Cellular and Molecular Life Sciences (2022) 79:183
https://doi.org/10.1007/s00018-022-04218-0

REVIEW

Multifaceted roles of YEATS domain-containing proteins and novel links to neurological diseases

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Received: 17 November 2021 / Revised: 17 February 2022 / Accepted: 22 February 2022

Abstract

The so-called Yaf9, ENL, AF9, Taf14, and Sas5 (YEATS) domain-containing proteins, hereafter referred to as YD proteins, take control over the transcription by multiple steps of regulation either involving epigenetic remodelling of chromatin or guiding the processivity of RNA polymerase II to facilitate elongation-coupled mRNA 3′ processing. Interestingly, an increasing amount of evidence suggest a wider repertoire of YD protein's functions spanning from non-coding RNA regulation, RNA-binding proteins networking, post-translational regulation of a few signalling transduction proteins and the spindle pole formation. However, such a large set of non-canonical roles is still poorly characterized. Notably, four paralogous of human YEATS domain family members, namely eleven-nineteen-leukaemia (ENL), ALL1-fused gene from chromosome 9 protein (AF9), YEATS2 and glioma amplified sequence 41 (GAS41), have a strong link to cancer yet new findings also highlight a potential novel role in neurological diseases. Here, in an attempt to more comprehensively understand the complexity of four YD proteins and to gain more insight into the novel functions they may accomplish in the neurons, we summarized the YD protein's networks, systematically searched and reviewed the YD genetic variants associated with neurodevelopmental disorders and finally interrogated the model organism *Drosophila melanogaster*.

Keywords YEATS domain · Epigenetic regulation · Neurological diseases · *Drosophila melanogaster*

Introduction

Cells deploy a multitude of different transcriptional regulatory proteins and orchestrate them to accomplish the fine regulation of gene expression. Due to the packaging of DNA into chromatin, the activity of an array of diverse remodellers with the ability to read and write the specific histone marks (i.e. methylation, acetylation, and others) is required to restructure nucleosomes and thus regulate the dynamic access of transcriptional factors to DNA.

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Published online: 12 March 2022

Bromodomain (BRD) has long been thought to be the sole protein module that specifically recognises acetyl-lysine motifs which are enriched in transcriptionally active chromatin [1]. However, it is now clear that also the Yaf9 ENL AF9 Taf14, and Sas5 (YEATS) domain of the so-called YEATS domain containing (YD) proteins, specifically binds to acetylated histone H3 lysine 9/18/27 marks (H3K9/18/27ac) and varies from BRD for its additional ability to read non-acetyl acylation of histone lysine, including crotonylation, butyrylation, propionylation [2–13].

The YEATS domain is highly conserved in more than 100 proteins from over 50 organisms, with eleven-nineteen-leukaemia (ENL), ALL1-fused gene from chromosome 9 protein (AF9) and glioma amplified sequence 41 (GAS41) (also known as mixed-lineage leukaemia translocated to 1 (MLLT1), MLLT3 and YEATS4, respectively) being the best characterized in humans [14, 15]. Notably, the aromatic sandwich pocket in the YEATS domain of YEATS2, another human YD protein, is unique among others in terms of the pocket residues and aromatic stacking contributing substantially to its preferential acyl-lysine readout [6, 16].

Overall, the YD proteins involve diverse fundamental steps of gene transcription regulation serving not only as epigenetic marks readers but also as a hub of transcriptionally active chromatin for multiple transcriptional regulators, including the histone-lysine N-methyltransferase, H3 lysine-79 specific (DOT1L) as well as a few complexes such as the ALL1-fused gene from chromosome 4 protein (AF4), ENL, positive transcription elongation factor (P-TEFb) also known as AEP complex and the Polycomb repressive complex 1 (PRC1) [17–19]. Moreover, much evidence also pointed out the mechanistic roles of YD proteins in regulating gene transcription by driving the assembly and modulating the function of Super Elongation Complex (SEC) among others [20].

Given such a critical role in transcription regulation, it is not surprising that human YEATS domain family members have a strong link to cancer. For instance, GAS41 is amplified in glioblastoma and astrocytoma and either ENL or AF9 is known to be the most frequent translocation partner of the mixed lineage leukaemia (MLL) gene [21–23]. However, new evidence yet largely unexplored may link a loss of function of the YD proteins to abnormal neuronal differentiation, thus suggesting a role also in neurological diseases [24].

Here, we summarized the major contribution of YD proteins in gene transcription and discussed their emerging roles with a particular emphasis on the functions that the YD proteins may accomplish in neurons. We aimed to create a novel framework that can help to understand the complexity of YD proteins more comprehensively. To gain more insight into such a novel paradigm of regulation, we also interrogated the model organism *Drosophila melanogaster* which the dysfunction of a few YD orthologs also suggests a similar novel link to neurological disorders.

Functions of YD proteins in epigenetic regulation

The YD protein serves as a histone acylated reader of various chromatin remodelling complex, thereby playing a role in regulating gene expression at the chromatin level. Four YD paralogous in humans, namely ENL, AF9, YEATS2, and GAS41, not only prefer distinct histone lysine positions but also reside in different chromatin associated complexes, consequently inferring their impact on subsequent epigenetic changes responsible for chromatin accessibility.

Upon binding with specific monoacetylated histone H3 via the YEATS domain, the C-terminal domain (CTD) of ENL, AF9, and YEATS2 interacts with partner proteins belonging to histone-modifying complexes that function to open the chromatin. ENL and AF9 form distinct Dot1L-containing multisubunit complex (DotCom) through the association with the histone methyltransferase DOT1L, which in turn methylates the histone H3K79 to induce local chromatin opening and sustain transcription (Fig. 1a) [10, 25]. In contrast, YEATS2 prompts gene transcription activation by the recruitment of the conserved histone acetyltransferase (HAT) complex named Ada-two-A-containing (ATAC) complex that is capable to regulate histone acetylation and maintain an active chromatin state (Fig. 1b) [10, 11, 25, 26]

The ENL/AF9-targeted gene regulation has also been linked to a multisubunit complex involved in chromatin compaction named PRC1. In response to DNA damage, either ENL or AF9 is phosphorylated at a well-conserved SQ site by the master kinase Ataxia-telangiectasia mutated (ATM). The modified ENL/AF9 next recruits PRC1 onto H2A and guides the ubiquitylation of H2A to induce transcriptional repression and DNA repair (Fig. 1c) [27, 28].

Distinct from other YD paralogous that modified histone tails, GAS41 has been described as a common component of the SNF2-related CBP activator protein (SRCAP)-contained remodelling complex, termed SRCAP complex and 60 kDa Tat-interactive protein/E1A-binding protein p400 (TIP60/p400) which are the complexes with abilities to control H2A histone exchange (Fig. 1d). The Gas41-mediated H2A.Z deposition regulates chromatin dynamics and contributes to either active or repressive transcription, depending on its location in specific chromatin regions (Fig. 1d) [12, 29, 30]. Moreover, GAS41 is likely the only YD protein that forms homodimer via the C-terminal coiled-coil domain and its YEATS domain can recognise the diacyl-lysine histone marks (Fig. 1e) [31], implying the specific targeted genes and unique biological functions of Gas41. Nevertheless,

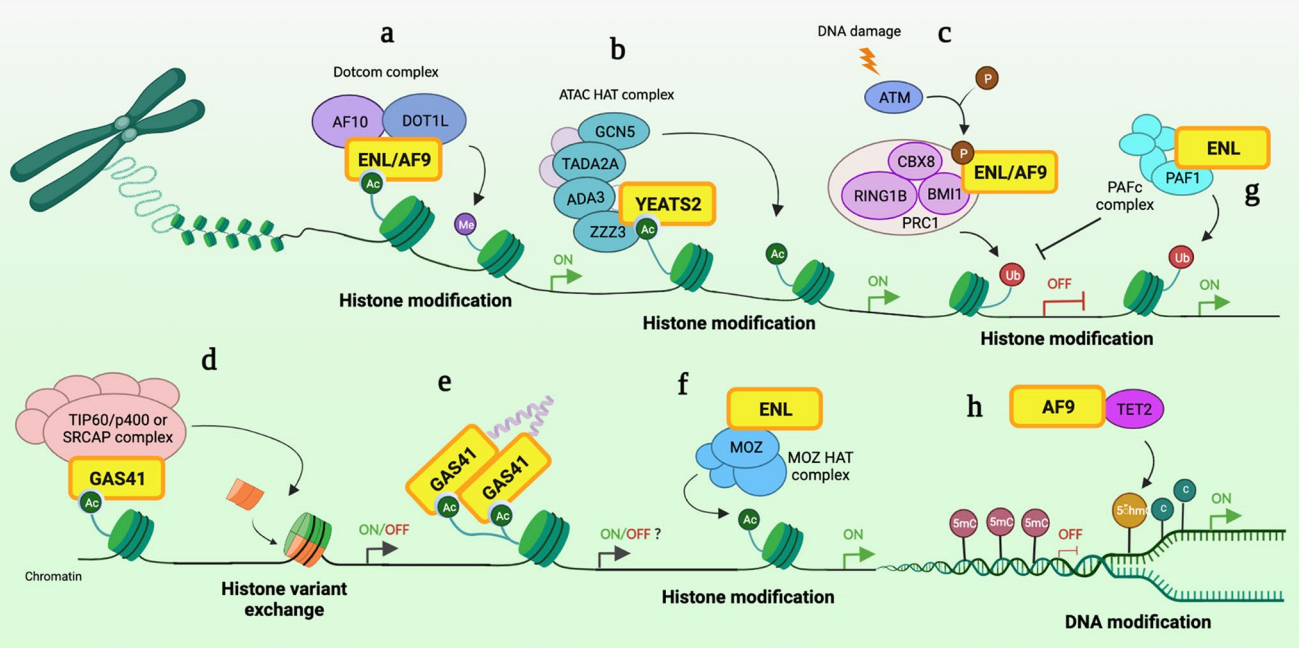


Fig. 1 Functions of YD proteins in epigenetic regulation. **a** Either ENL or AF9 (ENL/AF9) recognises the modified histone H3 tails via the well conserved YEATS domain and its C-terminal ANC1 Homology Domain (AHD) interacts with AF10 and histone methyltransferase DOT1L, which the latter eventually methylates the histone H3 to induce local chromatin opening. **b** YEATS2 serves as a selective histone reader of conserved histone acetyltransferase (HAT) complexes, named the Ada-two-A-containing (ATAC) complex that contains the transcriptional cofactors GCN5, TADA2A, ADA3, and ZZZ3. The recognition of specific histone marks by its YEATS domain is needed to recruit the ATAC complex to the chromatin and maintain ATAC-mediated histone H3 acetylation. **c** The ATM kinase phosphorylates ENL/AF9 at SQ site in response to DNA damage. This phosphorylation prompts ENL/AF9 to interact with BMI1 (a subunit of PRC1 complex that also contains RINGB and CBX8) and recruits the PRC1 complex to ubiquitinate histone H2A, leading to the closed, inactive chromatin. **d** GAS41 resides in either TIP60/p400 or SRCAP complexes that control the gene expression by exchanging the canonical histone H2A for the H2A.Z variant in specific chromatin regions. **e** GAS41 can form homodimer via the C-terminal coiled-coil domain and its YEATS domain recognises the diacyl-lysine histone H3 marks. **f** The ENL YEATS domain interacts with MOZ HAT complex that acetylates the histone H3 at the promotor of actively transcribed genes. **g** Polymerase-associated factor 1 (PAF1), a component of a promoter associating factor complex (PAFc), mechanistically competes with acetylated histone H3 in binding with the YEATS domain of ENL. This association contributes to the hypo-ubiquitylation of histone H2A and hyper-ubiquitylation of H2B, then overcoming PRC1-induced transcriptional repression and inducing the opening of chromatin, respectively. **h** By binding with the C-terminal catalytic domain of 5-methylcytosine (5mC) dioxygenase TET2, AF9 recruits TET2 to occupy the C-rich DNA regions and converse 5mC to 5-hydroxymethylcytosine (5hmC), subsequently allowing the specific targeted gene activation. The figure was created using ©BioRender (https://biorender.com)

whether this complex is required for gene activation is still not clear.

Although the YEATS domain has a preference for certain histone H3 acylation, a few pieces of evidence showed that it retains some acyl-lysine independent binding abilities that enhance the YD functions as positive regulators of transcription. Recently, the YEATS domain of ENL has been reported to interact with the HAT complex monocytic leukaemia zinc finger protein (MOZ) and the polymerase-associated factor 1 (PAF1) (Fig. 1f, g) [32–34]. In particular, it was shown that the association between the ENL YEATS domain and PAF1 contributes to either hypo or hyper-ubiquitylation of histone H2A and H2B (Fig. 1g), respectively, and has two profound effects on gene transcription by increasing the accessibility of chromatin to transcriptional factors and by inhibiting PRC1-induced transcriptional repression [35–37]. These findings add to the evidence on the functions of YD protein in terms of chromatin remodellers and illustrate the anti-repressive properties of ENL that contribute to transcription activation in an acetyl/acyl-lysine independent manner.

Remarkably, AF9 is also capable of physically interacting with the carboxyterminal catalytic domain of Tet Methylcytosine Dioxygenase 2 (TET2) through its CTD [24], thus serving not only as histone modifier but also to methylate DNA (Fig. 1h). Mechanistically, AF9 interacts and guides TET2 to specific gene loci where a conversion of 5-methylcytosine (5mC) to 5-hydroxymethylcytosine (5hmC) eventually triggers the activation of an array of targeted genes [24]. Such evidence provides additional context for the epigenetic regulatory functions of the YD protein, beyond the well-described mechanisms mainly related to histone modification.

Functions of YD proteins in the context of general transcription machinery

The chromatin remodelling is an intrinsic process towards the regulation of gene expression that factors involving the nucleosome dynamics are naturally linked to the activity of transcription machinery. Likewise, YD proteins often function as a bridge between chromatin remodellers and transcriptional factors; thus the gene expression regulation of their targets can be seen as result of a joined action of epigenetic mark's reading and RNA polymerase II (RNAPII) processivity. Just for simplicity, in this chapter, we summarized a few of YD proteins' activities that seem to mainly occur in the context of the general transcription machinery.

Recent findings have shown that an intrinsically disordered region of ENL triggers the liquid–liquid phase separation (LLPS) of P-TEFb (Fig. 2a), thus permitting the rapid assembly and action of the SEC (Fig. 2b) [38]. Similar to ENL, the YEATS domain of AF9 is capable of binding to a promoter associating factor complex (PAFc) in a fashion that recruits SEC on elongating Pol II (RNAPII) at a specific chromatin template (Fig. 2b) [20]. Therefore, both ENL and AF9 drive the positioning of SEC next to RNAPII and allow SEC to synergistically stimulate the processivity of RNAPII, thus facilitating elongation-coupled mRNA 3′ processing (Fig. 2b).

The study of transcriptional elongation in specific cellular stress conditions, such as those driven by MLL-fusion oncoproteins, and HIV-1 trans-activator protein Tat, has greatly contributed to our understanding of transcription elongation by RNAPII and the roles of YD associating proteins like AF9 and ENL [39, 40]. For instance, SEC, which contains transcription elongation activators/coactivators P-TEFb, RNA polymerase II elongation factor ELL2, AFF4/1, ENL, and AF9, is also recruited by HIV-1 Tat to activate the expression of HIV-1 (Fig. 2c). In this context, both AF9 and ENL have been found to interact with Tat to form the Tat complex 1 (Tatcom1) containing both PAFc and P-TEFb, among others (Fig. 2c). Here, AF9 plays at least two fundamental roles that have a profound effect on transcription elongation, including the regulation of CDK9/P-TEFb kinase activity and the recruitment of ELL to Tatcom1. Notably, while P-TEFb regulates RNAPII processivity through phosphorylation of CTD at Ser2, ELL is known to

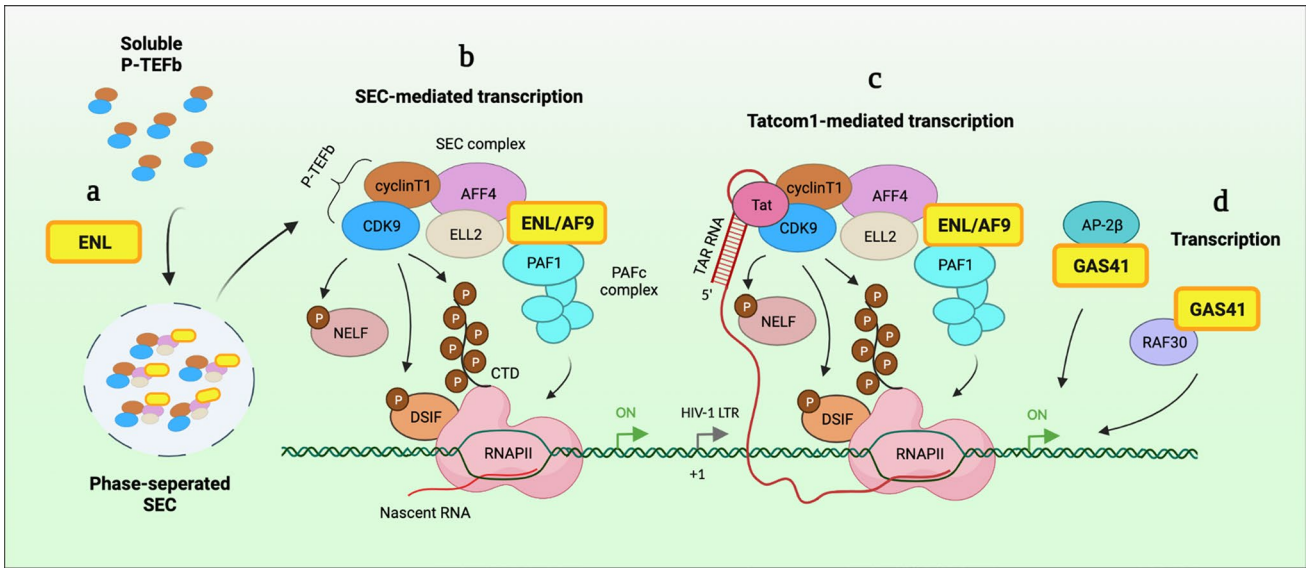


Fig. 2 Functions of YD proteins in the context of the general transcription machinery. **a** ENL guides the liquid–liquid phase separation (LLPS) of the positive transcription elongation factor b (P-TEFb), consisting of CDK9 and cyclin T, to form the super elongation complex (SEC) that also contains AFF4 and ELL2. **b** As a part of SEC, P-TEFb phosphorylates negative elongation factor (NELF), DRB sensitivity-inducing factor (DSIF) and the C-terminal domain (CTD) of RNA polymerase II (RNAPII) at serine 2. Under these phosphorylation events, NELF loses its ability to interact with RNAPII and DSIF becomes a positive elongation factor, thereby promoting the release of paused RNAPII into productive elongation. Besides, either ENL or AF9 (ENL/AF9) bind to a subunit of promoter associating factor complex (PAFc) PAF1 via its YEATS domain in a mutually exclusive manner, driving SEC to locate adjacent to RNAPII and then allowing the processivity of RNAPII. **c** ENL/AF9 is a component of multiprotein complex linked to transcriptional elongation from HIV-1 promotor long terminal repeat (LTR), named Tat complex 1 (Tatcom1). Shortly after promoter-proximal pausing of RNAPII, HIV-1 produces short RNA transcript TAR and encodes Tat protein to bind with host cellular SEC complex. In this setting, AF9 possesses great impacts on transcription elongation by regulating CDK9 CTD-kinase activity and engaging ELL2 to reside in Tatcom1. **d** GAS41 directly interacts with transcription factors, including AP-2β and a TFIIF subunit RAP30, and then enhances their DNA binding abilities. The figure was created using ©BioRender (https://biorender.com)

stimulate RNAPII activity by suppressing transient pausing and preventing backtracking [39, 41–43]. As a result, the recruitment of PAFc by either ENL or AF9 not only contributes to the transcription activation but also guides the transcription elongation via SEC (Fig. 2b).

Finally, functional characterization of AF9 domains collectively revealed the pivotal role of AF9 in gene transcription regulation as follows: the C-terminal ANC1 Homology Domain (AHD) domain mediates its incorporation into the SEC through interactions with AF4 or AFF4 [23, 44, 45]; the N-terminal YEATS domain interacts with both the histone acetylation and crotonylation marks [4, 6, 10] and PAFc [20] to facilitate SEC recruitment and RNAPII-mediated transcription events; the poly-Serine domain interacts with distinct TATA-binding protein (TBP)-associated factors (TAFs) subunits of transcription factor IID (TFIID) for the release of paused Pol II for productive elongation [46].

Other studies have shown that GAS41 can also play critical roles in the regulation of gene transcription by directly binding a few transcription factors. For instance, in vitro and in vivo assays revealed that GAS41 direct binds to either activating enhancer-binding protein 2-beta (AP-2β) or a TFIIF subunit named RAP30 and contributes to enhancing the DNA binding abilities of those transcription factors (Fig. 2d) [47, 48]. Given the TFIIF has critical functions in the pre-initiation complex formation, it is likely that GAS41 might exert a more general action in gene transcription.

Extra-transcriptional functions of YD proteins

Even though the epigenetic regulation of gene transcription has been known to be a common role of all human YD proteins, a few studies suggested that the YD proteins harbour extra-transcriptional functions, including the regulation of a few cell signalling networks. Besides, the association with non-histone proteins provides clues for additional features of the YD proteins involving crucial biological processes in the cells.

Evidence for the alternative roles of the YD protein on signal transduction stem from GAS41 that can modulate the p53-p21 pathway. GAS41 forms a heterodimer with protein phosphatase 2 catalytic subunit beta (PP2Cβ) and leads to the PP2Cβ-mediated dephosphorylation of serine residue on p53, subsequently reducing the stability of p53 (Fig. 3a) [49]. This finding is consistent with previous studies showing that GAS41 serves as a negative regulator of the p53-p21 pathway through the downregulation of either p53 or p21 expression [50, 51]. Additionally, GAS41 also promotes the phosphorylation of Akt and leads to a reduction of p21 (Fig. 3b) [52], suggesting a critical role of GAS41 in controlling such intracellular signalling.

There is also some evidence for the YD proteins being involved in Wnt signalling pathway. By direct binding with β-catenin, GAS41 not only enhances the interaction between β-catenin and T cell-factor 4 (TCF4) but also induces the expression of several downstream targets of the canonical Wnt/β-catenin/TCF4 pathway (Fig. 3c) [53]. On the other hand, AF9 associates with Diversin in the nucleus and prompts Diversin to activate transcriptional response in the non-canonical Wnt/c-Jun N-terminal Kinase (JNK) signalling pathway (Fig. 3d) [54].

Despite being a nuclear protein, AF9 is able to concentrate in the cytoplasm under perturbation of its chaperone protein HSP90 (Fig. 3e) [55]. The impaired HSP90 causes changes in either the localization or DNA-binding activity of AF9 (Fig. 3e) [55], indicating the mechanism controlling subcellular trafficking and action of the YD protein. In addition to mainly acting as the histone reader, previous studies speculated that AF9 possesses some properties related to RNA processing, such as microRNA (miRNA) maturation and small nucleolar RNA (snoRNA) formation, which is retained in MLL fusions [56, 57]. AF9 activates MYC/LIN28 axis and eventually inhibits precursor miRNA-150 (pre-miR-150) from being cleaved in the cytoplasm to create mature miRNA (Fig. 3f) [56], whereas the molecular mechanism underlying AF9-associated snoRNA formation in the nucleus is incompletely characterized [57]. Otherwise, these data demonstrate the involvement of the YD protein in the post-transcriptional regulation of non-coding RNAs.

Of note, GAS41 has been described as one of the spindle pole proteins [58]. During cell mitosis, GAS41 distributes to the spindle poles where it especially interacts with pericentrosomal material (PCM), including transforming acidic coiled-coil-containing protein 1 (TACC1), nuclear mitotic apparatus protein 1 (NuMA), α-tubulin and γ-tubulin (Fig. 3g) [58–60]. It has been proposed that the alteration of GAS41 expression provokes either abnormal spindle assembly or chromosome misalignment [58], implying that the YD protein plays a fundamental role in spindle pole formation. However, to better understand its influences on establishing proper bipolar spindle, the downstream players of GAS41 have yet to be clarified.

Genetic variations of YEATS-domain-containing genes and associated human phenotypes

Dysfunctional YD proteins have been demonstrated as a factor driving the development of several diseases, especially cancers [15]. Remarkably, ENL positively regulates the gene transcription at various levels as mentioned above by either complexing with chromatin remodellers at specific histones markers or joining transcription elongation

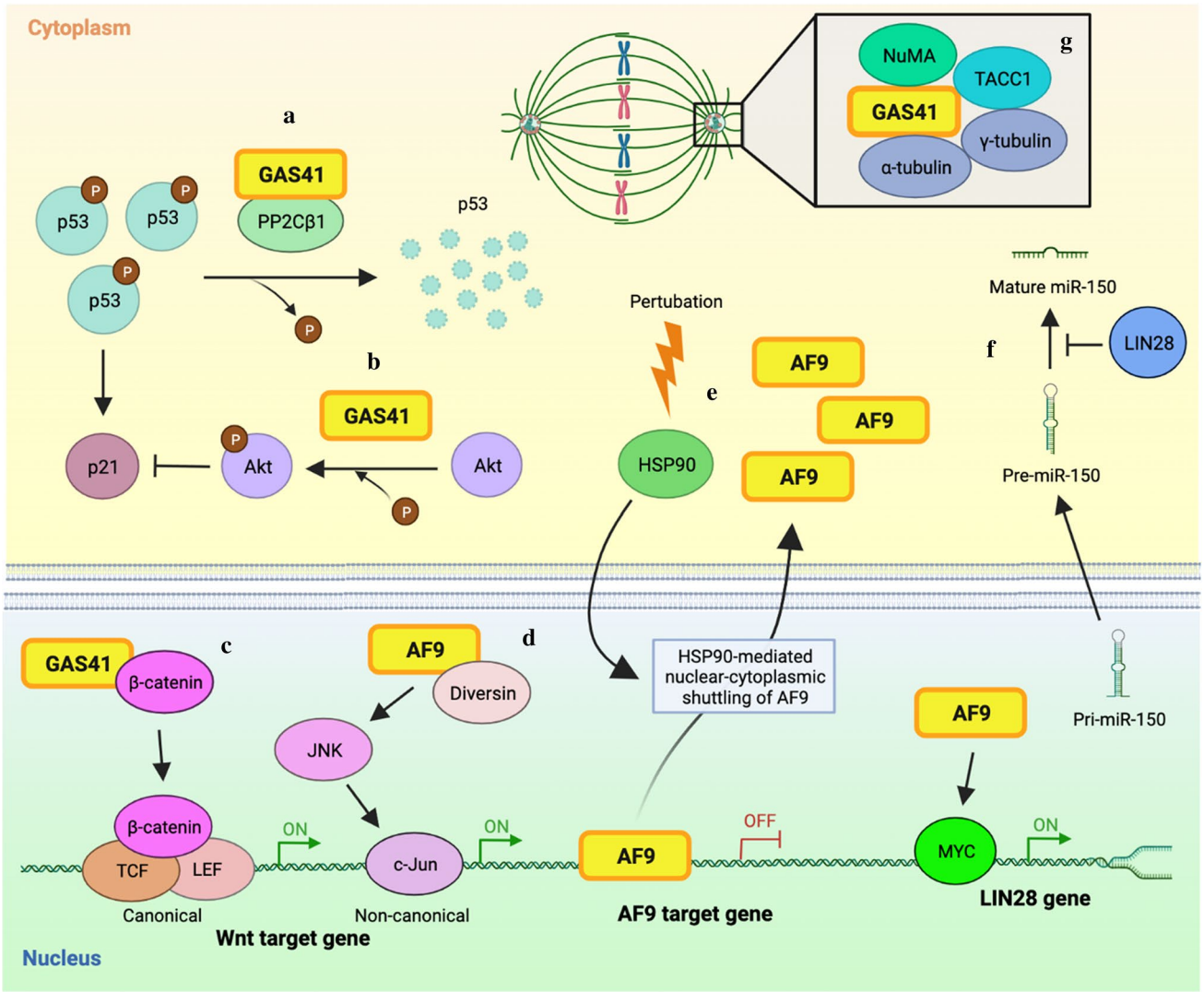


Fig. 3 Extra-transcriptional functions of YD proteins. **a** GAS41 binds to protein phosphatase 2 catalytic subunit beta (PP2Cβ) which in turn dephosphorylates p53 at serine residue, resulting in the reduction of p53 stability. **b** GAS41 induces the phosphorylation activation of Akt which then contributes to the low production of p21. **c** By physically binding with β-catenin, GAS41 promotes the β-catenin-T-cell factor/lymphoid enhancer factor (TCF/LEF) interaction and upregulates the expression of canonical Wnt target genes. **d** AF9 modulates the transcriptional activation of the non-canonical Wnt/c-Jun N-terminal Kinase (JNK) target gene via a direct association with Diversin in the nucleus. **e** Perturbation of HSP90 chaperone, such as pharmacologic inhibition and siRNA knock-down, not only disrupts the DNA-binding activity but also leads to the cytoplasmic translocation and accumulation of AF9. **f** AF9 plays a role in inhibiting the miRNA-150 maturation via a MYC/LIN28 axis. Onco-fusion MLL-AF9 protein activates a transcription factor MYC which in turn drives the expression of LIN28 and then blocks the miR-150 processing. **g** Upon cell mitosis, GAS41 colocalizes and binds with pericentrosomal materials (PCM), including TACC1, NuMA, α-tubulin and γ-tubulin. The distribution of GAS41 and PCM at the spindle pole is required for proper bipolar spindle assembly and chromosome alignment. The figure was created using ©BioRender (https://biorender.com)

complexes. Therefore, oncogenic fusion proteins have been found to undermine such an ENL-centric transactivation system involving tumourigenesis.

Oncogenic fusion proteins of MLL and a component of AF4 family (AF4, AF5Q31) or ENL family (ENL, AF9) actively recruit either the so-called AEP complex or SEC to MLL target promoters. These events result in constitutive activation of key leukemic genes, including *HOXA9* and *MEIS1* that eventually promote leukemic transformation [23, 61, 62]. Moreover, mutations in the YEATS domain of ENL have been reported in a subset of childhood cancers that start in the kidneys (Wilms tumours) marked by a relative overexpression of *HOX* genes, particularly *HOXA13* [63]. To date, eight *ENL* mutations have been identified, essentially in Wilms tumours [63, 64]. On the other hand, the increased copy number of *GAS41* has been reported in glioblastoma multiforme and astrocytoma III and at a high frequency in astrocytoma grades I and II,

making GAS41 responsible for nearly 40% of tumour formation associated with the central nervous system (CNS) [21, 65, 66]. Overall, somatic mutations occurring within the YEATS domains of AF9, ENL and GAS41 in different cancer tissues of patients have been recently reviewed based on the Catalogue of Somatic Mutations in Cancer (COSMIC) database [15].

Along with the well-documented association of *AF9*, *ENL* and *GAS41* gene mutations with carcinogenesis, emerging evidence suggested that an alteration of the YD protein functions might also be deleterious for neuronal activities. In fact, a few germline variations of *AF9* have been associated with neurodevelopmental diseases. A t(4;9)(q35;p22) leading to a 10-bp deletion within the first intron has been detected in a 6-year-old girl [67] and t(4;9)(q34;p22) translocation causing disruption of exons 3–4 of *AF9* gene has been detected in a 9-year-old girl [68]. Interestingly, both clinical cases presented neuromotor developmental disorders, body ataxia and epilepsy. These genetic variations have been proposed to segregate in an autosomal recessive manner [67, 68]. Additionally, a large 97,992 bp deletion of the genomic locus hg38 9p21.3 (chr9:20380587–20478578) which include *AF9*, *MIR4473* and the pseudogene *RNU4-26P* has also been reported to implicate in an intellectual disability [69]. Moreover, a missense variation of *ENL* (p.Arg473Gln) has been classified as likely pathogenic by Lupski Lab, Baylor-Hopkins Centre for Mendelian Genomics (BHCMG) (ClinVar, rs749203329), due to its association with one clinical case of cerebral atrophy with global developmental delay and hypertelorism. Recently, a repeat expansion mutation within the first intron of *YEATS2* has been recently identified in a Thai pedigree of benign familial adult myoclonic epilepsy type 4 (BAFME4) [70]. However, whether such a repeat expansion leads to a loss of function (pLoF) of YEATS2 or involves the disease via an RNA toxicity mechanism still remains unknown.

Of note, an investigation of the Genome Aggregation Database (gnomAD) revealed additional 30 genetic variants of *YD* genes with predicted pLoF effects in a non-cancer dataset. These variants are absent from controls and have an allele frequency < 0.00001 (last search September 2021) (Table S1). Nevertheless, none of the gnomAD annotated variants has been reported so far in ClinVar. The molecular functions of YD proteins in the CNS are largely unknown. Likewise, the pathogenic mechanism of how dysfunctional YD proteins lead to neurological diseases is yet to be explored. Therefore, further functional characterization studies are needed to validate the cause-effects relationship of these novel YD genetic variants. Such a study might reveal new clues on the biological functions of YD proteins and their potential roles in human neurological diseases.

Drosophila YD proteins: what can we learn from flies?

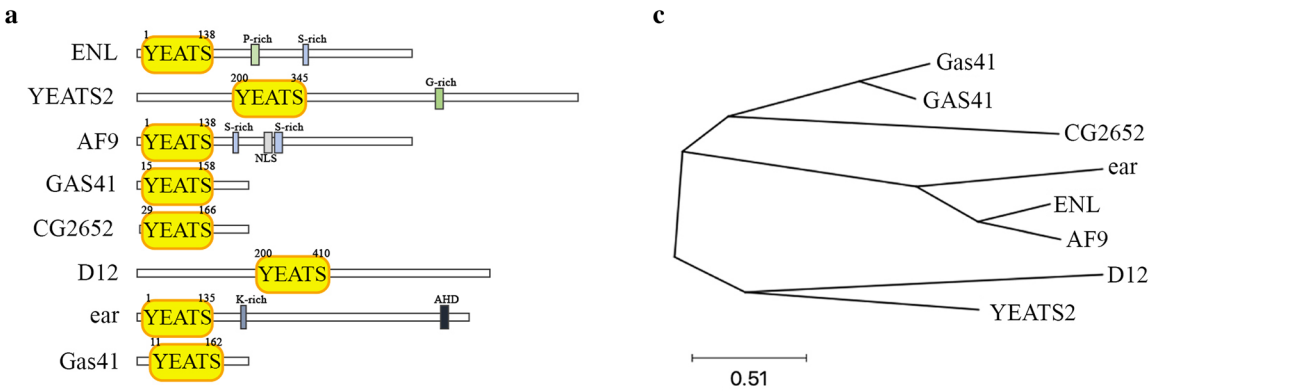
The evolutionary conservation of YD proteins has enabled to develop a few mouse models to shed light on the many aspects of YD protein's biology and their relevance in human cancer like acute myeloid leukaemia [3, 5, 16, 71]. To date, no model organism has been employed to investigate the molecular functions of YD proteins in neurons. However, some pieces of evidence are recently arising from the model organism *Drosophila melanogaster* which could prove novel functions of the YD proteins in neuronal activities.

Drosophila carries three orthologs of the human YD proteins (ear, D12, Gas41) with a high degree of sequence conservation as shown in Fig. 4 and Table S1–S4. Protein identity is higher within the YEATS domain (Table 1) and perhaps accounts for the similar function that the *Drosophila* YD proteins retain as epigenetic regulators and in gene transcription regulation. A fourth YD protein also exists in *Drosophila*, namely CG2652, which shows a lesser degree of similarity with human YD proteins (Fig. 4, Table 1 and S3). Despite CG2652 remaining largely uncharacterized, a previous genome-wide analysis (GWAS) study revealed its association with life span and fecundity of the fly [72].

Notably, like the human YD proteins, *Drosophila* ear (ENL, AF9), D12 (YEATS2) and Gas41 (GAS41) are components of different complexes involving either chromatin remodelling such as Dotcom, ATAC, Tip60 or transcription elongation such as SEC and TFIID [73–79]. Other similarities with the human YD proteins can also be observed regarding the extranuclear compartmentalization and roles in cancers. In fact, in addition to the nuclear complexes, D12 has been identified in the cytoplasm as a novel component of the cytoplasmic transient ribonucleoprotein (RNP) aggregates, namely stress granules (SGs), albeit its role in such stress-dependent membraneless organelles needed to be clarified [80]. Moreover, an abnormal activity of Gas41 has been linked to an altered hematopoietic progenitor niche cell production and differentiation, confirming an evolutionary conserved role in carcinogenesis [81, 82].

Interestingly, a decline of ear function by pan-neuronal RNA interference (RNAi) expression has proven to impair memory formation in *Drosophila*, possibly due to a disruption of the neuronal development program or by impairing the neurophysiological mechanisms underlying memory formation [83].

Remarkably, a strong link between *Drosophila* YD orthologs and motor neuron disorders (MNDs) is emerging since independent studies have shown that knocking down either *ear* or *D12* can rescue the toxicity of amyotrophic



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ENL_HUMAN/1-559          1 - - - MDNQCTVQVR - - - - - - - - - - - - - - - - - - - - - - - - - - - - - LE  12
YEATS2_HUMAN/1-1422    197 LTDETSRLFVKKT - - - - - - - - - - - - - - - - - - - - - - - - - - - - - IV  211
AF9_HUMAN/1-568          1 - - - MASSCAVQVK - - - - - - - - - - - - - - - - - - - - - - - - - - - - - LE  12
GAS41_HUMAN/1-227       14 - - GRVKGVTIVKP - - - - - - - - - - - - - - - - - - - - - - - - - - - - - IV  26
CG2652_DROME/1-235      26 PITVTGRCVISRD - - - - - - - - - - - - - - - - - - - - - - - - - - - - - IV  40
D12_DROME/1-969        209 QPEQEPPISIKLEDEQPCTSRQAHERQVELNASRLNNKNKFNFV  252
ear_DROME/1-945          1 - - - - - - - MAVKVQ - - - - - - - - - - - - - - - - - - - - - - - - - FE  8
Gas41_DROME/1-227       10 - - GRLKGVTIVKP - - - - - - - - - - - - - - - - - - - - - - - - - - - - - IV  22

ENL_HUMAN/1-559          13 LGHRAQL - - - RKKPTTEGF - - - - - THDWMVFVRGPEQC - DIQHF  47
YEATS2_HUMAN/1-1422     212 VGNVSKYIPPDKREENDQS - - - - - THKWMVYVRGSRREPSINHF  250
AF9_HUMAN/1-568          13 LGHRAQV - - - RKKPTVEGF - - - - - THDWMVFVRGPEHS - NIQHF  47
GAS41_HUMAN/1-227        27 YGNVARYF - - GKKREEDGH - - - - - THQWTVYVKPYRNE - DMSAY  62
CG2652_DROME/1-235       41 IGCRME - - - - QCDPDMPYM - - - - LEPTWGVYLRPGRDGGDLSRF  76
D12_DROME/1-969         253 VGNTSKYI - - GEDSRENGTGGNALTYKWLVYVQGKDLPEPLEKY  294
ear_DROME/1-945           9 IGHTSKLRS - KKTPHPQAF - - - - - THDWEIYVQGVNKA - DISAF  45
Gas41_DROME/1-227        23 YGNIARSF - - GKKREEDGH - - - - - THQWKVYLKPYFNE - DMSIY  58

ENL_HUMAN/1-559          48 VEKVVFWLHDSF - PKPRRVCKEPPYKVEESGYAGFIMPIEVHFK  90
YEATS2_HUMAN/1-1422     251 VKKVWFFLHPSYKPNDLVEVREPPFHLTRRGWGEFPVRVQVHFK  294
AF9_HUMAN/1-568          48 VEKVVFHLHESF - PRPKRVCKDPPYKVEESGYAGFILPIEVYFK  90
GAS41_HUMAN/1-227        63 VKKIQFKLHESY - GNPLRVVTKPPYEITETGWGEFEIIIKIFFI  105
CG2652_DROME/1-235       77 VRRVTFKMSPRL - PLRLHVADSAPFEIGEVLGSDFPVEVQVQYM  119
D12_DROME/1-969         295 IKKVRFHLHPSYRPNDIVDVHRSPFQLNRHGWGEFPMRIQLFFQ  338
ear_DROME/1-945          46 VEKVVFVLHESF - PKPKRVVKEPPYAIQESGYAGFLLPVEIYFR  88
Gas41_DROME/1-227        59 VKKVHFKLHESY - ANPNRIVVKPPYEITETGWGEFEVIIKIYFN  101

ENL_HUMAN/1-559          91 NK - EEPRKVCFTYDLF - - - - - - LNLEGNPPVNHLRCEKLTF - - -  124
YEATS2_HUMAN/1-1422     295 DS - QNKRIDIIHNLKLDRTYTGLQTLGAETVVDVELHRHSLGED  337
AF9_HUMAN/1-568          91 NK - EEPRKVRFDYDLF - - - - - - LHLEGHPPVNHLRCEKLTF - - -  124
GAS41_HUMAN/1-227       106 DP - NERPVTLYHLLKL - - - - - - - - - - - - - - - - - - - - - - - - - - -  120
CG2652_DROME/1-235      120 DA - - - - RMSATSYI - - - - - - - - - - - - - - - - - - - - - - - - - - -  129
D12_DROME/1-969         339 EHLQQKPVQLMHTVVLDKTMCGLHTMGAETTVEIWLRAKQA - - -  379
ear_DROME/1-945          89 NR - DEPKRIVYQYDLV - - - - - - LQSTG - PPQHHVEVKTHIF - - -  121
Gas41_DROME/1-227       102 DQ - SERPVTCYHILKL - - - - - - - - - - - - - - - - - - - - - - - - - - -  116
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Fig. 4 Evolutionary conservation of YD proteins between humans and *Drosophila*. **a** Schematic representation of both human and *Drosophila* YEATS-domain containing proteins. Domains, families and functional sites of human and *Drosophila* YEATS-domain containing proteins were identified by Prosite tools (prosite.expasy.org). The position of YEATS domains and other non-annotated elements are highlighted (note: protein lengths and YEATs domains are to scale). **b** Primary sequence alignment shows the conservation of YEATS domains among the human and *Drosophila* proteins. Comparison of the primary structure was ruled out by Clustal Omega (ebi.ac.uk) and further by MEGAX (Molecular Evolution Genetic Analysis, megasoftware.net) with TcoffeWS and default settings. **c** Phylogenetic tree: The evolutionary history of both human and *Drosophila* YEATS-domain containing proteins was inferred using the Maximum Likelihood method and JTT matrix-based model [127]. The tree with the highest log likelihood (− 13329.07) is shown. Initial tree(s) for the heuristic search were obtained automatically by applying Neighbor-Join and BioNJ algorithms to a matrix of pairwise distances estimated using the JTT model, and then selecting the topology with a superior log likelihood value. The tree is drawn to scale, with branch lengths measured in the number of substitutions per site. This analysis involved 8 amino acid sequences. There were a total of 1509 positions in the final dataset. Evolutionary analyses were conducted in MEGA X [128, 129]

lateral sclerosis (ALS)-associated proteins like Fused in Sarcoma (FUS) (ALS6, Mendelian Inheritance in Man (MIM) entry #608030), VAMP Associated Protein B (VAPB) (ALS8, MIM #608627) and Tar DNA-binding protein 43 (TDP43) (ALS10, MIM #612069) [80, 84, 85]. Briefly, expression of human ALS causing genes like the RNA-binding proteins *FUS* and *TDP43* or the transmembrane protein VAPB are known to cause neuronal

Table 1 Similarity of human and *Drosophila* YEATS domains

	CG2652	D12	Ear	Gas41	ENL	YEATS2	AF9	GAS41
CG2652	100%							
D12	29.71%	100%						
ear	28.88%	40%	100%					
Gas41	35.50%	32.50%	37.03%	100%				
ENL	31.88%	29.71%	**64.44%**	40.57%	100%			
YEATS2	32.60%	**59.58%**	37.03%	40.41%	35.50%	100%		
AF9	33.33%	29.71%	**66.66%**	40.57%	**87.68%**	35.50%	100%	
GAS41	39.13%	34.96%	38.51%	**80.41%**	39.13%	42.65%	39.13%	100%

Primary structures of the YEATS domain have been retrieved from uniprot (uniprot.org). CLUSTAL omega (ebi.ac.uk) with default setting has been used to generate sequence alignment. Further, aligned sequences have been exported in FASTA through MEGAX (megasoftware.net). SIAS tool (imed.med.ucm.es/) has been employed to search for similarities

Bold characters mark similarity > 50%

degeneration in the fly in a fashion that recapitulates some clinical features observed in related human MNDs like shortened life span, locomotive and behavioural dysfunctions [86–90]. Given the pathogenic mechanism of ALS remains to be fully elucidated and therapeutics are still lacking, *Drosophila* lines ectopically expressing human ALS-causing proteins are often used in genetic modifiers screening. In a few such screenings, a reduction of the ear has been found to partially suppress the external and internal retinal deterioration conferred by TDP-43 and VAPB, while RNAi of *D12* has been shown to improve pigmentation, ommatidial structure and glossiness phenotypes impaired by TDP-43 and FUS toxicity [80, 84, 85]. Although this evidence supports a model wherein a crosstalk between TDP-43 and SEC components plays a critical role in the TDP-43 pathology, the mechanism of how a decline of ear and D12 can rescue FUS and VAPB toxicity also remains elusive.

Concluding remarks

The four human proteins ENL, YEATS2, AF9 and GAS41 which contain a YEATS domain are widely recognised as epigenetic regulators with critical roles in cancers. Nonetheless, new evidence is emerging that the so-called YD proteins also execute extra-transcriptional functions and can localize in extra-nuclear compartments. These new findings clearly rindicae that there is still much to discover for the YD proteins. For instance, all the epigenetic functions attributed to YD proteins pertain to their ability to coordinate and cooperate with chromatin remodellers for the regulation of chromatin structure so far. However, AF9 and GAS41 have been found to also regulate the DNA methylation and processing of non-coding RNAs, yet the relevance of these new paradigms of regulation is still poorly understood.

Furthermore, several genetic variations have been reported to associate with human neurological disorders, including neurodevelopmental disorders, yet we have just recently begun to explore the functions of YD proteins in neurons and hence certain biological questions still remain open, such as whether and how an alteration of YD protein's activities becomes detrimental for neurons. In this regard, it is noteworthy that several YD protein's downstream targets, such as Akt, Wnt and p53, are known to involve cellular signalling cascades, which are critical for neurodevelopment. For instance, the PI3K-Akt-mTOR pathway, identified originally as cancer regulatory pathway, has now been demonstrated to play a primary role in brain development, since also pointed out by the widespread p-Akt localization in the developing cortex, with remarkable enrichment in neural progenitor cells in the ventricular zone [91]. It is, therefore, not surprising that dysregulation of this node leads to neuronal apoptosis in multiple neurocomplications and has been regarded as a root cause of several neurodevelopmental diseases, such as megalocephaly ("big brain"), microcephaly ("small brain"), autism spectrum disorders (ASD), intellectual disability, schizophrenia, and epilepsy [92–96].

Moreover, both canonical and non-canonical Wnt signalling pathways are known to play crucial roles in neural development and related neurodevelopmental disorders [97]. Remarkably, the Wnt signalling is fundamental for neurodevelopmental and post-neurodevelopmental processes, such as CNS regionalization, differentiation of neural progenitor cells (NPCs), neuronal migration, axon guidance, dendrite development, synaptogenesis, adult neurogenesis as well as neural plasticity [98–104]. As such, perturbation in Wnt signalling has proven to be detrimental for CNS structures and functions, hence leading to related disorders including ASD and intellectual disability [105–109].

Finally, the ability of p53 in regulating the balance among apoptosis, proliferation and differentiation, which has been well known for a long time to be critical in carcinogenesis,

is emerging to be equally important in brain organogenesis. For instance, lack of p53 was shown to promote the expansion of NPCs and alter their differentiation [110, 111], whereas augmentation of p53 in neurons has been found to trigger developmental programmed cell death [112–114]. In addition, a decline of p53 expression was suggested to alter the neuronal architecture in human brain organoids, hence resulting in a disorganized stem cell layer and reduced number of NPCs and neurons [115]. Therefore, altered p53 activity can contribute to developmental defects in different human genetic syndromes [116].

Overall, an intriguing scenario seems to emerge that, in addition to the epigenetic regulation of genes involving differentiation and neurodevelopmental outcomes, the YD proteins may play a role in neurodevelopment and related disorders via a few extra-transcriptional functions by controlling either Akt, Wnt or p53 signalling cascades that are critical for synaptic plasticity and behaviour.

The evolutionary conservation of YD proteins in small animals like the highly tractable and versatile model *Drosophila* might be taken into consideration for future investigation in this matter. In fact, the Akt, Wnt and p53 pathways are very well studied in *Drosophila*, making the fruit fly an excellent model candidate to investigate further whether an alteration of YD protein's activities becomes detrimental for neurons due to any dysfunction of the above YD protein's downstream targets.

Nonetheless, at the present time, the study of *Drosophila* YD orthologous has already provided new clues on the potential role of YD protein in neurological disorders. In fact, a prominent link between YD proteins and ALS-causative RNA binding proteins has recently emerged in the fly that a decline of the *Drosophila* orthologs AF9/ENL or YEATS2 seems to alleviate the neuronal toxicity caused by abnormal TDP-43, FUS and VAPB. Evidence points out a remarkable role of YD proteins in the dynamics of specific cytoplasmic granules that are critical during cellular stress and are known to be abnormally accumulating during the pathogenic process leading to MNDs. However, further investigations are required to understand the novel role of *Drosophila* YD proteins in the cellular response to stress, as well as whether the human YD proteins retain similar functions. These novel findings would be of relevance especially since many data highlight an impairment of SG's dynamics to be a trigger of neuronal toxicity not only in ALS but also in other neurological diseases [117, 118].

Recently, several YEATS domain-selective drug inhibitors have been developed with a general preference towards the AF9 and ENL YEATS domains to suppress their target genes, including HOXA9/10, MYB, MYC and several other leukaemia proto-oncogenes [28, 119–126]. Such an array of drugs targeting the YD proteins may represent a good source of available therapeutics to test also with respect to the potential roles of YD proteins in neurological disorders. Overall, more studies are needed to better explore the intricate pathways of YD proteins in neurons and whether any approaches to normalize the activity of human orthologs of the SEC components like the YD proteins may have any therapeutic benefit also in MNDs and neurodevelopmental disorders. Once again, *Drosophila* might be a suitable candidate for novel functional studies and used to validate the potential efficacy of novel therapeutics targeting the YD proteins.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00018-022-04218-0.

Author contributions Conceptualization: RY and LLP; Validation: RY, PC, SJ and LLP; Formal analysis: RY and LLP; Investigation: RY and LLP; Resources: RY and LLP; Data curation: RY and LLP; Writing—original draft preparation: RY and LLP; Writing—review and editing: RY, PC, SJ, DP, VS and LLP; Visualization: RY and PC; Supervision LLP; Project administration: LLP; Funding acquisition: LLP. All authors have read and agreed to the published version of the manuscript.

Funding This study was supported by Genomics Thailand, Health Systems Research Institute (HSRI) under grants 64/122 and 64/132 and partially supported by the Faculty of Medicine, Chiang Mai University under grant 030/2564 and by the Medical Council of Thailand under grant 012/2534. This work was partially supported by Chiang Mai University and Chulalongkorn University (CU_FRB640001_01_30_10 and 764002-HE01).

Availability of data and material All data used to support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Conflicts of interest The authors declare no conflict of interest.

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