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Study of the Evolutionary History of FBXO41

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Abstract: ***F-box proteins are a part of SCF (SKP1-Cullin1-RBX1-F-box-protein) ubiquitin ligase complexes that ubiquitinate cellular proteins. They are essential for normal functioning of several important cellular processes, including cellular signaling, cell cycle progression, stress response and cell death pathways. Deregulation of F-box proteins results in multiple disorders, however their role often remains elusive. FBXO41 has emerged as a key regulator in many cellular processes, notably in neurobiology and cancer. FBXO41 gene is mapped to human chromosome 2p13.2, which is located in PARK3 gene locus (2p13). FBXO41 is shown to disrupt neuronal primary cilia and affects the hedgehog signaling, which is crucial for brain development and function (King et al., 2019). It also plays a role in synaptic transmission and hippocampal network maturation; its loss leading to behavioral defects and impaired brain development (Quadros et al., 2022). Additionally, FBXO41 contributes to cancer biology, particularly in arsenic trioxide (ATO)-mediated autophagic cell death, highlighting its potential as a therapeutic target (Agrawal et al., 2022). Our study aims to construct a comprehensive phylogenetic tree of FBXO41 across species, identifying the conserved protein domains and motifs. By analyzing evolutionary relationships and the conserved and divergent regions, we aim to better understand the functions and implications of FBXO41 in neurodegenerative diseases. We have identified two undocumented conserved motifs and are working on understanding their potential roles. This could provide new insights into FBXO41 activity and pave the way for further research into FBXO41's molecular mechanisms and involvement in cellular development.***

Keywords: FBXO41, evolution, phylogenetics, conserved motifs

1. Introduction

The F-box protein family, characterized by an approximately 40 amino acid motif, encompasses diverse members, each with distinct protein-protein interaction modules or no recognizable motifs. Among these, FBXO41 stands out as a member of the FBXO class and a vital component of the Skp1-Cullin1-F-box protein (SCF) complex—a type of E3 ubiquitin ligase. Operating within this complex, FBXO41, like other F-box proteins, engages in substrate recognition, specifically identifying target proteins for ubiquitination and subsequent degradation. The SCF complex, consisting of Skp1, Cullin1, RING-box 1 (RBX1), and FBXO41, collaborates to form a functional E3 ubiquitin ligase. FBXO41's primary role revolves around ubiquitinating specific target proteins, marking them for degradation by the proteasome.

FBXO41 is expected to assume a regulatory function in a myriad of cellular processes, encompassing cell cycle progression, signal transduction, and responses to cellular stressors- not dissimilar from the primary function attributed to F-box proteins. Despite the pivotal regulatory functions that F-box proteins carry out, there has not yet been a comprehensive investigation into the phylogenetic tree and gene evolutionary analysis of FBXO41. This paper aims to explain the evolutionary dynamics of FBXO41 within the framework of the SCF complex- through phylogenetic tree analysis. This research clarifies the distinct evolutionary pathway of FBXO41, as well as provides valuable input into the broader patterns that influence the evolution of the SCF complex.

HGNC. "150726 - Gene ResultFBXO41 F-box protein 41 [(human)]." NCBI, 10 October 2023, https://www.ncbi.nlm.nih.gov/gene/150726.

2. Methods

Steps followed -

- Step 1 – Went to the pathways common website
- Step 2 – In the search database entered our search "Antigen processing: Ubiquitination & Proteasome degradation"
- Step 3 – Got 73 pathways
- Step 4 – Selected the pathway "Antigen processing: Ubiquitination & Proteasome degradation"
- Followed the same process for "Neddylation"

3. Results and discussions

The results are given below:

Subcellular Localization

FBXO41, a crucial component of the SCF complex, exhibits distinct localization patterns within cells, primarily in the cytosol and nucleus. These localization patterns provide critical insights into the functional roles of FBXO41 in various cellular processes.

Cytosol:

FBXO41 is prominently localized in the cytosol, where it plays a significant role in the ubiquitination process. The cytosolic presence facilitates its interactions with substrates and other components of the SCF complex, leading to the targeted degradation of proteins. This localization is crucial for maintaining protein homeostasis and regulating various cellular pathways.

Nucleus:

FBXO41 is also localized in the nucleus, implicating its role in nuclear processes such as transcriptional regulation, cell cycle control, and DNA repair. Nuclear localization suggests that FBXO41 may influence the stability and function of nuclear proteins, contributing to gene expression regulation and genomic integrity. This dual localization pattern

underscores the multifunctional nature of FBXO41 within the cell.

Additional Localizations:

While primarily found in the cytosol and nucleus, FBXO41 is also detected in other cellular compartments, including the mitochondrion, membrane, and secretory pathways. These localizations suggest potential roles in mitochondrial dynamics, energy metabolism, and protein transport, adding layers of complexity to FBXO41's functional repertoire (Ghahramani Seno et al., 2013).

Tissue-Specific Expression

FBXO41 exhibits varied expression patterns across different tissues, indicating its diverse functional roles:

- Reproductive Cells: FBXO41 is expressed in male germ cells, sperm, and oocytes, suggesting a role in reproductive biology and possibly in processes such as gametogenesis or fertilization.
- Pancreatic Cells: The presence of FBXO41 in epithelial cells and type B pancreatic cells implies a potential involvement in pancreatic functions or diseases like diabetes and pancreatic cancer.

These tissue-specific expressions highlight the physiological significance of FBXO41 in different biological contexts (Quadros et al., 2022).

Pathway Associations

FBXO41 is involved in several critical pathways, contributing to its diverse functional roles:

- **Ubiquitination and Proteasome Degradation**: FBXO41 plays a pivotal role in the ubiquitination process, marking proteins for degradation by the proteasome. This function is essential for regulating protein levels and maintaining cellular homeostasis (Agrawal et al., 2022).
- **Neddylation**: In addition to ubiquitination, FBXO41 is involved in the neddylation pathway, a process that modifies proteins and influences their stability and function. This pathway is crucial for the regulation of various cellular processes, including cell cycle progression and signal transduction.

These pathway associations underscore the multifaceted roles of FBXO41 in cellular regulation and its potential impact on cellular physiology and pathology (King et al., 2019).

Protein Interactions and Functional Implications

FBXO41 interacts with several key proteins within the SCF complex, such as CUL1, SKP1, and RBX1. These interactions facilitate its role in substrate recognition and ubiquitination, highlighting its importance in protein regulation and cellular homeostasis.

- **CUL1 (Cullin-1)**: Acts as a scaffold for the assembly of the SCF complex, enabling the proper function of FBXO41.
- **SKP1**: Serves as an adaptor, linking FBXO41 to the SCF complex and facilitating its interaction with target proteins.
- **RBX1 (RING-box 1)**: Involved in the transfer of ubiquitin to the target proteins, completing the ubiquitination process.

These interactions are critical for the proper functioning of the SCF complex and the regulatory roles of FBXO41 in various cellular processes (Agrawal et al., 2022).

Drug Interactions and Therapeutic Potential

FBXO41's involvement in critical pathways and interactions with key proteins make it a potential target for therapeutic interventions. Drugs targeting the ubiquitination pathway could modulate FBXO41's activity, offering potential treatments for diseases where protein degradation is disrupted, such as cancer and neurodegenerative disorders.

- **DrugBank ID DB07448:** ((2S)-3-[(R)-(1S)-1-amino-3-phenylpropylphosphoryl]-2-benzylpropanoic acid)
- **DrugBank ID DB08766:** (L-PROLINE, 1-[(2S)-3-MERCAPTO-2-METHYL-1-OXOPROPYL]-4-(PHENYLTHIO)-, 4S)

These compounds highlight the therapeutic potential of targeting FBXO41 and its associated pathways for treating various pathological conditions (Ghahramani Seno et al., 2013).

FBXO41's localization in the cytosol and nucleus, along with its presence in other cellular compartments, reflects its multifaceted roles in cellular processes. Its involvement in critical pathways and interactions with key proteins within the SCF complex underscores its importance in cellular regulation. Understanding these localization patterns and functional interactions provides valuable insights into FBXO41's potential as a therapeutic target.

4. Interactions between FBXO41 and other proteins

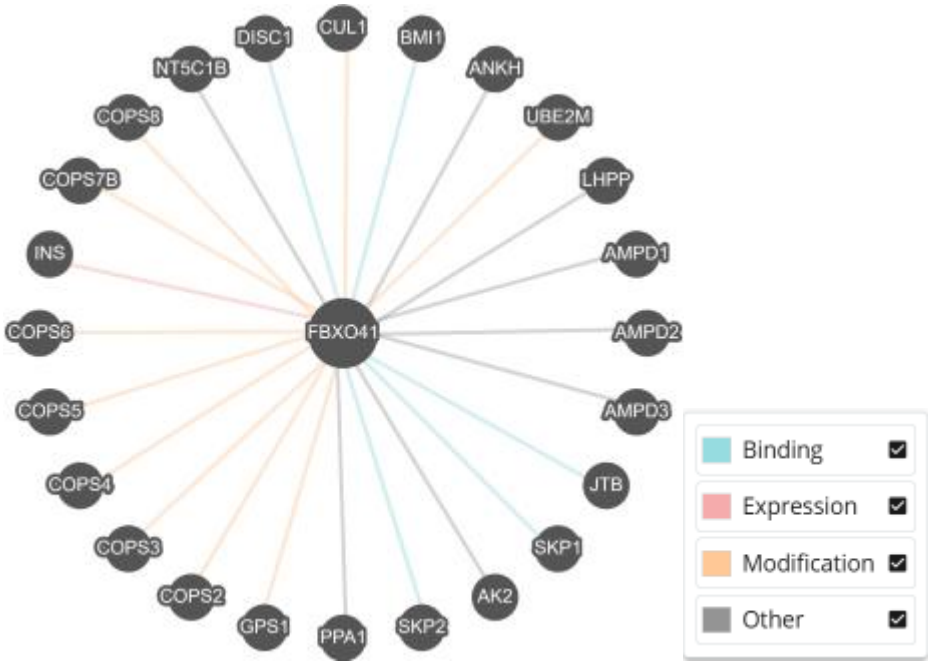


Figure 1: Interaction network of FBXO41

Analysis of FBXO41 Interaction Network
This analysis provides an understanding of the FBXO41 interaction network, integrating its functional roles, interactions, and potential therapeutic applications.

Subcellular Localization and Functional Interactions
Figure 1 above illustrates the interaction network of FBXO41, depicting its interactions with various proteins within the cell. These interactions highlight the multifaceted roles of FBXO41 in different cellular processes, especially within the ubiquitin-proteasome system and other regulatory pathways.

Key Interacting Proteins:

CUL1 (Cullin 1):
- Interaction suggests involvement in the SCF (Skp1-Cullin1-F-box protein) complex.
- Plays a critical role in ubiquitin-mediated protein degradation (Agrawal et al., 2022).

SKP1 (S-phase kinase-associated protein 1):
- Essential component of the SCF complex.
- Facilitates the interaction between FBXO41 and CUL1, and targets proteins for ubiquitination (King et al., 2019).

SKP2 (S-phase kinase-associated protein 2):
- Works in conjunction with SKP1 and CUL1 within the SCF complex.
- Involved in regulating the cell cycle by targeting cell cycle regulators for degradation (Quadros et al., 2022).

COPS (COP9 signalosome subunits, including COPS2, COPS3, COPS4, COPS5, COPS6, COPS7B, COPS8):
- Involved in the deneddylation of cullin-RING ligases, thus regulating their activity.
- Critical for maintaining the balance between neddylation and deneddylation processes, impacting protein degradation (Rouault, 2006).

UBE2M (Ubiquitin-conjugating enzyme E2M):
- Participates in neddylation by transferring NEDD8 to cullin proteins.
- Regulates the activity of cullin-RING ligases, thus controlling protein ubiquitination (Tong & Rouault, 2007).

DISC1 (Disrupted in schizophrenia 1):
- Interacts with FBXO41, suggesting a role in neurodevelopmental and neuropsychiatric processes.
- Implicated in neuronal migration, synaptic transmission, and neural network formation (King et al., 2019).

BMI1 (B lymphoma Mo-MLV insertion region 1 homolog):
- Involved in chromatin remodeling and regulation of gene expression.
- Interaction with FBXO41 indicates a role in epigenetic regulation and possibly in stem cell maintenance (Ghahramani Seno et al., 2013).

AK2 (Adenylate kinase 2):
- Regulates energy metabolism by catalyzing the interconversion of adenine nucleotides.
- Interaction with FBXO41 might influence cellular energy homeostasis (Tong & Rouault, 2007).

AMPD (Adenosine monophosphate deaminase 1, 2, and 3):
- Involved in the purine nucleotide cycle, regulating energy metabolism.

- FBXO41 interaction could impact cellular metabolic processes (Agrawal et al., 2022).

JTB (Jumping translocation breakpoint):
- Implicated in cell proliferation and apoptosis.
- Interaction with FBXO41 suggests a role in cell survival and growth regulation (Rouault, 2006).

FBXO41's interaction network illustrates its multifaceted roles in cellular processes such as protein degradation, neurodevelopment, epigenetic regulation, and energy metabolism. Understanding these interactions provides valuable insights into its potential as a therapeutic target for various diseases.

5. Observed in Experiments

I used the publicly accessible database peptideAtlas, to access organ distribution of FBXO41 in mammals. PeptideAtlas is an experimental database for peptides from large set of tandem mass spectrometry proteomics experiments.

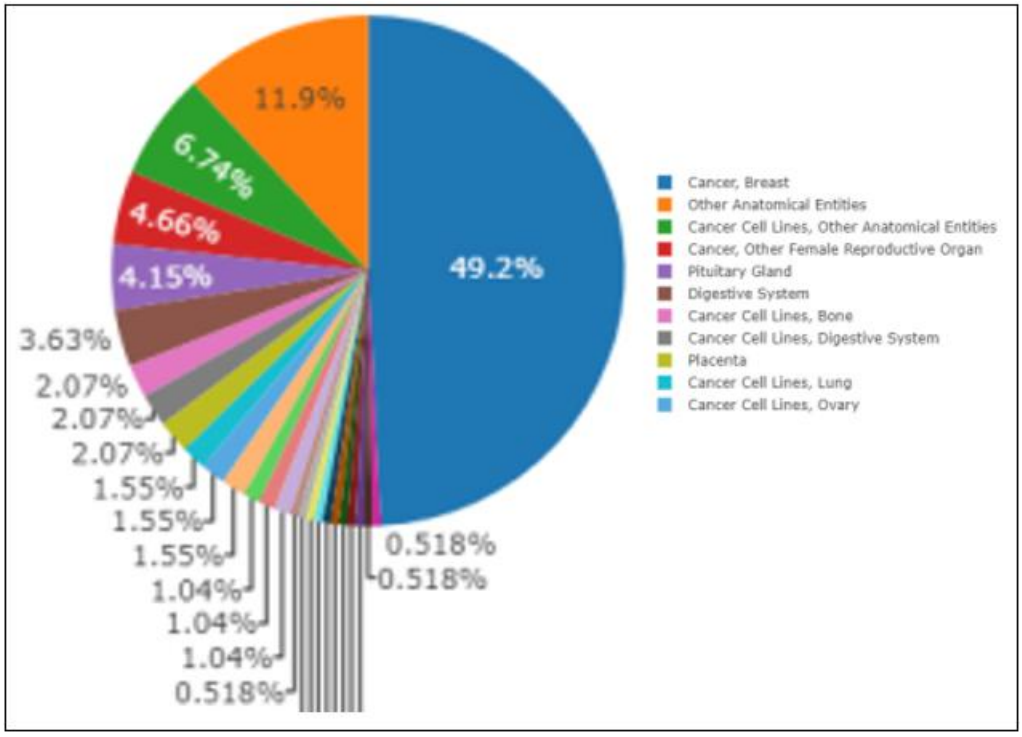


Figure 2: Tissue specific expression of a particular gene or protein

Tissue-Specific Expression in Cancer Cell Lines and Anatomical Entities

The pie chart (Figure 2) depicts the tissue-specific expression of a particular gene or protein across various cancer cell lines and anatomical entities. Each segment represents the percentage of total expression within a specific tissue or cancer cell line. The legend provides a key to the colors used in the chart, indicating the corresponding tissue types or cancer cell lines.

The tissue-specific expression profile depicted in the pie chart reveals the gene/protein's significant roles in breast cancer and its broad biological functions across various tissues and cancer cell lines. Understanding these expression patterns provides valuable insights for cancer research, potential therapeutic targets, and exploring its roles in normal physiology.

6. Human Brain RNA expression

I found that FBXO41 is highly expressed in brain. To analyze its RNA expression in specific regions of the brain, I used The Human Protein Atlas. It is an open access for exploration of the human proteome.

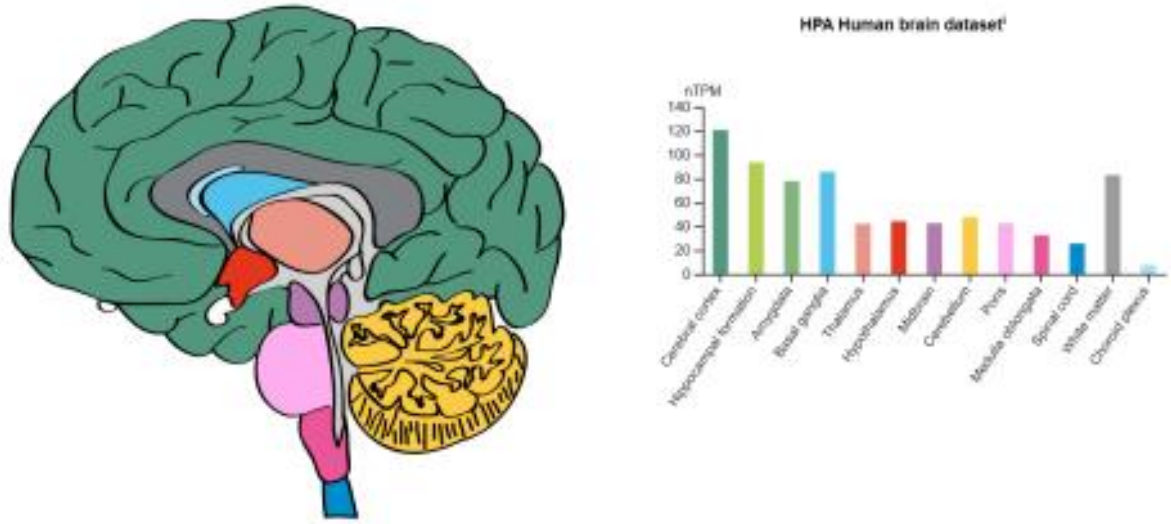


Figure 3: Gene expression levels across regions of the human brain.

Gene Expression in Human Brain Regions

Figure 3 above depicts gene expression levels across various regions of the human brain, as represented in the HPA (Human Protein Atlas) Human brain dataset. The graph displays normalized transcript per million (nTPM) values, indicating the relative expression levels in different brain regions. The brain diagram alongside helps to locate these regions visually. This analysis provides an understanding of the gene expression profile in various human brain regions, integrating its functional roles, interactions, and potential therapeutic applications.

Tissue-Specific Expression and Functional Roles

- **Expression in Brain Regions:**
  The differential expression levels across various brain regions indicate that the gene/protein has region-specific roles, contributing to diverse functions from higher cognitive processing to basic autonomic control.
- **Potential Implications for Neurological Disorders:**
  Dysregulation of this gene/protein in specific brain regions could contribute to neurological and psychiatric disorders. For instance, high expression in the hippocampus and cortex might link to cognitive disorders, while expression in the amygdala and basal ganglia could relate to emotional and movement disorders.

Drug Interactions and Therapeutic Potential

Therapeutic Targeting:

- Understanding the specific expression patterns in brain regions can guide the development of targeted therapies for neurological and psychiatric conditions.
- Potential therapies could aim to modulate the activity of this gene/protein in specific regions to address dysfunctions related to overexpression or under expression.

The differential expression of the gene/protein across various brain regions underscores its diverse roles in cognitive functions, sensory processing, emotional regulation, motor control, and autonomic functions. These insights are crucial for understanding the molecular basis of brain function and developing targeted therapies for neurological disorders.

7. Interactions

The cullin protein (CUL1) acts as a scaffold to assemble RING box-domain protein (RBX1), the adaptor protein (SKP1) and a substrate receptor. CUL1 consists of an N-terminal helical region that binds the SKP1-F box protein, and a C-terminal globular domain that binds RBX1.

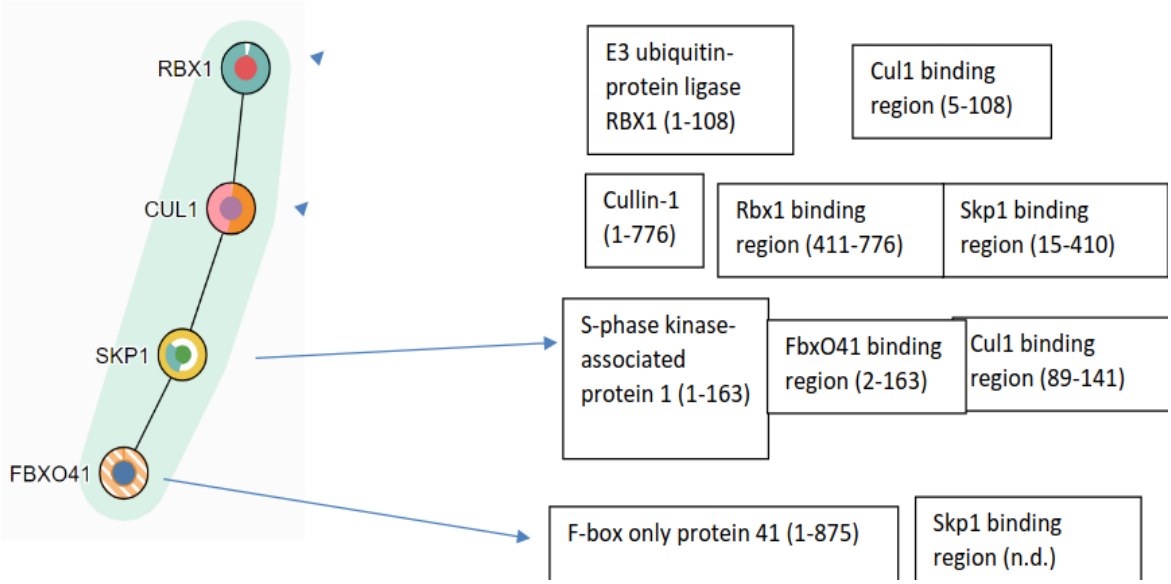


Figure 4: Interaction network of FBXO41 with SCF complex.

FBXO41 and SCF Complex Components Interaction Network

This analysis provides an understanding of the interaction network of FBXO41 with SCF complex components, integrating its functional roles, interactions, and potential therapeutic applications.

Figure 4 above depicts the interaction network of FBXO41 with components of the SCF complex, highlighting the specific binding regions on each protein involved in the complex formation. The SCF complex is crucial for ubiquitin-mediated protein degradation, which regulates various cellular processes.

Key Components and Binding Regions:

RBX1 (E3 ubiquitin-protein ligase RBX1):
- Binding Region: 1-108
- Function: Facilitates the transfer of ubiquitin from E2 enzymes to the substrate proteins.

CUL1 (Cullin-1):
- Binding Regions: 1-776 (overall protein), 5-108 (RBX1 binding region), 411-776 (RBX1 binding region), 15-410 (SKP1 binding region), 89-141 (FBXO41 binding region)
- Function: Acts as a scaffold for the assembly of the SCF complex, connecting SKP1 and RBX1.

SKP1 (S-phase kinase-associated protein 1):
- Binding Regions: 1-163 (overall protein), 2-163 (FBXO41 binding region), 89-141 (CUL1 binding region), n.d. (SKP1 binding region)
- Function: Adaptor protein that links F-box proteins (like FBXO41) to the SCF complex, enabling substrate specificity.

FBXO41 (F-box only protein 41):
- Binding Regions: 1-875 (overall protein), 2-163 (SKP1 binding region)
- Function: Acts as a substrate recognition component, targeting specific proteins for ubiquitination.

Functional Implications of Interactions

SCF Complex Formation and Function:
Assembly:
- CUL1 serves as the scaffold, connecting RBX1, SKP1, and FBXO41.
- RBX1 binds to the C-terminal region of CUL1, facilitating the transfer of ubiquitin to the substrates.
- SKP1 acts as a bridge between CUL1 and FBXO41, enabling the recognition of specific substrates.

Protein Degradation:
- The SCF complex targets specific proteins for ubiquitination and subsequent degradation by the proteasome.
- This process is crucial for regulating protein levels and maintaining cellular homeostasis.

Specific Roles of Each Component:

RBX1:
- Catalyzes the ubiquitination process, crucial for tagging proteins for degradation.
- Interaction with CUL1 is essential for its function.

CUL1:
- Provides structural integrity to the SCF complex.
- Binds to both RBX1 and SKP1, facilitating the assembly and function of the complex.

SKP1:
- Acts as an adaptor, linking F-box proteins (like FBXO41) to CUL1.
- This linkage is essential for the specificity of the SCF complex towards different substrates.

FBXO41:
- Functions as a substrate receptor within the SCF complex.
- Its interaction with SKP1 is critical for recognizing and binding specific substrates for ubiquitination.

Tissue-Specific Expression and Functional Roles

- **Broad Expression:**
  The components of the SCF complex, including FBXO41, are expressed in various tissues, reflecting their fundamental role in regulating protein degradation across different cell types.
- **Specific Tissues:**
  The expression patterns of these proteins in specific tissues can influence the regulation of protein turnover and the maintenance of cellular functions

Drug Interactions and Therapeutic Potential

Therapeutic Targeting:

- Targeting the SCF complex components, especially the interactions between CUL1, RBX1, SKP1, and FBXO41, could provide therapeutic benefits in diseases where protein degradation is dysregulated, such as cancer and neurodegenerative disorders.
- Modulating these interactions can offer new avenues for drug development, aiming to restore or inhibit the function of the SCF complex in specific pathological conditions.

The interaction network of FBXO41 with the SCF complex components underscores its crucial role in ubiquitin-mediated protein degradation. Understanding these interactions provides valuable insights into the regulation of protein turnover and potential therapeutic targets for various diseases

8. Phylogenetic tree

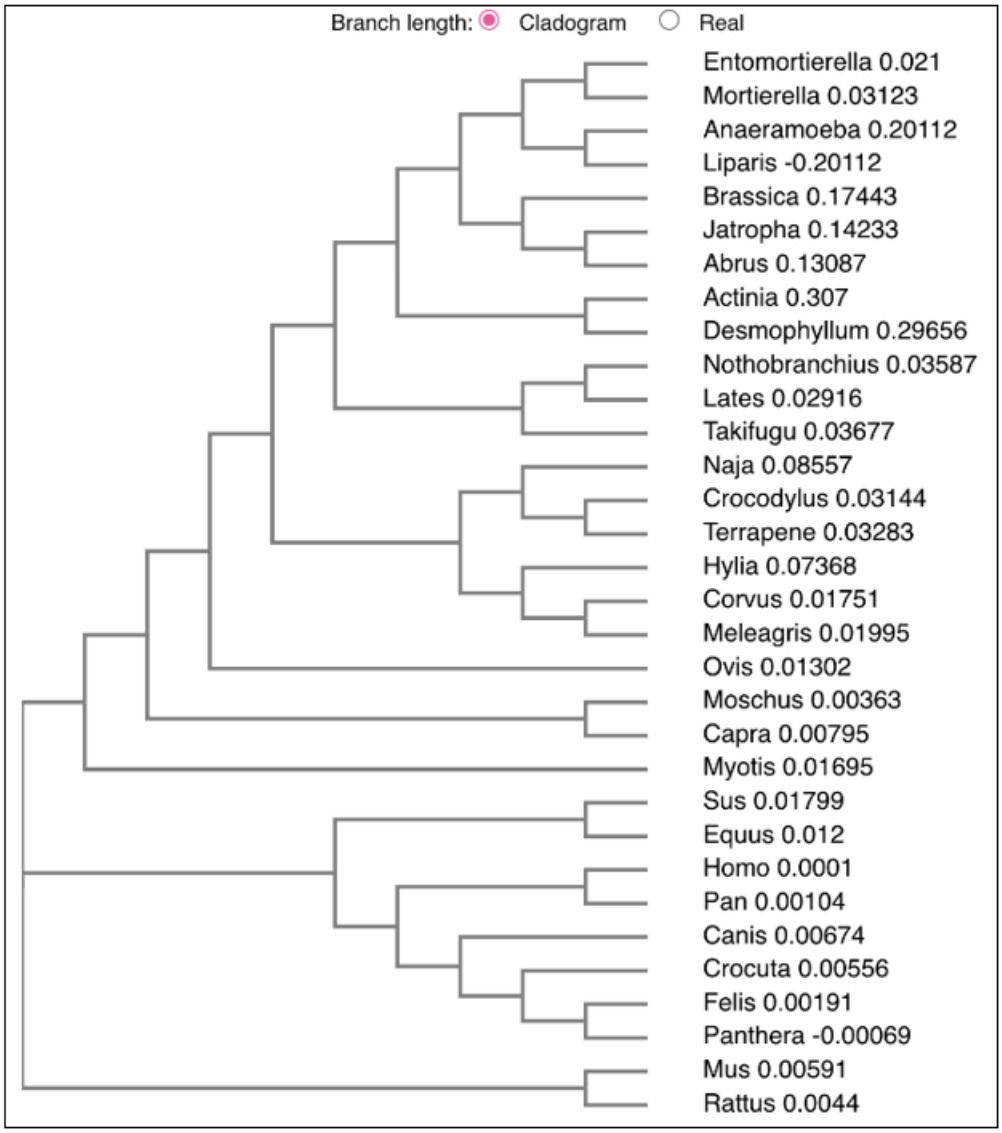


Figure 5: Phylogenetic tree

Data Retrieval:

I started by going to the UniProt website (https://www.uniprot.org/) to obtain the protein sequences for FBXO41 from various species. After conducting an online search, I obtained the sequences in FASTA format, creating a collection of FBXO41 protein sequences from other animals.

Sequence Alignment using Clustal W:

I then went ahead and downloaded and set up Clustal W, which is a software for multiple sequence alignment. I

prepared Clustal W and entered the accumulated sequences of the FBXO41 protein for alignment.

Phylogenetic Tree Construction:

I used Clustal W to build a phylogenetic tree, which is a graphic depiction of the evolutionary relationships of FBXO41 proteins in different species, based on the matched sequences. The phylogenetic tree proved to be an effective method for clarifying the evolutionary landscape of the FBXO41 protein since it ensured accurate labelling and a clear representation of evolutionary links

9. Similar Proteins

90% identity (9 sequences taken)

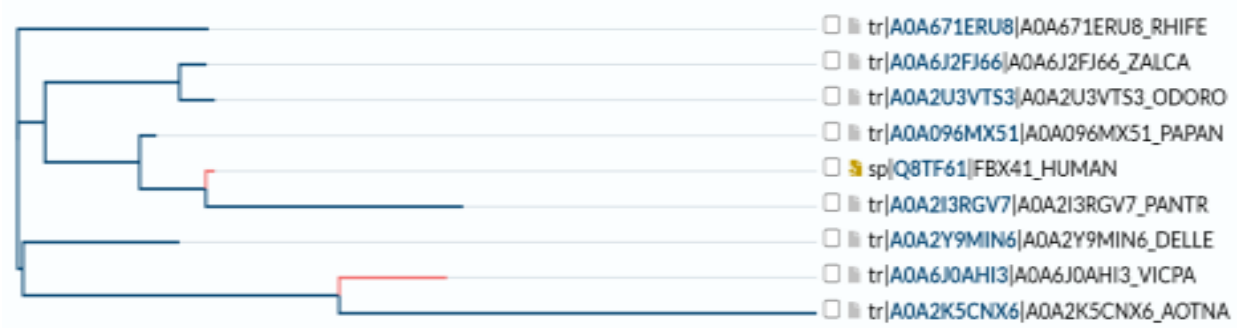


Figure 6: Phylogenetic tree for FBXO41

Phylogenetic Tree for FBXO41

Figure 6 above is a phylogenetic tree depicting the evolutionary relationships of the FBXO41 protein across different species. The tree illustrates the genetic divergence and similarities among the FBXO41 homologs in various organisms. This analysis provides an understanding of the evolutionary relationships of FBXO41, integrating its functional roles, interactions, and potential applications in health and disease research.

Key Observations:

FBXO41_HUMAN (Q8TF61):
- Located centrally in the phylogenetic tree, indicating its relationship with other FBXO41 homologs across different species.

Closest Homologs:

A0A2I3RGV7_PANTR (Pan troglodytes):
- The closest homolog to human FBXO41, suggesting a recent common ancestor and high sequence similarity.

A0A2Y9MN6_DELLE (Delphinapterus leucas):
- Another close homolog, indicating evolutionary conservation of FBXO41 in marine mammals.

Distant Homologs:

A0A671ERU8_RHIFE (Rhinolophus ferrumequinum):
- A more distantly related homolog, suggesting greater evolutionary divergence from the human FBXO41.

A0A6J2FJ66_ZALCA (Zalophus californianus):
- Indicates divergence within the mammalian lineage, showing the evolutionary breadth of FBXO41.

Intermediate Homologs:

A0A2U3VTS3_ODORO (Odocoileus virginianus):
- Shows intermediate divergence, representing a broader spectrum of mammalian FBXO41 evolution.

A0A096MX51_PAPAN (Papio anubis):
- Closer to the human homolog, reflecting evolutionary conservation among primates.

Other Homologs:

A0A2K5CNX6_AOTNA (Aotus nancymaae):
- Positioned with moderate divergence, indicating a mix of evolutionary conservation and divergence in primates.

A0A6J0AHI3_VICPA (Vicugna pacos):
- Represents an example of divergence within the mammalian clade.

Functional Implications of Phylogenetic Relationships

Evolutionary Conservation:

The close relationship between human FBXO41 and homologs from primates and marine mammals suggests that the protein's function is conserved across these species. This conservation indicates the essential nature of FBXO41 in fundamental cellular processes.

Divergence in Function:

The greater divergence seen in species like Rhinolophus ferrumequinum and Zalophus californianus might suggest adaptations specific to these species, potentially leading to variations in the function or regulation of FBXO41.

Comparative Analysis:

Pan troglodytes (A0A2I3RGV7):
- High sequence similarity to human FBXO41, useful for studying functional conservation and potential differences in regulatory mechanisms.

Delphinapterus leucas (A0A2Y9MN6):
- Insights into how FBXO41 functions in marine environments, which can be compared to terrestrial environments.

Papio anubis (A0A096MX51):
- Close evolutionary relationship with humans, relevant for understanding primate-specific functions and adaptations.

Applications and Future Research

Functional Studies:

Comparative Functional Analysis:
- Investigating the functional similarities and differences in FBXO41 across these species can shed light on the evolutionary pressures and adaptations that have shaped its role.

Cross-Species Studies:
- Functional assays in model organisms like Pan troglodytes and Papio anubis can provide insights into the conserved functions of FBXO41 and its role in human health and disease.

Therapeutic Implications:

Disease Models:
- Understanding the evolutionary conservation of FBXO41 can aid in developing animal models for studying diseases related to FBXO41 dysfunction.

Targeted Therapies:
- Insights from phylogenetic analysis can inform the development of targeted therapies that consider evolutionary conservation and species-specific variations in FBXO41.

The phylogenetic analysis of FBXO41 reveals significant evolutionary conservation among closely related species, highlighting its essential role in cellular functions. The divergence observed in more distantly related species suggests potential adaptations and functional variations. This analysis provides a foundation for future comparative and functional studies, with implications for understanding the role of FBXO41 in health and disease.

10. Position of domain

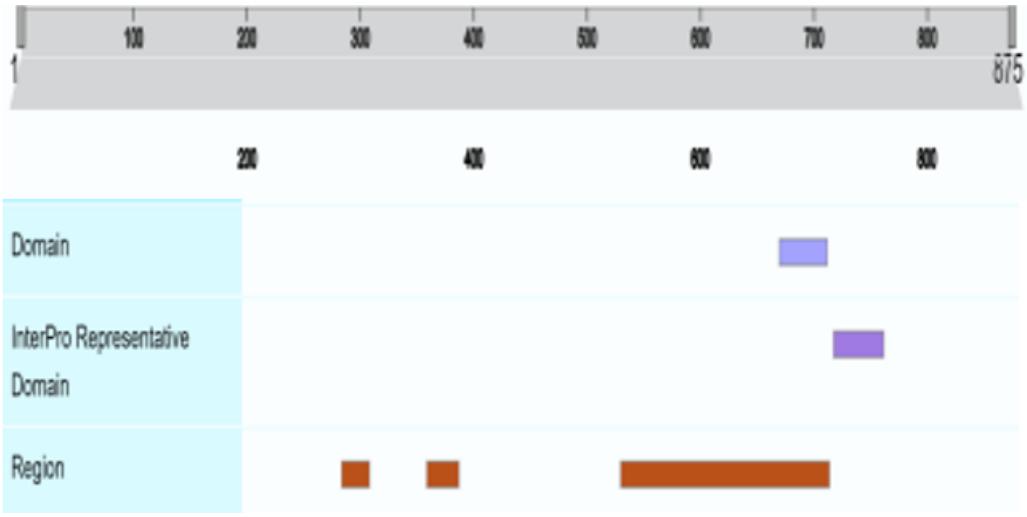


Figure 7: Domain and region structure for FBXO41

Protein Domain and Region Structure for FBXO41
Figure 7 above depicts the domain and region structure of the FBXO41 protein, highlighting specific domains and regions identified by InterPro and other bioinformatics tools. This information is essential for understanding the functional aspects of FBXO41 and its role in various cellular processes. The analysis below provides an understanding of the domain and region structure of FBXO41, integrating its functional roles, interactions, and potential applications in research and therapy.

Key Observations:

Protein Length:
- The total length of the FBXO41 protein is 875 amino acids.

Domain Annotations:
- **Domain:** Specific functional units within the protein structure.
- **InterPro Representative Domain:** Domains identified and characterized by InterPro database.
- **Region:** Non-domain regions that may have specific roles or structural properties.

Potential Research and Therapeutic Applications

Functional Studies:

Domain Characterization:
- Further research is needed to characterize the specific activities of the InterPro-identified domain.
- Functional assays can elucidate the role of this domain in ubiquitination or protein-protein interactions.

Mutational Analysis:
- Investigating mutations within the identified regions can reveal their impact on FBXO41 function.
- Helps in understanding disease mechanisms where FBXO41 is implicated.

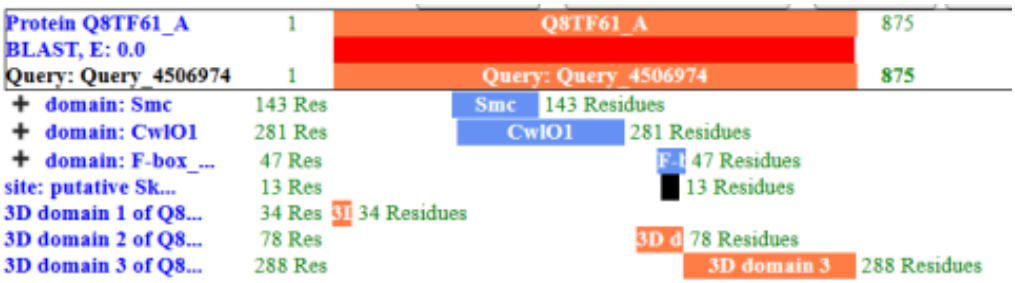
Therapeutic Targeting:

Drug Development:

- Targeting the critical domain identified by InterPro could lead to the development of specific inhibitors or modulators.
- Potential for therapeutic intervention in diseases related to FBXO41 dysfunction, such as cancer or neurodegenerative disorders.

The domain and region analysis of FBXO41 provides insights into its structural and functional organization. The identified InterPro domain and significant regions highlight areas critical for the protein's function, guiding future research and potential therapeutic strategies.

11. Annotation of FBXO41 (with conserved domains and Functional sites)



Motif 9 – LEERASELSRQVDVS (a.a. – 265-280)

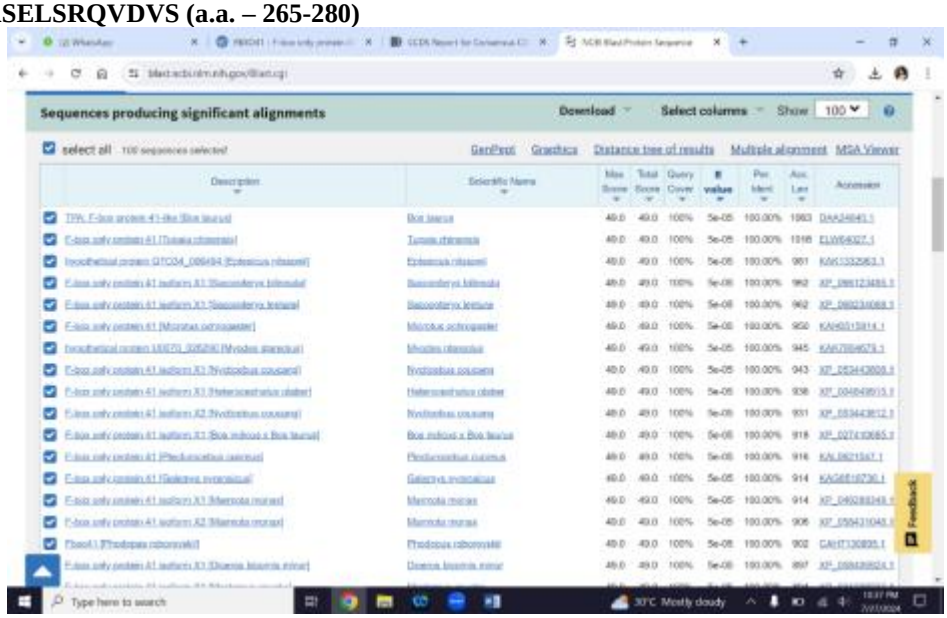


Figure 8: FBXO41 BLAST results and Domain structure

FBXO41 BLAST Results and Domain Structure

Figure 8 above includes multiple sections displaying the results from a BLAST search, domain annotations, and compositional bias analysis for the FBXO41 protein. These sections highlight significant alignments, domain structures, and regions of interest within the FBXO41 sequence. This analysis provides an understanding of the BLAST results and domain structure of FBXO41, integrating its functional roles, interactions, and potential applications in research and therapy.

Key Observations:

1) BLAST Results:

Query: Query_4506974:
- The query sequence is compared against the FBXO41 protein (Q8TF61_A), showing complete alignment (1-875 amino acids).

Domains Identified:
- **Smc Domain:** 143 residues
- **CwlO1 Domain:** 281 residues
- **F-box Domain:** 47 residues
- **Other Regions:** Including 13 residues, and 3D domains of varying lengths (31-288 residues).

2) Sequence Alignment:

Significant Alignments:
- Top hits include F-box only protein 41 homologs from various species (e.g., Bos taurus, Tupaia chinensis).
- These alignments suggest strong evolutionary conservation across different organisms.
- E-values and percentage identities indicate high similarity, with values close to zero and 100% identity in many cases.

3) Disordered Regions and Compositional Bias:

Disordered Regions:
- **Region 85-110**
- **Region 165-194**
- **Region 347-542**

Compositional Bias:
- **Proline-rich Regions:** 170-188
- **Polar Residue Regions:** 391-419, 447-467

Functional Implications of Domains and Regions

Domain Functions:

Smc Domain (143 Residues):
- Involved in structural maintenance of chromosomes and protein interactions.
- Plays a role in chromosome segregation and DNA repair.

CwlO1 Domain (281 Residues):
- Associated with cell wall hydrolases.
- May indicate a role in protein-protein interactions or enzymatic activity within the FBXO41 protein.

F-box Domain (47 Residues):
- Critical for mediating protein-protein interactions within the SCF complex.
- Facilitates substrate recognition and ubiquitination.

Sequence Alignment and Evolutionary Conservation:

High Similarity Across Species:
- Strong conservation of the F-box domain and other regions, suggesting essential functional roles conserved through evolution.
- Alignments with species such as Bos taurus and Tupaia chinensis indicate functional similarities.

Disordered Regions and Compositional Bias:

Disordered Regions:
- Indicate flexible regions that may be involved in regulatory functions or interactions with multiple partners.
- Could facilitate conformational changes necessary for FBXO41 function.

Proline-rich and Polar Residue Regions:
- Proline-rich regions may play a role in protein-protein interactions or structural stability.
- Polar residue regions suggest areas that may be involved in solvent interactions or protein folding.

Potential Research and Therapeutic Applications

Functional Studies:

Domain Characterization:
- Further experimental studies to characterize the function of Smc, CwlO1, and F-box domains.
- Understanding the role of these domains in protein interactions and cellular functions.

Mutational Analysis:
- Investigating the impact of mutations in disordered and compositional bias regions to determine their functional significance.
- Insight into how these regions contribute to FBXO41's regulatory roles.

Therapeutic Targeting:

Drug Development:
- Targeting conserved domains, such as the F-box domain, for therapeutic interventions in diseases related to protein ubiquitination dysregulation.
- Developing inhibitors or modulators that can specifically interact with these domains.

12. Conclusion

FBXO41 is a critical protein with very diverse functional roles in cellular regulation, conserved across species, and involved in important biological processes. Understanding its structure, evolutionary relationships, and expression patterns provides valuable insights for future research and therapeutic development, particularly in targeting protein degradation pathways and addressing disorders related to FBXO41 dysfunction.

Later in our analysis of FBXO41, we identified a highly conserved motif sequence, LEERASELSRQVDVS, located within the coiled-coil domain of the protein (amino acids 265-280). This motif is conserved across various species, showing its potential significance in the protein's function. The coiled-coil domain, known for facilitating protein-protein interactions, suggests that this motif may play a critical role in mediating these interactions, thereby contributing to the diverse functional roles of FBXO41 in cellular processes.

The conservation of this motif across species underscores its evolutionary importance and hints at a fundamental role that has been preserved throughout evolution. This motif's presence in the coiled-coil domain suggests it may be involved in stabilizing the structure of FBXO41 or in mediating interactions with other proteins within the ubiquitin-proteasome system.

The function of the LEERASELSRQVDVS motif warrants further investigation considering its potential significance. Both in vitro and in vivo experiments should be conducted to explain the specific role of this motif in FBXO41's function. In vitro studies could focus on identifying interaction partners and assessing the motif's contribution to the structural stability of FBXO41. In vivo studies could investigate the physiological relevance of this motif in cellular contexts, potentially uncovering its role in processes such as protein degradation, signal transduction, and cellular homeostasis.

The discovery of the LEERASELSRQVDVS motif in the coiled-coil domain of FBXO41 highlights a potentially critical functional element that is highly conserved across species. Further studies are necessary to fully understand its role, which could provide significant insights into the broader functions of FBXO41 and its involvement in essential biological processes. This knowledge could also contribute to the development of targeted therapeutic strategies for diseases related to FBXO41 dysfunction including neurological disorders and can be used as a potential biomarker for breast cancer.

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