution. *Nucleic Acids Res.* 2017; 45(D1): D777-D783.
- Frattini V, Trifonov V, Chan JM, Castano A, Lia M, Abate F, Keir ST, Ji AX, Zoppi P, Niola F, Danussi C, Dolgalev I, Porrati P, Pellegatta S, Heguy A, Gupta G, Pisapia DJ, Canoll P, Bruce JN, McLendon RE, Yan H, Aldape K, Finocchiaro G, Mikkelsen T, Privé GG, Bigner DD, Lasorella A, Rabadan R, Iavarone A.. The integrated landscape of driver genomic alterations in glioblastoma. *Nat Genet.* 2013; 45: 1141-1149.
- Gangisetty O, Lauffart B, Sondarva GV, Chelsea DM, Still IH.. The transforming acidic coiled coil proteins interact with nuclear histone acetyltransferases. *Oncogene* 2004; 23(14): 2559-63.
- Gergely F, Kidd D, Jeffers K, Wakefield JG, Kilmartin J, Raff JW.. D-TACC: a novel centrosomal protein required for normal spindle function in the early *Drosophila* embryo. *EMBO J.* 2000; 19(2): 241-252.
- Gupta GD, Coyaud J, Gonçalves J, Mojarad BA, Liu Y, Wu Q, Gheiratmand L, Comartin D, Tkach JM, Cheung SW, Bashkurov M, Hasegan M, Knight JD, Lin ZY, Schueler M, Hildebrandt F, Moffat J, Gingras AC, Raught B, Pelletier L.. A dynamic protein interaction landscape of the human centrosome-cilium interface. *Cell* 2015; 163(6): 1484-99.
- Guyot R, Vincent S, Bertin J, Samarut J, Ravel-Chapuis P.. The transforming acidic coiled coil (TACC1) protein modulates the transcriptional activity of the nuclear receptors TR and RAR. *BMC Mol Biol.* 2010; 11: 3.
- Harborth J, Weber K, Osborn M.. GAS41, a Highly Conserved Protein in Eukaryotic Nuclei, Binds to NuMA. *J. Biol. Chem.* 2000; 275(41): 31979-31985.
- Haren L, Gnadt N, Wright M, Merdes A.. NuMA is required for proper spindle assembly and chromosome alignment in prometaphase. *BMC Res Notes.* 2009; 2: 64.
- Hein MY, Hubner NC, Poser I, Cox J, Nagaraj N, Toyoda Y, Gak IA, Weisswange I, Mansfeld J, Buchholz F, Hyman AA, Mann M.. A human interactome in three quantitative dimensions organized by stoichiometries and abundances. *Cell* 2015; 163(3): 712-723.
- Heisel S, Habel NC, Schuetz N, Ruggieri A, Meese E.. The YEATS family member GAS41 interacts with the general transcription factor TFIIF. *BMC Mol Biol.* 2010; 11: 53.
- Hornbeck PV, Zhang B, Murray B, Kornhauser JM, Latham V, Skrzypek E.. PhosphoSitePlus, 2014: mutations, PTMs and recalibrations. *Nucleic Acids Res.* 2015; 43 (D1): D512-D520.
- Huttlin EL, Bruckner RJ, Paulo JA, Cannon JR, Ting L, Baltier K, Colby G, Gebreab F, Gygi MP, Parzen H, Szpyt J, Tam S, Zarraga G, Pontano-Vaites L, Swarup S, White AE, Schweppe DK, Rad R, Erickson BK, Obar RA, Guruharsha KG, Li K, Artavanis-Tsakonas S, Gygi SP, Harper JW.. Architecture of the human interactome defines protein communities and disease networks. *Nature* 2017; 545(7655): 505-509.
- Italiano A, Bianchini L, Keslair F, Bonnafous S, Cardot-Leccia N, Coindre JM, Dumollard JM, Hofman P, Leroux A, Mainguené C, Peyrottes I, Ranchere-Vince D, Terrier P, Tran A, Gual P, Pedeutour F.. HMGA2 is the partner of MDM2 in well-differentiated and dedifferentiated liposarcomas whereas CDK4 belongs to a distinct inconsistent amplicon. *Int J Cancer* 2008; 122(10): 2233-41.
- Ji S, Zhang Y, Yang B.. YEATS domain containing 4 promotes gastric cancer cell proliferation and mediates tumor progression via activating the Wnt/ β -catenin signaling pathway. *Oncol Res. E-pub* March 2, 2017.
- Jixiang C, Shengchun D, Jianguo Q, Zhengfa M, Xin F, Xuqing W, Jianxin Z, Lei C.. YEATS4 promotes the tumorigenesis of pancreatic cancer by activating beta-catenin/TCF signaling. *Oncotarget* 2017; 8(15): 25200-25210.
- Lauffart B, Gangisetty O, Still IH.. Molecular cloning, genomic structure and interactions of the putative breast tumor suppressor TACC2. *Genomics* 2003; 81(2): 192-201.
- Le Masson I, Yu DY, Jensen K, Chevalier A, Courbeyrette R, Boulard Y, Smith MM, Mann C.. Yaf9, a novel NuA4 histone acetyltransferase subunit, is required for the cellular response to spindle stress in yeast. *Mol Cell Biol.* 2003; 23(17):6086-6102.
- Lee JC, Lu TP, Changou CA, Liang CW, Huang HN, Lauria A, Huang HY, Lin CY, Chiang YC, Davidson B, Lin MC, Kuo KT.. Genomewide copy number analysis of Müllerian adenocarcinoma identified chromosomal instability in the aggressive subgroup. *Mod Pathol.* 2016; 29: 1070-1082.
- Leon A, Omri B, Gely A, Klein C, Crisanti P.. QN1/KIAA1009: a new essential protein for chromosome segregation and mitotic spindle assembly. *Oncogene* 2006; 25(13): 1887-1895.
- Li X, Wang W, Wang J, Malovannaya A, Xi Y, Li W, Guerra R, Hawke DH, Qin J, Chen J.. Proteomic analyses reveal distinct chromatin-associated and soluble transcription factor complexes. *Mol Syst Biol.* 2015; 11(1): 775.
- Llanos S, Efeyan A, Monsech J, Dominguez O, Serrano M.. A high-throughput loss-of-function screening identifies novel p53 regulators. *Cell Cycle* 2006; 5(16): 1880-1885.
- Munnia A, Schütz N, Romeike BFM, Maldener E, Glass B, Maas R, Nastainczyk W, Feiden W, Fischer U, Meese E.. Expression, cellular distribution and protein binding of the glioma amplified sequence (GAS41), a highly conserved putative transcription factor. *Oncogene* 2001; 20: 4853-4863.
- Ohata H, Miyazaki M, Otomo R, Matsushima-Hibiya Y, Otsubo C, Nagase T, Arakawa H, Yokota J, Nakagama H, Taya Y, Enari M.. NuMA is required for the selective induction of p53 target genes. *Mol Cell Biol.* 2013; 33(12): 2447-2457.
- Park JH, Roeder RG.. GAS41 is required for repression of the p53 tumor suppressor pathway during normal cellular proliferation. *Mol Cell Biol.* 2006; 26(11): 4006-4016
- Park JH, Smith RJ, Shieh SY, Roeder RG.. The GAS41-PP2C β complex dephosphorylates p53 at serine 366

YEATS4 (YEATS domain containing 4)

- and regulates its stability. *J Biol Chem.* 2011; 286(13): 10911-10917
- Piccinni E, Chelstowska A, Hanus J, Widlak P, Loreti S, Tata AM, Augusti-Tocco G, Bianchi MM, Negri R.. Direct interaction of Gas41 and Myc encoded by amplified genes in nervous system tumours. *Acta Biochim Pol.* 2011; 58(4): 529-34.
- Pikor LA, Lockwood WW, Thu KL, Vucic EA, Chari R, Gazdar AF, Lam S, Lam WL.. YEATS4 is a novel oncogene amplified in non-small cell lung cancer that regulates the p53 pathway. *Cancer Res.* 2013; 73(24): 7301-7312.
- Rhodes DR, Yu J, Shanker K, Deshpande N, Varambally R, Ghosh D, Barrette T, Pandey A, Chinnaiyan AM.. ONCOMINE: a cancer microarray database and integrated data-mining platform. *Neoplasia* 2004; 6: 1-6.
- Sadek CM, Jalaguier S, Feeney EP, Aitola M, Damdimopoulos AE, Pelto-Huikko M, Gustafsson JA.. Isolation and characterization of AINT: a novel ARNT interacting protein expressed during murine embryonic development. *Mech Dev.* 2000; 97(1-2): 13-26.
- Schmitt J, Fischer U, Heisel S, Strickfaden H, Backes C, Ruggieri A, Keller A, Chang P, Meese E.. GAS41 amplification results in overexpression of a new spindle pole protein. *Genes Chromosomes Cancer* 2012; 51(9): 868-880.
- Schulze JM, Wang AY, Kobor MS.. Reading chromatin. Insights from yeast into YEATS domain structure and function *Epigenetics* 2010; 5(7): 573-577.
- Shah N, Lankerovich M, Lee H, Yoon JG, Schroeder B, Foltz G.. Exploration of the gene fusion landscape of glioblastoma using transcriptome sequencing and copy number data. *BMC Genomics* 2013; 14: 818.
- Simpson RJ, Yi Lee SH, Bartle N, Sum EY, Visvader JE, Matthews JM, Mackay JP, Crossley M.. A classic zinc finger from friend of GATA mediates an interaction with the coiled-coil of transforming acidic coiled-coil 3. *J Biol Chem.* 2004; 279(38): 39789-97.
- Tao K, Yang J, Hu Y, Deng A.. Knockdown of YEATS4 inhibits colorectal cancer cell proliferation and induces apoptosis. *Am J Transl Res.* 2015; 7(3): 616-623.
- Verhaak RG, and co-workers.. TUMOR FUSION GENE DATA PORTAL <http://54.84.12.177/PanCanFusV2> accessed 7/13/2017.
- Vettaikorumakankauv AKLB, Gangisetty O, Cincotta MA, Hawthorne LA, Cowell JK, Still IH.. The TACC proteins are coregulators of the retinoid-X-Receptor ?. *Cancer Therapy.* 2008; 6: 805-816.
- Wang YL, Faiola F, Xu M, Pan S, Martinez E.. Human ATAC Is a GCN5/PCAF-containing acetylase complex with a novel NC2-like histone fold module that interacts with the TATA-binding protein. *J Biol Chem.* 2008; 283(49): 33808-33815.
- Yoshihara K, Wang Q, Torres-Garcia W, Zheng S, Vegesna R, Kim H, Verhaak RG.. The landscape and therapeutic relevance of cancer-associated transcript fusions. *Oncogene* 2015; 34: 4845-4854.
- Zeng X, Neupert W, Tzagoloff A.. The metalloprotease encoded by ATP23 has a dual function in processing and assembly of subunit 6 of mitochondrial ATPase. *Mol Biol Cell* 2007; 18: 617-626.
- Zheng S, Fu J, Vegesna R, Mao Y, Heathcock LE, Torres-Garcia W, Ezhilarasan R, Wang S, McKenna A, Chin L, Brennan CW, Yung WK, Weinstein JN, Aldape KD, Sulman EP, Chen K, Koul D, Verhaak RG.. A survey of intragenic breakpoints in glioblastoma identifies a distinct subset associated with poor survival. *Genes Dev.* 2013; 27: 1462-1472.
-
- This article should be referenced as such:*
- Still IH, Lauffart B. YEATS4 (YEATS domain containing 4). *Atlas Genet Cytogenet Oncol Haematol.* 2018; 22(7):263-277.
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