



WD40 Repeat Proteins: Signalling Scaffold with Diverse Functions

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Abstract

The WD40 domain is one of the most abundant and interacting domains in the eukaryotic genome. In proteins the WD domain folds into a β -propeller structure, providing a platform for the interaction and assembly of several proteins into a signalosome. WD40 repeats containing proteins, in lower eukaryotes, are mainly involved in growth, cell cycle, development and virulence, while in higher organisms, they play an important role in diverse cellular functions like signal transduction, cell cycle control, intracellular transport, chromatin remodelling, cytoskeletal organization, apoptosis, development, transcriptional regulation, immune responses. To play the regulatory role in various processes, they act as a scaffold for protein–protein or protein–DNA interaction. So far, no WD40 domain has been identified with intrinsic enzymatic activity. Several WD40 domain-containing proteins have been recently characterized in prokaryotes as well. The review summarizes the vast array of functions performed by different WD40 domain containing proteins, their domain organization and functional conservation during the course of evolution.

Keywords WD40 protein · Scaffold · Cell signalling · STRIPAK

1 Introduction

WD40 repeat proteins, as the name suggests, are characterized by the presence of a tandem repeats (4–16) of ~40–60 amino acids having tryptophan (W)–aspartic acid (D) at the C terminus and glycine (G)–histidine (H) residues at 11–24 amino acids downstream from the N terminus. However, the GH and WD dipeptides are not the absolutely necessity for these proteins (<http://BMERC-www.bu.edu/wdrepeat>). These dipeptides are also flanked by core sequences that are conserved in nature [1, 2]. Although the internal sequences of the repeating units in different proteins are highly variable, there are occurrences of most probable residues at each position with a characterizing spacing between them [1, 2]. The WD40 repeats were first identified in the β subunit of transducin, a GTP binding protein and therefore, it is also

referred to as transducin repeats. Structurally, they are characterized by a β propeller fold comprising of 4–8 antiparallel sheets; each sheet, in turn, has 4 β strands. These sheets are arranged as the blades of a propeller around a central cavity, while each WD repeat is a part of these antiparallel strands [3]. They form a platform at which protein–protein or protein–DNA interactions take place [3, 4].

It has been postulated that the WD40 repeats have arisen from intragenic duplication and recombination events [5]. Up to date, based on the available genome sequences and the proteomic data, it is predicted that there are about 200 putative WD-containing proteins in plants [6, 7], and 349 such proteins in the human [8]. Their presence in prokaryotes is rare, and only a few have been reported yet [3, 9].

The WD40 repeats are among the top ten most abundant domains in eukaryotes. Proteins containing WD40 repeats take part in diverse processes viz., transcriptional regulation, vesicular trafficking, cytoskeletal assembly, apoptosis, cell cycle control, chromatin modification and signal transduction. Owing to the numerous roles of WD-repeat proteins in cellular processes, any malfunctions in these proteins might lead to diseases [1]. Studying these proteins is thus of prime importance. Although the interaction of WD repeats with other molecules, and their structure and evolution have been extensively reviewed [2, 3, 10], their functional aspect

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and distribution among the five kingdoms of life has not yet received adequate attention. Here in this review, we are summarising the functions and the distribution of WD40 repeat proteins from the simplest kingdom Monera to the highly complex metazoans.

2 Structure of WD40 Domain

The crystal structure of the prototype WD40 repeat protein, the β -subunit of G-protein, was first determined by Wall et al. in 1995. It showed that the WD40 domain forms a symmetrical β propeller fold. Subsequent studies with other proteins have shown that the propeller fold commonly comprises of 4–8 β sheets which, in turn, has four antiparallel β strands, named a, b, c and d. The repeating WD unit is a part of these strands, while the a blade of the propeller starts

from one strand (d strand) of the adjacent repeating unit [3] (Fig. 1). Accordingly, strand d from the adjacent unit along with a, b and c strands of the same unit form a blade. In the G β protein containing seven blades, the outer strand of the last i.e., the seventh blade is formed from the N terminal region of the first repeat that overlaps the three strands at its C terminus region. This kind of arrangement leads to the formation of a “Velcro snap” that closes the ring and provides stability [2]. Some proteins like Aip1 (an actin-interacting protein) and DDB1 (a DNA damage-binding protein) have multiple WD40 β propeller structures. While Aip1 has two 7-bladed β propeller structures, DDB1 comprises of three. The first propeller structure of DDB1 lacks the Velcro, while it is present in the second and third propeller structures [11]. This suggests that the Velcro closure is dispensable and the WD40 domains devoid of it stabilise the propeller structure by other mechanisms to close their ring.

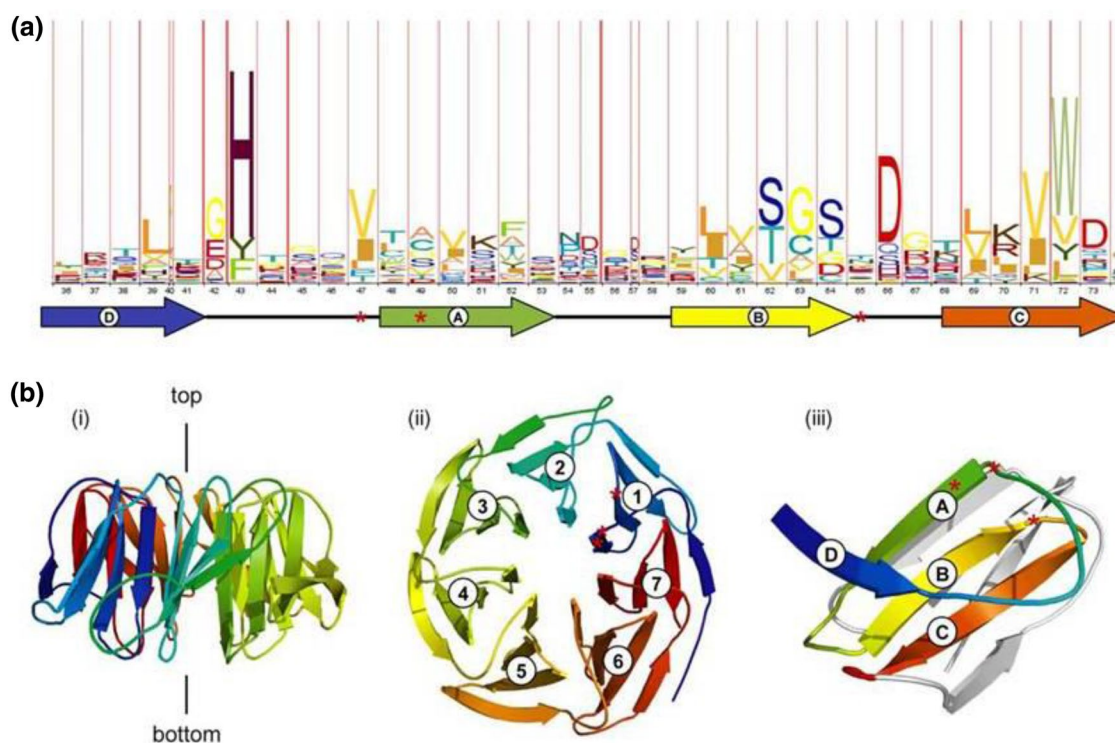


Fig. 1 Sequence and structural features of WD40 domains, which contain several copies of the 44–60 residues WD40 repeat. WD40 repeats typically fold into seven-bladed beta propellers with each blade comprising a four-stranded anti-parallel beta-sheet. **a** Sequence logo for WD40 repeats. The letter plots represent amino acid conservation at each position. The corresponding β -strands within a repeat are depicted below. Each WD40 repeat typically contains a variable region of 11–24 residues followed by key signature sequence features: a glycine–histidine (GH) dipeptide at the end of strand D, three small amino acids (serine, glycine etc.) at the C-terminal end of strand B and a tryptophan–aspartate (WD) dipeptide at the end of strand C. The logo was created with HMM logo [15] based on a structural alignment [16] of WD40 domains as classified in SCOP

(PDB IDs 1tbq, 1erj, 2ce8, 1u2 v, 1nex, 1p22, 1nr0, 1pi6, 1sq9, 1vyh, 2ovr and 1yfq) [17]. **b** WD40 domains often fold into seven-bladed beta-propellers with a funnel-like shape and, by convention, the narrower part of the funnel containing the DA and BC loops is defined as the top domain and the wider part as the bottom of the propeller (i). The WD40 sequence repeat corresponds to strand D of one blade followed by strands A, B and C of the next blade (iii). The WD40 sequence repeat therefore is not equivalent to a single propeller blade. The main chain is coloured using a gradient from red at the N-terminus to blue at the C-terminus (ii, iii). Residues often involved in peptide interactions on the top surface are highlighted with red asterisks. Reproduced with permission from Stirnimann et al. [3], with permission from Elsevier. (Color figure online)

As an example, in hemopexin protein, which scavenges the heme released during the turnover of heme proteins, a disulphide bond connects the first and the last blade [2, 12]. Inter sheet hydrophobic interactions also play a role in stabilizing these structures [4]. By geometrical modelling, it has been predicted that the sevenfold β propeller is the most ideal and stable β sheet geometry [13]. At least 7 WD40 repeats are required to make such structures. It has been found that the proteins with lesser number of repeats dimerize to form at least seven propellers for attaining stability. One example is Sec13, which functions as a component of coat protein II (COPII) in the nuclear pore complex. Although it has 6 WD-40 domains, in order to gain stability, it shares 1 WD40 domain with its complex partner ancestral coatomer element 1 (ACE1) [14]. As described by Xu and Min in 2011, WD40 domains recruit their substrates/partners by different mechanisms that are listed below [4].

- *Acting as interchangeable substrate receptor to selectively target different substrates* In SCF ubiquitin ligase complex containing SKP1, CUL1, and an F-box, approximately 70 F box proteins serve as interchangeable substrate receptors; thereby recruiting various substrates for ubiquitination followed by proteasomal degradation;
- *Recruiting different substrates in a similar way by the same WD40 protein* The N terminal repeat of clathrin protein is a WD40 β propeller structure which loads the cargo in the coated pit during endocytosis;
- *Recruiting different substrates in different ways by the same WD40 domain* During GPCR signalling, the G β protein binds to G α , G γ , and phosducin in different modes.
- *Ligand binding through its insertion motif of the WD40 domain* As in case of the Bub3 protein which plays a role in the spindle assembly checkpoint. It has 2 insertion motifs which enable its binding to Bub1 and Mad3;
- *Ligand binding through inter-blade binding grooves of the WD40 domain* This type of binding mode is found in the PALB2–BRCA2 peptide complex. PALB2 protein recruits BRCA2 and RAD51 in the homologous recombination repair mechanism [4].

3 Distribution and Origin of WD Repeats

The evolutionary origin of WD40 repeat-containing proteins remains enigmatic as the diversity in their structures and functions is quite large, thus questioning the existence of a common ancestor. The members of the family which arose during the early evolution were less similar, while those with more similarity evolved later. They are exclusive to eukaryotes and are uncommon in prokaryotes. Interestingly, in archaea, YVTN and YWTD repeat proteins have

seven-bladed β propeller structures with homology to metazoan cell surface proteins [18]. They are considered as WD40 repeat like proteins with a common ancestral origin and acquired from the eukaryotes via horizontal gene transfer [18, 19]. The high degree of similarity in structures rather than the primary sequences are the determining features of the WD40 repeat proteins thereby making their phylogenetic analysis very difficult. The sequence repeats that form a stable propeller-like structure have remained conserved during evolution; however, the functional selection of the residues found on their surfaces has evolved depending on the domains where the ligand interactions take place [2]. Accordingly, the grouping of WD-repeat proteins has been done by clustering them on the basis of the sequence other than the internal repeat residues.

3.1 WD40 Repeats Proteins in Monera

Although the WD40 repeat proteins are confined to the eukaryotes and are absent in prokaryotes, the first prokaryotic protein PkwA was identified in *Thermomonospora curvata* [9, 20, 21]. Subsequently, several WD40 proteins were characterized in other prokaryotes like the WdlA in *Streptomyces lincolnensis* [22], and WdpB and WdpC in *Streptomyces coelicolor* [23]. However, they have not been studied in depth as compared to their eukaryotic counterparts. Several WD40 domain-containing proteins have also been reported in cyanobacteria and other archaea [24], but they remained uncharacterized. Their functions need to be elucidated to find their potential involvement in various biological processes. Systematic analysis of various WD repeat-containing proteins in prokaryotes suggests the existence of around 4000 such proteins, with abundance in cyanobacteria and planctomycetes [24]. In prokaryotes, those proteins for which the functions are known, mainly participate in signalling and nutrient synthesis [24].

3.2 WD40 Repeats Proteins in Protista

Few reports are available regarding the presence of the WD40 proteins in the unicellular eukaryotes. In the unicellular green alga *Chlamydomonas reinhardtii*, a WD40 repeat protein encoded in the gene *mut11* is essential for the transcriptional repression [25]. The WD40 repeat-containing myosin F protein in *Gregarina polymorpha* contributes to actin remodelling. It contains several WD40 repeats at its C-terminal, along with several other domains like the myosin motor domain, a coiled coil structure and a neck domain with 6 IQ motif [26]. In *Leishmania*, LACK protein, an ortholog of mammalian RACK1, maintains the level of LmCOX4; a subunit of the mitochondrial cytochrome complex required for maintaining the membrane potential generated by the electron transport chain. LACK is indispensable

for the thermostability and pathogenicity of the organism [27]. The ortholog of RACK1 in *Trypanosoma brucei* is termed TRACK. It is a part of the translational machinery as it binds to eEF1A and associates with the ribosome and polysomes. It has also been shown to take part in cytokinesis [28, 29].

In *Plasmodium falciparum*, there are several WD40 repeat proteins viz., PfSEC13, PfRACK and PfAMA1. PfSEC13 forms the nuclear pore complex, associates with chromatin and other nucleic acid binding proteins, regulating transcription [30]. PfRACK is expressed during the replication of the parasite and it inhibits Ca^{2+} signalling in the host erythrocytes. It also associates with integrin, src, and protein kinase C, playing a role in cell migration [31]. PfWLP1 interacts with cell adhesion proteins PfAMA1 and PfCCp, stabilizing the cell adhesion protein complex during the blood stage progeny of the parasite [32].

3.3 WD40 Repeats Proteins in Fungi

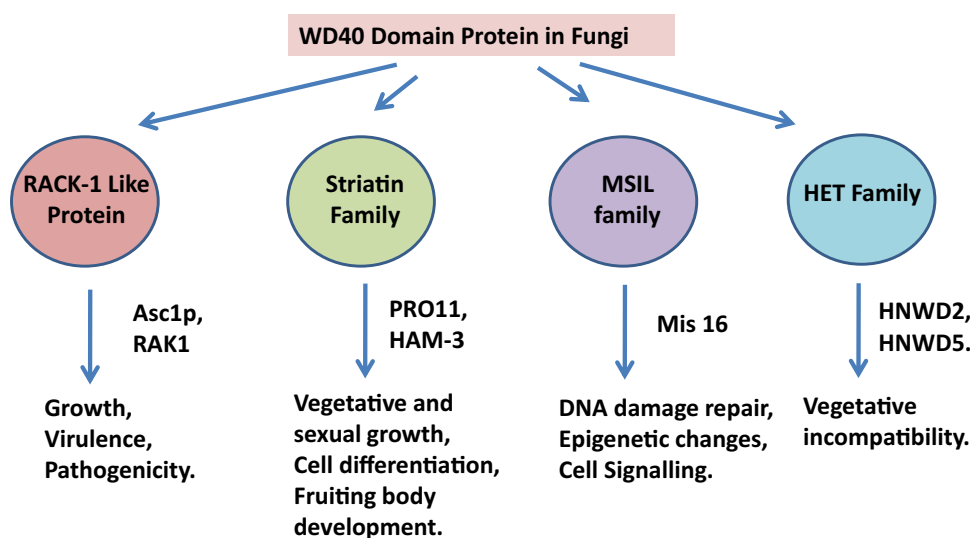
Various WD40 domain-containing proteins have been extensively studied in pathogenic as well as non pathogenic fungi, which play prominent roles in many cellular and biological processes (Fig. 2). Based on those studies, the WD40 domain-containing proteins in fungi are broadly categorized into four groups: RACK1 like proteins, Striatin family, MSIL family and HET family.

- Receptor for activated C kinase (RACK1) like protein is a WD repeat-containing protein in *Verticillium dahlia*. It affects the level of ribosomal proteins and the expression of genes which regulate the hyphal growth, virulence, and pathogenicity [33]. In *Saccharomyces cerevisiae*, the RACK1 homolog is Asc1p. It consists of 7 WD repeats, it is localized at the smaller subunit of the ribosome and

is involved in kinase signalling and repression of translation [34, 35]. It binds to GDP-Gpa2, thereby blocking the guanine nucleotide exchange activity of Gpa2. It binds to Cyr1 that catalyzes the synthesis of cAMP, causing a reduction in the cAMP level. It also represses the MAP kinase signalling [36]. It is a core component of 40S ribosomal subunit and is required for the Flo-11 dependent adhesive growth under amino acid starvation [35]. Another RACK1 homolog protein in *Ustilago maydis* (RAK1) plays a role in cell wall formation, growth, mating and virulence [37]. It regulates the expression of *rop1*, a transcriptional regulator of *pfr1* that regulates the pheromone (*mfa*) and pheromone-receptor genes [37].

- In *S. macrospora*, the pro 11 mutant is found to be defective in early sexual development and in the formation of fruiting bodies. The meiosis process is affected in the mutants, thereby resulting in the sterile phenotype which is unable to form sexual spores. Mouse striatin is able to restore the fertility in the *pro11* mutant of *Sordaria macrospora*, as the process of meiosis is restored in it. This suggests the functional conservation of striatin [38]. GPI anchored protein smGPI-1 and the kinase activator smMOB3 are the core components of the fungal STRIPAK (striatin-interacting phosphatase and kinase) complex. smMOB3 interacts with the C terminal of PRO11. The fungal SLMAP (Pro45) interacts with PRO11 and smMOB3 in this multiprotein STRIPAK complex. Pro45 localizes at the nuclear envelope, endoplasmic reticulum, and mitochondria and plays an important role in development [39]. In *Neurospora crassa*, striatin ortholog *Ham-3* is essential for the vegetative and reproductive development [40]. Members of STRIPAK complex HAM2 (Strip) and HAM3 (Striatin) are the core components of the multiprotein assembly at the nuclear envelope that regulate the MAP-kinase pathway (MAK-1) [41].

Fig. 2 The functions performed by different protein families in Yeast with the WD40 domain



- In fungi, Msi1-like (MSIL) protein family members have been extensively characterized with diverse roles in the regulation of numerous processes as DNA damage response, epigenetic modifications etc. The members of this family have evolutionary divergent roles in different families of fungi [42]. Mis16, a MSIL protein is essential for survival in *S. pombe*, it plays an important role in the kinetochore assembly in mitosis [43].
- HET-D and HET-E (heterokaryon incompatibility protein), both belong to a family of proteins encoded by the *het* gene family with as many as 11 loci in *Neurospora crassa*. The members of this family comprise WD40 repeat domains at their C-terminus and are responsible for vegetative incompatibility in filamentous fungi like *Podospora anserina* and *Neurospora crassa* [44, 45].

Other than these four main groups, there are some other examples of the WD40 domain-containing proteins in fungi. For instance, the G β like protein in *Aspergillus fumigatus* (CpcB, Cross pathway control B) participates in virulence and drug sensitivity of fungus [46]. In yeasts, CDC4 protein, which is a member of SCF ubiquitin E3 ligase complex, contains the F-box and WD40 repeats. It plays a significant role in the growth, filamentation, and morphogenesis of the yeast [47]. CreC, a WD40 repeat-containing protein was characterized in *Aspergillus nidulans* as a component of CRC (carbon catabolite repression) pathway which is a regulatory mechanism for using glucose as the preferential carbon source by the microorganism. The homolog of CreC in *Magnaporthe oryzae*, a pathogen of rice plants, (MoCreC) plays important roles in the vegetative and sexual growth, conidium formation and pathogenicity by modulating the CRC pathway [48].

3.4 Functions of WD40 Repeat Proteins in Plants

In plants the WD40 repeat proteins play key roles in the regulation of various processes as summarized below.

3.4.1 Immunity

The WD repeat proteins involved in plant immunity are—G β family, that are present in a variety of eukaryotes [49, 50]; and Transparent testa glabra1 (TTG1) family, which is found only in higher plants. G protein complexes are directly associated with the ligand binding innate immune receptors [e.g., EF-Tu receptor (EFR)]. In response to the fungal and bacterial infections, these complexes convert the pathogen-associated molecular patterns into intracellular defence responses like production of ROS, activation of defence genes, deposition of callose and apoptosis [15–17, 51–55]. A combination of various G protein isoforms viz., XLG2, AGG1/2, and AGB1 are needed to impart the immunity to

the plants. Similarly, the G α isoform GPA1 mediates the stomatal closure which in turn inhibits the entry of microbes through the stomata [56]. Under DNA damage, the immune response also involves the RACK1 protein, a member of the WD repeat family.

Another WD repeat containing protein TTG1, has been associated with the defence mechanism in dicots. It associates with the oomycetes specific receptor PAR1, and activates the immune response by increasing the ROS production and apoptosis [57]. TTG1 has been associated with the transcription factors MYB and GL3 to form a ternary complex where TTG1 act as a scaffolding platform facilitating their interactions. This ternary complex binds to the promoters of the genes for the production of secondary metabolites like anthocyanin and proanthocyanidin [58, 59]. These secondary metabolites (also known as defence metabolites) are the primary means of defence against the microbial attack and are essential for the survival of plants in a complex environment [60, 61].

3.4.2 Cell Wall Formation

Three WD repeat proteins viz., LEUNIG Homolog (LUH), FRAGILE FIBER3 (FRA3) and TWD40-2 have been associated with cell wall formation in plants. The *luh-1* mutants are defective in mucilage extrusion, thereby suggesting its role in the expression of genes associated with mucilage maturation [62]. FRA3 is an inositol polyphosphate 5-phosphatase with an N terminal WDR domain [63]. Mutations in the *fra3* gene reduce secondary cell wall thickness in the xylem vessels and fibres. Another WD40 protein TWD40-2 mediates the endocytosis of cellulose synthase during cellulose biosynthesis [64]. Mutation of the *twd40-2* gene causes impaired endocytosis and stunted plant growth due to the decreased cellulose content [65].

3.4.3 Gene Regulation

CYP71, HOS15 and MS11 are the major WD repeat proteins that are associated with gene regulation in plants. CYP71 is a regulator of histone modification for chromatin based gene silencing. It directly interacts with the histone H3 and its absence causes reduced lateral organ development as well as reduced root elongation [66]. HOS15 causes the repression of genes associated with abiotic stress tolerance. It causes histone deacetylation and its mutation results in the cold hypersensitivity [67]. MS11 is a histone binding protein and is part of a histone deacetylase complex. It associates with the histone deacetylase 19 (HDA19) as a part of a core complex and upregulates the abscisic acid (ABA) receptor genes [68].

3.4.4 Proteasomal Degradation

Various WD repeat proteins are E3 ubiquitin ligases e.g., COP1. COP1 interacts with the adapter protein Trib for the transcriptional regulator C/EBP α , resulting in its degradation [69]. In *Arabidopsis thaliana*, the ULCS1 gene encodes a WD40 protein that interacts with the subunit of E3 Cullin ring ligase, thereby regulating the degradation of various proteins involved in the developmental process [70].

3.4.5 Microtubule Organisation

In *Nicotiana tabacum*, the deficiency of WD40 protein RAE1 serves as a platform for the assembly of proteins required for the organisation of spindle fibres [71]. Another WD40 protein NEDD in *Arabidopsis thaliana* interacts with γ tubulin complex and plays a role in microtubule organisation [72].

As summarised above, various WD repeat proteins in plants control cellular processes primarily by acting as an interaction platform for various proteins.

3.5 Functions of WD40 Repeat Proteins in Animalia

As summarized below, like in the case of plants, WD repeat proteins also control numerous processes in the kingdom Animalia (Fig. 3).

3.5.1 Signal Transduction

There are several WD40 repeat proteins viz., the β subunit of heterotrimeric G protein, RACK1, striatins, STE4, LIS1, MSI1, PR55, PLAP etc., that are involved in signal transduction. They help in the signalling process by providing platforms for the assembly of other proteins involved in the process. Receptor for activated kinase 1 (RACK1) has seven WD40 repeats with a β propeller structure that functions as an adaptor or scaffold for protein–protein interactions. It acts as a receptor that binds to activated protein kinase C, regulating its signalling [73].

Striatin subfamily, which comprises three members (striatin, SG2NA and zinedin) belongs to the WD40 repeat super family. They are primarily membrane associated proteins but are also present in the cytoplasm. Striatin family members were the first among the WD40 repeat proteins shown to bind calmodulin in presence of calcium. They are thus

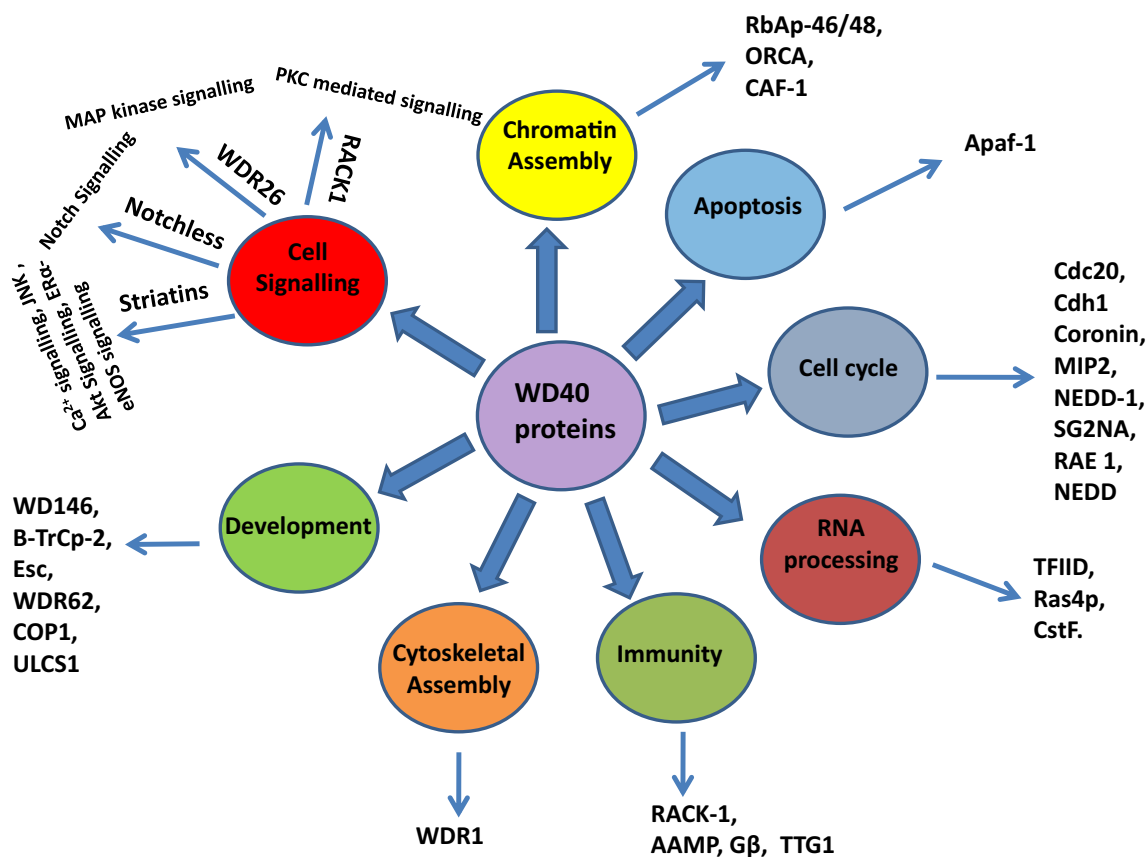


Fig. 3 Summary of diverse functions assigned to WD40 domain containing proteins in higher eukaryotes

involved in the Ca^{2+} signalling in a Ca^{2+} /Cam dependent manner [74]. Striatin and SG2NA have been independently shown to interact with phocein and protein phosphatase 2A (PP2A), thereby attributing them to vesicular trafficking and cell signalling respectively [75]. Noticeably, *Drosophila* has only one homolog of Striatin/SG2NA i.e., CKA, which acts as a platform for organizing the components of JNK signalling [76]. SG2NA recruits Akt to the plasma membrane and mitochondria along with the antioxidant protein DJ-1 to protect cells from oxidative stress. Cells with down-regulated expression of SG2NA are more susceptible to the oxidative stress while the cells over-expressing it are resistant [77]. SG2NA enhances the cancer cell survival by inhibiting the proteasomal degradation of DJ-1 and stabilizes it which, in turn activates Akt to increase the rate of cell proliferation [78].

Notchless gene in *Drosophila* and *Xenopus* encodes a novel WD40 repeat-containing protein that modulates the Notch signalling involved in cell fate decision during development. This protein binds to the cytoplasmic domain of Notch and increases its signalling activity [79]. WDR26, a G β like protein, suppresses the mitogen-activated protein kinase (MAPK) signalling pathway. It is highly conserved in evolution and inhibits the transcriptional activities of ETS proteins ELK1 and is a negative regulator of MAPK signalling [80].

3.5.2 Chromatin Assembly

ORC-associated (ORCA) is another WD40 domain-containing protein which facilitates assembly of the origin recognition complex (ORC), thereby playing a critical role in DNA replication during the initiation and cell cycle progression. Depletion of ORCA in human primary cells and embryonic stem cells results in the loss of ORC association to chromatin and thus the cells accumulate in the G1 phase [81]. Chromatin assembly factor-1 (CAF-1), has three subunits—p48, p60, and p150, of which the p48 is a WD repeat protein and binds to histone H4 in the absence of p150 and p60. It is also a component of histone acetylase. Together, these three subunits of CAF-1, H3 and H4 form the chromatin assembly complex (CAC) [82, 83].

3.5.3 Apoptosis

Apoptosis is an essential process for embryonic development and for maintaining homeostasis in adult tissues. The product of CED4 gene in *C. elegans* participates in the proapoptotic signal. In human, Apaf (Apoptotic protease activating factor 1, a homolog of CED-4) is an activator of Caspase 9 that induces the release of cytochrome C from the mitochondria, inducing apoptosis. Apaf1 associates with Caspase 9 and cytochrome C to form a proteasomal complex and 12

WD40 repeats at the C terminal region of Apaf1 mediate its interaction with those proteins [84, 85].

3.5.4 Cell Cycle

The cell cycle is primarily controlled by numerous CDKs that get activated at different stages by their respective cyclins. While the concentration of CDKs remains constant throughout the cell cycle; their activation and inactivation depends on the availability of different cyclins. The ubiquitin ligase complexes bring out their proteolytic degradation by attaching ubiquitin chain to their targets. Two polyubiquitinating E3 complexes that affect the cell cycle are SCF (Skp1, Cullin, and F-box) and the anaphase-promoting complex or cyclosome (APC/C). Several WD40 proteins act as scaffolds which facilitate the interactions between E3 enzymes and their substrate through the multiprotein assemblies. The WD40 domain-containing proteins Cdc20 and Cdh1 act as activators for APC/C, E3 ligase. They interact with APC/C and through their WD40 domains, recruit substrates to E3 ligase and increase the specific activity of APC/C [86]. The SCF complex remains active throughout the cell cycle and plays a prominent role in different stages. The WD40 domain of F-box protein mediates the substrate recognition in SCF complex and promotes its auto-ubiquitination and turnover [87].

Human Aurora-A is a key regulator of the mitotic spindle. It is required for proper formation of the mitotic spindle and separation of centrosome. It ensures proper alignment of chromosomes and exit from mitosis. Human Aurora-A is turned over through the APC/C mediated ubiquitin proteasome pathway and in vivo degradation of Aurora-A depends on hCdh1 [88].

Coronin, a 55 kDa protein isolated from *Dictyostelium discoideum*, is an actin-binding protein which interacts with microtubules and also has a role in phagocytosis [89]. It is a WD40 repeat-containing protein with a β propeller structure. It plays a role in organizing the normal actin cytoskeleton and cell division [90]. Myocardial ischemic preconditioning up-regulated protein-2 (MIP2) is a member of the WD40 repeat family having five WD40 domains. Over-expression of MIP2 in rat cardiomyocytes resulted in shorter cell cycle and increased cellular proliferation, suggesting its role in cell proliferation [91]. Centrosome, the primary microtubule organizing center, and γ tubulin are required for microtubule nucleation. The recruitment of γ tubulin to centrosome is mediated by its interaction with NEDD1, a WD40 repeat protein [92, 93].

Striatin family members play a significant role in different events of the cell cycle. Striatin interacts with PP2A and regulates MAP2 phosphorylation and microtubule dynamics. Inhibition of striatin results in hyperphosphorylation of MAP2 and microtubule destabilization that arrests cells

in G0/G1 phase inhibiting proliferation [94]. Mammalian misshapen like kinase 1 (MINK1) is a member of GCK family which functions in cytoskeletal assembly and cell senescence. It directly interacts with STRN4 (zinedin) in the multiprotein complex STRIPAK [95]. Knockdown of MINK results in multinucleated cells. SG2NA, a cell cycle-regulated protein, regulates the cell cycle process. Downregulation of 78 kDa isoform of SG2NA extends the G1 phase and its over-expression delays the entry into M phase. The expression of SG2NA is dynamically regulated by pGSK-3 β and pERK at different stages of the cell cycle [96]. Loss of the 78 kDa isoform decreases the CyclinD1 level and increases the number of cells in G1 phase [97].

3.5.5 Transcription and RNA Processing

TFIID, is a multiprotein complex of TATA-box binding protein (TBP) and several transcription associated factors (TAFs). Most of TAFs contain multiple WD40 repeats. Although TAFs are not required for the basal transcription activity, they regulate the transcription process and behave as coactivators. Cleavage stimulation factor (CstF) is required for the polyadenylation of mammalian pre mRNAs. It is composed of three subunits of molecular weight 77, 64 and 50 kDa. The 50 kDa subunit shows homology with G protein β subunit and has multiple WD40 repeats. It is required for mRNA processing [98]. Similarly, another WD repeat-containing protein WDR5 is a core component of Set/MLL histone methyltransferase complex. It catalyses methylation of histone H3, leading to the activation of transcription [99–101].

3.5.6 Innate Immunity

Some WD40 repeat proteins play important roles in innate immune responses. RACK1, with seven tandem WD40 domains, is a scaffolding protein involved in signalling and development. It also has a role in innate immunity. FcRACK1 protein from Chinese white shrimp is characterized by seven WD40 repeat domains. Its expression increases upon microbial infection, suggesting a role in innate immunity [102]. Angio-associated migratory cell protein (AAMP) is a WD40 repeat-containing protein that binds to the nucleotide binding domain of Nod2, a leucine-rich repeat (NLR) containing protein, mediating the activation of NF- κ B during innate immune responses [103].

3.5.7 Cytoskeletal Assembly

A novel 67 kDa WD40 repeat protein 1 [WDR1, also known as actin-interacting protein (Aip1)], consists of nine WD repeats. It helps inducing the disassembly of actin filaments [104, 105]. In *Drosophila*, it assists depolymerisation of

F-actin [106], thereby regulating various processes like cytokinesis, cell migration and muscle contractility [107].

3.5.8 Development

Some WD40 repeat proteins also have roles in different stages of development. β -TrCp-2 is a highly conserved protein belonging to the F-box family of ubiquitin ligase specificity factors. In *Xenopus* embryo it negatively regulates the Wnt/ β catenin signalling pathway and its expression reduces the dorsal axis formation [108]. The extra sex comb (esc) protein is composed of multiple copies of the WD40 domain. It participates in the repression of homeotic genes involved in determining the developmental fate of cells [109]. Another protein WDR62, which is the second most mutated gene in microcephaly patients, interacts with mitotic signalling kinase AURKA. Upon glial specific deletion of WDR62, brain volume decreases, suggesting its role in brain growth and development [110].

In addition to above, a brief summary of functions of few more WD40 repeat proteins is summarised below in Table 1. Also, owing to the diverse functions carried out by various WD repeat-containing proteins, any dysfunction in them may lead to various anomalies. The list of such diseases is given below in Table 2, and a list of the WD40 repeats containing proteins we have discussed in this manuscript, the organisms from which they were studied, corresponding functions and relevant references, are also provided in Table 3.

4 Conclusion

WD40 repeats were first identified in the β -subunit of the heterotrimeric G protein and CDC-4 protein [144]. It was found to consist of a repetitive sequence motif of 40 amino acids with highly conserved glycine, histidine (GH) and an aspartic acid residing before the signature tryptophan and aspartic acid (WD) residues. Later it was clarified as a sequence of 44–60 residues with the GH dipeptide at the N-terminus and the WD dipeptide at the C-terminus [2, 10]. WD40 domains are involved in diverse cellular processes by acting as an adaptor for protein–protein and protein–DNA interactions. They are involved in varied functions like signal transduction, transcription, development, cell cycle regulation, apoptosis. They thus play a significant role in maintaining the homeostasis and proper functioning of the body. Most of the WD40 domain-containing proteins possess additional domains with catalytic or other functional activities. Their way of interaction with respective partners in different cellular processes and their functional variability are yet to be fully explored. Their occurrence and widespread diversity in the higher order of organisms suggest their involvement

Table 1 List of the functions of various WD repeat proteins

Protein	Function	References
WDR5	Differentiation of osteoblast and chondrocytes	[111]
TFIID	Transcription initiation complex	[112]
IC138/IC140/IFTA-1	Cilia assembly	[113]
MHCK-A/B/C	Cytoskeleton and myosin assembly	[114]
Lis-1	Regulates microtubule motor cytoplasmic dynein	[115]
Swd2	Polyadenylation in transcription	[116]
SPA1	Part of phytochrome A signal transduction complex in Arabidopsis	[117]
Mad2/BubR1	Form kinetochore complex which is involved in interaction with histone deacetylase	[118]
Bop1/GRWD1	Part of pre-ribosomal complex in ribosome biogenesis	[119]
STE4	Subunit of heterotrimeric G protein signal transducing in yeasts	[120]
MSI1	Negatively regulates the Ras-mediated increase in cAMP	[121]
PR55	Regulatory subunit of protein phosphatase 2A	[122, 123]
PLAP	Activator protein of phospholipase A2	[124]
PRP4/PRP17	Role in splicing in yeasts	[125]
HIR1	Acts as repressor of histone gene transcription	[126]
SEC13	Formation of mature transport vesicle from ER membrane	[127]
TAFII80	Component of RNA polymerase II transcriptional apparatus	[128]
Mdv1p	Role in division of mitochondria	[129]
Leucine rich repeat kinase-1 (LRRK-1)	Regulates osteoclast function	[130]
Tomosyn	Inhibits vesicle priming and synaptic transmission	[131]
SG2NA	Maintains the Endoplasmic reticulum homeostasis Protects cells from oxidative injury	[77, 97]

Table 2 List of the diseases caused by the various WD repeat proteins

Protein	Disease	References
Endonuclein	A cell cycle regulated protein which act as an oncogene when upregulated	[132]
STRAP	Oncogenic effect through interaction with TGF- β	[133]
G protein β -3	Spliced variants are found in case of hypertension	[134]
AAAS	Mutation in it causes triple A syndrome	[135, 136]
Gurcho	Role in colorectal cancer suppression by Wnt signalling pathway	[137]
AHI 1	Mutation in it is responsible for Joubert syndrome	[138]
LIS1	Mutation in it causes Lissencephaly	[20, 139]
CSA	Mutation causes Cockayne syndrome	[140]
TBL1	Deletion in it leads to late-onset sensory neural deafness phenotype	[141]
SG2NA and zinedin	Cancer cell survival and progression	[78, 142]

in sustaining the complexity of those organisms. Although recent studies have shed light on the structure, mechanism of action and abnormalities that are caused due to any impairment in their functions, a detailed analysis of these proteins throughout the five kingdoms of life have never been performed. Once thought to be confined as a eukaryotic protein, its presence has now been detected in prokaryotes as well. However, due to the lack of detailed characterization and knowledge of functional aspects of these proteins in prokaryotes, the question of their evolution is still unanswered. We have summarised their functions and the diversity in various

kingdoms of life. Accumulative evidences indicate that they primarily serve as an interacting platform for various proteins that are the key regulator of diverse processes. None of the known WD repeats containing protein has any catalytic activity, while they can possess other subunits performing the catalytic functions. Therefore, understanding the role of WD repeat-containing proteins is of paramount importance to understand the critical processes they regulate. The growing research on these proteins highlights the significance of the role played by them.

Table 3 Summary of the various WD repeat proteins amongst the five kingdoms

Protein	Organism	Function	References
Protista			
Mut11	<i>Chlamydomonas reinhardtii</i>	Gene regulation by transcriptional repression	[25]
Myosin F protein	<i>Gregarina polymorpha</i>	Actin remodelling	[26]
LACK1 (homologue of RACK1)	<i>Leishmania</i>	Role in thermostability and pathogenicity	[27]
TRACK (homologue of RACK1)	<i>Trypanosoma brucei</i>	Role in cytokinesis	[28, 29]
PfSEC13	<i>Plasmodium falciparum</i>	Role in regulation of transcription	[30]
PfRACK	<i>Plasmodium falciparum</i>	Signalling and cell migration	[31]
pfWLP1	<i>Plasmodium falciparum</i>	Stabilizes cell adhesion complex	[32]
Fungi			
Receptor for activated C kinase (RACK1) like protein	<i>Verticillium dahliae</i>	Role in regulation of the hyphal growth, virulence and pathogenicity	[33]
Asc1p (RACK1 protein homologue)	<i>Saccharomyces cerevisiae</i>	Phosphosignalling and translation repression	[34, 35]
RAK1 (RACK1 protein homologue)	<i>Ustilago maydis</i>	Role in cell wall formation, growth, mating and virulence	[37]
Pro11 (mammalian striatin homologue)	<i>Sordaria macrospora</i>	Role in fungal cell differentiation during fruiting body development	[38]
Ham-3 (Striatin orthologue)	<i>Neurospora crassa</i>	Role in vegetative and reproductive development	[40]
Mis16 (MSIL protein)	<i>S. pombe</i>	Role in kinetochore assembly in mitosis	[43]
HET-D and HET-E (heterokaryon incompatibility protein)	<i>Podospira anserine</i>	Responsible for vegetative incompatibility	[44, 45]
Gβ like protein (CpcB, Cross pathway control B)	<i>Aspergillus fumigatus</i>	Participates in virulence and drug sensitivity	[46]
CreC homologue	<i>Magnaporthe oryzae</i>	Role in vegetative and sexual growth, conidium formation and pathogenicity by modulating CRC pathway	[48]
Plants			
Gβ (member of G protein complex)	<i>Arabidopsis thaliana</i>	Role in the production of ROS, defence gene activation, callose deposition or apoptosis in response to fungal and bacterial infections	[15–17, 51–55]
Transparent testa glabra1 (TTG1)	<i>Nicotiana tabacum</i>	Activates immune response of plants by ROS production and apoptosis	[57]
LEUNIG Homolog (LUH), FRAGILE FIBER3 (FRA3) and TWD40-2	<i>Arabidopsis thaliana</i>	Cell wall formation	[62, 63, 65]
CYP71	<i>Arabidopsis thaliana</i>	Development and root elongation	[66]
HOS15	<i>Arabidopsis thaliana</i>	Repression of abiotic stress tolerant genes by mediating their histone deacetylation	[67]
MS11	<i>Arabidopsis thaliana</i>	Part of histone deacetylase complex and regulate abscisic acid signalling	[68]
ULCS1	<i>Arabidopsis thaliana</i>	Controls proteasomal degradation of different proteins involved in developmental	[70]
RAE1	<i>Nicotiana tabacum</i>	Role in spindle fibre organisation	[71]
NEDD	<i>Arabidopsis thaliana</i>	Role in microtubule organisation	[72]
Animals			
RACK1 (Receptor for activated kinase1)	Mammals	Role in PKC mediated signalling	[73]
Striatins	Mammals	Ca ²⁺ signalling pathway, vesicular trafficking	[74, 75]
CKA (homologue of striatin/SG2NA)	<i>Drosophila</i>	JNK signalling	[76]
SG2NA	Mouse, Human	Protects cells from oxidative stress and role in cancer cell proliferation	[77, 78]
Notchless gene	<i>Drosophila</i> and <i>Xenopus</i>	Modulates Notch signalling activity during development	[79]

Table 3 (continued)

Protein	Organism	Function	References
WDR26	<i>Drosophila</i> , Mouse, Human	Suppresses MAPK (Mitogen activated protein kinase) signalling pathway	[80]
ORC-associated (ORCA)	Human	DNA replication initiation and cell cycle progression	[81]
CAF-1 (chromatin assembly factor-1)	<i>Drosophila</i> , Mammals	Role in chromatin assembly and histone modification	[82, 83]
Cdc20	Mammals	Activates APC/C and plays role in different cell cycle stages	[86, 87]
Coronin	<i>C. elegans</i> , <i>Drosophila</i> , Mammals	Organizing normal actin cytoskeleton and in cell division	[90]
Myocardial Ischemic preconditioning up regulated protein-2 (MIP2)	Rat	Cell proliferation	[91]
NEDD1	Mouse, Human	Role in correct localization of γ tubulin	[92, 93]
Striatin	Human	Interacts with PP2A to regulate MAP2 phosphorylation and microtubule dynamics. Striatin inhibition arrests cells in G0/G1 phase and inhibit proliferation	[94]
SG2NA	Mouse, Human	Affects cell cycle progression	[96, 97]
50 kDa subunit of Cleavage stimulation factor (CstF)	Human	Role in mRNA processing	[98]
WDR5	Mammals	Activation of transcription of genes and development	[99–101, 143]
FcRACK1	Chinese white shrimp	Innate immunity A WD40 repeats containing protein binds to nucleotide binding domain of Nod2, a Leucine rich repeat containing (NLR) family member. It modulates Nod2 and Nod1 mediated NF- κ B activation, thus	[102]
Angio-associated migratory cell protein (AAMP)	Human	Regulates innate immune response	[103]
Actin interacting protein (Aip1)	<i>Drosophila</i>	Induces disassembly of actin filaments and regulates various processes as cytokinesis, cell migration, muscle contractility	[104, 105, 107]
β -TrCp-2	<i>Xenopus</i>	Regulates the Wnt/ β catenin signalling pathway	[108]
Extra sex comb protein (esc)	<i>Drosophila</i>	Repression of homeotic genes (polycomb gene repressor)	[109]
WDR62	<i>Drosophila</i>	Brain growth and development	[110]

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Research Involving Human and Animal Participants This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Li D, Roberts R (2001) WD-repeat proteins: structure characteristics, biological function, and their involvement in human diseases. *Cell Mol Life Sci* 58:2085–2097
2. Smith TF, Gaitatzes C, Saxena K, Neer EJ (1999) The WD repeat: a common architecture for diverse functions. *Trends Biochem Sci* 24:181–185
3. Stirnimann CU, Petsalaki E, Russell RB, Müller CW (2010) WD40 proteins propel cellular networks. *Trends Biochem Sci* 35:565–574. <https://doi.org/10.1016/j.tibs.2010.04.003>

4. Xu C, Min J (2011) Structure and function of WD40 domain proteins. *Protein Cell* 2:202–214. <https://doi.org/10.1007/s13238-011-1018-1>
5. Andrade MA, Perez-Iratxeta C, Ponting CP (2001) Protein repeats: structures, functions, and evolution. *J Struct Biol* 134:117–131. <https://doi.org/10.1006/jsbi.2001.4392>
6. van Nocker S, Ludwig P (2003) The WD-repeat protein superfamily in Arabidopsis: conservation and divergence in structure and function. *BMC Genomics* 4:50. <https://doi.org/10.1186/1471-2164-4-50>
7. Ouyang Y, Huang X, Lu Z, Yao J (2012) Genomic survey, expression profile and co-expression network analysis of OsWD40 family in rice. *BMC Genomics* 13:100. <https://doi.org/10.1186/1471-2164-13-100>
8. Letunic I, Doerks T, Bork P (2009) SMART 6: recent updates and new developments. *Nucleic Acids Res* 37:D229–D232. <https://doi.org/10.1093/nar/gkn808>
9. Janda L, Tichý P, Spížek J, Petříček M (1996) A deduced *Thermomonospora curvata* protein containing serine/threonine protein kinase and WD-repeat domains. *J Bacteriol* 178:1487–1489
10. Neer EJ, Schmidt CJ, Nambudripad R, Smith TF (1994) The ancient regulatory-protein family of WD-repeat proteins. *Nature* 371:297–300. <https://doi.org/10.1038/371297a0>
11. Voegtli WC, Madrona AY, Wilson DK (2003) The structure of Aip1p, a WD repeat protein that regulates Cofilin-mediated actin depolymerization. *J Biol Chem* 278:34373–34379. <https://doi.org/10.1074/jbc.M302773200>
12. Faber HR, Groom CR, Baker HM et al (1995) 1.8 Å crystal structure of the C-terminal domain of rabbit serum haemopexin. *Structure* 3:551–559
13. Murzin AG (1992) Structural principles for the propeller assembly of beta-sheets: the preference for seven-fold symmetry. *Proteins* 14:191–201. <https://doi.org/10.1002/prot.340140206>
14. Whittle JRR, Schwartz TU (2010) Structure of the Sec13-Sec16 edge element, a template for assembly of the COPII vesicle coat. *J Cell Biol* 190:347–361. <https://doi.org/10.1083/jcb.201003092>
15. Lee S, Rojas CM, Ishiga Y et al (2013) Arabidopsis heterotrimeric G-proteins play a critical role in host and nonhost resistance against *Pseudomonas syringae* pathogens. *PLoS ONE* 8:e82445. <https://doi.org/10.1371/journal.pone.0082445>
16. Liu J, Ding P, Sun T et al (2013) Heterotrimeric G proteins serve as a converging point in plant defense signaling activated by multiple receptor-like kinases. *Plant Physiol* 161:2146–2158. <https://doi.org/10.1104/pp.112.212431>
17. Llorente F, Alonso-Blanco C, Sánchez-Rodríguez C et al (2005) ERECTA receptor-like kinase and heterotrimeric G protein from Arabidopsis are required for resistance to the necrotrophic fungus *Plectosphaerella cucumerina*. *Plant J Cell Mol Biol* 43:165–180. <https://doi.org/10.1111/j.1365-3113X.2005.02440.x>
18. Jing H, Takagi J, Liu JH et al (2002) Archaeal surface layer proteins contain beta propeller, PKD, and beta helix domains and are related to metazoan cell surface proteins. *Structure* 10(10):1453–1464
19. Ponting CP, Aravind L, Schultz J et al (1999) Eukaryotic signaling domain homologues in archaea and bacteria. Ancient ancestry and horizontal gene transfer. *J Mol Biol* 289(4):729–745
20. Neer EJ, Schmidt CJ, Smith T (1993) LIS is more. *Nat Genet* 5:3–4. <https://doi.org/10.1038/ng0993-3>
21. Petříčková K, Hasek J, Benada O, Petříček M (2006) The WD-40 repeat protein PkwA of *Thermomonospora curvata* is associated with rapid growth and is localized in the tips of growing hyphae. *FEMS Microbiol Lett* 258:187–193. <https://doi.org/10.1111/j.1574-6968.2006.00215.x>
22. Stoytcheva Z, Joshi B, Spížek J, Tichý P (2000) WD-repeat protein encoding genes among prokaryotes of the Streptomyces genus. *Folia Microbiol* 45:407–413
23. Ulrych A, Goldová J, Petříček M et al (2013) The pleiotropic effect of WD-40 domain containing proteins on cellular differentiation and production of secondary metabolites in *Streptomyces coelicolor*. *Mol Biosyst* 9:1453–1469. <https://doi.org/10.1039/c3mb25542e>
24. Hu X-J, Li T, Wang Y et al (2017) Prokaryotic and highly-repetitive WD40 proteins: a systematic study. *Sci Rep* 7:10585. <https://doi.org/10.1038/s41598-017-11115-1>
25. Zhang C, Wu-Scharf D, Jeong B, Cerutti H (2002) A WD40-repeat containing protein, similar to a fungal co-repressor, is required for transcriptional gene silencing in Chlamydomonas. *Plant J Cell Mol Biol* 31:25–36
26. Heintzelman MB, Mateer MJ (2008) GpMyoF, a WD40 repeat-containing myosin associated with the myonemes of *Gregarina polymorpha*. *J Parasitol* 94:158–168. <https://doi.org/10.1645/GE-1339.1>
27. Cardenas D, Carter PM, Nation CS et al (2015) LACK, a RACK1 ortholog, facilitates cytochrome c oxidase subunit expression to promote Leishmania major fitness. *Mol Microbiol* 96:95–109. <https://doi.org/10.1111/mmi.12924>
28. Regmi S, Rothberg KG, Hubbard JG, Ruben L (2008) The RACK1 signal anchor protein from *Trypanosoma brucei* associates with eukaryotic elongation factor 1A: a role for translational control in cytokinesis. *Mol Microbiol* 70:724–745. <https://doi.org/10.1111/j.1365-2958.2008.06443.x>
29. Rothberg KG, Burdette DL, Pfannstiel J et al (2006) The RACK1 homologue from *Trypanosoma brucei* is required for the onset and progression of cytokinesis. *J Biol Chem* 281:9781–9790. <https://doi.org/10.1074/jbc.M600133200>
30. Dahan-Pasternak N, Nasereddin A, Kolevzon N et al (2013) PfSec13 is an unusual chromatin-associated nucleoporin of *Plasmodium falciparum* that is essential for parasite proliferation in human erythrocytes. *J Cell Sci* 126:3055–3069. <https://doi.org/10.1242/jcs.122119>
31. Buensuceso CS, Obergfell A, Soriani A et al (2005) Regulation of outside-in signaling in platelets by integrin-associated protein kinase C beta. *J Biol Chem* 280:644–653. <https://doi.org/10.1074/jbc.M410229200>
32. von Bohl A, Kuehn A, Simon N et al (2015) A WD40-repeat protein unique to malaria parasites associates with adhesion protein complexes and is crucial for blood stage progeny. *Malar J* 14:435. <https://doi.org/10.1186/s12936-015-0967-x>
33. Yuan L, Su Y, Zhou S et al (2017) A RACK1-like protein regulates hyphal morphogenesis, root entry and in vivo virulence in *Verticillium dahliae*. *Fungal Genet Biol* 99:52–61. <https://doi.org/10.1016/j.fgb.2017.01.003>
34. Schmitt K, Smolinski N, Neumann P et al (2017) Asc1p/RACK1 connects ribosomes to eukaryotic phosphosignaling. *Mol Cell Biol*. <https://doi.org/10.1128/MCB.00279-16>
35. Valerius O, Kleinschmidt M, Rachfall N et al (2007) The Saccharomyces homolog of mammalian RACK1, Cpc2/Asc1p, is required for FLO11-dependent adhesive growth and dimorphism. *Mol Cell Proteomics* 6:1968–1979. <https://doi.org/10.1074/mcp.M700184-MCP200>
36. Zeller CE, Parnell SC, Dohlman HG (2007) The RACK1 ortholog Asc1 functions as a G-protein beta subunit coupled to glucose responsiveness in yeast. *J Biol Chem* 282:25168–25176. <https://doi.org/10.1074/jbc.M702569200>
37. Wang L, Berndt P, Xia X et al (2011) A seven-WD40 protein related to human RACK1 regulates mating and virulence in *Ustilago maydis*. *Mol Microbiol* 81:1484–1498. <https://doi.org/10.1111/j.1365-2958.2011.07783.x>
38. Pöggeler S, Kück U (2004) A WD40 repeat protein regulates fungal cell differentiation and can be replaced functionally by the mammalian homologue striatin. *Eukaryot Cell* 3:232–240

39. Nordzicke S, Zobel T, Fränzel B et al (2015) A fungal sarcolemmal membrane-associated protein (SLMAP) homolog plays a fundamental role in development and localizes to the nuclear envelope, endoplasmic reticulum, and mitochondria. *Eukaryot Cell* 14:345–358. <https://doi.org/10.1128/EC.00241-14>
40. Simonin AR, Rasmussen CG, Yang M, Glass NL (2010) Genes encoding a striatin-like protein (ham-3) and a forkhead associated protein (ham-4) are required for hyphal fusion in *Neurospora crassa*. *Fungal Genet Biol* 47:855–868. <https://doi.org/10.1016/j.fgb.2010.06.010>
41. Dettmann A, Heilig Y, Ludwig S et al (2013) HAM-2 and HAM-3 are central for the assembly of the *Neurospora* STRIPAK complex at the nuclear envelope and regulate nuclear accumulation of the MAP kinase MAK-1 in a MAK-2-dependent manner. *Mol Microbiol* 90:796–812. <https://doi.org/10.1111/mmi.12399>
42. Yang D-H, Maeng S, Bahn Y-S (2013) Msi1-like (MSIL) proteins in fungi. *Mycobiology* 41:1–12. <https://doi.org/10.5941/MYCO.2013.41.1.1>
43. Hayashi T, Fujita Y, Iwasaki O et al (2004) Mis16 and Mis18 are required for CENP-A loading and histone deacetylation at centromeres. *Cell* 118:715–729. <https://doi.org/10.1016/j.cell.2004.09.002>
44. Espagne E, Balhadère P, Penin M-L et al (2002) HET-E and HET-D belong to a new subfamily of WD40 proteins involved in vegetative incompatibility specificity in the fungus *Podospora anserina*. *Genetics* 161:71–81
45. Paoletti M, Saupe SJ, Clavé C (2007) Genesis of a fungal non-self recognition repertoire. *PLoS ONE* 2:e283. <https://doi.org/10.1371/journal.pone.0000283>
46. Cai Z, Chai Y, Zhang C et al (2015) The Gβ-like protein CpcB is required for hyphal growth, conidiophore morphology and pathogenicity in *Aspergillus fumigatus*. *Fungal Genet Biol* 81:120–131. <https://doi.org/10.1016/j.fgb.2015.04.007>
47. Chin C, Lai W-C, Lee T-L et al (2013) Dissection of the *Candida albicans* Cdc4 protein reveals the involvement of domains in morphogenesis and cell flocculation. *J Biomed Sci* 20:97. <https://doi.org/10.1186/1423-0127-20-97>
48. Matar KAO, Chen X, Chen D et al (2017) WD40-repeat protein MoCreC is essential for carbon repression and is involved in conidiation, growth and pathogenicity of *Magnaporthe oryzae*. *Curr Genet* 63:685–696. <https://doi.org/10.1007/s00294-016-0668-1>
49. Adams DR, Ron D, Kiely PA (2011) RACK1, a multifaceted scaffolding protein: structure and function. *Cell Commun Signal* 9:22. <https://doi.org/10.1186/1478-811X-9-22>
50. Bradford W, Buckholz A, Morton J et al (2013) Eukaryotic G protein signaling evolved to require G protein-coupled receptors for activation. *Sci Signal* 6:ra37. <https://doi.org/10.1126/scisignal.2003768>
51. Delgado-Cerezo M, Sánchez-Rodríguez C, Escudero V et al (2012) Arabidopsis heterotrimeric G-protein regulates cell wall defense and resistance to necrotrophic fungi. *Mol Plant* 5:98–114. <https://doi.org/10.1093/mp/ssr082>
52. Torres MA, Morales J, Sánchez-Rodríguez C et al (2013) Functional interplay between Arabidopsis NADPH oxidases and heterotrimeric G protein. *Mol Plant Microbe Interact* 26:686–694. <https://doi.org/10.1094/MPMI-10-12-0236-R>
53. Trusov Y, Rookes JE, Chakravorty D et al (2006) Heterotrimeric G proteins facilitate Arabidopsis resistance to necrotrophic pathogens and are involved in jasmonate signaling. *Plant Physiol* 140:210–220. <https://doi.org/10.1104/pp.105.069625>
54. Trusov Y, Rookes JE, Tilbrook K et al (2007) Heterotrimeric G protein gamma subunits provide functional selectivity in Gbetagamma dimer signaling in Arabidopsis. *Plant Cell* 19:1235–1250. <https://doi.org/10.1105/tpc.107.050096>
55. Trusov Y, Sewelam N, Rookes JE et al (2009) Heterotrimeric G proteins-mediated resistance to necrotrophic pathogens includes mechanisms independent of salicylic acid-, jasmonic acid/ethylene- and abscisic acid-mediated defense signaling. *Plant J Cell Mol Biol* 58:69–81. <https://doi.org/10.1111/j.1365-313X.2008.03755.x>
56. Zhang W, He SY, Assmann SM (2008) The plant innate immunity response in stomatal guard cells invokes G-protein-dependent ion channel regulation. *Plant J Cell Mol Biol* 56:984–996. <https://doi.org/10.1111/j.1365-313X.2008.03657.x>
57. Wang Y, Liu R, Chen L et al (2009) *Nicotiana tabacum* TTG1 contributes to ParA1-induced signalling and cell death in leaf trichomes. *J Cell Sci* 122:2673–2685. <https://doi.org/10.1242/jcs.049023>
58. Morohashi K, Zhao M, Yang M et al (2007) Participation of the Arabidopsis bHLH factor GL3 in trichome initiation regulatory events. *Plant Physiol* 145:736–746. <https://doi.org/10.1104/pp.107.104521>
59. Zhao M, Morohashi K, Hatlestad G et al (2008) The TTG1-bHLH-MYB complex controls trichome cell fate and patterning through direct targeting of regulatory loci. *Development* 135:1991–1999. <https://doi.org/10.1242/dev.016873>
60. Dixon RA (2001) Natural products and plant disease resistance. *Nature* 411:843–847. <https://doi.org/10.1038/35081178>
61. Kliebenstein DJ (2013) Making new molecules—evolution of structures for novel metabolites in plants. *Curr Opin Plant Biol* 16:112–117. <https://doi.org/10.1016/j.pbi.2012.12.004>
62. Bui M, Lim N, Sijacic P, Liu Z (2011) LEUNIG_HOMOLOG and LEUNIG regulate seed mucilage extrusion in Arabidopsis. *J Integr Plant Biol* 53:399–408. <https://doi.org/10.1111/j.1744-7909.2011.01036.x>
63. Zhong R, Burk DH, Morrison WH, Ye Z-H (2004) FRAGILE FIBER3, an Arabidopsis gene encoding a type II inositol polyphosphate 5-phosphatase, is required for secondary wall synthesis and actin organization in fiber cells. *Plant Cell* 16:3242–3259. <https://doi.org/10.1105/tpc.104.027466>
64. Bashline L, Li S, Zhu X, Gu Y (2015) The TWD40-2 protein and the AP2 complex cooperate in the clathrin-mediated endocytosis of cellulose synthase to regulate cellulose biosynthesis. *Proc Natl Acad Sci USA* 112:12870–12875. <https://doi.org/10.1073/pnas.1509292112>
65. Zhang Y, Persson S, Hirst J et al (2015) Change your TPLATE, change your fate: plant CME and beyond. *Trends Plant Sci* 20:41–48. <https://doi.org/10.1016/j.tplants.2014.09.002>
66. Li H, He Z, Lu G et al (2007) A WD40 domain cyclophilin interacts with histone H3 and functions in gene repression and organogenesis in Arabidopsis. *Plant Cell* 19:2403–2416. <https://doi.org/10.1105/tpc.107.053579>
67. Zhu J, Jeong JC, Zhu Y et al (2008) Involvement of Arabidopsis HOS15 in histone deacetylation and cold tolerance. *Proc Natl Acad Sci USA* 105:4945–4950. <https://doi.org/10.1073/pnas.0801029105>
68. Mehdi S, Derkacheva M, Ramström M et al (2016) The WD40 domain protein MSI1 functions in a histone deacetylase complex to fine-tune abscisic acid signaling. *Plant Cell* 28:42–54. <https://doi.org/10.1105/tpc.15.00763>
69. Uljon S, Xu X, Durzynska I et al (2016) Structural basis for substrate selectivity of the E3 ligase COP1. *Structure* 24:687–696. <https://doi.org/10.1016/j.str.2016.03.002>
70. Beris D, Kopolas G, Livanos P et al (2016) RNAi-mediated silencing of the *Arabidopsis thaliana* ULCS1 gene, encoding a WDR protein, results in cell wall modification impairment and plant infertility. *Plant Sci Int J Exp Plant Biol* 245:71–83. <https://doi.org/10.1016/j.plantsci.2016.01.008>
71. Lee J-Y, Lee H-S, Wi S-J et al (2009) Dual functions of *Nicotiana benthamiana* Rae1 in interphase and mitosis. *Plant J*

- Cell Mol Biol 59:278–291. <https://doi.org/10.1111/j.1365-313X.2009.03869.x>
72. Zeng CJT, Lee Y-RJ, Liu B (2009) The WD40 repeat protein NEDD1 functions in microtubule organization during cell division in *Arabidopsis thaliana*. Plant Cell 21:1129–1140. <https://doi.org/10.1105/tpc.109.065953>
 73. Ron D, Chen CH, Caldwell J et al (1994) Cloning of an intracellular receptor for protein kinase C: a homolog of the beta subunit of G proteins. Proc Natl Acad Sci USA 91:839–843
 74. Castets F, Bartoli M, Barnier JV et al (1996) A novel calmodulin-binding protein, belonging to the WD-repeat family, is localized in dendrites of a subset of CNS neurons. J Cell Biol 134:1051–1062
 75. Baillat G, Moqrach A, Castets F et al (2001) Molecular cloning and characterization of phocein, a protein found from the Golgi complex to dendritic spines. Mol Biol Cell 12:663–673
 76. Chen H-W, Marinissen MJ, Oh S-W et al (2002) CKA, a novel multidomain protein, regulates the JUN N-terminal kinase signal transduction pathway in *Drosophila*. Mol Cell Biol 22:1792–1803
 77. Tanti GK, Goswami SK (2014) SG2NA recruits DJ-1 and Akt into the mitochondria and membrane to protect cells from oxidative damage. Free Radic Biol Med 75C:1–13. <https://doi.org/10.1016/j.freeradbiomed.2014.07.009>
 78. Tanti GK, Pandey S, Goswami SK (2015) SG2NA enhances cancer cell survival by stabilizing DJ-1 and thus activating Akt. Biochem Biophys Res Commun 463:524–531. <https://doi.org/10.1016/j.bbrc.2015.05.069>
 79. Royet J, Bouwmeester T, Cohen SM (1998) Notchless encodes a novel WD40-repeat-containing protein that modulates Notch signaling activity. EMBO J 17:7351–7360. <https://doi.org/10.1093/emboj/17.24.7351>
 80. Zhu Y, Wang Y, Xia C et al (2004) WDR26: a novel Gbeta-like protein, suppresses MAPK signaling pathway. J Cell Biochem 93:579–587. <https://doi.org/10.1002/jcb.20175>
 81. Shen Z, Sathyan KM, Geng Y et al (2010) A WD-repeat protein stabilizes ORC binding to chromatin. Mol Cell 40:99–111. <https://doi.org/10.1016/j.molcel.2010.09.021>
 82. Tyler JK, Collins KA, Prasad-Sinha J et al (2001) Interaction between the *Drosophila* CAF-1 and ASF1 chromatin assembly factors. Mol Cell Biol 21:6574–6584
 83. Verreault A, Kaufman PD, Kobayashi R, Stillman B (1996) Nucleosome assembly by a complex of CAF-1 and acetylated histones H3/H4. Cell 87:95–104
 84. Hu Y, Ding L, Spencer DM, Núñez G (1998) WD-40 repeat region regulates Apaf-1 self-association and procaspase-9 activation. J Biol Chem 273:33489–33494
 85. Zou H, Henzel WJ, Liu X et al (1997) Apaf-1, a human protein homologous to *C. elegans* CED-4, participates in cytochrome c-dependent activation of caspase-3. Cell 90:405–413
 86. van Leuken R, Clijsters L, Wolthuis R (2008) To cell cycle, swing the APC/C. Biochim Biophys Acta 1786:49–59. <https://doi.org/10.1016/j.bbcan.2008.05.002>
 87. Skaar JR, Pagan JK, Pagano M (2013) Mechanisms and function of substrate recruitment by F-box proteins. Nat Rev Mol Cell Biol 14:369–381. <https://doi.org/10.1038/nrm3582>
 88. Taguchi S-ichi, Honda K, Sugiura K et al (2002) Degradation of human Aurora-A protein kinase is mediated by hCdh1. FEBS Lett 519:59–65
 89. de Hostos EL, Bradtke B, Lottspeich F et al (1991) Coronin, an actin binding protein of *Dictyostelium discoideum* localized to cell surface projections, has sequence similarities to G protein beta subunits. EMBO J 10:4097–4104
 90. Rybakina V, Clemen CS (2005) Coronin proteins as multifunctional regulators of the cytoskeleton and membrane trafficking. BioEssays 27:625–632. <https://doi.org/10.1002/bies.20235>
 91. Wei X, Song L, Jiang L et al (2010) Overexpression of MIP2, a novel WD-repeat protein, promotes proliferation of H9c2 cells. Biochem Biophys Res Commun 393:860–863. <https://doi.org/10.1016/j.bbrc.2010.02.099>
 92. Manning J, Kumar S (2007) NEDD1: function in microtubule nucleation, spindle assembly and beyond. Int J Biochem Cell Biol 39:7–11. <https://doi.org/10.1016/j.biocel.2006.08.012>
 93. Manning JA, Shalini S, Risk JM et al (2010) A direct interaction with NEDD1 regulates gamma-tubulin recruitment to the centrosome. PLoS ONE 5:e9618. <https://doi.org/10.1371/journal.pone.0009618>
 94. Kązmierzak-Barańska J, Pęczek Ł, Przygodzka P, Cieślak MJ (2015) Downregulation of striatin leads to hyperphosphorylation of MAP2, induces depolymerization of microtubules and inhibits proliferation of HEK293T cells. FEBS Lett 589:222–230. <https://doi.org/10.1016/j.febslet.2014.12.003>
 95. Hyodo T, Ito S, Hasegawa H et al (2012) Misshapen-like kinase 1 (MINK1) is a novel component of striatin-interacting phosphatase and kinase (STRIPAK) and is required for the completion of cytokinesis. J Biol Chem 287:25019–25029. <https://doi.org/10.1074/jbc.M112.372342>
 96. Pandey S, Talukdar I, Jain BP, Goswami SK (2017) GSK3β and ERK regulate the expression of 78 kDa SG2NA and ectopic modulation of its level affects phases of cell cycle. Sci Rep 7:7555. <https://doi.org/10.1038/s41598-017-08085-9>
 97. Jain BP, Pandey S, Saleem N et al (2017) SG2NA is a regulator of endoplasmic reticulum (ER) homeostasis as its depletion leads to ER stress. Cell Stress Chaperones. <https://doi.org/10.1007/s12192-017-0816-7>
 98. Takagaki Y, Manley JL (1992) A human polyadenylation factor is a G protein beta-subunit homologue. J Biol Chem 267:23471–23474
 99. Ang Y-S, Tsai S-Y, Lee D-F et al (2011) Wdr5 mediates self-renewal and reprogramming via the embryonic stem cell core transcriptional network. Cell 145:183–197. <https://doi.org/10.1016/j.cell.2011.03.003>
 100. Wysocka J, Swigut T, Xiao H et al (2006) A PHD finger of NURF couples histone H3 lysine 4 trimethylation with chromatin remodelling. Nature 442:86–90. <https://doi.org/10.1038/nature04815>
 101. Wysocka J, Swigut T, Milne TA et al (2005) WDR5 associates with histone H3 methylated at K4 and is essential for H3 K4 methylation and vertebrate development. Cell 121:859–872. <https://doi.org/10.1016/j.cell.2005.03.036>
 102. Ren Q, Zhou J, Zhao X-F, Wang J-X (2011) Molecular cloning and characterization of a receptor for activated protein kinase C1 (RACK1) from Chinese white shrimp; *Fenneropenaeus chinensis*. Dev Comp Immunol 35:629–634. <https://doi.org/10.1016/j.dci.2011.01.004>
 103. Biegel H, Zurek B, Kutsch A et al (2009) A function for AAMP in Nod2-mediated NF-kappaB activation. Mol Immunol 46:2647–2654. <https://doi.org/10.1016/j.molimm.2009.04.022>
 104. Adler HJ, Sanovich E, Brittan-Powell EF et al (2008) WDR1 presence in the songbird basilar papilla. Hear Res 240:102–111. <https://doi.org/10.1016/j.heares.2008.03.008>
 105. Luxenburg C, Heller E, Pasolli HA et al (2015) Wdr1-mediated cell shape dynamics and cortical tension are essential for epidermal planar cell polarity. Nat Cell Biol 17:592–604. <https://doi.org/10.1038/ncb3146>
 106. Poukkula M, Hakala M, Pentimikko N et al (2014) GMF promotes leading-edge dynamics and collective cell migration in vivo. Curr Biol 24:2533–2540. <https://doi.org/10.1016/j.cub.2014.08.066>
 107. Yuan B, Wan P, Chu D et al (2014) A cardiomyocyte-specific Wdr1 knockout demonstrates essential functional roles for actin disassembly during myocardial growth and maintenance

- in mice. *Am J Pathol* 184:1967–1980. <https://doi.org/10.1016/j.ajpath.2014.04.007>
108. Marikawa Y, Elinson RP (1998) beta-TrCP is a negative regulator of Wnt/beta-catenin signaling pathway and dorsal axis formation in *Xenopus embryos*. *Mech Dev* 77:75–80
 109. Simon J, Bornemann D, Lunde K, Schwartz C (1995) The extra sex combs product contains WD40 repeats and its time of action implies a role distinct from other Polycomb group products. *Mech Dev* 53:197–208
 110. Lim NR, Shohayeb B, Zaytseva O et al (2017) Glial-specific functions of microcephaly protein WDR62 and interaction with the mitotic kinase AURKA are essential for *Drosophila* brain growth. *Stem Cell Rep* 9:32–41. <https://doi.org/10.1016/j.stemcr.2017.05.015>
 111. Gori F, Friedman L, Demay MB (2005) Wdr5, a novel WD repeat protein, regulates osteoblast and chondrocyte differentiation in vivo. *J Musculoskelet Neuronal Interact* 5:338–339
 112. Roberts SG (2000) Mechanisms of action of transcription activation and repression domains. *Cell Mol Life Sci* 57:1149–1160
 113. Hendrickson TW, Perrone CA, Griffin P et al (2004) IC138 is a WD-repeat dynein intermediate chain required for light chain assembly and regulation of flagellar bending. *Mol Biol Cell* 15:5431–5442. <https://doi.org/10.1091/mbc.E04-08-0694>
 114. Steimle PA, Naismith T, Licate L, Egelhoff TT (2001) WD repeat domains target dictyostelium myosin heavy chain kinases by binding directly to myosin filaments. *J Biol Chem* 276:6853–6860. <https://doi.org/10.1074/jbc.M008992200>
 115. Tarricone C, Perrina F, Monzani S et al (2004) Coupling PAF signaling to dynein regulation: structure of LIS1 in complex with PAF-acetylhydrolase. *Neuron* 44:809–821. <https://doi.org/10.1016/j.neuron.2004.11.019>
 116. Cheng H, He X, Moore C (2004) The essential WD repeat protein Swd2 has dual functions in RNA polymerase II transcription termination and lysine 4 methylation of histone H3. *Mol Cell Biol* 24:2932–2943
 117. Hoecker U, Tepperman JM, Quail PH (1999) SPA1, a WD-repeat protein specific to phytochrome A signal transduction. *Science* 284:496–499
 118. Yoon Y-M, Baek K-H, Jeong S-J et al (2004) WD repeat-containing mitotic checkpoint proteins act as transcriptional repressors during interphase. *FEBS Lett* 575:23–29. <https://doi.org/10.1016/j.febslet.2004.07.089>
 119. Gratenstein K, Heggstad AD, Fortun J et al (2005) The WD-repeat protein GRWD1: potential roles in myeloid differentiation and ribosome biogenesis. *Genomics* 85:762–773. <https://doi.org/10.1016/j.ygeno.2005.02.010>
 120. Klein S, Reuveni H, Levitzki A (2000) Signal transduction by a nondissociable heterotrimeric yeast G protein. *Proc Natl Acad Sci USA* 97:3219–3223. <https://doi.org/10.1073/pnas.050015797>
 121. Zhu X, Démolis N, Jacquet M, Michaeli T (2000) MS11 suppresses hyperactive RAS via the cAMP-dependent protein kinase and independently of chromatin assembly factor-1. *Curr Genet* 38:60–70
 122. Mayer RE, Hendrix P, Cron P et al (1991) Structure of the 55-kDa regulatory subunit of protein phosphatase 2A: evidence for a neuronal-specific isoform. *Biochemistry* 30:3589–3597
 123. Pallas DC, Weller W, Jaspers S et al (1992) The third subunit of protein phosphatase 2A (PP2A), a 55-kilodalton protein which is apparently substituted for by T antigens in complexes with the 36- and 63-kilodalton PP2A subunits, bears little resemblance to T antigens. *J Virol* 66:886–893
 124. Clark MA, Bomalaski JS, Conway TM et al (1990) The role of phospholipase A2 activating protein (PLAP) in regulating prostanoid production in smooth muscle and endothelial cells following leukotriene D4 treatment. *Adv Exp Med Biol* 275:125–144
 125. Sapra AK, Arava Y, Khandelia P, Vijayraghavan U (2004) Genome-wide analysis of pre-mRNA splicing: intron features govern the requirement for the second-step factor, Prp17 in *Saccharomyces cerevisiae* and *Schizosaccharomyces pombe*. *J Biol Chem* 279:52437–52446. <https://doi.org/10.1074/jbc.M408815200>
 126. Spector MS, Raff A, DeSilva H et al (1997) Hir1p and Hir2p function as transcriptional corepressors to regulate histone gene transcription in the *Saccharomyces cerevisiae* cell cycle. *Mol Cell Biol* 17:545–552
 127. Pryer NK, Salama NR, Schekman R, Kaiser CA (1993) Cytosolic Sec13p complex is required for vesicle formation from the endoplasmic reticulum in vitro. *J Cell Biol* 120:865–875
 128. Hampsey M (1998) Molecular genetics of the RNA polymerase II general transcriptional machinery. *Microbiol Mol Biol Rev* 62:465–503
 129. Tieu Q, Okreglak V, Naylor K, Nunnari J (2002) The WD repeat protein, Mdv1p, functions as a molecular adaptor by interacting with Dnm1p and Fis1p during mitochondrial fission. *J Cell Biol* 158:445–452. <https://doi.org/10.1083/jcb.200205031>
 130. Zeng C, Goodluck H, Qin X et al (2016) Leucine-rich repeat kinase-1 regulates osteoclast function by modulating RAC1/Cdc42 small GTPase phosphorylation and activation. *Am J Physiol Endocrinol Metab* 311:E772–E780. <https://doi.org/10.1152/ajpendo.00189.2016>
 131. Ashery U, Bielopolski N, Barak B, Yizhar O (2009) Friends and foes in synaptic transmission: the role of tomosyn in vesicle priming. *Trends Neurosci* 32:275–282. <https://doi.org/10.1016/j.tins.2009.01.004>
 132. Honoré B, Baandrup U, Nielsen S, Vorum H (2002) Endonuclein is a cell cycle regulated WD-repeat protein that is up-regulated in adenocarcinoma of the pancreas. *Oncogene* 21:1123–1129. <https://doi.org/10.1038/sj.onc.1205186>
 133. Halder T, Pawelec G, Kirkin AF et al (1997) Isolation of novel HLA-DR restricted potential tumor-associated antigens from the melanoma cell line FM3. *Cancer Res* 57:3238–3244
 134. Benjafield AV, Jeyasingam CL, Nyholt DR et al (1998) G-protein beta3 subunit gene (GNB3) variant in causation of essential hypertension. *Hypertension* 32:1094–1097
 135. Handschug K, Sperling S, Yoon SJ et al (2001) Triple A syndrome is caused by mutations in AAAS, a new WD-repeat protein gene. *Hum Mol Genet* 10:283–290
 136. Tullio-Pelet A, Salomon R, Hadj-Rabia S et al (2000) Mutant WD-repeat protein in triple-A syndrome. *Nat Genet* 26:332–335. <https://doi.org/10.1038/81642>
 137. Polakis P (2000) Wnt signaling and cancer. *Genes Dev* 14:1837–1851
 138. Parisi MA, Doherty D, Eckert ML et al (2006) AHI1 mutations cause both retinal dystrophy and renal cystic disease in Joubert syndrome. *J Med Genet* 43:334–339. <https://doi.org/10.1136/jmg.2005.036608>
 139. Lo Nigro C, Chong CS, Smith AC et al (1997) Point mutations and an intragenic deletion in LIS1, the lissencephaly causative gene in isolated lissencephaly sequence and Miller-Dieker syndrome. *Hum Mol Genet* 6:157–164
 140. Henning KA, Li L, Iyer N et al (1995) The Cockayne syndrome group A gene encodes a WD repeat protein that interacts with CSB protein and a subunit of RNA polymerase II TFIIF. *Cell* 82:555–564
 141. Bassi MT, Ramesar RS, Caciotti B et al (1999) X-linked late-onset sensorineural deafness caused by a deletion involving OA1 and a novel gene containing WD-40 repeats. *Am J Hum Genet* 64:1604–1616. <https://doi.org/10.1086/302408>

142. Wong M, Hyodo T, Asano E et al (2014) Silencing of STRN4 suppresses the malignant characteristics of cancer cells. *Cancer Sci* 105:1526–1532. <https://doi.org/10.1111/cas.12541>
143. Wang KC, Yang YW, Liu B et al (2011) A long noncoding RNA maintains active chromatin to coordinate homeotic gene expression. *Nature* 472:120–124. <https://doi.org/10.1038/nature09819>
144. Fong HK, Hurley JB, Hopkins RS et al (1986) Repetitive segmental structure of the transducin beta subunit: homology with the CDC4 gene and identification of related mRNAs. *Proc Natl Acad Sci USA* 83:2162–2166