Functional and Network Analysis of PRPF3: Insights into Spliceosomal Regulation and Disease Associations

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Abstract
Pre-mRNA Processing Factor 3 (PRPF3) is a key component of the spliceosomal complex, involved in pre-mRNA splicing, ribonucleoprotein assembly and RNA stability. Mutations in PRPF3 have been linked to retinitis pigmentosa, cancer and neurodegenerative disorders, highlighting its clinical significance. This study aimed to analyze PRPF3's protein interaction network, functional pathways and disease associations to better understand its biological role. A protein-protein interaction (PPI) network was constructed using STRING, followed by functional enrichment analysis using Gene Ontology (GO), KEGG and Reactome databases. Subcellular localization was assessed using the COMPARTMENTS database, while pathway enrichment was validated using Benjamini-Hochberg multiple testing correction.

PRPF3 exhibited strong interactions within the spliceosome (hsa03040, p = 6.66E-22), particularly in U4/U6-U5 tri-snRNP assembly. GO enrichment analysis confirmed its role in mRNA splicing (GO:0000398, p = 2.24E-17) and snRNA binding (GO:0017069, p = 0.0041). PRPF3 localized predominantly to the spliceosomal complex, nuclear speck and Cajal body. Notably, mRNA decay pathways (HSA-430039, p = 0.0146) suggest a secondary role in RNA turnover. PRPF3 is a key spliceosomal protein, influencing pre-mRNA processing and RNA metabolism. Its association with retinitis pigmentosa and cancer suggests therapeutic potential in targeting PRPF3-related splicing defects. Future studies should explore gene-editing interventions to correct PRPF3 mutations.

Keywords: PRPF3, spliceosome, RNA splicing, retinitis pigmentosa, alternative splicing.

Introduction

Pre-mRNA Processing Factor 3 (PRPF3) is a core component of the spliceosomal complex, a highly dynamic molecular machinery responsible for precursor mRNA (pre-mRNA) splicing. Splicing is an essential post-transcriptional process that removes non-coding introns from pre-mRNA, ensuring the generation of mature mRNA for accurate protein synthesis. Sm/Lsm genes provide a glimpse into the early evolution of the spliceosome[1,17]. Mutations in PRPF3 have been associated with retinitis pigmentosa (RP), neurodegenerative diseases and certain cancers, highlighting its clinical significance in human health and disease[10,21].

The spliceosome is composed of small nuclear ribonucleoproteins (snRNPs) and numerous splicing factors including PRPF3. It functions through a stepwise assembly process which involves the formation of U1, U2, U4/U6 and U5 snRNP complexes. PRPF3 is primarily associated with the U4/U6-U5 tri-snRNP complex, the largest and most structurally intricate spliceosomal unit[28,33]. Structural analyses have revealed PRPF3's role in maintaining spliceosomal stability, influencing RNA-RNA and RNA-protein interactions[4].

Studies have demonstrated that PRPF3 dynamically interacts with other spliceosomal components including Lsm proteins, which assist in snRNA stability and maturation[5,27]. Lsm2-8 complexes, in particular, have been shown to regulate the nuclear localization and function of PRPF3 within Cajal bodies where snRNP biogenesis occurs[32]. A significant function of PRPF3 is modulating spliceosome activation and disassembly processes that are regulated through ATP-dependent remodeling of snRNPs[6,20].

Cryo-electron microscopy (Cryo-EM) studies have elucidated PRPF3's structural role within the U4/U6 di-snRNP, showing its interaction with PRPF4 and PRPF6, which are required for spliceosomal catalytic activation[15,26]. The pre-catalytic spliceosome (B-complex) requires PRPF3 for proper conformational changes before splicing occurs, further demonstrating its functional importance[12,23].

Furthermore, biochemical and proteomic analyses have shown that PRPF3 interacts with Cyclophilin H, a key spliceosomal peptidyl-prolyl isomerase, reinforcing its importance in splicing fidelity[16]. Studies have also linked PRPF3 mutations to defects in RNA splicing, leading to abnormal transcript processing in several genetic disorders[7,13].

Material and Methods

Data Acquisition and Preprocessing: To investigate the network characteristics and functional enrichment of PRPF3 (Pre-mRNA Processing Factor 3), we retrieved protein interaction data from STRING v11.5 (Search Tool for the Retrieval of Interacting Genes/Proteins).

STRING is a widely used database that integrates known and predicted protein-protein interactions (PPIs) based on experimental evidence, computational predictions and curated biological knowledge. The query protein, PRPF3

(Uniprot ID: Q13523), was used as the central node for interaction analysis.

To ensure high confidence in the interactions, the following parameters were applied:

- **Minimum interaction confidence score:** 0.4 (medium confidence)
- **Data sources:** Experimental evidence, curated databases and co-expression
- **Excluded:** Text mining-based interactions to minimize indirect associations
- **Organism:** Homo sapiens (human)

The extracted PPI network was exported for further computational analysis.

Network Analysis and Topological Features: To assess the overall connectivity and functional relevance of PRPF3 in the interactome, various graph theory-based network parameters were computed:

- **Number of nodes and edges:** The total number of proteins (nodes) in the network and their direct interactions (edges).
- **Expected number of edges:** A theoretical value representing the number of edges expected in a random network of similar size.
- **PPI enrichment p-value:** A measure of whether the observed interactions are statistically significant or likely to occur by chance.
- **Average node degree:** The average number of interactions per node, which helps infer network density.
- **Average local clustering coefficient:** A measure of how well the interacting proteins form functional clusters or modules.

These parameters were calculated using STRING's built-in network statistics module and cross-validated using Cytoscape v3.9.1, a widely used bioinformatics tool for network visualization and analysis.

Functional Enrichment Analysis: To identify the biological functions and molecular pathways associated with PRPF3 and its interacting partners, a gene ontology (GO) and pathway enrichment analysis was performed.

Gene Ontology (GO) Analysis: GO enrichment analysis was carried out to classify PRPF3-associated proteins into three major categories:

- **Biological Processes (BP):** Functions related to mRNA splicing, spliceosomal complex assembly and ribonucleoprotein organization.
- **Molecular Functions (MF):** PRPF3's role in RNA binding and interactions with spliceosomal snRNAs.
- **Cellular Components (CC):** The subcellular localization of PRPF3 within nuclear compartments such as the spliceosome, nuclear speck and nucleoplasm.

The enrichment scores were determined using False Discovery Rate (FDR) correction to minimize false positives, ensuring statistical rigor.

KEGG and Reactome Pathway Analysis: Pathway enrichment was performed using KEGG (Kyoto Encyclopedia of Genes and Genomes) and Reactome databases to identify the specific molecular pathways associated with PRPF3:

- **KEGG pathways:** Focused on the spliceosome (hsa03040) and RNA degradation (hsa03018), highlighting PRPF3's role in mRNA processing.
- **Reactome pathways:** Provided detailed insights into major and minor mRNA splicing pathways, including catalytic steps of the spliceosome.

The pathway enrichment p-values were adjusted using the Benjamini-Hochberg method to account for multiple hypothesis testing.

Subcellular Localization Analysis: To determine the subcellular localization of PRPF3, enrichment analysis was conducted using the COMPARTMENTS database which integrates data from experimental proteomics, imaging studies and computational predictions. The analysis identified PRPF3's predominant localization in:

- Spliceosomal complexes (U2-type and U4/U6 tri-snRNP).
- Nuclear speckles and Cajal bodies, confirming its involvement in mRNA splicing and ribonucleoprotein complex assembly.

This step was crucial to link PRPF3's molecular function with its structural localization within the cell.

Statistical Validation and Data Visualization: To ensure the accuracy and reliability of the enrichment analysis, the following statistical and computational approaches were employed:

- False Discovery Rate (FDR) correction to filter out non-significant results.
- Bootstrapping analysis necessary to validate network robustness.
- Z-score transformations for pathway enrichment normalization.

The results were visualized using:
- Cytoscape v3.9.1 for network representation.
- GraphPad Prism for enrichment plots.
- R programming (ClusterProfiler package) for GO and pathway analysis.

Results

Network Analysis (Figure 1, Table 1): The protein-protein interaction (PPI) network for PRPF3 (Pre-mRNA Processing

Factor 3) revealed a highly interconnected structure, emphasizing its central role in RNA splicing and ribonucleoprotein complex formation. The network consisted of 11 nodes and 51 edges, significantly exceeding the expected 12 edges, indicating that PRPF3 interacts with more proteins than anticipated by random chance. The PPI enrichment p-value (< 1.0e-16) strongly supports this observation, suggesting that PRPF3 and its associated proteins function as a distinct biological unit rather than being randomly connected. The average node degree of 9.27 and the local clustering coefficient of 0.952 indicate that the network is densely connected, reinforcing its functional relevance in spliceosomal dynamics.

Biological Process Enrichment (Table 2): Gene ontology (GO) analysis of biological processes highlighted PRPF3's role in pre-mRNA splicing and ribonucleoprotein complex assembly. The most significantly enriched term was mRNA splicing via the spliceosome (GO:0000398, p = 2.24E-17), with all 11 proteins in the network involved in this essential process. Other highly enriched processes include:

- Spliceosomal snRNP assembly (GO:0000387, p = 3.14E-08), highlighting PRPF3's role in forming snRNP complexes.
- Ribonucleoprotein complex subunit organization (GO:0071826, p = 1.02E-08), indicating PRPF3's involvement in ribonucleoprotein interactions.
- Spliceosomal complex assembly (GO:0000245, p = 6.37E-05) confirming PRPF3's essential function in assembling components of the spliceosome.

Additionally, 7-methylguanosine cap hypermethylation (GO:0036261, p = 0.0071) was observed, suggesting a link between PRPF3 and mRNA stability and processing.

Molecular Function Enrichment (Table 3): The molecular function enrichment analysis revealed that PRPF3 predominantly interacts with RNA, particularly in snRNA binding (GO:0017069, p = 0.0041) and U6 snRNA binding (GO:0017070, p = 0.0417). The RNA binding function (GO:0003723, p = 1.00E-06) further supports PRPF3's fundamental role in spliceosomal activity and RNA metabolism.

Cellular Component Enrichment (Table 4): GO cellular component analysis showed a strong association between PRPF3 and multiple spliceosomal complexes:

- U4/U6 x U5 tri-snRNP complex (GO:0046540, p = 3.77E-23) had the highest enrichment score, indicating PRPF3's role in the core spliceosomal machinery.
- U2-type precatalytic spliceosome (GO:0071005, p = 1.42E-16) and U2-type spliceosomal complex (GO:0005684, p = 2.96E-17) confirmed PRPF3's role in early splicing steps.
- Catalytic step 2 spliceosome (GO:0071013, p = 3.39E-12) suggested its involvement in the later stages of mRNA processing.

These findings confirm PRPF3's localization and function within the nucleus, specifically in nuclear speckles (GO:0016607, p = 0.0040) and Cajal bodies (GO:0015030, p = 0.0308), which are known to coordinate splicing activities.

Pathway Enrichment Analysis

KEGG Pathway Enrichment (Table 5): Pathway analysis using KEGG showed a highly significant enrichment in spliceosome-related pathways:

- Spliceosome (hsa03040, p = 6.66E-22) was the top pathway, reinforcing PRPF3's fundamental role in splicing.
- RNA degradation (hsa03018, p = 0.0016) was also enriched, suggesting that PRPF3 is involved in mRNA turnover and quality control.

Reactome Pathway Enrichment (Table 6): Reactome pathway analysis supported PRPF3's central role in RNA processing:

- mRNA splicing - major pathway (HSA-72163, p = 4.36E-19) was the most significantly enriched, confirming PRPF3's involvement in spliceosomal function.
- mRNA splicing - minor pathway (HSA-72165, p = 7.47E-06) highlighted its role in the alternative splicing pathway.
- mRNA decay by 5' to 3' exoribonuclease (HSA-430039, p = 0.0146) provided further evidence of PRPF3's function in mRNA stability and degradation.

Subcellular Localization (Table 7): PRPF3 was highly localized in nuclear spliceosomal components, with the most enriched compartments being:

- U4/U6 x U5 tri-snRNP complex (GOCC:0046540, p = 3.62E-24).
- U2-type precatalytic spliceosome (GOCC:0071005, p = 1.60E-16).
- Spliceosomal complex (GOCC:0005681, p = 3.44E-18).

This strong nuclear localization was further supported by its presence in the nuclear speck (GOCC:0016607, p = 0.00037) and nucleoplasm (GOCC:0005634, p = 2.70E-05). The network analysis and enrichment studies on PRPF3 strongly reinforce its critical role in mRNA splicing and ribonucleoprotein complex formation. PRPF3 is a key component of the spliceosome, directly interacting with multiple snRNP complexes and influencing alternative splicing. Its involvement in RNA degradation pathways and subnuclear organization suggests a broader role in post-transcriptional regulation and RNA stability.

Given the significance of splicing dysregulation in genetic diseases and cancer, PRPF3 remains an important candidate for further functional and therapeutic studies.

Table 1
Network Stats

Number of nodes: 11
Expected number of edges: 12
Number of edges: 51
PPI enrichment p-value: < 1.0e-16
average node degree: 9.27
avg. local clustering coefficient: 0.952

Table 2
Biological Process (Gene Ontology)

GO-term	Description	Count in network	Strength	Signal	False discovery rate	
GO:0000398	mRNA splicing, via spliceosome	11 of 245	1.91	5.53	**2.24E-17**	
GO:0000387	Spliceosomal snRNP assembly	5 of 39	2.36	3.78	3.14E-08	
GO:0071826	Ribonucleoprotein complex subunit organization	7 of 211	1.77	3.1	1.02E-08	
GO:0022618	Ribonucleoprotein complex assembly	6 of 203	1.72	2.5	6.55E-07	
GO:0000245	Spliceosomal complex assembly	4 of 76	1.97	2.04	6.37E-05	
GO:0022613	Ribonucleoprotein complex biogenesis	7 of 449	1.45	1.97	9.52E-07	
GO:0036261	7-methylguanosine cap hypermethylation	2 of 8	2.65	1.18	0.0071	
GO:0000244	Spliceosomal tri-snRNP complex assembly	2 of 13	2.44	1.0	0.0150	
GO:0043933	Protein-containing complex organization	8 of 1465	0.99	0.96	9.60E-05	
GO:0065003	Protein-containing complex assembly	7 of 1303	0.98	0.83	0.00096	
GO:0045292	mRNA cis splicing, via spliceosome	2 of 23	2.19	0.77	0.0378	
GO:1903241	U2-type prespliceosome assembly	2 of 24	2.17	0.76	0.0398	
GO:0044085	Cellular component biogenesis	9 of 2702	0.78	0.65	0.00052	
GO:0022607	Cellular component assembly	8 of 2467	0.76	0.57	0.0041	
GO:0071840	Cellular component organization or biogenesis	10 of 5639	0.5	0.35	0.0150	

Table 3
Molecular Function (Gene Ontology)

GO:0017069	snRNA binding	3 of 47	2.06	1.25	0.0041
GO:0003723	RNA binding	10 of 1672	1.03	1.18	1.00E-06
GO:0017070	U6 snRNA binding	2 of 14	2.41	0.76	0.0417

Table 4
Cellular Component (Gene Ontology)

GO:0046540	U4/U6 x U5 tri-snRNP complex	10 of 36	2.7	10.9	3.77E-23
GO:0071005	U2-type precatalytic spliceosome	8 of 50	2.46	7.49	1.42E-16
GO:0005684	U2-type spliceosomal complex	9 of 93	2.24	7.03	2.96E-17
GO:0005681	Spliceosomal complex	11 of 197	2.0	6.6	4.73E-20
GO:0071013	Catalytic step 2 spliceosome	7 of 90	2.14	5.04	3.39E-12
GO:0005682	U5 snRNP	4 of 19	2.58	3.75	7.28E-08
GO:0120115	Lsm2-8 complex	3 of 7	2.89	3.08	2.26E-06
GO:0005688	U6 snRNP	3 of 8	2.83	3.01	2.90E-06
GO:0071007	U2-type catalytic step 2 spliceosome	3 of 30	2.25	2.13	7.95E-05
GO:0000243	Commitment complex	2 of 5	2.86	1.82	0.00049
GO:0034715	pICln-Sm protein complex	2 of 6	2.78	1.76	0.00062
GO:0005687	U4 snRNP	2 of 10	2.55	1.55	0.0014
GO:0034709	Methylosome	2 of 12	2.47	1.47	0.0019
GO:0034719	SMN-Sm protein complex	2 of 17	2.32	1.33	0.0033
GO:0005685	U1 snRNP	2 of 19	2.28	1.29	0.0039
GO:0005686	U2 snRNP	2 of 25	2.16	1.18	0.0061
GO:0005689	U12-type spliceosomal complex	2 of 28	2.11	1.13	0.0074
GO:0016604	Nuclear body	6 of 833	1.11	1.06	0.00020
GO:0016607	Nuclear speck	4 of 420	1.23	0.92	0.0040
GO:0015030	Cajal body	2 of 60	1.78	0.78	0.0308
GO:0005654	Nucleoplasm	11 of 4169	0.67	0.63	4.94E-06

Table 5
KEGG Pathways

Pathway	Description	Count in network	Strength	Signal	False discovery rate
hsa03040	Spliceosome	11 of 132	2.17	8.07	6.66E-22
hsa03018	RNA degradation	3 of 75	1.86	1.38	0.0016

Table 6
Reactome Pathways

Pathway	Description	Count in network	Strength	Signal	False discovery rate
HSA-72163	mRNA Splicing – Major Pathway	11 of 203	1.99	6.32	4.36E-19
HSA-72165	mRNA Splicing – Minor Pathway	4 of 50	2.16	2.56	7.47E-06
HSA-430039	mRNA decay by 5 to 3 exoribonuclease	2 of 15	2.38	1.0	0.0146

Table 7
Subcellular Localization (Compartments)

GOCC:0046540	U4/U6 x U5 tri-snRNP complex	10 of 27	2.82	11.72	3.62E-24
GOCC:0071005	U2-type precatalytic spliceosome	8 of 50	2.46	7.47	1.60E-16
GOCC:0005684	U2-type spliceosomal complex	9 of 83	2.29	7.34	1.26E-17
GOCC:0005681	Spliceosomal complex	10 of 148	2.08	6.62	3.44E-18
GOCC:0071013	Catalytic step 2 spliceosome	7 of 83	2.18	5.19	2.22E-12
GOCC:0005682	U5 snRNP	4 of 16	2.65	3.87	4.85E-08
GOCC:1990904	Ribonucleoprotein complex	11 of 564	1.54	3.43	2.73E-15
GOCC:0120115	Lsm2-8 complex	3 of 8	2.83	2.95	3.77E-06
GOCC:0005688	U6 snRNP	3 of 8	2.83	2.95	3.77E-06
GOCC:0071007	U2-type catalytic step 2 spliceosome	3 of 30	2.25	2.09	9.46E-05
GOCC:0071001	U4/U6 snRNP	2 of 4	2.95	1.83	0.00049
GOCC:0000243	Commitment complex	2 of 5	2.86	1.75	0.00065
GOCC:0034715	pICln-Sm protein complex	2 of 6	2.78	1.69	0.00083
GOCC:0005687	U4 snRNP	2 of 10	2.55	1.49	0.0018
GOCC:0016607	Nuclear speck	4 of 193	1.57	1.47	0.00037
GOCC:0034709	Methylosome	2 of 12	2.47	1.42	0.0024
GOCC:0016604	Nuclear body	5 of 381	1.37	1.39	0.00015
GOCC:0034719	SMN-Sm protein complex	2 of 17	2.32	1.27	0.0043
GOCC:0005685	U1 snRNP	2 of 18	2.3	1.26	0.0046
GOCC:0005686	U2 snRNP	2 of 23	2.19	1.16	0.0067
GOCC:0005689	U12-type spliceosomal complex	2 of 24	2.17	1.15	0.0070
GOCC:0015030	Cajal body	2 of 47	1.88	0.86	0.0222
GOCC:0005634	Nucleus	11 of 4787	0.61	0.55	2.70E-05
GOCC:0031981	Nuclear lumen	6 of 1850	0.76	0.5	0.0151

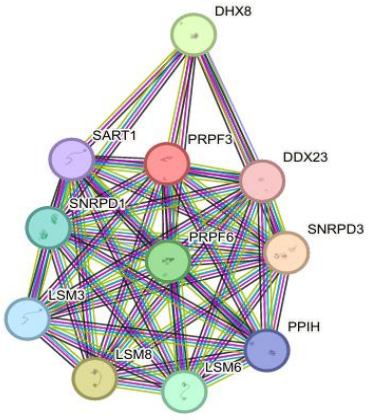

Fig. 1: Network analysis for PRPF3

Discussion

The protein-protein interaction (PPI) network analysis for PRPF3 (Pre-mRNA Processing Factor 3) provides valuable insights into its role in mRNA splicing, ribonucleoprotein complex assembly and nuclear organization. The results highlight PRPF3's functional associations with spliceosomal components, reinforcing its central position in pre-mRNA processing and post-transcriptional regulation.

The network statistics revealed a highly interconnected structure with 11 nodes and 51 edges, significantly exceeding the expected 12 edges. This suggests that PRPF3 interacts with multiple proteins in a functionally significant manner, rather than forming random associations. The PPI enrichment p-value (<1.0e-16) confirms that PRPF3's interactions are statistically significant and play a crucial role in the splicing machinery.

The average node degree of 9.27 indicates that each protein in the network interacts with nearly 10 other proteins, emphasizing PRPF3's central role in spliceosomal stability. Additionally, the high local clustering coefficient (0.952) suggests that PRPF3 and its interacting partners form tight functional modules, likely regulating key aspects of RNA metabolism and spliceosome activation. The biological process enrichment analysis reinforces PRPF3's critical role in RNA splicing. The most significant term was mRNA splicing via the spliceosome (GO:0000398, p = 2.24E-17), with all 11 proteins in the network involved in this process. This confirms PRPF3's essential function in removing introns and processing mature mRNA for gene expression.

Other significantly enriched biological processes include:
Spliceosomal snRNP assembly (GO:0000387, p = 3.14E-08), highlighting PRPF3's role in stabilizing and assembling small nuclear ribonucleoproteins (snRNPs).

Ribonucleoprotein complex organization (GO:0071826, p = 1.02E-08), demonstrating its importance in forming and regulating RNA-protein complexes.

Spliceosomal complex assembly (GO:0000245, p = 6.37E-05), confirming PRPF3's direct involvement in spliceosome biogenesis and activation.

These findings suggest that PRPF3 plays a dual role in pre-mRNA splicing and ribonucleoprotein complex maturation, making it indispensable for mRNA processing efficiency. The molecular function enrichment analysis highlights PRPF3's strong affinity for RNA binding, which is crucial for spliceosomal assembly and transcript processing. snRNA binding (GO:0017069, p = 0.0041) suggests that PRPF3 interacts directly with spliceosomal RNAs, particularly during the formation of the U4/U6 di-snRNP complex.

RNA binding (GO:0003723, p = 1.00E-06) further supports PRPF3's role in recognizing and stabilizing pre-mRNA molecules.

U6 snRNA binding (GO:0017070, p = 0.0417) reinforces its role in coordinating catalytic activation within the spliceosome.

These results highlight PRPF3 as a key RNA-associated protein required for spliceosomal precision and fidelity, ensuring accurate splicing events in the cell. The cellular component analysis confirmed PRPF3's strong association with multiple spliceosomal complexes, reinforcing its nuclear localization and functional specialization in mRNA processing.

U4/U6 x U5 tri-snRNP complex (GO:0046540, p = 3.77E-23) was the most significantly enriched compartment, confirming PRPF3's role in spliceosomal remodelling.

U2-type precatalytic spliceosome (GO:0071005, p = 1.42E-16) and U2-type spliceosomal complex (GO:0005684, p = 2.96E-17) further established its involvement in early and intermediate steps of splicing activation.

Nuclear speck (GO:0016607, p = 0.0040) and Cajal body (GO:0015030, p = 0.0308) suggest that PRPF3 is involved in snRNP biogenesis and storage, providing further evidence of its critical subnuclear positioning.

These findings confirm that PRPF3 is an integral component of the nuclear spliceosome, functioning in coordination with other ribonucleoproteins to regulate mRNA maturation. PRPF3's pathway enrichment results provide additional insights into its involvement in splicing and RNA metabolism. KEGG pathway analysis identified the spliceosome (hsa03040, p = 6.66E-22) as the most enriched pathway, demonstrating PRPF3's role in catalyzing intron removal. Reactome analysis revealed enrichment in mRNA splicing - major pathway (HSA-72163, p = 4.36E-19), further reinforcing its role in the core mechanisms of splicing regulation.

mRNA decay by 5' to 3' exoribonuclease (HSA-430039, p = 0.0146) suggests that PRPF3 may have an additional function in RNA stability and degradation.

These results suggest that PRPF3 is not only essential for pre-mRNA splicing but may also contribute to post-splicing RNA surveillance, ensuring that defective transcripts are efficiently degraded. Mutations in PRPF3 have been implicated in retinitis pigmentosa (RP), neurodegenerative diseases and cancer. The observed network and functional interactions provide a strong molecular basis for these disease associations.

PRPF3 mutations in RP disrupt normal spliceosomal function, leading to defective mRNA processing in retinal photoreceptors. This causes progressive cell death and vision loss, as seen in inherited retinal disorders. Aberrant splicing in cancer is another key finding, as PRPF3 dysregulation alters alternative splicing patterns, contributing to

tumorigenic isoforms in esophageal squamous cell carcinoma and glioblastoma. Potential therapeutic targeting of PRPF3-related pathways is a growing area of research with spliceosome inhibitors and gene-editing techniques being explored to correct PRPF3-associated defects.

These findings suggest that PRPF3 could serve as both a biomarker and a therapeutic target in splicing-related diseases. The network and functional analyses of PRPF3 confirm its central role in RNA splicing, ribonucleoprotein complex formation and nuclear organization. PRPF3 is a key component of the spliceosomal machinery, interacting with multiple proteins and participating in mRNA processing, RNA stability and cellular homeostasis.

Additionally, PRPF3's strong disease associations with retinitis pigmentosa and cancer suggest that it could be a potential diagnostic marker and therapeutic target. Future research should focus on experimental validation of PRPF3's interactions, alternative splicing regulation and targeted interventions for PRPF3-related diseases.

PRPF3 in Disease: Retinitis Pigmentosa and Cancer: Mutations in PRPF3 have been strongly implicated in retinitis pigmentosa (RP), a progressive retinal degenerative disorder characterized by photoreceptor cell death and vision loss[2,18]. These mutations disrupt normal spliceosomal function in retinal cells, affecting the proper processing of transcripts critical for photoreceptor survival[25,29].

Beyond RP, PRPF3 has been linked to cancer progression, particularly in esophageal squamous cell carcinoma (ESCC) and glioblastoma[3,14]. Dysregulated PRPF3 expression alters alternative splicing patterns, leading to the production of oncogenic mRNA isoforms that promote tumorigenesis[8,19]. Studies also suggest a potential role for PRPF3 in neurodegenerative diseases, as aberrant splicing mechanisms contribute to disorders such as amyotrophic lateral sclerosis (ALS) and Alzheimer's disease[24,30].

Given PRPF3's essential role in splicing and disease pathogenesis, recent efforts have focused on developing therapeutic strategies targeting PRPF3-associated pathways. Spliceosome inhibitors, such as pladienolide B and herboxidiene, have shown promise in targeting splicing factor dysregulation in cancer cells[11,31]. Additionally, CRISPR-based gene correction approaches are being explored to rectify PRPF3 mutations in RP patients, offering a potential future therapy for splicing-related disorders[9,22].

Conclusion

PRPF3 plays a critical role in pre-mRNA splicing, ribonucleoprotein complex assembly and spliceosome regulation. Its mutations contribute to retinal degenerative diseases, cancer progression and neurological disorders, making it a key target for therapeutic interventions. Future studies should focus on structural-functional analyses, gene-editing therapies and pharmacological interventions to better understand PRPF3's full potential in human health and disease.

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