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이학박사학위논문

mRNA-단백질 상호작용에 대한
시계열 분석

Time-resolved profiling of
mRNA-protein interaction through the
mRNA life cycle

2023년 8월

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Abstract

Time-resolved profiling of mRNA-protein interaction through the mRNA life cycle

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mRNAs continually change their protein partners throughout their life cycle, yet our understanding of mRNA-protein complexes (mRNPs) is limited by a lack of temporal information. Here, we present time-resolved mRNA interactome data by combining pulse metabolic labeling with photoactivatable ribonucleoside, UVA crosslinking, poly(A)+ RNA isolation, and mass spectrometry. This approach allows the quantification of over 700 mRNA-binding proteins (mRBPs) across ten distinct time points.

The chronological orders of RNA binding were consistent with the known functions, subcellular localizations and protein-protein interactions of the RBPs. Stress granule proteins were found to be enriched in "aged" mRNPs, implying their roles in the terminal stages of the mRNA life cycle. Many late binding RBPs were previously known as viral RBPs, suggesting their regulatory activities on viruses. We also built a computational model to systematically identify RBPs with unexpected binding dynamics based on their Gene Ontology annotations, indicating that they may have some unknown functions. We identify numerous mRBPs with unexpected dynamics, implying undiscovered functions and regulatory mechanisms. For data exploration, we have developed a web application available at chronology.rna.snu.ac.kr. By introducing a time dimen-

sion, this study offers a unique resource and insights into mRNP remodeling.

Keywords: mRNA; RNA-binding proteins; mRNP remodeling; Time-resolved mRNA interactome

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Nomenclature

3' UTR	3' untranslated region
4sU	4-thio-uridine
5' UTR	5' untranslated region
6sG	6-thioguanosine
BP	Biological process
CC	Cellular component
CDS	coding sequence
GO term	Gene ontology term
hnRNP	heterogeneous nuclear ribonucleoprotein
HPLC	High-performance liquid chromatography
LC-MS	liquid chromatography and mass spectrometry
MCA	multiple correspondence analysis
mRBP	mRNA-binding protein
mRNP	mRNA-protein complex
NMD	nonsense mediated decay

PABP	poly(A) binding protein
PAR-crosslinking	Photoactivatable ribonucleoside (PAR)-enhanced crosslinking
PPI	protein-protein interaction
RBD	RNA binding domain
RIC	RNA interactome capture
RIP	RNA immunoprecipitation
SG	stress granule
vRBP	viral RNA binding protein

1. Introduction

1.1 Life cycle of mRNA and its protein complexes

The life cycle of eukaryotic mRNA involves several distinct stages: transcription, pre-mRNA processing, nuclear export, translation, and decay. After transcription by RNA polymerase II, mRNA undergoes several processing steps, including 5' capping, splicing, 3' end cleavage, and polyadenylation. Once processed, the mRNA is exported from the nucleus to the cytoplasm. In the cytoplasm, mRNAs interact with translational initiation factors, facilitating 40S ribosome complex recruitment. After translation, poly(A) tail of mRNA is shortened by deadenylases. Following deadenylation, the mRNA can be subjected to decapping, exposing the mRNA to degradation (66) (Figure 1.1).

In each stage, mRNA interacts with a specific set of RNA binding proteins (RBPs) to form mRNA-protein complexes (mRNPs) (66; 52). These RBPs govern the activity, localization, and stability of mRNA, and influence its transition to the subsequent stage of the life cycle. Therefore, unveiling the stage-specific repertoire of RBPs is vital for understanding mRNA regulation.

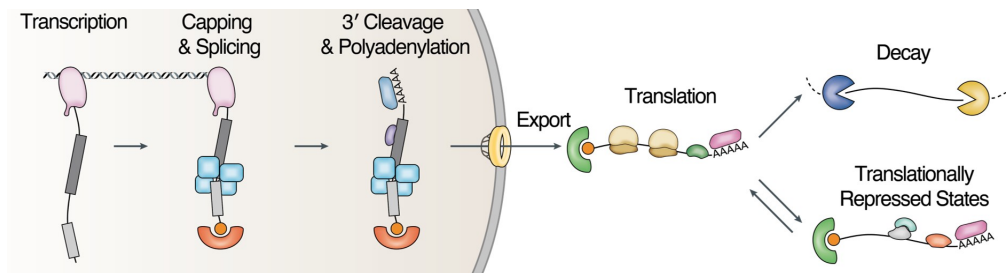


Figure 1.1 Life cycle of mRNA.

Since mRNP was first observed in the 1950s, many researchers have biochemically purified mRNPs and discovered core mRNP components, such as cap-binding proteins, heterogeneous nuclear ribonucleoproteins (hnRNPs), serine/arginine-rich (SR) splicing factors, and poly(A) binding proteins (PABPs) (22; 15; 66).

1.2 RNA interactome capture (RIC)

Studies have explored the interaction between mRNAs and RBPs comprehensively, employing high-throughput approaches such as the RNA interactome capture (RIC) (Figure 1.2). In RIC experiments, RNA-protein partners are first crosslinked either with UV light or chemical crosslinkers, followed by RNP enrichment methods such as oligo-dT capture, protein extraction, liquid chromatography and mass spectrometry (LC-MS) (10; 5). MS-based techniques collectively reported more than 6000 human proteins as potential RBPs (11), and it is believed that the human genome encodes at least 1,542 RBPs (24). These methods have been applied to numerous biological contexts, revealing the diverse biological roles of RBPs (69; 23; 57; 87).

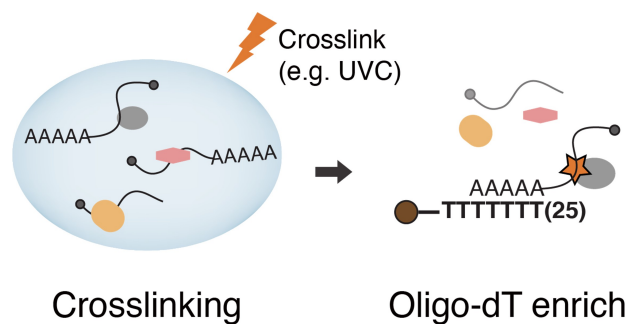


Figure 1.2 RNA interactome capture (RIC).

1.3 Photoactivatable Ribonucleoside (PAR) -enhanced crosslinking

PAR-crosslinking, also known as Photoactivatable Ribonucleoside-enhanced crosslinking, is a technique utilized to investigate RNA-protein interactions. Unlike crosslinking methods that use short-wavelength UV light, PAR-crosslinking employs modified ribonucleosides, such as 4-thio-uridine (4sU) and 6-thioguanosine (6sG), which can be photoactivated by UV light more efficiently. This photoactivation leads to the formation of covalent crosslinks between the RNA and the proteins in close proximity (Figure 1.3).

The photoactivatable ribonucleosides, such as 4sU, are specifically excited by long-wavelength UV light, typically around 365nm, which is in the UVA light range. Natural nucleotides are not excited by this wavelength. When the photoactivatable ribonucleosides are exposed to UVA light, the sulphur atom within them is released, forming photoadducts with amino acid side chains of nearby proteins. Amino acids with aromatic rings, such as phenylalanine, tyrosine, and tryptophan, as well as other amino acids like lysine and cysteine, can undergo PAR-crosslinking. The loss of the sulphur atom in 4sU during crosslinking causes the crosslinked 4sU to be recognized as a C during reverse transcription (4).

By employing PAR-crosslinking, researchers can capture and identify RNA-protein interactions in a spatially and temporally controlled manner. The technique

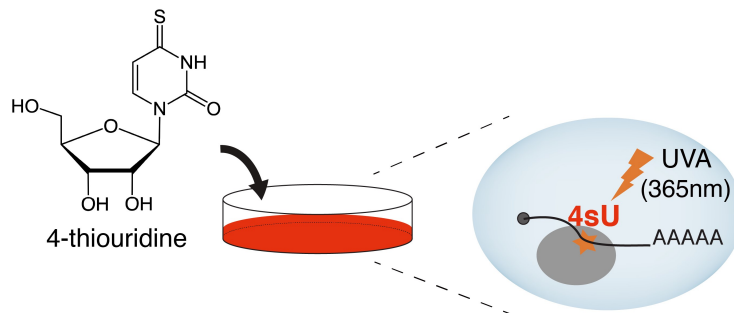


Figure 1.3 Photoactivatable Ribonucleoside-enhanced crosslinking.

enables the study of dynamic RNA-protein interactions, providing valuable insights into the roles of specific proteins in RNA-related processes (5).

2. Chronological profiling of mRNA-protein interaction

2.1 Background

While the previous approaches greatly advanced our knowledge of RNA-protein interactions, their limitation lies in providing unsynchronized mixed pools of mRNPs without temporal resolution. Since mRNPs involved in distinct stages of the mRNA life cycle (e.g. co-transcriptional processing vs. translating) are expected to be fundamentally different from each other, there is a need to collect and analyze mRNPs specific to each stage. Time-resolved profiling would help reveal the compositional changes in mRNPs throughout the mRNA life cycle, offering a more comprehensive understanding of RBP functions. An earlier study examined nascent RNPs by using 5-ethynyluridine labeling followed by click chemistry-based RNA capture, but this approach mainly yielded proteins bound to abundant noncoding RNAs and had a limited temporal resolution (0.5, 2, and 16 hours) (6).

In this study, we aimed to investigate the remodeling of mRNPs over time by developing a time-resolved RNA interactome capture technique. We enriched mRNAs of specific “ages” using pulse-chase metabolic labeling with 4sU and selective crosslinking under 365 nm light (UVA) across 10 time points (28; 42). This longitudinal analysis revealed the RNA binding dynamics of 734 mRBPs. We further integrated these temporal RNA interaction data with subcellular localization, protein-protein interaction, RNA granule formation, viral RNA interaction, and gene ontology data to identify RBPs with as-yet-unknown functions and provide new insights into mRNP remodeling. The chronological data of mRNA-protein interaction from this study can be accessed at: <https://chronology.rna.snu.ac.kr/>

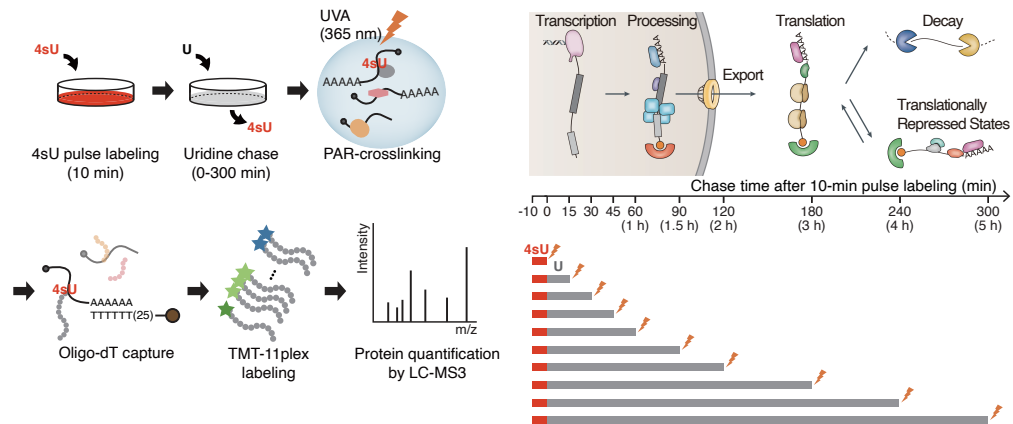


Figure 2.1 Experimental scheme. (A) Schematic of modified RIC for time-resolved mRNP capture. (B) Design of high-temporal resolution mRNP pulse-chase labeling using 4sU and U nucleosides.

2.2 Results

2.2.1 Time-resolved mRNA interactome profiling using RIC with 4sU pulse-labeling

To identify RBPs that associate with mRNAs at specific time points following RNA synthesis, I employed a pulse-labeling approach (Figure 2.1). HeLa cells were metabolically labeled with 4sU for 10 minutes, which is the shortest period yielding sufficient amounts of crosslinked materials needed for our proteomic analyses. This short duration of labeling did not notably affect cell viability (data not shown) or the transcriptome as determined by RNA-seq (Figure 2.2). After a washing procedure and chasing with unmodified uridine until the required time points, cells were exposed to UVA irradiation (365 nm) to induce photoactivatable ribonucleoside (PAR)-enhanced crosslinking between 4sU-labeled RNA and its associated proteins. We selected ten time points, spanning from 0 to 5 hours (0, 15, 30, 45, 60, 90, 120, 180, 240, and 300 min), which likely cover most stages of the mRNA life cycle, considering the median half-life of human mRNAs is 3.4 hours (average half-life, 6.9 hours) (73). For control, we omitted 4sU labeling (“no-4sU”) to identify non-specific proteins and assess background levels.

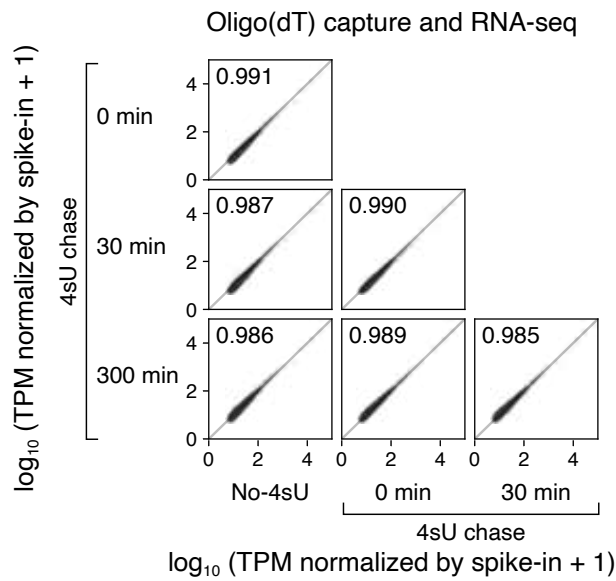


Figure 2.2 mRNA expression was not influenced substantially by 10-min 4sU treatment, as analyzed by RNA-seq. "No-4sU" refers to the oligo(dT) captured RNA population from unlabeled cells. The "4sU chase (0, 30, 300 min)" category corresponds to the oligo(dT) captured RNA populations from cells that were pulse-labeled with 4sU for 10 minutes and then chased with unmodified uridine for the respective time period. The Pearson's correlation coefficient for each sample-sample pair is indicated. The thin gray line represents the line of identity ($y=x$).

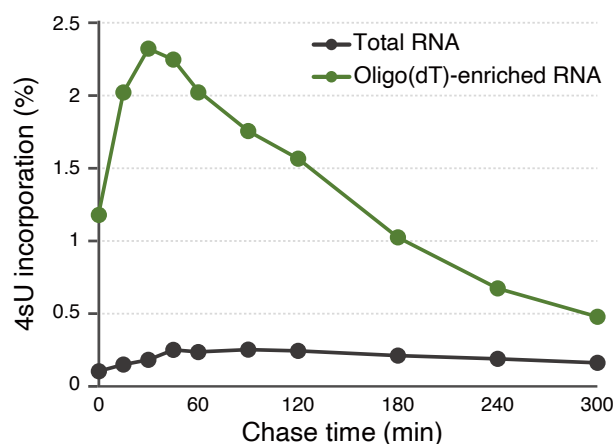


Figure 2.3 Proportion of 4sU relative to total U as measured by HPLC after single nucleotide digestion, using total RNA (black) or oligo(dT)-enriched RNA (green).

To estimate the 4sU incorporation rate under our conditions, I digested RNA into single nucleosides and analyzed them by high-performance liquid chromatography (HPLC) (Figure 2.3).¹ Immediately after the 10-minute labeling period (chase time=0 min), 4sU constituted approximately 1.2% of total uridines in the oligo(dT)-captured RNAs. The 4sU fraction increased to 2.3% within the next 30 minutes, likely because of residual intracellular 4sU and delayed phosphorylation of 4sU into 4sUTP (16). Subsequently, this 4sU fraction decreased likely because of intron removal and decay of labeled transcripts. These findings suggest that our pulse-chase conditions labeled approximately 2% of uridine residues, which corresponds to about ten 4sU incorporated per an mRNA molecule of 2 kb. Labeling occurs within a relatively narrow time window of about 30-40 minutes, without substantially affecting cell physiology.

Silver-staining of captured proteins revealed a peak at 30 min point, which gradually decreased over time, mirroring the pattern of 4sU incorporation into RNA (Figure 2.4). Protein bands were barely visible in the unlabeled negative control, indicating robust enrichment of PAR-crosslinked RBPs. The seized

¹HPLC were performed by Dr. Yongwoo Na

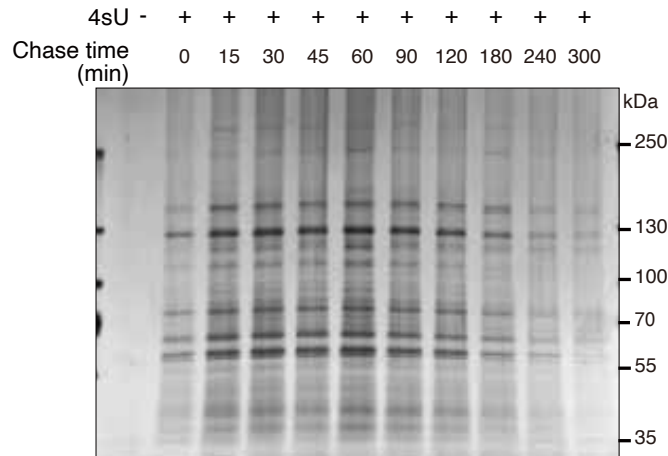


Figure 2.4 Silver staining visualizing the proteins eluted in the RIC experiments.

proteins were digested with trypsin, labeled with TMT 11-plex, and analyzed using LC-MS3 (74; 76). Protein quantities from triplicate samples were tested for enrichment against the unlabeled control (Figure 2.5).²

We determined “confidently quantified RBPs” based on two criteria: enrichment over unlabeled control and reproducibility across replicates (Figure 2.6 and Methods). This analysis yielded 801 confidently quantified proteins. To examine the specificity of our method in identifying RBPs, we compared our confidently quantified proteins with previously identified RBPs (11). More than 90% (734/801) of the confidently quantified proteins from our study were previously reported as mRNA interactors, and >80% of them were annotated with “RNA binding” Gene Ontology (GO) term (Figure 2.7). Regarding domains, we found 58 Pfam domains significantly enriched over all human proteins at a false discovery rate (FDR) of 1% (19) (Figure 2.8 and Methods). The majority of these enriched domains (35 out of 58), such as RRM, Helicase C, DEAD, and KH, have been experimentally verified as RNA binding domains (RBDs) or enriched in previous

²Jeesoo Kim generated the LC-MS3 data. All the bioinformatic analyses were done by Dr. Yeon Choi

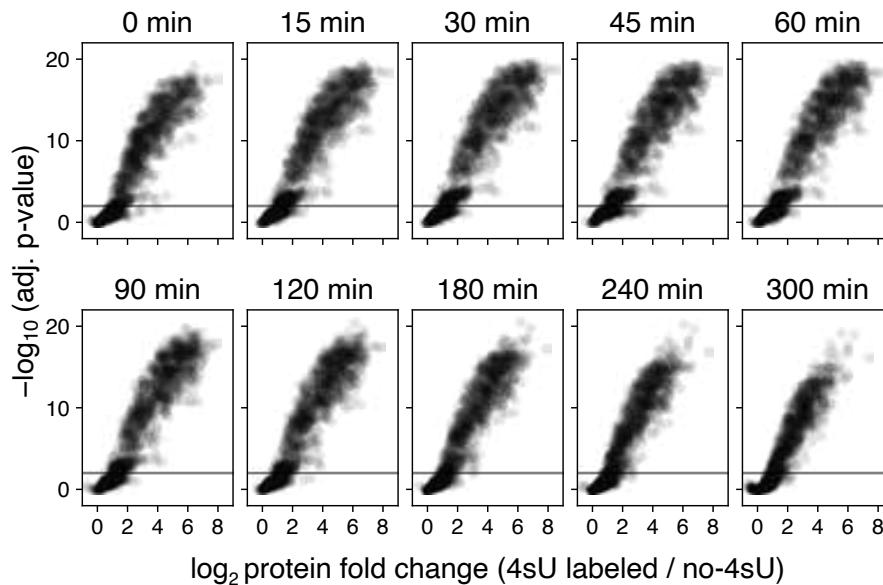


Figure 2.5 Volcano plots of protein differential expression, between no-4sU and 4sU labeled samples. The protein quantities were measured as TMT reporter ion intensities in triplicate. Fold changes between the no-4sU and 4sU-labeled samples were calculated, log2 transformed, and then averaged to obtain the log2 fold changes. P-values were determined using the DEqMS R library and adjusted by the Benjamini-Hochberg method.

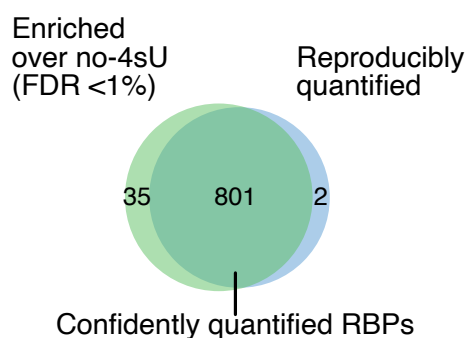


Figure 2.6 Venn diagram showing the number of proteins enriched over the control (no-4sU) and of those that are reproducibly quantified.

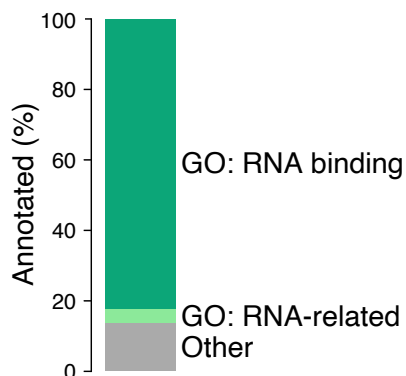


Figure 2.7 Gene Ontology (GO) annotations of the confidently quantified RBPs (n=801). RNA-related GO term was defined as any GO term containing ‘RNA’.

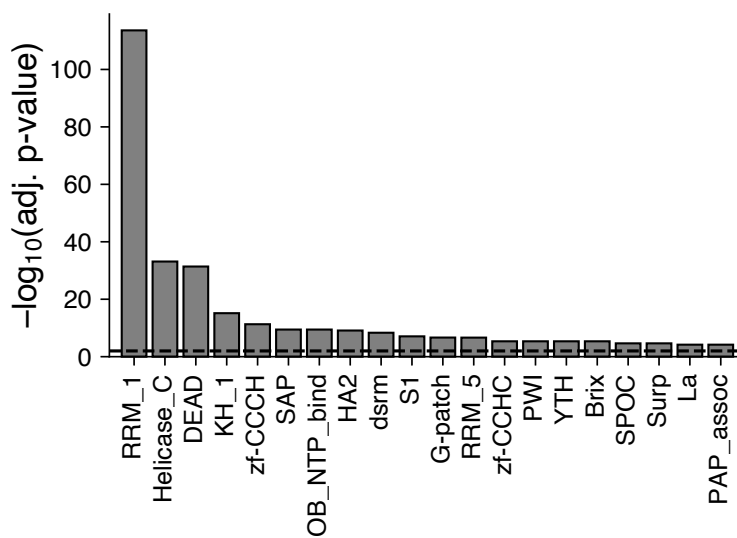


Figure 2.8 Top 20 enriched Pfam protein domains among the confidently quantified proteins (n=801). P-values were calculated by Fisher’s exact test and adjusted by Benjamini-Hochberg method. Dashed line indicates an adjusted p-value of 0.01.

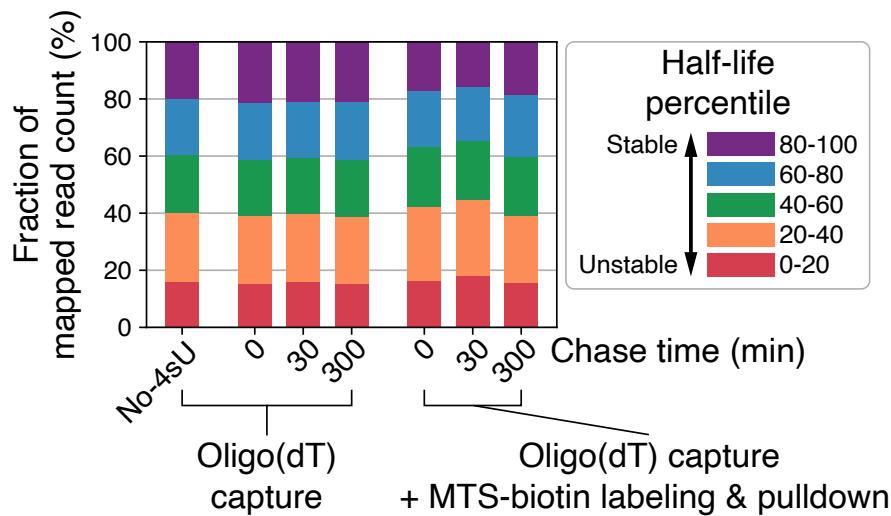


Figure 2.9 Fraction of RNA-seq read counts mapped to mRNAs within each half-life range. mRNA half-lives in HeLa cells were determined by (73). “Oligo(dT)” refers to the same RNA-seq experiments used in panel (A). “Oligo(dT) capture + MTS-biotin labeling & pulldown” means that the oligo(dT) captured RNAs were subsequently treated with methylthiosulfonate-biotin, which labels 4sU, and precipitated with streptavidin beads. indicates RNAs labeled by 4sU for 10 minutes and then chased with unmodified uridine, which resembles the mRNA population captured in our RIC experiment. For these samples, oligo(dT) capture followed by methylthiosulfonate-biotin (MTS-biotin) pulldown was applied, to enrich the 4sU labeled RNAs.

RIC studies (10) (Table 2.1). Collectively, these results indicate that our method successfully captured RBPs.

To monitor the differences in the captured RNA populations over time, I performed RNA-seq on oligo(dT)-captured RNAs with an extra precipitation step which isolates 4sU-labeled RNAs. Comparing chase times 0 and 300 min (Figure 2.9), we observed only a modest reduction (from 16.5% to 15.5% in read proportion) of of unstable mRNAs (bottom 20% in half-life) and a slight increase (from 17.1% to 18.6% in read proportion) of stable mRNAs (top 20% in half-life).

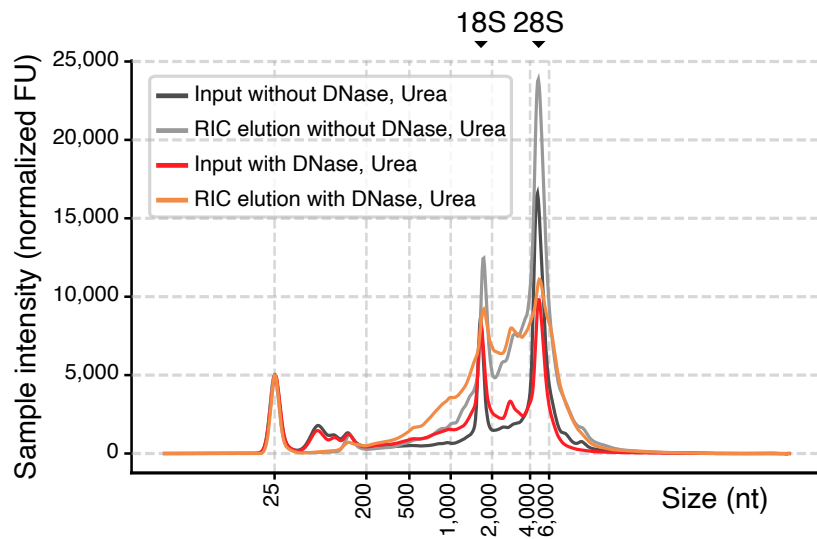


Figure 2.10 Electrophoreogram graphs of RNAs obtained using the conventional RNA interactome capture (RIC) method (without DNase treatment or urea lysis) and the modified RIC method (with DNase treatment and urea lysis), analyzed by TapeStation 4150. The input sample refers to the total RNA extracted using Trizol with or without DNase and urea, and used for RIC. FU indicates fluorescence units. Black triangles indicate the size of 18S and 28S rRNAs.

The majority (97.5%) of genes observed at 0 min remained detectable until 300 min (TPM>1), indicating that our experimental conditions represent the majority of mRNA species although we do not exclude a possibility that differential mRNA decay rates influence the mRBP repertoire over time to some extent.

Our RNA-seq data also showed that some RNAs with oligo(A) tails such as mitochondrial mRNAs and long noncoding RNAs, as well as abundant RNAs were partially precipitated (Figures 2.10 and 2.11) although our method enriched poly(A)+ mRNAs via oligo(dT) capture under a stringent condition with 4M urea and DNase treatment. Our list of RBPs contains 65 mitochondrial RBPs and 65 noncoding RNA-related proteins with established roles in snoRNA and rRNA

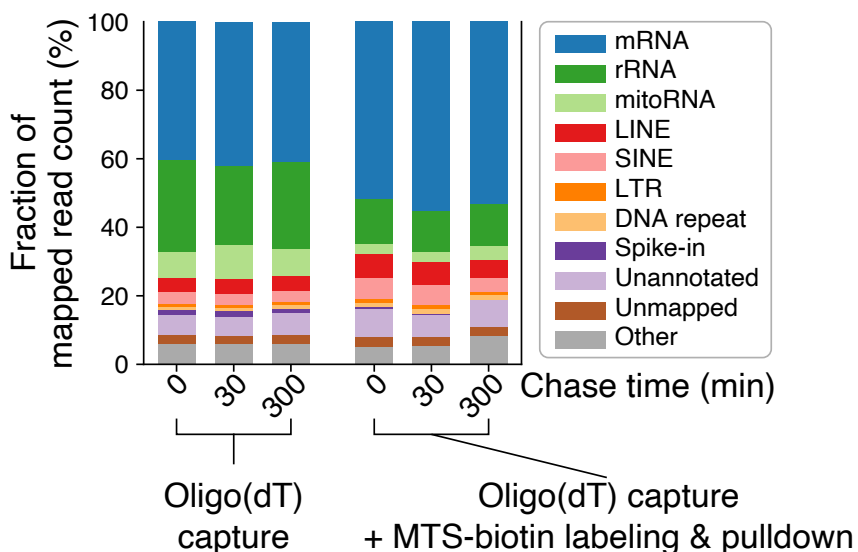


Figure 2.11 Fraction of RNA-seq read counts mapped to each RNA class. “Oligo(dT)” and “MTS-biotin labeling & pulldown + oligo(dT) capture” are the same as in 2.9.

processing. While their RNA binding dynamics may provide interesting insights into the noncoding RNA biogenesis pathways, and they could potentially have roles in the mRNA pathway, we excluded these proteins from further analysis due to our study’s focus on nuclear genome-encoded mRNAs.

2.2.2 High-resolution profiling of RNA-binding dynamics

To investigate the mRNA binding dynamics of each RBP, we merged normalized protein quantities using a univariate spline (Figure 2.12). We defined the “peak binding time” for each RBP as the moment when the spline curve hits its maximum (Figure 2.12). This approach facilitated a quantitative comparison of the binding dynamics among RBPs. It should be noted that this “peak binding time” is actually delayed by approximately 30 minutes from the true maximal binding time due to the persistence of 4sU labeling after washing, as mentioned above.

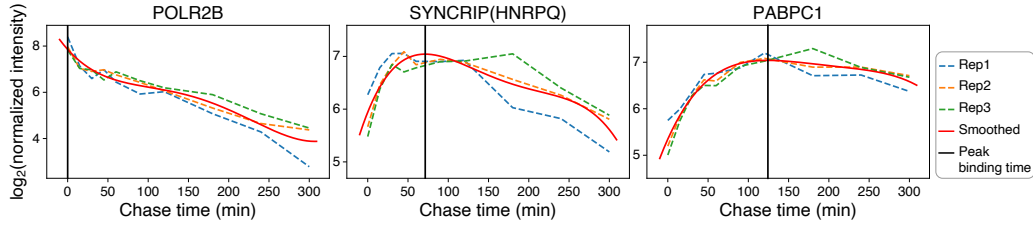


Figure 2.12 Processing of the mRNA binding dynamics from triplicated TMT intensities. Initially, the protein quantity of the no-4sU sample was subtracted from the quantity in the given sample at each time point to eliminate background levels. Subsequently, quantities from triplicates were normalized to achieve equal total quantities, and merged using a univariate spline. The peak binding time was determined from the resulting spline curve.

I initially examined representative RBPs with well-established roles (Figure 2.13). Subunits of RNA polymerase II (POLR2A and POL2R2B) exhibited the highest level of interaction at chase time 0 min, then swiftly declined, along with other transcription-related factors such as SUPT5H, SSRP1, SCAF8 (Figure 2.13A). Subsequently, pre-mRNA processing factors involved in 5' capping, splicing, and 3' end processing emerged (Figure 2.13B). Notably, some of the 3' cleavage and polyadenylation factors (such as CSTF3, CSTF2T, and FIP1L1) are recruited even earlier than cap binding protein CBP20 (also known as NCBP2) and splicing factors. This concurs with the notion that premature 3' cleavage and transcriptional termination are pervasive, and that short transcripts are extensively produced (35). Promoter-proximal polyadenylation sites are frequent in the antisense orientation from the promoter, leading to the generation of upstream short antisense transcripts (3), which may also partially explain the early association of the 3'-processing factors in our experiment.

The binding of the nuclear export factor (NXF1) and the Transcription-Export complex (TREX) components aligned with the replacement of nuclear PABP (PABPN1) by cytoplasmic PABPs (PABPC1 and PABPC4), reflecting mRNP remodeling during nuclear export (Figure 2.13C and 2.14). Translation factors like EIF4G and PABPC bind to mRNA between 1.5 and 4 hours (Figure

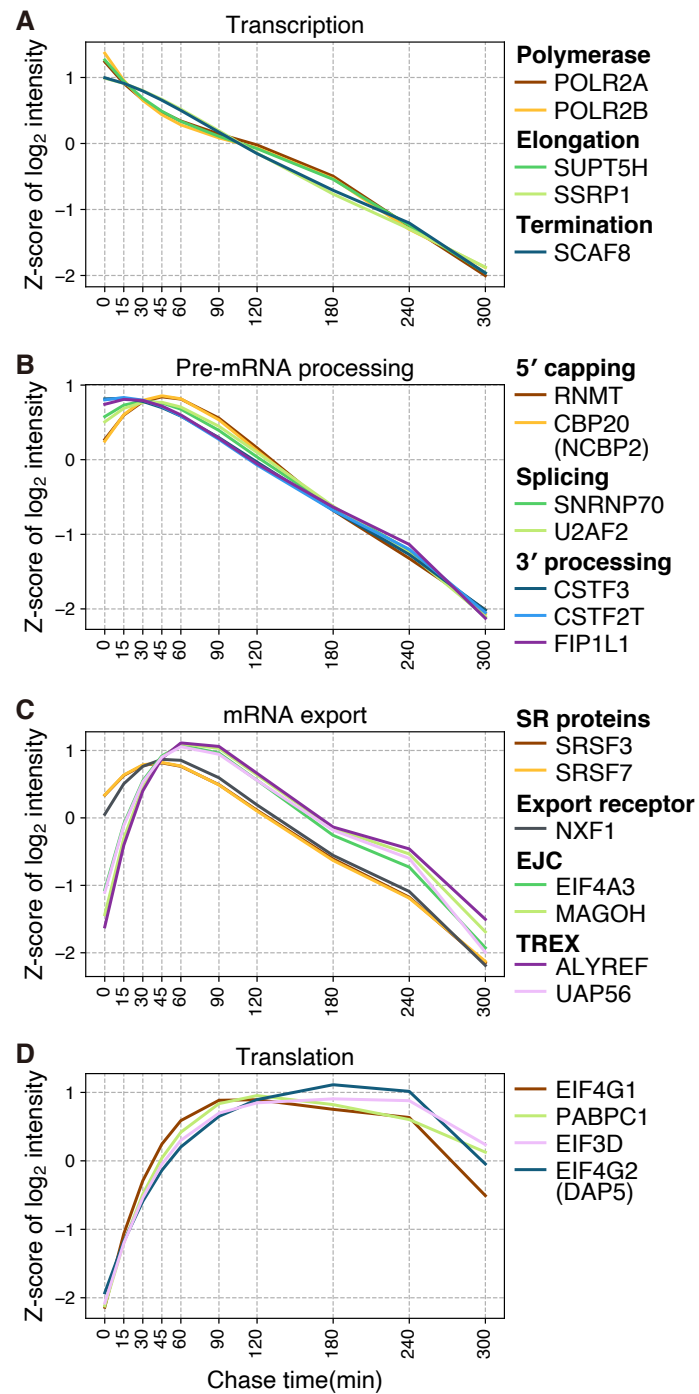


Figure 2.13 (A-D) mRNA binding dynamics of RBPs known to participate in mRNA transcription (A), pre-mRNA processing (B), mRNA nuclear export (C), and translation (D).

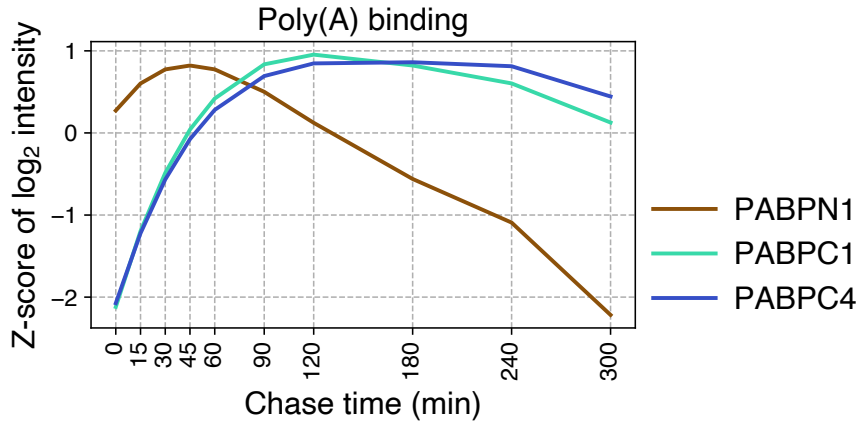


Figure 2.14 mRNA binding dynamics of poly(A) binding proteins

2.13D). The canonical cap binding protein in the cytoplasm, EIF4E, was not detected, possibly due to its low abundance and low crosslinkability. An alternative cap binding protein, EIF3D, was detected alongside its cofactor EIF4G2/DAP5, exhibiting slightly delayed dynamics compared with EIF4G, which may reflect their preferential binding to aged mRNAs or stable mRNAs.

The high temporal resolution of our data allowed us to observe even subtle differences in RNA interaction. For instance, HnRNPs and SR proteins, which bind and regulate pre-mRNAs, showed strikingly similar dynamics (Figures 2.15 and 2.16), indicating their primary function as general constituents of nuclear pre-mRNPs, even though some can shuttle between the nucleus and cytoplasm. One notable exception was HNRPQ (also known as hnRNP Q or SYNCRIP), detected at a substantially later time point than the other hnRNPs. This observation supports previous findings that HNRPQ/SYNCRIP modulates mRNA translation and decay (68; 82) (Figure 2.15). Furthermore, the core components of the exon junction complex (EJC) such as EIF4A3, RBM8A/Y14, and MAGOH precede CASC3/MLN51/BTZ, which is not essential for EJC formation and is mainly located in the cytoplasm, and PYM1, which functions in EJC recycling in the cytoplasm (63) (Figure 2.17).

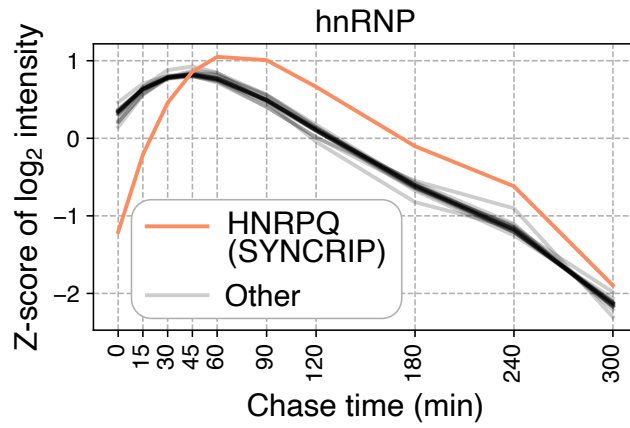


Figure 2.15 mRNA binding dynamics of hnRNP proteins

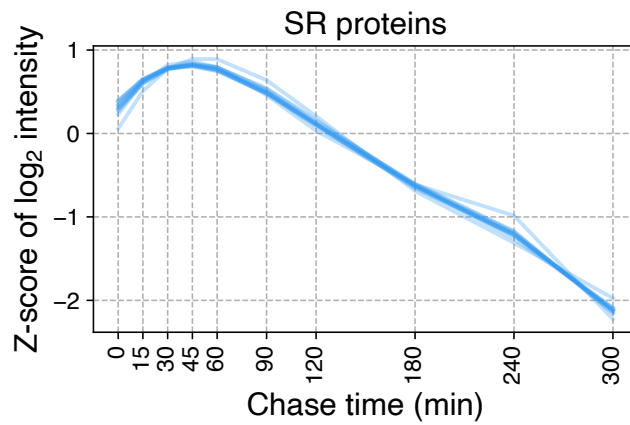


Figure 2.16 mRNA binding dynamics of SR proteins

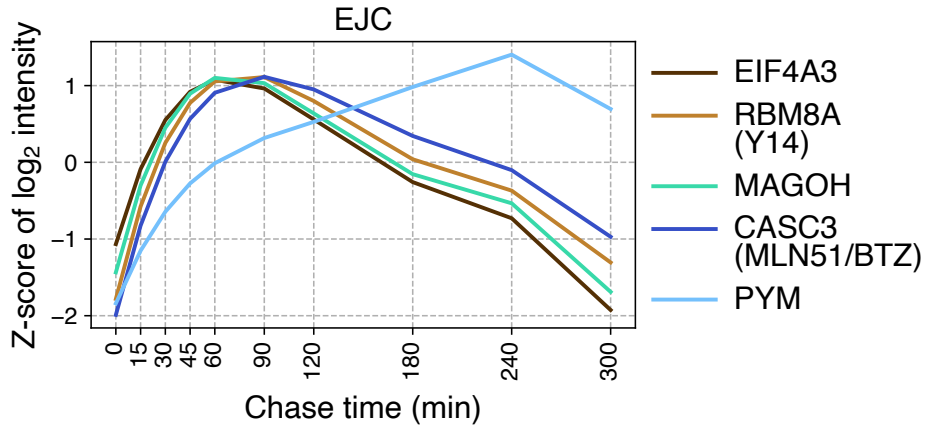


Figure 2.17 mRNA binding dynamics of EJC proteins

Moreover, proteins involved in splicing demonstrated a cascade of RNA association/dissociation (Figure 2.18), overall consistent with the known sequence of spliceosome assembly/disassembly, starting with the U1 and U2 snRNP components and proteins recruited to A complex, followed by the U4/U6.U5 tri-snRNP components and proteins recruited to B, B_{act}, and C complexes (Figure 2.18). Factors involved in m6A modification present another notable example of dynamic mRNA interaction (Figure 2.19); the nuclear writer complex components (RBM15 and ZC3H13) are followed by the nuclear reader (YTHDC1), nuclear eraser (ALKBH5), and cytoplasmic readers (e. g. YTHDC2, YTHDF1, YTHDF2, and YTHDF3) (21; 34) (Figure 2.19).

Our data also show the mRNA binding dynamics of proteins associated with human diseases; for instance, TDP43, EWS, TAF15, FUS, and hnRNPA1 implicated in Amyotrophic Lateral Sclerosis (Figure 2.20).

For validation, I conducted Western blotting analyses on RBPs detected in our analyses (Figure 2.21). Consistent with the mass spectrometry data, a pol II subunit POLR2 was detected primarily at the earliest time point, while nuclear RBPs such as hnRNPA1, SRSF7, PABPN, and TDP-43 peaked at 30–60 min, followed by the shuttling export factor ALYREF and subsequently by cytosolic

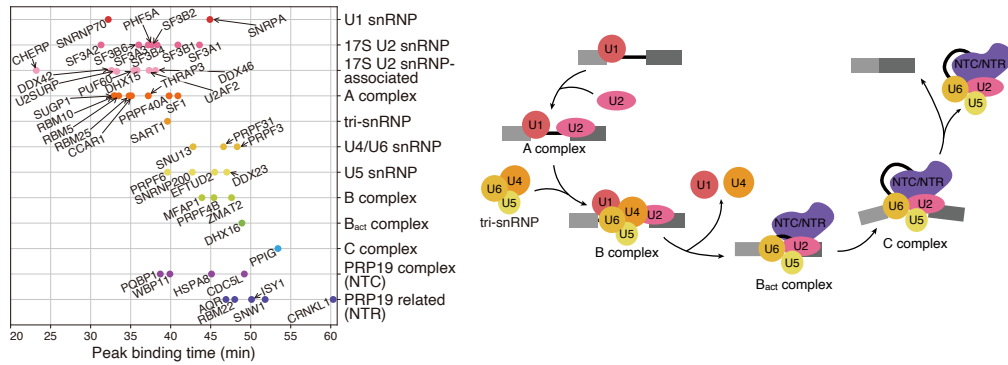


Figure 2.18 Peak binding times of splicing machinery proteins. For visualization, only the proteins quantified in all three replicates are shown. (Right) Schematic diagram of pre-mRNA splicing.

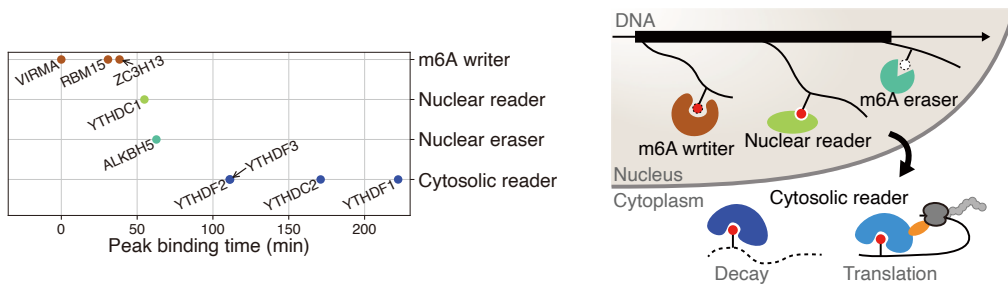


Figure 2.19 Peak binding times of m6A RNA modification-related proteins. Check Figure S3F for the known functions of m6A RNA modification-related proteins. (Right) Schematic diagram of m6A RNA modification

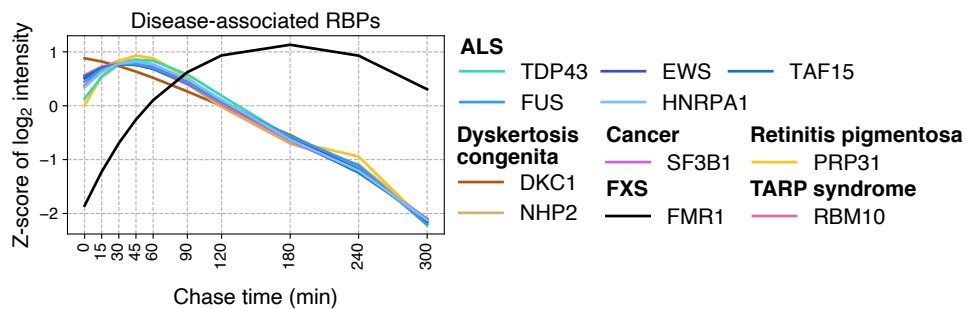


Figure 2.20 mRNA binding dynamics of RBP associated with human diseases.

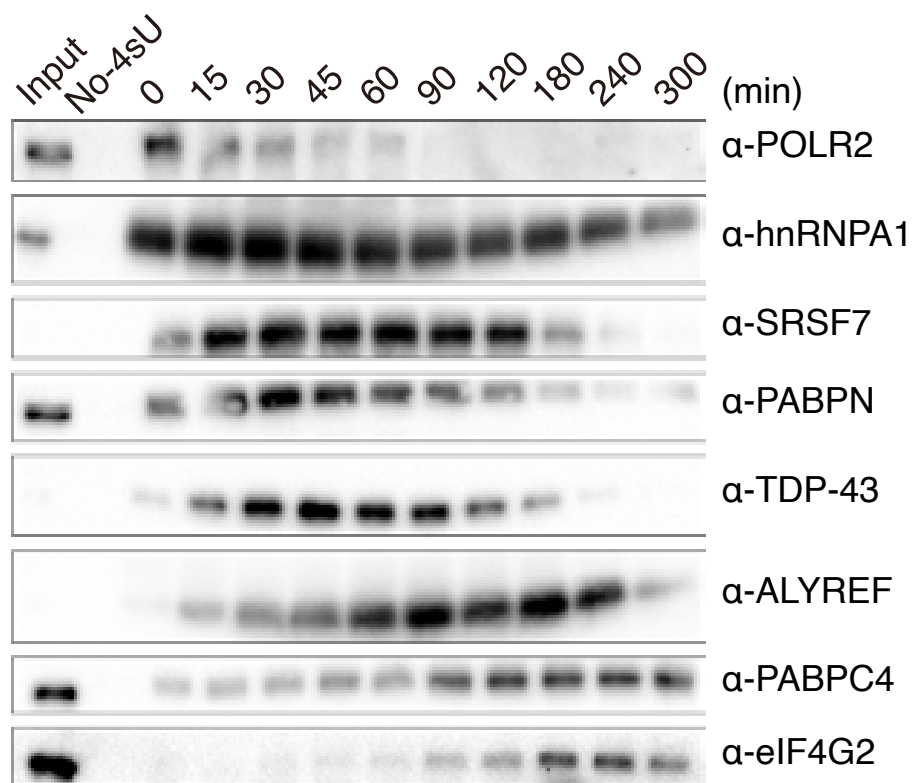


Figure 2.21 Validation by western blotting. Input represents 0.01% of the lysate that is used in the 0 min RIC sample. No-4sU means the RIC elution sample obtained from unlabeled cells.

translation factors, PABPC4 and EIF4G2. Thus, our dataset successfully reflects the known localizations and functions of the representative RBPs.

2.2.3 Clustering analysis of RBPs

To categorize mRBPs according to their temporal RNA-binding dynamics, we executed k-means clustering, utilizing z-score-normalized log₂ protein intensity and peak binding time (Figure 2.22 and Table 2.2 ; also see Methods). “Biological process” (BP) GO term analyses revealed unique enrichment within each cluster (2)(Figure 2.23). Cluster I frequently displays transcription-related terms, whereas cluster II is enriched with pre-mRNA processing and splicing related terms. Export-related terms are observed in cluster III, whereas clusters IV and V were significantly associated with translation and nonsense mediated decay (NMD). Clusters VI and VII were enriched with translation regulation, stress granule (SG), and RNA decay terms.

Orthogonally, we calculated the mean peak binding time of the proteins within a given GO term group. Proteins with transcription-related terms show the earliest mean peak binding times (Figure 2.24, shown in x-axis) and belonged mainly to clusters I or II (Figure 2.24, indicated by colors). Proteins with processing-related terms and translation-related terms followed in the anticipated order. We repeated this test on “cellular component (CC)” GO terms to monitor the temporal changes in mRNP organizations (Figure 2.25). Proteins with “RNA polymerase complex” and “transcription elongation factor complex” terms were detected initially, followed by proteins with “cleavage and polyadenylation complex” and spliceosome-related terms. Proteins with translation-related terms (e.g. polysome, EIF4F complex, EIF3 complex) and decay/mRNA storage-related terms (e.g. P-body) took longer to bind to mRNA. Both BP and CC term analyses suggested that the transition from nuclear to cytoplasmic processes occurs at around 60-100 minutes and between clusters IV and V. Considering the inevitable lag period of approximately 30 minutes in our labeling scheme, this transition time aligns with the time required for mRNA export (30-40 minutes) (33; 53).

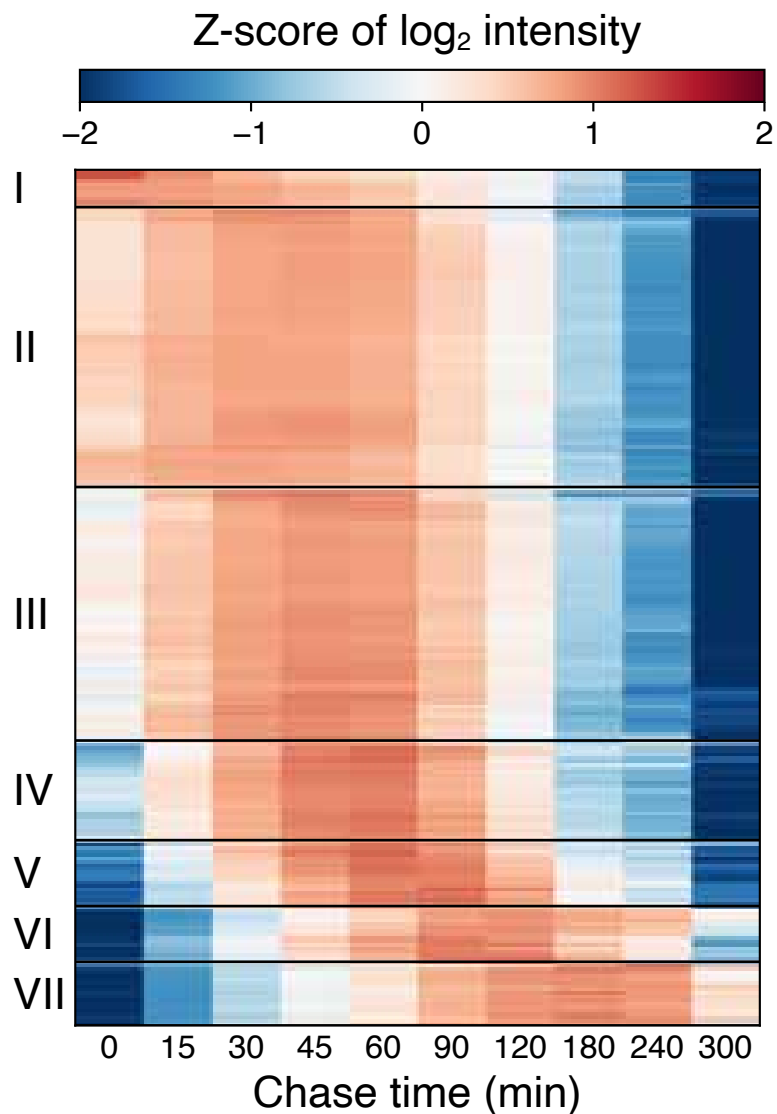


Figure 2.22 Clustering analysis based on mRNA binding dynamics. Each row of the heatmap represents the z-score normalized mRNA binding dynamics of a protein. Out of 801 confidently quantified proteins, 734 proteins that were previously reported as mRNA binders were used for clustering analysis. Mitochondrial mRNA binders (n=65) and potential non-coding RNA binders (n=65, e.g. ribosomal proteins, snoRNA binders) were excluded from this and following analyses (see methods for the list).

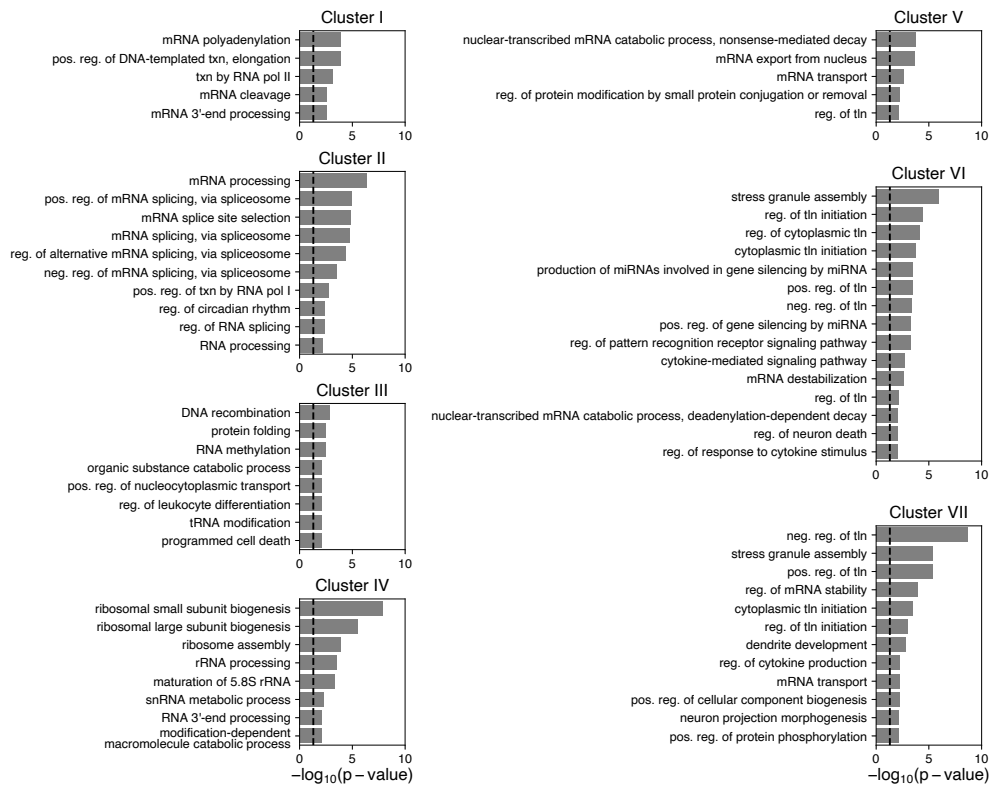


Figure 2.23 GO: BP term enrichment analysis on each cluster, using TopGO R library. For the background group for the enrichment test, all proteins identified (FDR 1%) in this study were included. pos.: positive, neg.: negative, txn: transcription, tln: translation, reg.: regulation.

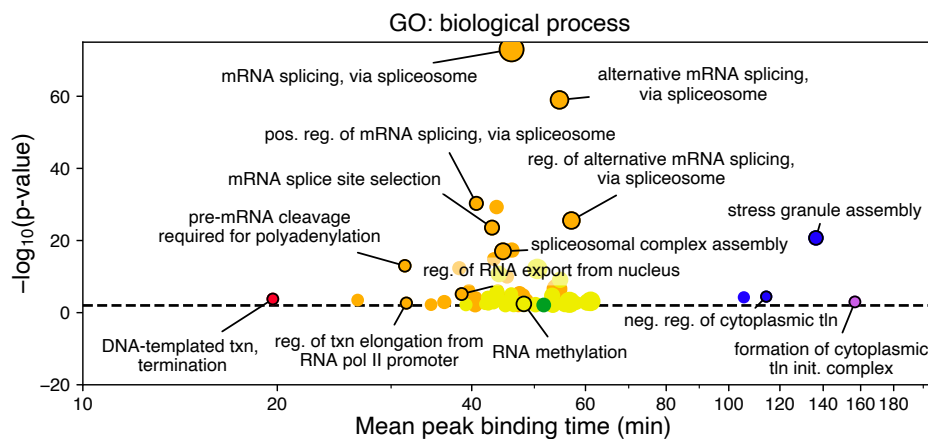


Figure 2.24 Bubble plot showing the mean peak binding time (x-axis) of the RBPs sharing the same GO : biological process (BP) terms. The significance of similarity in mRNA binding dynamics of the RBP group sharing the same terms are shown in y-axis, as p-values derived from two-sided Mann-Whitney U test on the Euclidean distances between proteins with the same GO annotations vs. those between proteins without the same GO annotations. Dashed line indicates $P=0.01$. To reduce the over-representation of general (higher level) GO terms, the elim algorithm described in (2) was applied during the p-value calculation. Color code indicates the most frequently occurring cluster among the RBPs annotated with each GO term. Area of each circle is proportional to the number of RBPs annotated with each GO.

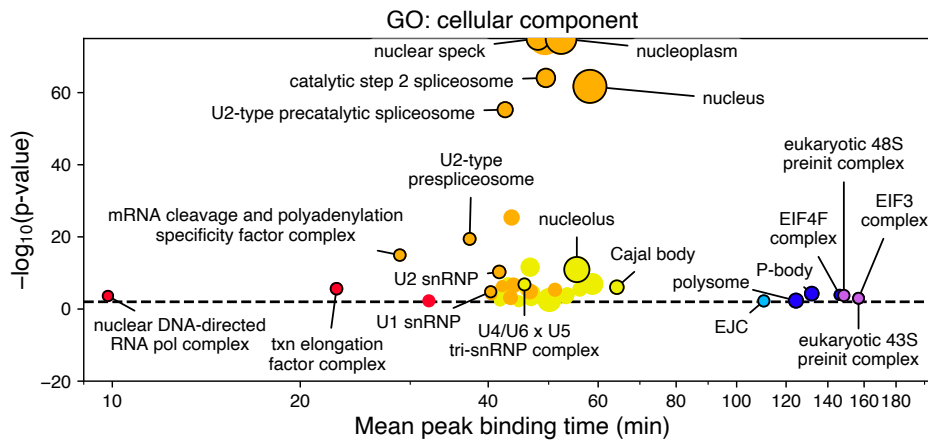


Figure 2.25 The same as 2.24 except for using GO: cellular component.

Comparing our data with protein localization data from the Human Protein Atlas (HPA), based on immunofluorescence staining (75), we found that proteins in cluster I are predominantly nuclear and that the fraction of nuclear proteins decreases gradually in later clusters (Figure 2.26). We also cross-referenced proximity labeling-based localization data (26) and found that most early binders are associated with chromatin, nucleoplasm, nuclear body, paraspeckles and/or spliceosomal complexes, while late binders are primarily in cytoplasmic RNP granules (Figure 2.27).

Next, we examined the enhanced crosslinking and immunoprecipitation followed by high-throughput sequencing (eCLIP) data from the ENCODE project, which revealed protein interaction sites on transcripts for 85 and 76 RBPs in K562 and HepG2 cells, respectively (80; 79; 81). We calculated the proportion of eCLIP peaks mapped to the intron, 5' untranslated region (5' UTR), coding sequence (CDS), and 3' UTR (Figure 2.28). Although some clusters are not represented well by the eCLIP data, we observed an overall consistent pattern from both cell lines. Early binders in clusters I, II, and III bind mainly to intronic regions, indicating their major role in the pre-mRNA complex. In contrast, late binders in clusters V, VI, and VII exhibited fewer eCLIP peaks in introns and large number of peaks in CDS and 3' UTR, consistent with their role in mature mRNA complexes.

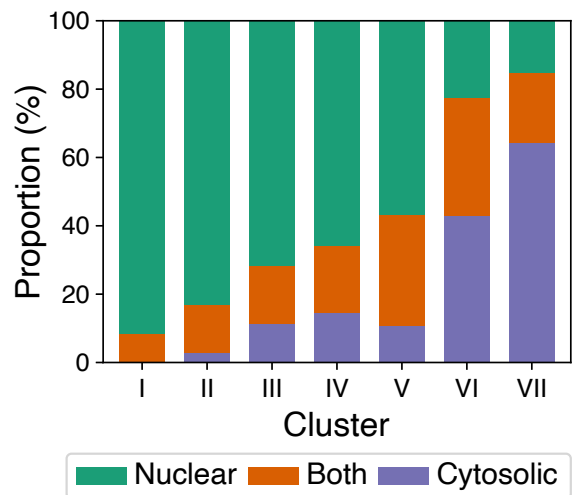


Figure 2.26 Proportion of nuclear and cytosolic proteins in each cluster, according to the annotation in HumanProteinAtlas.

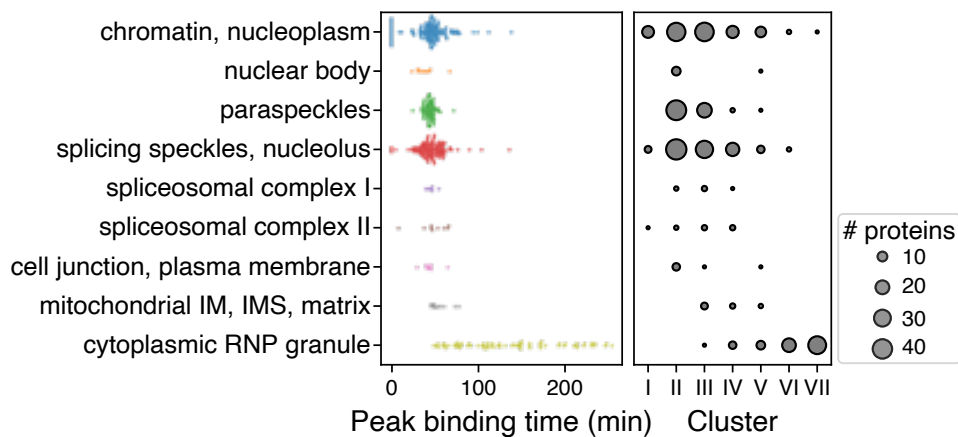


Figure 2.27 Beeswarm plot (left) and dot plot (right) of subcellular localization of RBPs. The y-axis of both plots indicates proximity-labeling based prediction of subcellular location, provided by the HumanCellMap. The x-axis of the left plot shows the peak binding time of each protein, and the x-axis of the right plot represents the cluster of each circle. The radius of each circle in the right plot is proportional to the number of proteins belonging to each category.

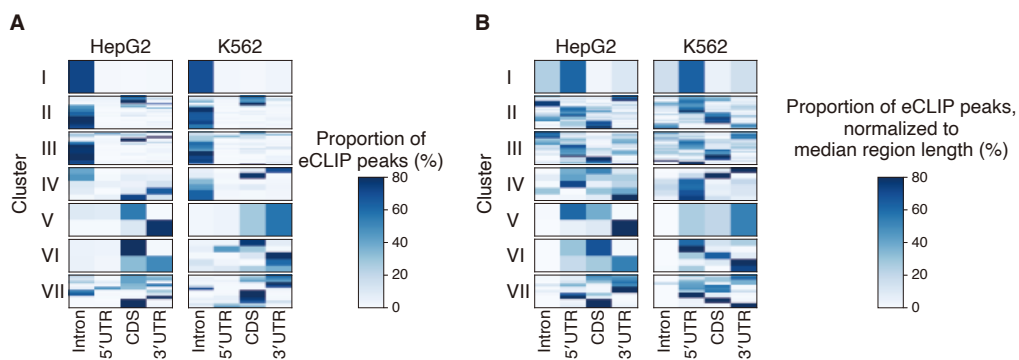


Figure 2.28 (A) Location of eCLIP peaks of 76 RBPs in HepG2 and 85 RBPs in K562, which overlap between our data and the ENCODE data. (B) Density of eCLIP peaks in intronic regions, 5' UTR, CDS, and 3' UTR. Density was calculated by normalizing the raw read proportion by the length of the intron, 5' UTR, CDS, and 3' UTR of highly expressed genes (TPM>10). Prior to normalization, eCLIP peaks that do not overlap with any protein coding gene were removed. The lengths used for normalization are as follows: intron: 21603 (K562) and 22541 (HepG2), 5' UTR: 124 (K562) and 123 (HepG2), CDS: 1212 (K562) and 1237.5 (HepG2), and 3' UTR: 959.5 (K562) and 979 (HepG2).

Notably, some late binders in cluster VI and VII are preferentially associated with CDS, suggesting that they may arrive after ribosome is cleared away from CDS, potentially forming translationally inert complexes on aged mRNAs. Thus, the eCLIP analyses further demonstrate the validity of our time-resolved mRNA interactome data, reflecting the mRNP life cycle.

2.2.4 Protein-protein interactions in mRNP complexes

Our data presents a comprehensive interactome of direct RNA binders. However, RNPs also contain proteins that associate via protein-protein interactions (PPI), contributing to the RNP function (48; 12). To extend the temporal map of RNP, we incorporated indirect RNA binders by merging our data with PPI information and generating a PPI network, using the RBPs identified in our study as seeds (Figure 2.29). This extended PPI network enriches our understanding of time-resolved RNP components.

Our analysis also showed PPIs between direct RNA binders identified in this study. Proteins within the same cluster tend to interact frequently with each other (2.29, shown in color). By measuring the number of PPIs between the seed proteins, we confirmed that the frequency of PPIs within the same cluster or between neighboring clusters (particularly clusters VI and VII) were significantly higher than randomly selected protein pairs (Figure 2.30A). Similar patterns were observed when we included proteins interacting indirectly via one neighbor (Figure 2.30B). These results suggest that proteins interacting with each other bind to mRNAs at similar time points, via PPIs as well as RNA-protein interactions, collectively forming stage-specific RNP complexes. To statistically validate this result orthogonally, we quantified temporal differences in mRNA binding by calculating the Euclidean distance of RNA binding dynamics between protein pairs (see Methods). Protein pairs with physical interaction evidence showed similar RNA binding dynamics, resulting in small Euclidean distances, compared to non-interacting protein pairs (Figure 2.31). Additionally, we cross-examined known protein complexes (“CORUM complexes”) (25), by comparing the Euclidean distances of mRNA binding dynamics. RBPs within the same

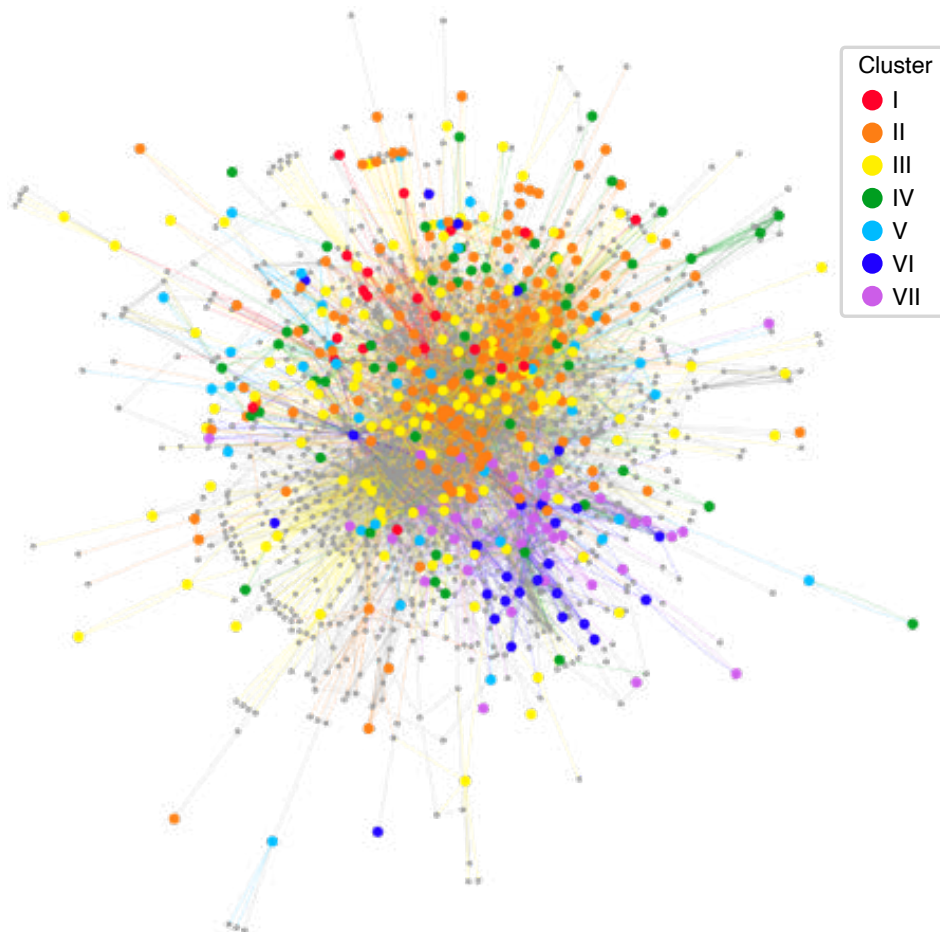


Figure 2.29 A protein-protein interaction (PPI) network of direct RBPs found in this study (color-coded to indicate their respective clusters) and their interactors. A graph with the largest number of connected proteins ($n=1620$) was chosen for visualization.

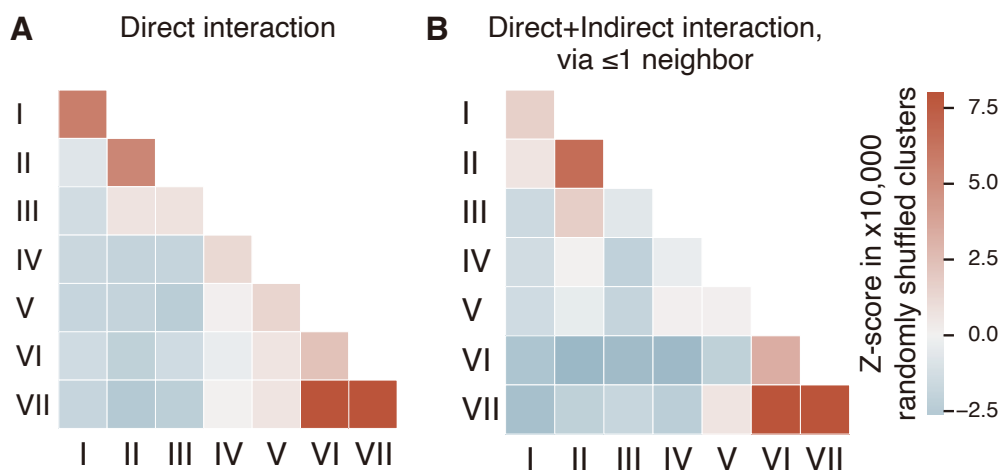


Figure 2.30 (A) PPIs within and between clusters. To calculate the normalized enrichment of PPIs, z-scores were calculated through 10,000 iterations of randomly shuffling clusters. This generated null distributions for PPI counts, from which the z-scores were derived. (B) PPIs within and between clusters. Same analysis as (A), except for using direct PPIs as well as indirect PPIs via one neighbor protein interactor.

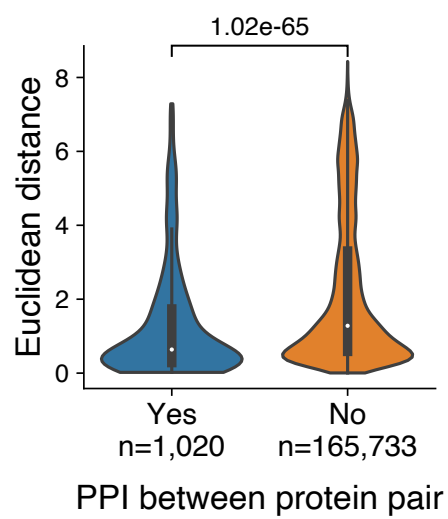


Figure 2.31 Violin plots visualizing the dissimilarities in terms of mRNA binding dynamics (represented by Euclidean distances, y-axis) between protein pairs that interact or do not interact. Box plots inside the violin plots show the median (center dot), first and third quartiles (lower and upper box limits, respectively), and 1.5 times the interquartile range (whiskers). P-value was calculated by the two-sided Mann-Whitney U test.

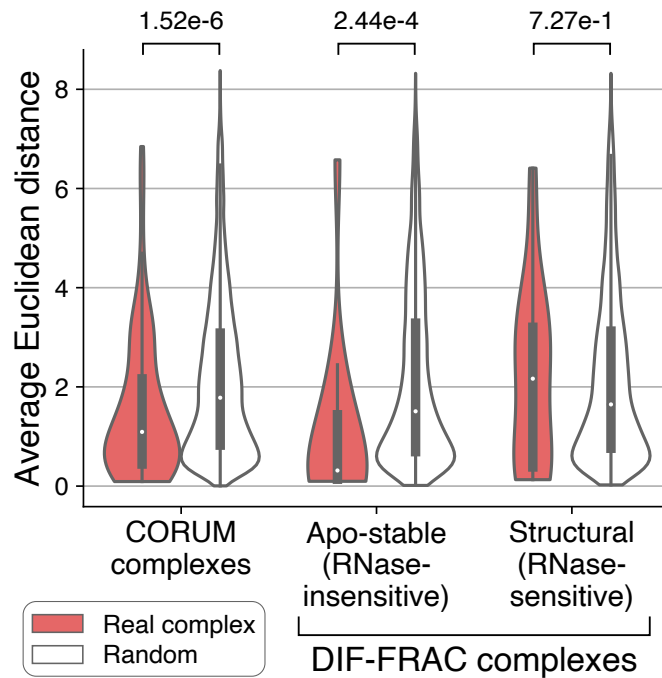


Figure 2.32 Violin plots of average Euclidean distances of mRNA binding dynamics, per protein complex. P-values were calculated by the two-sided Mann-Whitney U test. Mini box plots inside the violin plot indicate the same quantile range as (C). CORUM: all protein complexes in the CORUM database. DIF-FRAC complexes: RNA binding protein complexes, defined by (48).

complexes (Figure 2.32, left, red) displayed significantly lower Euclidean distances in RNA binding dynamics compared to randomly selected proteins (2.32, left, white), indicating that the components of these complexes join the mRNPs at similar temporal stages. Another earlier study grouped mRNP complexes (“DIF-FRAC” complexes) (48) into two groups based on RNase-sensitivity: “apo-stable” RNPs (RNase-insensitive; RNA-independent) and “structural” RNPs” (RNase-sensitive; RNA-dependent). Notably, apo-stable RNP components demonstrated significantly smaller Euclidean distances in RNA dynamics compared to random protein sets (2.32, middle), while structural RNP components did not (2.32, right).

Thus, proteins interacting with each other independently of RNA may join mRNP simultaneously as a pre-formed complex.

Overall, PPI and mRNA binding dynamics are in good agreement, indicating that proteins interacting with each other constitute stage-specific RNPs. However, some RBPs display markedly different dynamics from their PPI partners, represented by large Euclidean distances (Figure 2.33 and Table 2.3). The discrepancy between mRNA binding dynamics and PPI information implies that these RBPs may be multifunctional and/or have unidentified functions. For instance, a late binder MOV10 (cluster VII) has been reported to interact with both early binders (such as XRN2) and late binders (such as UPF1, STAU2, and IGFBPs) (Figure 2.34). Although MOV10 targets 3' UTR regions and associates with regulators of mRNA stability and translation, it is also known to bind introns and interact with splicing factors (37; 20). The RNA binding time revealed in this study suggests that the majority of MOV10 molecules act in the late stage of the mRNA life cycle, at least under our experimental conditions.

2.2.5 Aged mRNPs and RNA granules

It was unanticipated that the late clusters were highly enriched with GO terms related to 'cytoplasmic RNP granules' and 'stress granule (SG) assembly' (Figures 2.24, and 2.27), even though I did not expose the cells to any stressors. When I performed immunofluorescence imaging using a G3BP1 antibody, a known SG marker, no visible foci were detected (Figure 2.35), indicating that SGs were not formed under our experimental conditions.

We examined the proteins interacting with G3BP1 ("G3BP1 protein interactome") (49), discovering that about 49% and 63% of cluster VI and VII proteins, respectively, overlap with G3BP1 interactors (Figure 2.36). The majority of these proteins have been reported to bind to G3BP1 independently of stress (49), suggesting that naturally aged mRNPs are similar to SGs in the protein composition.

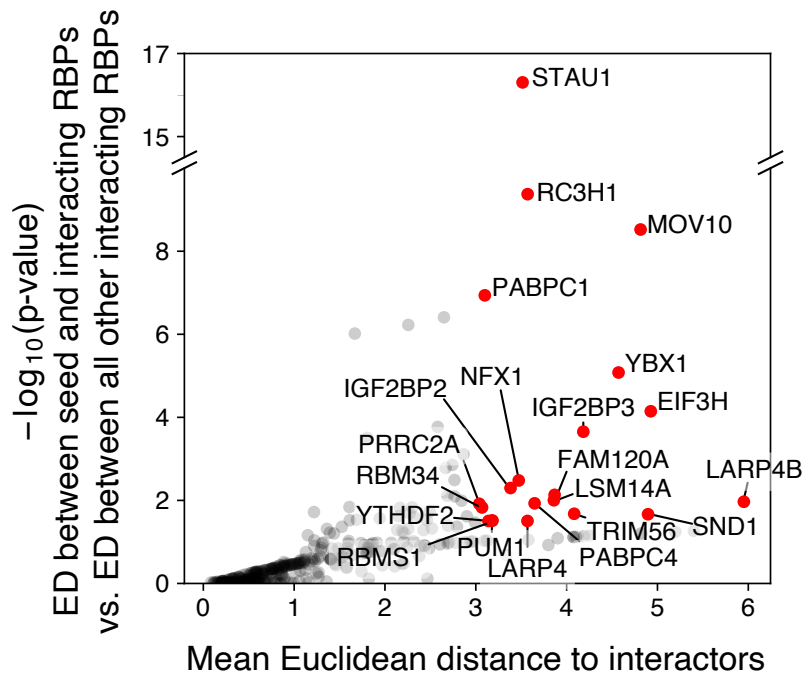


Figure 2.33 Scatter plot illustrating differential mRNA binding dynamics between RBPs and their protein interactors. The x-axis shows the average Euclidean distances (ED) of mRNA binding dynamics for a seed protein and its interactors. The y-axis represents differential p-values, comparing the ED between the seed protein and its interactors to the ED between other pairs of interacting proteins. P-values were calculated using the one-sided Mann-Whitney U test. RBPs meeting $P < 0.05$ and mean Euclidean distance to interactors > 3 are marked in red on the plot.

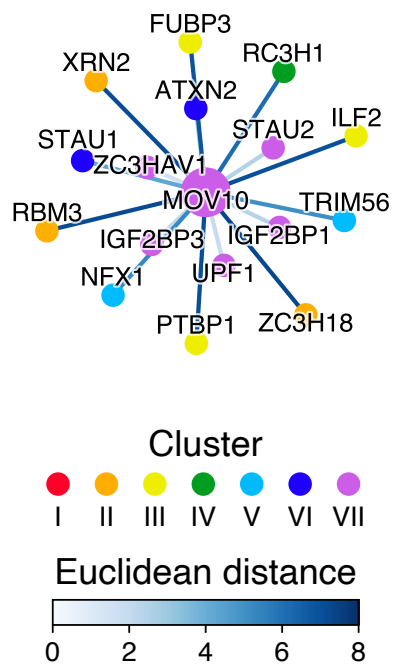


Figure 2.34 Euclidean distances between mRNA binding dynamics of MOV10 and its interactors. Edge colors represent the Euclidean distance between mRNA binding dynamics of two proteins. Protein nodes are colored according to their assigned cluster.

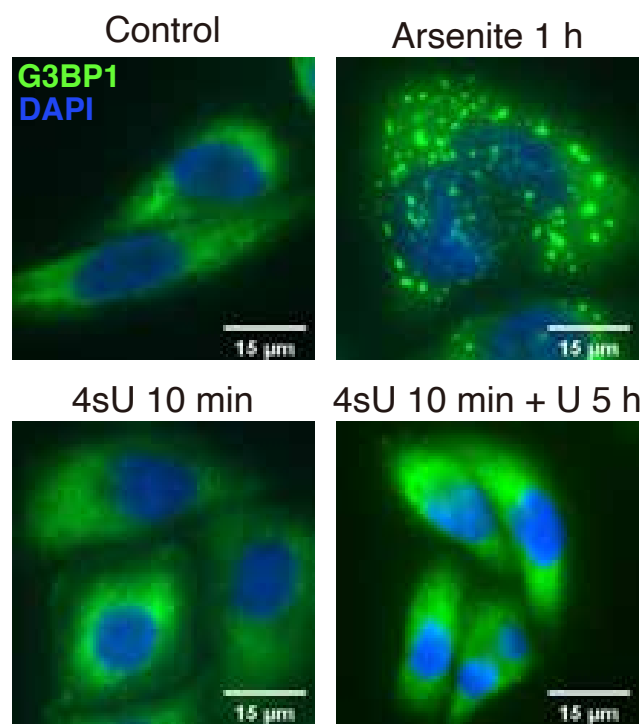


Figure 2.35 Immunofluorescence against G3BP1 (green) and DAPI (blue) in HeLa cells. Sodium arsenite treatment was used as a control for SG formation.

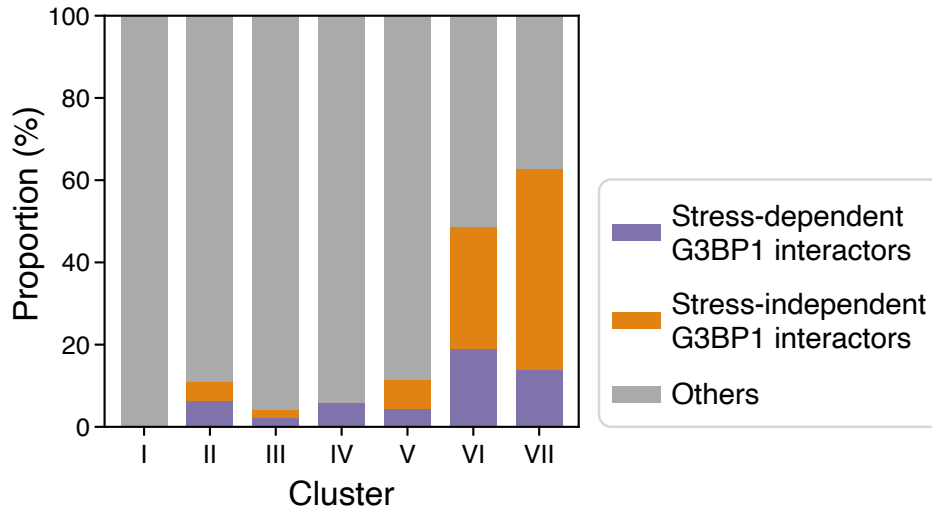


Figure 2.36 Proportion of stress-dependent (purple) or stress-independent (orange) G3BP1 interactors in each cluster. The list of G3BP1 protein interactors were from (49).

To validate our findings, we conducted 4sU pulse-labeling, UVA crosslinking, poly(A) RNA capture, and western blotting analyses on late binders which are known to localize to SGs (Figure 2.37). Our data confirm that LARP1, FMR1, IGF2BP3, and G3BP1 are indeed captured at late time points.

We further compared our RBPs with those known to localize to SGs and P-bodies (86; 85; 32). Remarkably, 67% and 74% of cluster VI and VII proteins were annotated as SG proteins, respectively, while PB proteins are not strongly enriched in late clusters (Figure 2.38A and Table 2.4). Furthermore, 26% of cluster VII proteins were annotated as the regulators of SG formation as well as the structural core proteins of SG (Figure 2.38B). Out of 36 proteins previously reported as SG regulators and core proteins, 16 proteins belong to cluster VI and VII (Figure 2.38C).

We observed frequent PPIs within and between clusters VI and VII (Figure 2.30). The majority of these interacting proteins in clusters VI and VII are indeed SG proteins, while those not participating in the interaction networks are

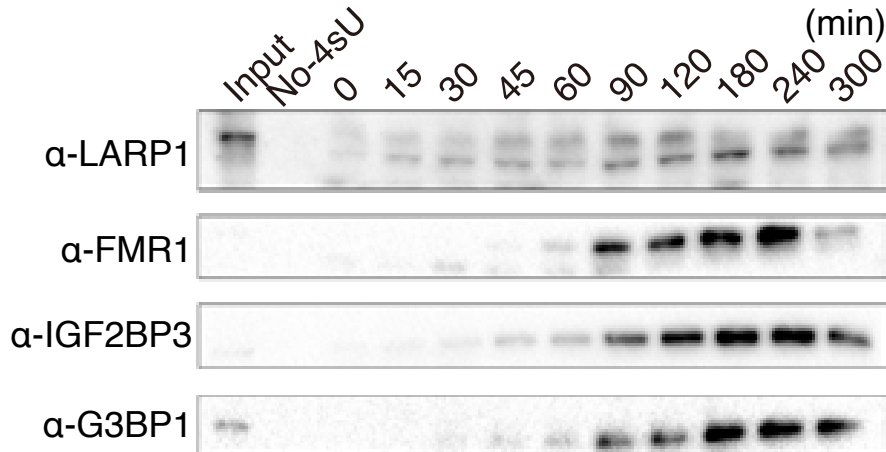


Figure 2.37 Validation of mRNA binding dynamics of SG proteins by western blotting. Input means 0.01% of lysate from chase time 0 min. No-4sU indicates the RIC elution sample obtained from unlabeled cells.

predominantly non-SG proteins (Figure 2.39). The considerable overlap between the SG proteome and late mRNPs, along with the frequent PPIs among late binders, suggests that late mRNPs may form submicroscopic RNP condensates with similar properties to SGs, which might be natural process of mRNA aging under unstressed conditions.

2.2.6 Interaction between viral RNAs and late binders

RNA viruses interact with a wide range of host RBPs for viral proliferation and immune evasion (31). Proteomics-based approaches have identified a large number of viral RNA binding proteins (vRBPs) (45; 56; 43; 38). Most of the vRBPs have also been reported as host RNA interactors. In line with this, 354 of RBPs found in our study have previously been described as vRBPs (Figure 2.40 and Table 2.4).

All temporal clusters contain vRBPs; however, we observed marked enrichment of vRBPs among late binders, most notably in cluster VII (Figure 2.40B). This enrichment is not solely attributed to the cytosolic localization of late binders,

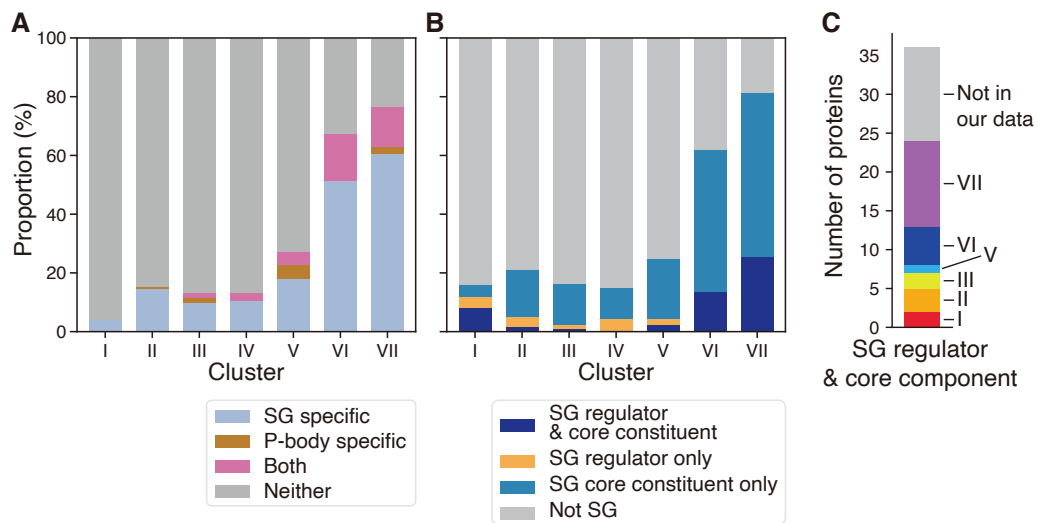


Figure 2.38 (A) Proportion of SG and P-body proteins in each cluster. Tier-1 SG and P-body list of RNA granule database (v1.0) was utilized. (B) Proportion of SG regulators (necessary for SG formation, identified by genetic screening) and SG core proteins (enriched in SG pull-down proteome) in each cluster. SG regulator and SG core protein lists were obtained from (85). (C) Number of SG proteins that belong to different temporal clusters. SG regulator and SG core protein were from (85).



Figure 2.39 (A) Interaction network map of proteins belonging to cluster VI, cluster VII, and their interactors (n=298). SG core proteins are marked as square nodes. Gene names of cluster VI and VII proteins are marked above their respective nodes. (B) The number of SG and non-SG proteins among the connected cluster VI, VII proteins in (A) and not connected (singleton) cluster VI, VII proteins.

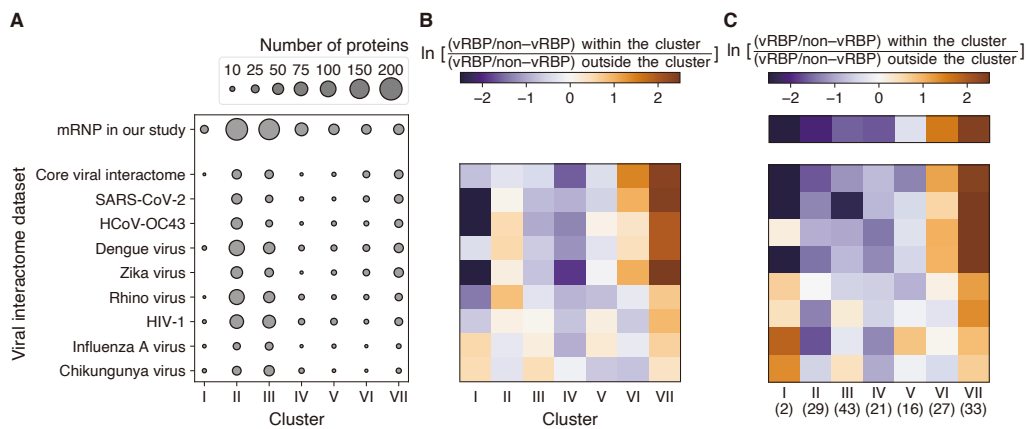


Figure 2.40 (A) Number of mRBPs found in viral RBPs, per each cluster. (B) Enrichment of vRBPs in each cluster, measured in log odds ratio. (C) Enrichment of vRBPs in each cluster, measured in log odds ratio, as in (B). But, unlike (B), we used only cytosolic proteins (annotated in HumanProteinAtlas) in this analysis. Numbers below the clusters indicate the number of cytosolic proteins, which include those located in both nucleus and cytosol and those restricted in the cytosol. Used vRBP dataset: Core viral interactome: (31); SARS-CoV-2: sgRNA, (45); HCoV-OC43: sgRNA at 36 hours post infection, (45); Dengue virus, Zika virus, Rhinovirus: (56); HIV-1: All splice variant captures, (43); Influenza A virus: (38); Chikungunya virus: 1 hour post infection, without interferon, (38)

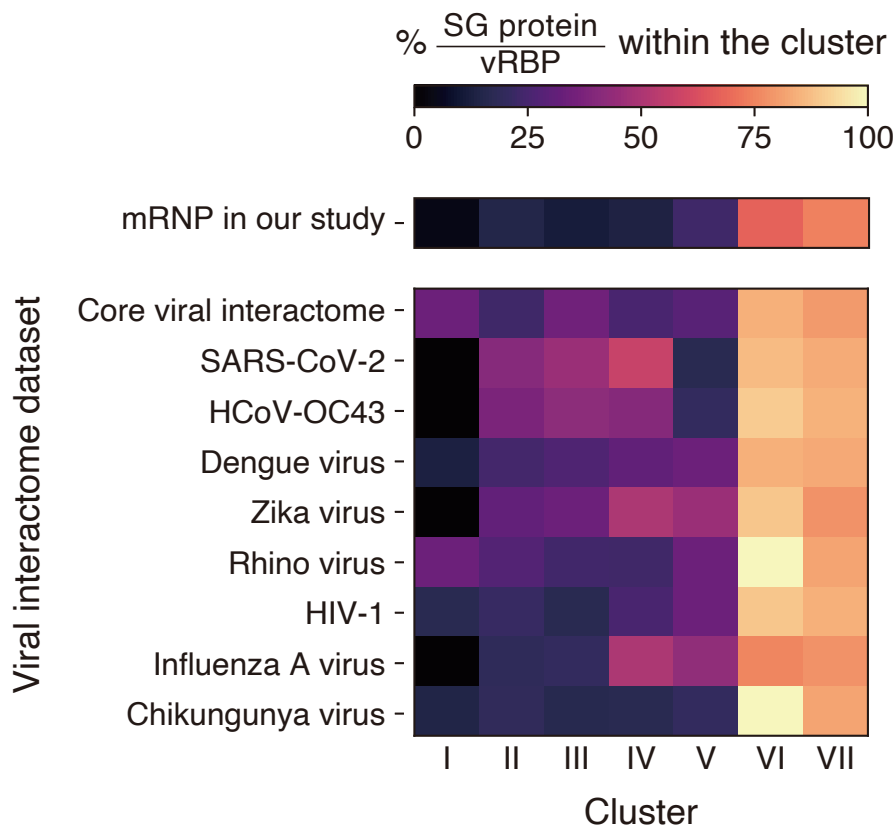


Figure 2.41 Proportion of SG proteins among viral RBPs, per each cluster.

as the same analysis restricted to the cytosolic proteins also exhibited higher enrichment in cluster VI and VII (Figure 2.40C). Transcripts of coronaviruses (SARS-CoV-2 and HCoV-OC43) and flaviviruses (dengue virus and zika virus) showed particularly strong enrichment with late clusters. We also noticed that SG proteins frequently appeared among vRBPs in the cluster VI and VII (Figure 2.41). This pattern mirrors the host mRNA interactome, but the SG protein proportion among vRBPs was higher than that in the host mRNA interactome across all clusters (Figure 2.41). The intersection of cluster VII, SG, and vRBP includes well-known antiviral proteins DDX3X and ZC3HAV1 (ZAP). These observations support the notion that the granule-forming late binders may play a

role in antiviral defense by sequestering viral RNAs, while some of them may be repurposed by viruses to facilitate viral proliferation (55; 7).

2.2.7 Systemic identification of RBPs with unexpected RNA binding dynamics

While mRNA binding dynamics generally align well with previously reported features, some RBPs display significant discrepancies between their RNA binding times and known functions, localizations, and PPIs. This suggests that these RBPs may possess yet-undiscovered functions. To systematically identify RBPs with unexpected dynamics, we developed a regression method that predicts mRNA binding dynamics based on annotated characteristics (Figure 2.42; for detailed information, please refer to the Methods section). We compiled a gene-GO term table that includes the RBPs identified in this study along with their corresponding GO term annotations. Due to the redundancy of certain GO terms (e.g. ‘RNA binding’ and ‘nucleic acid binding’), we applied multiple correspondence analysis (MCA) to compress the information into a lower dimension. Subsequently, with the MCA-converted GO annotations, we fitted a ridge regression model to predict the z-score of a given RBP’s quantity at each time point.

The coefficient of determination (R^2) between the observed and expected z-scores at each time point ranged 0.55–0.79 (Figure 2.43). To understand which specific GO terms our regression model relied on, we calculated each GO term’s contribution to the expected z-score (Table 2.5). For early timepoints (0–15 min), top positive contributors were GO terms related to transcription or splicing, while GO terms related to translation or cytoplasmic localization were the top negative contributors at these time points. At 1.5 hours, NMD was one of the positive contributors, whereas transcription and splicing-related terms contributed negatively. In later time points (3–5 hr), translation or cytoplasmic localization-related GO terms were the top positive contributors. Despite the overall high performance of our prediction model on well-annotated RBPs (Figure 2.44), we observed some RBPs with substantial differences between the expected and observed mRNA binding dynamics (Table 2.6 and Figure 2.45). Undercharacterized RBPs, sparsely

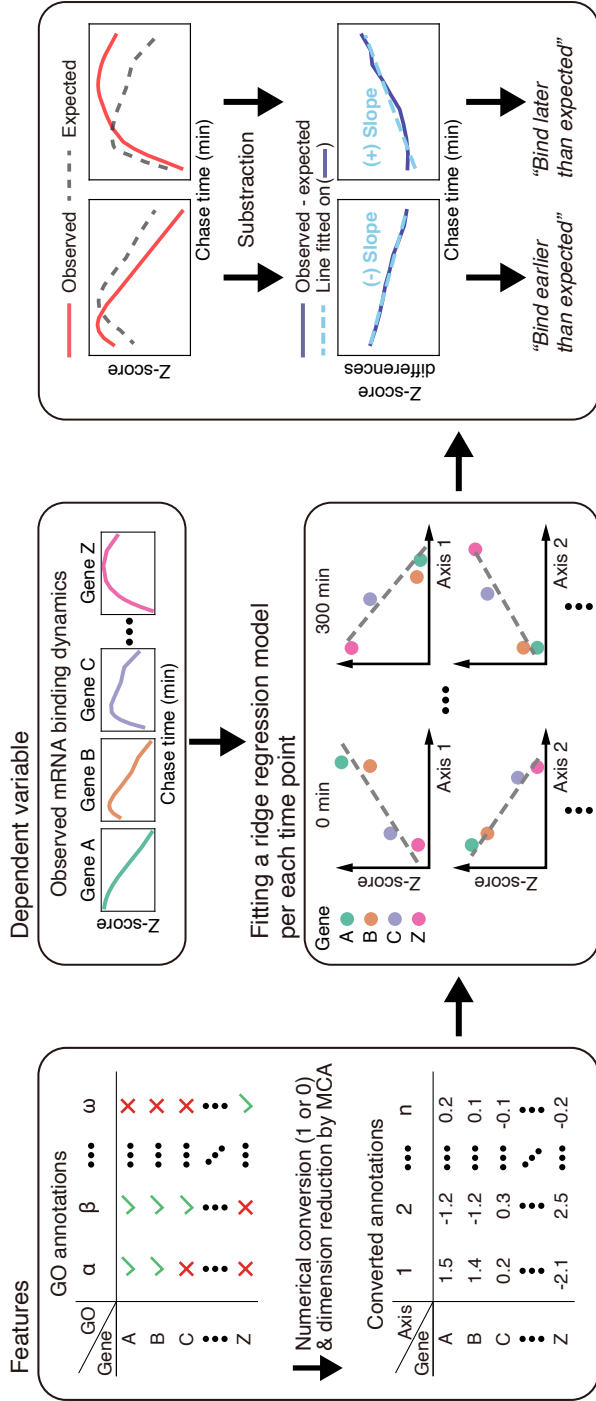


Figure 2.42 Schematic of the mRNA binding dynamics prediction model based on GO-term annotations. The gene-GO term table is encoded to numbers and transformed to the lower dimensions, by the Multiple Correspondence Analysis (MCA, left column). For each time point, a ridge regression model is fitted to find the relationship between the MCA-converted GO annotations and z-score normalized intensities. Model fitting was repeated for all 10 time points (middle column). The difference between the observed and expected values reveals RBPs that bind earlier or later than predicted (right column).

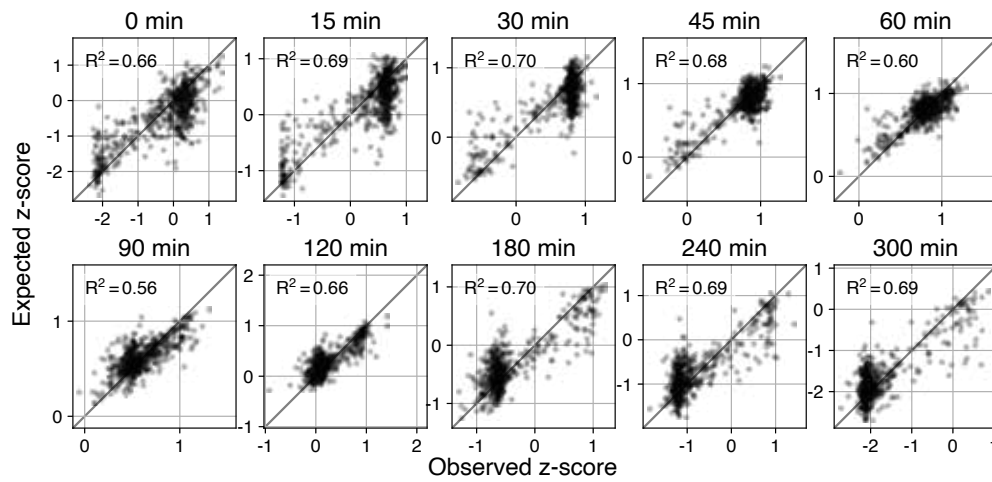


Figure 2.43 Comparison of the expected and observed z-scores at each time point. The coefficient of determination (R^2) between two values is marked on each plot.

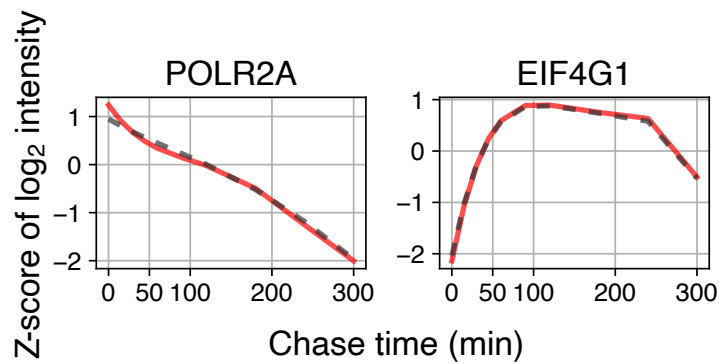


Figure 2.44 Observed and expected mRNA binding dynamics of well-studied RBPs, POLR2A and EIF4G1.

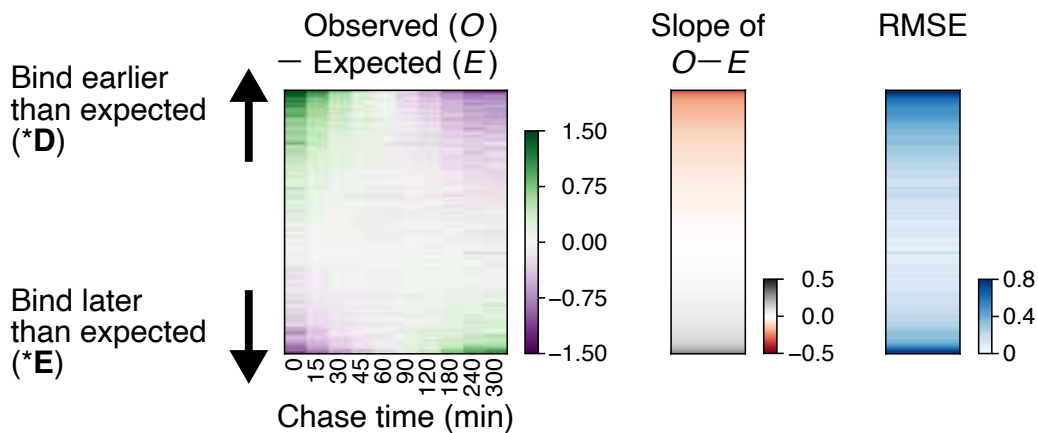


Figure 2.45 RBPs are sorted by the slope of the observed-minus-expected z-scores. RMSE: Root Mean Square Error

covered in literature, generally displayed high prediction errors (Figure 2.46). We sorted RBPs based on the difference between the expected and observed dynamics (Figure 2.47). RBPs at the top or bottom of this list bind to mRNA earlier or later than our model predicts. For example, LSM14B, FAM120A, and FAM120C, which are poorly studied and associated with only a few GO terms (“ribonucleoprotein complex”, “mRNA binding”, “RNA binding”, “regulation of translation”), were predicted as an intermediate binder (class V), but they actually associate with mRNAs at very late time points (cluster VII) (Figure 2.48). Thus, our temporal RNA interaction data supplement current knowledge and assist in functional studies on under-characterized RBPs.

2.2.8 CCDC86 as cytoplasmic mRNA binding protein

To validate the discrepancy between the predicted mRNA binding dynamics and the observed behavior, we focused on CCDC86. Previous studies have reported the nuclear localization of CCDC86, particularly in the nucleoli (78), leading to the prediction of its early association with mRNA (Figure 2.49). It has also been suggested that CCDC86 may be involved in ribosome biogenesis based on its domain architecture, which includes a coiled-coil domain and a Cgr1-like domain.

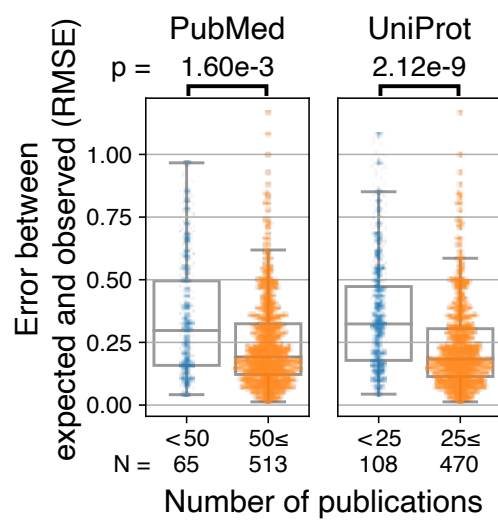


Figure 2.46 Box plots and beeswarm plots of root-mean-square-errors (RMSEs) between the observed and expected dynamics, for the RBPs with small or large number of publications. The number of publications were acquired from PubMed and UniProt web sites. Box plots show the median (center line), first and third quartiles (lower and upper box limits, respectively), and 1.5 times the interquartile range (whiskers). P-values were derived by the two-sided Mann-Whitney U test.

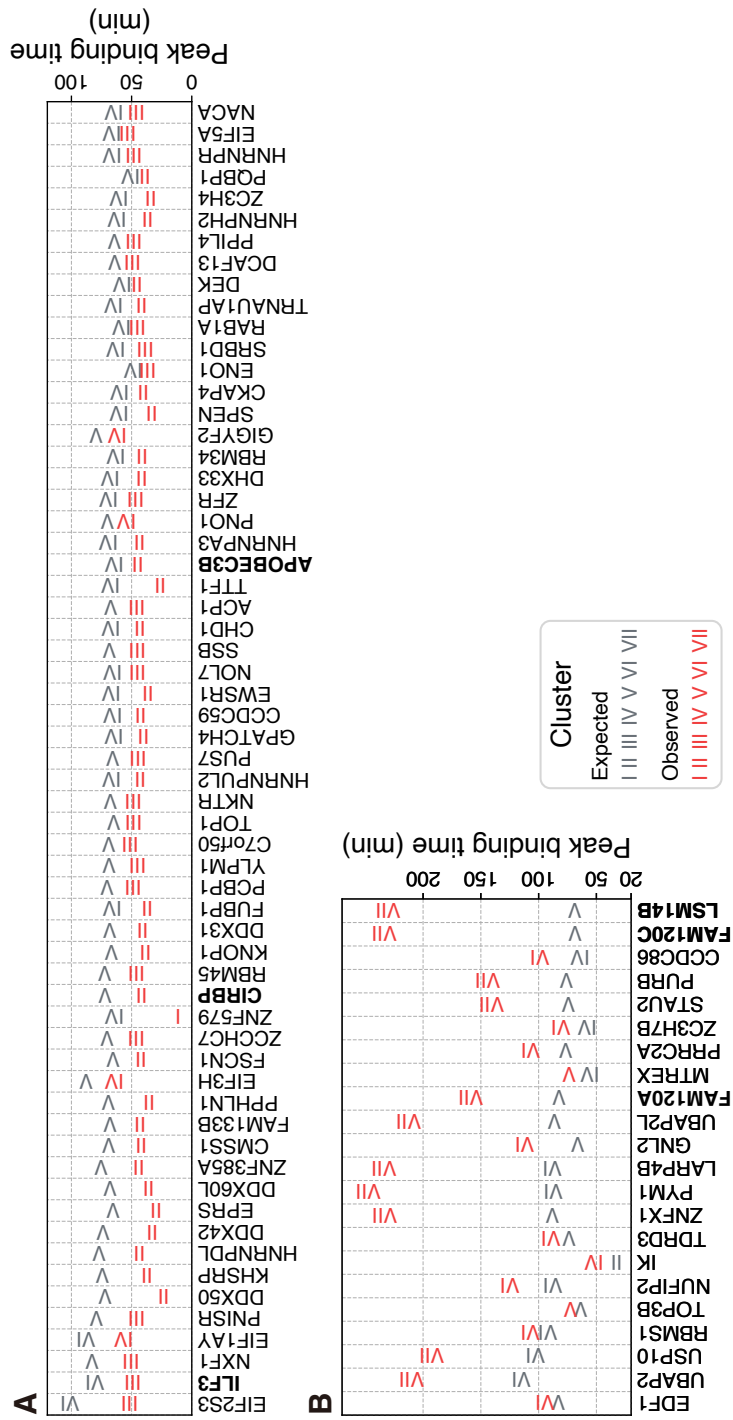


Figure 2.47 Unexpected early (A) or late (B) binders. Shown are RBPs whose slope of the observed-minus-expected z-score is higher than 0.15 or lower than -0.15.

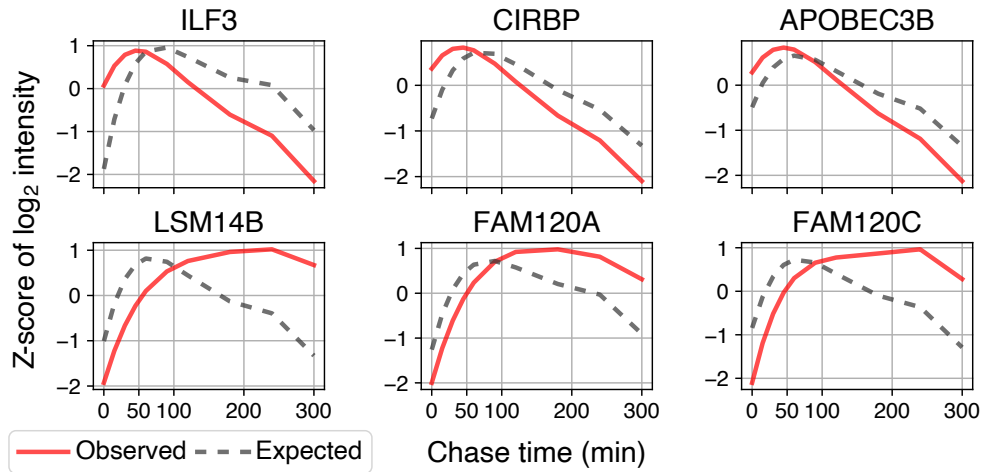


Figure 2.48 Observed and expected mRNA binding dynamics of selected RBPs.

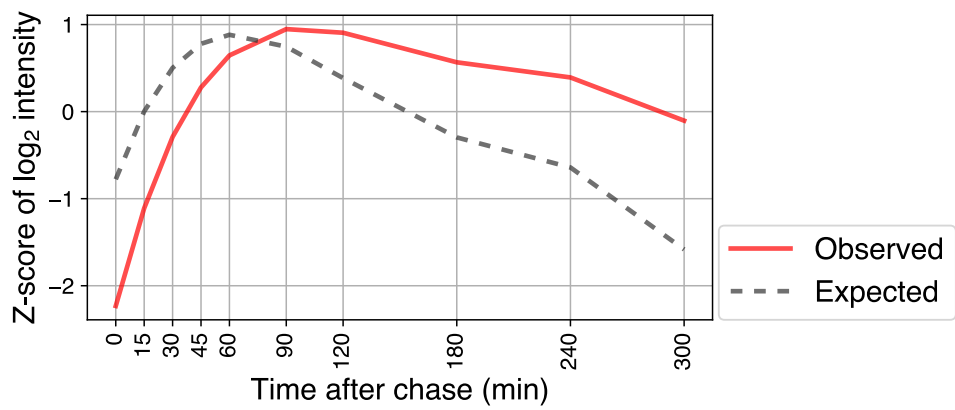


Figure 2.49 Observed and expected mRNA binding dynamics of CCDC86.

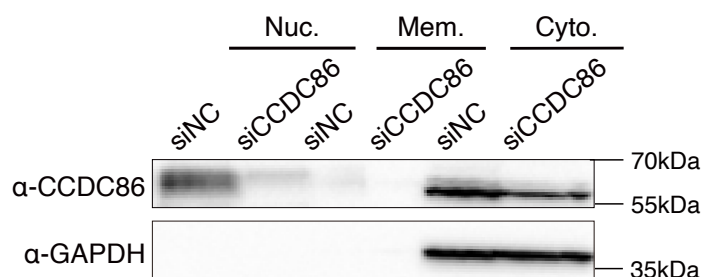


Figure 2.50 Western blotting of the subcellular fractionation after CCDC86 knockdown. HeLa cell was knockdowned with siCCDC86 for 48 hrs.

Cgr1, a yeast protein with nucleolar localization, plays a role in large subunit biogenesis through regulation of pre-rRNA processing in yeast (54). Another study based on Perturb-seq also suggested that CCDC86 is involved in ribosome biogenesis (62).

However, contrary to the initial prediction, our findings demonstrated that CCDC86 interacts with cytoplasmic mRNA until late time points (cluster VI), suggesting potential unknown functions in the cytoplasm. First, we performed cell fractionation experiments, confirming the presence of CCDC86 in both the nucleus and cytoplasm (Figure 2.50). Furthermore, RNA immunoprecipitation (RIP) experiments showed mRNA enrichment in the CCDC86 IP samples compared to the IgG control, even after EDTA treatment, which dissociates ribosomes from mRNA, indicating that the interaction is not mediated by ribosomes (Figure 2.51). Of note, RNA-seq analysis following CCDC86 knockdown revealed a limited number of significantly differentially expressed mRNAs (~200) (Figure 2.52). These findings suggest that CCDC86 may have a minimal impact on mRNA expression levels and stability. Notably, CCDC86 is not the only ribosome biogenesis factor that exhibits late mRNP binding. Proteins such as LSG1, GNL2, SDAD1, and SERBP1, found in clusters VI and VII, are known to be located in the nucleolus and influence rRNA processing (70). LSG1, GNL2, and SDAD1 function as 60s ribosome nuclear export factors, while SERBP1 is involved in mRNA 3'-UTR binding and mRNA stability regulation. These examples illustrate

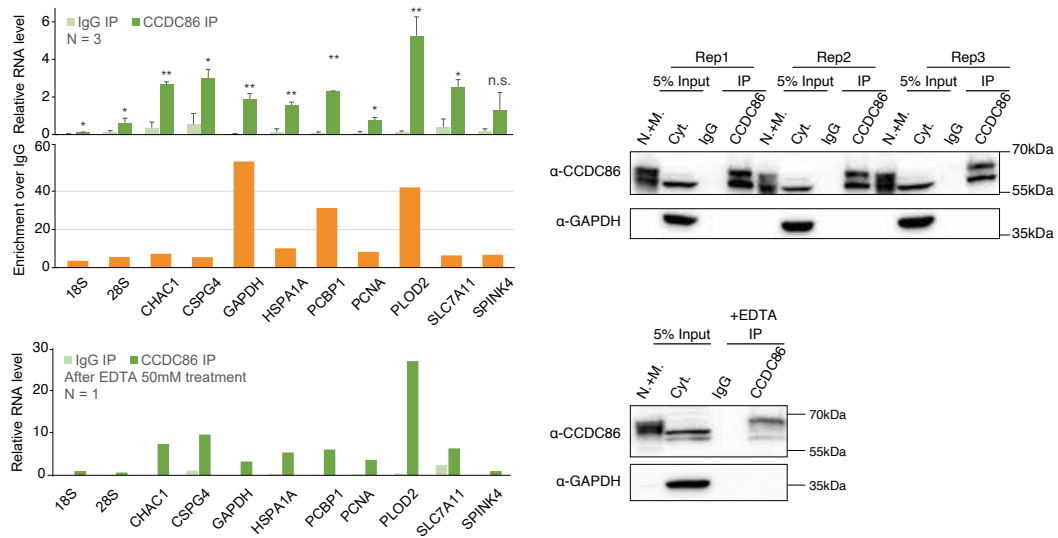


Figure 2.51 RIP-qPCR for CCDC86 in the cytoplasmic fraction. (right) Western blotting of RIP for CCDC86. (below) Same experiment except EDTA was treated in final 50mM. After immunoprecipitation (IP) of CCDC86 from the cytoplasmic fraction, one-fourth of the sample was used for Western blot analysis, while the remaining sample was subjected to RNA isolation using TRIzol for subsequent qPCR analysis. The relative abundance of various mRNAs, along with rRNAs, compared to 1% of input lysate, is shown in the graph. Data are represented as mean \pm SD ($n = 3$ independent experiments). Spike-in RNA used in RNA isolation step was used for normalization. * $p < 0.05$ and ** $p < 0.001$, two-sided Student's t test. N.+M.: nuclear and membrane fraction, Cyt.: cytosolic fraction.

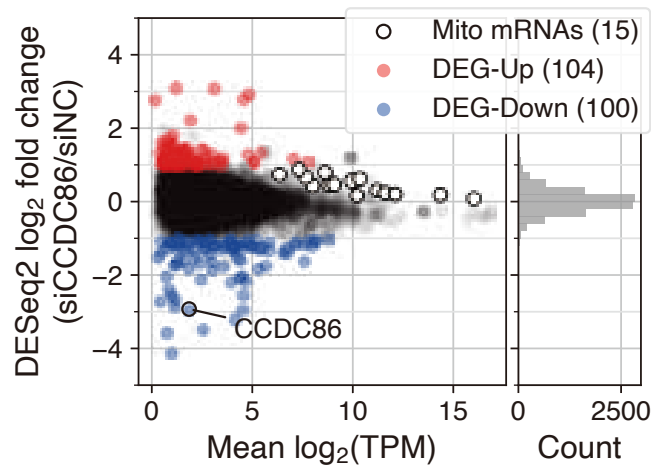


Figure 2.52 Knockdown RNA-seq was performed for CCDC86 in HeLa cell line. Red and blue dots indicate significantly up- or down-regulated genes (FDR 5% and $|\log_2 \text{fold change}| > 1$). The histogram in the right panel shows the distribution of log₂ fold changes. NC: negative control, DEG: differentially expressed genes, TPM: transcripts per million.

how certain RBPs can act as both nuclear rRNA-related factors and cytosolic mRNA regulators. Further studies are required to unravel the specific functions of CCDC86 in mRNA regulation during the later stages of their life cycle, extending beyond its known involvement in pre-rRNA biogenesis.

2.2.9 Studying late binding RBPs can provide valuable insights into the state of mRNA between translation and decay

FAM120A was previously known as an mRNA transport factor, which contradicts its late mRNA binding pattern as observed in our study (Figure 2.48) (44; 71). Recent papers have reported conflicting roles of FAM120A in miRNA targeting, with one study suggesting enhancement (Kim et al.) and another indicating suppression (36), further adding to the controversy surrounding its function. However, when we performed FAM120A knockdown in HepG2, K562, and HeLa cells, only a small number of mRNAs (<200) showed significant changes, suggesting that its major function may not be directly related to general mRNA stability control, at

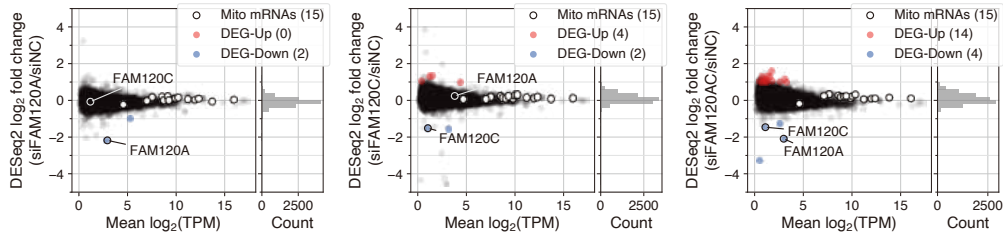


Figure 2.53 Knockdown RNA-seq was performed for FAM120A, FAM120C, and both (FAM120A/C) in HeLa, K562, and HepG2 cell lines. K562 and HepG2 data were re-analyzed from the ENCODE shRNA-seq dataset. Red and blue dots indicate significantly up- or down-regulated genes (FDR 5% and $|\log_2 \text{fold change}| > 1$). The histogram in the right panel shows the distribution of log₂ fold changes. NC: negative control, DEG: differentially expressed genes, TPM: transcripts per million.

least under normal conditions (Figure 2.53). Additionally, FAM120A knockdown did not affect overall protein production, as observed in the SUNSET assay which labels only nascent peptides with puromycin (Figure 2.54) (64).

To address the possibility of functional compensation between FAM120A and its close paralog FAM120C, which also exhibited a late binding pattern, we conducted a double knockdown of FAM120A and FAM120C. However, this double knockdown only minimally affected mRNA levels and global protein translation (Figure 2.53 and 2.54). These findings suggest that the functions of FAM120A and FAM120C may not be essential for general mRNA stability control or translation regulation.

Previous discussions on the final stages of the mRNA life cycle have primarily focused on mRNA translation and decay. However, the presence of several late binding RBPs with limited impact on mRNA stability or translation raises the possibility of an unknown processing step between translation and decay in the mRNA life cycle. Furthermore, our findings regarding the interaction of old mRNAs with the stress-independent G3BP1 interactome suggest a potential association between these RBPs and mRNAs in a state prior to decay, where

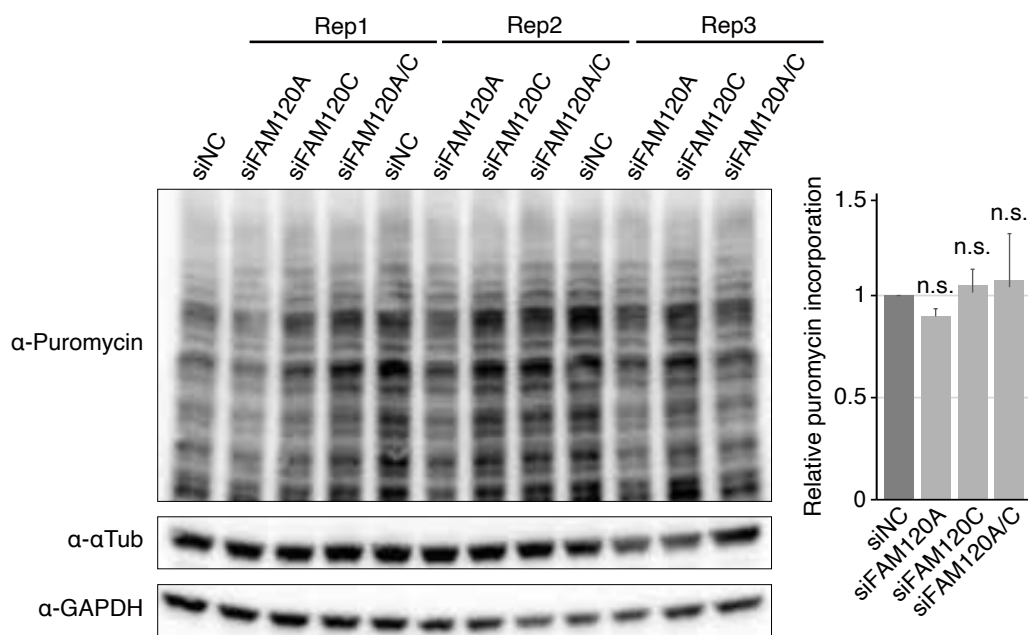


Figure 2.54 Western blot image of SUNSET analysis after FAM120A and FAM120C KD. The incorporation of puromycin was detected by anti-puromycin blot. -Tubulin and GAPDH immunoblots were used as loading controls. The graph show quantitative representation of puromycin incorporation observed in WB (right). Data are represented as mean \pm SD ($n = 3$ independent experiments). n.s. not significant, paired two-sided Student's t-test.

translation is no longer occurring. Conducting additional research on late binding RBPs that do not significantly affect mRNA stability or translation will contribute to our understanding of the state of mRNA prior to decay. Such investigations may provide valuable hints about the intermediate states of mRNA between translation and decay.

2.3 Discussion

The current study utilized an oligo(dT) capture method to analyze poly(A)+ mRNAs. Although we successfully enriched mRNAs using stringent conditions, the RNA pool also contains oligoadenylated mitochondrial mRNAs, poly(A)+ long noncoding RNAs, and contaminants from other noncoding RNA species like rRNAs. Hence, we have excluded RBPs with well-established functions in noncoding RNA pathways from our analyses. Also note that our protocol depletes mRNAs that either lack a poly(A) tail (such as nascent transcripts or replication-dependent histone mRNAs) or possess very short poly(A) tails (such as decay intermediates). Thus, the RBPs quantified in this study may not fully represent co-transcriptional processing factors or decay factors. Future studies might consider using organic phase separation-based methods to capture RNPs, although this could introduce its own limitations due to a lack of RNA specificity (60; 77). Furthermore, because our approach targeted bulk mRNAs with various half-lives, the proportion of stable mRNAs modestly increased over time (Figure 2.9), enriching RBPs that preferentially associate with stable mRNAs. Finally, our bulk analyses do not account for gene-specific regulatory mechanisms. To circumvent all these limitations, future studies should aim to isolate and analyze gene-specific mRNPs using specific antisense oligos as baits. This presents a major technical challenge due to the low concentration of individual mRNA species. In the meantime, temporal gene-specific analyses of more abundant RNAs, such as rRNAs and snRNAs, could be a more attainable goal and may offer valuable insights into the complex processes of ribosome biogenesis and spliceosome biogenesis.

This study introduces the first longitudinal proteomic analysis of mRNPs with a high temporal resolution. Although numerous studies have been performed for decades to assign the functions and localizations of RBPs, from which the temporal sequence of mRNA binding has been inferred, direct and quantitative evidence has not been available at the proteomic level. The high resolution of our data allows us to detect even subtle differences in mRNA binding dynamics, establishing the chronological orders of RNA-protein interactions throughout the mRNA life cycle. We observe the nascent transcripts collected at 0 min chase time are associated with pol II subunits and transcription factors, some 3' processing factors, and an m6A writer subunit VIRMA, revealing the initial pre-mRNP complex undergoing (or becoming committed to) the earliest events of co-transcriptional processing and modification. These early recruits are quickly followed by the other 3' processing factors, hnRNPs, SR proteins, splicing factors, and spliceosome components (U1/U2 followed by tri-snRNPs). Additional proteins join the assemblage, featuring capping-related proteins and nuclear export factors. Several translation-related factors known to interact with ribosomes appear at this stage possibly due to partial rRNA contamination, while the majority of ribosomal proteins and translation factors emerge later. Posttranscriptional regulators, such as AGO proteins and YTHDF proteins, appear in clusters VI and VII. Other proteins implicated in translational repression, such as FMR1, and mRNA destabilization, like UPF1, are found in the final stage.

This temporal sequence generally aligns with the known locations of RBPs. Early binders are predominantly nuclear proteins, while late binding groups are highly enriched with cytoplasmic proteins. Late binders in cluster VII frequently overlap with SG proteome, which includes FMR1/FXR1/FXR2, G3BP1/2, UPF1, MOV10, DDX3X, YBX1/3, LSM14A/B, STAU2, PURA/B, IGF2BP1/2/3, UBAP2/UBAP2L, FAM120A/C, LARP1/4B, SND1, and ZC3HAV1. One can envision that these proteins bind to old mRNAs, forming submicroscopic SG-like small condensates. Given that some of these proteins are implicated in translational repression and decay, this aged mRNP complex may be in a “retired” state, in which mRNAs are less active translationally compared to those in “younger”

mRNPs. Because SG formation per se does not prevent translation (51), the assembly of the SG proteins on old mRNAs is likely to be a consequence, rather than a cause, of the natural process of “translational retirement.” Whether or not this complex is indeed less active in translation, what triggers the changes in mRNP composition, and if liquid-liquid phase separation is involved, will be interesting topics for future studies. It is also noteworthy that this very late binding group is highly enriched with proteins that bind to viral transcripts, particularly those from coronaviruses and flaviviruses, with positive-sense single-stranded RNA genomes, whose structures are similar to those of cellular mRNAs. It will be interesting to investigate the functions of these vRBPs in viral infection.

Our experiments yielded some unexpected results. For instance, we detected pol II and 3′ end processing proteins among the earliest binders. Considering our experimental design which is based on oligo(dT) capture, their presence was unanticipated as they are supposed to function before the polyadenylation step. However, a recent report offers a potential explanation for these results: pol II and nascent transcripts readily incorporate into RNP complexes in nuclear matrix, where poly(A) tailed pre-mRNAs are held for further processing steps (72). Another intriguing observation involves the nuclear export factor NXF1. EJC components, SR proteins (SRSF3/SRp20 and SRSF7/9G8), and a TREX component (ALYREF/THOC4) have been reported to recruit NXF1 to promote mRNA export (41; 30; 88). However, our current data show that NXF1 is recruited soon after SR proteins but before EJC and TREX (Figure 2.13). This suggests that NXF1 might be recruited via direct RNA binding and/or assisted by early binders such as SR proteins. While we do not exclude the possibility that EJC and TREX also contribute to NXF1 recruitment, our results indicate a necessity to reassess the mechanisms of mRNA export.

To systematically identify RBPs with unanticipated binding dynamics, we trained a machine learning model to predict mRNA binding dynamics from GO annotations. This model was then applied to screen under-characterized RBPs by comparing the observed and expected dynamics. We found numerous RBPs that bind to mRNA earlier or later than expected, revealing proteins with

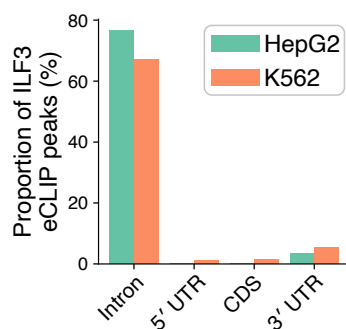


Figure 2.55 Proportions of ILF3 eCLIP peaks that are mapped to intron, 5' UTR, CDS, and 3' UTR regions. Both the HepG2 (green) and K562 (orange) eCLIP data are from the ENCODE project.

potentially unknown functions or multiple functions. For instance, we discovered ILF3 (also known as NF90) as an early binder belonging to cluster III. ILF3 has been implicated in various processes such as transcription, microRNA maturation, pre-mRNA splicing, RNA export, translation, and mRNA degradation (9; 27). However, recent eCLIP experiments showed a high proportion of intron peaks (Figure 2.55), suggesting ILF3's binding to pre-mRNAs rather than mature mRNAs. This observation aligns with our data and suggests a role of ILF3 mainly in pre-mRNA processing. Moreover, CIRBP (also termed hnRNP A18), which has been described as a regulator of mRNA stabilization and translational activation (84; 83), was identified as a cluster II protein in our study. CIRBP is predominantly found in the nucleus but partially relocates to the cytoplasm under stress conditions (13). Our dynamics data supports a nuclear function for CIRBP at least under the condition used in this study. The annotation-based prediction method and the temporal RNA binding information will provide a useful resource for further studies on these RBPs.

To foster community access to our data, we developed an interactive web application available at <https://chronology.rna.snu.ac.kr>. This platform enables the search for specific RBPs via their UniProt accessions or gene symbols. For each RBP, we provide detailed and comprehensive information on mRNA binding

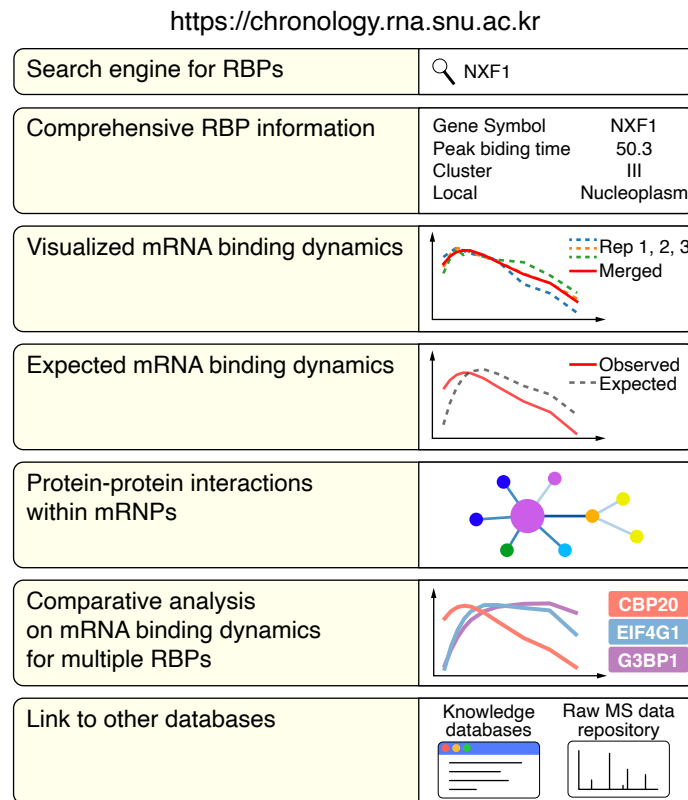


Figure 2.56 . A web application aiding community access to mRNA binding dynamics, accessible at <https://chronology.rna.snu.ac.kr>.

dynamics, subcellular localization, GO-based prediction of mRNA binding dynamics, and protein interactors within mRNPs. Furthermore, our web application allows researchers to compare the mRNA binding dynamics of multiple RBPs of interest and create combined line plots of the mRNA binding dynamics (Figure 2.56).

The methodology used in this study is readily adaptable to other biological contexts, provided that pulse-labeling and UVA cross-linking are feasible. For instance, a loss-of-function study could be combined to explore a gene's function in mRNP remodeling. Given that some RBPs are associated with genetic disorders (e.g. ALS caused by the defective TDP-43), examining the impact of

their mutations in disease models could yield intriguing results. One could also scrutinize the effects of pharmacological inhibitors/agonists on the mRNA life cycle. Investigating the molecular effects of splicing or translation inhibitors, currently under clinical trials or in use for cancer and genetic diseases, could be enlightening (18; 65; 46; 8). Moreover, mRNP profiling under stress conditions could reveal alterations in mRNP remodeling in cells coping with stressors such as amino acid deprivation, ER stress, heat shock, viral infection, and inflammation, adding new dimensions to the understanding of gene regulation.

2.4 Methods and Materials

Capture of the pulse-labeled RNA interactome

HeLa cells were maintained in DMEM (Welgene) supplemented with 9% FBS (Welgene, cat#S001-01) and cultured at 37°C with 5% CO₂. Four 150mm dishes were used for each time point sample. For pulse-labeling, cells were incubated with 0.5mM 4sU (Sigma-Aldrich, cat#T4509) for 10 min. After washing three times with PBS, cells were incubated with DMEM supplemented with 1mM uridine until UVA irradiation. A “no-labeling” sample which was also irradiated with UVA was used as a negative control. After incubation with the uridine supplemented DMEM for a certain designated incubation time (0-5 h), the pulse-labeled cells were washed with cold PBS and irradiated with 365nm UV for 0.45J/cm². After crosslinking, cells were immediately harvested and treated with TURBO DNaseI at 37°C for 30 min. The 2X lysis buffer (40mM Tris-HCl pH 7.5, 1M LiCl, 1% LiDS wt/vol, 1% NP40 wt/vol, 2mM EDTA, 10mM DTT, 8M Urea) were added to lyse the DNase treated cells. Lysates were homogenized by passing the lysate with a 21G needle. After measuring the amount of total protein with BCA assay, samples containing equal amounts of proteins (15mg) were used for RNA interactome capture (RIC). RIC was performed as in previous papers (10) with the following modifications. Oligo d(T) bead (NEB, cat#S1419S), which was washed with lysis/binding buffer (20mM Tris-HCl pH 7.5, 500mM LiCl, 0.5% LiDS wt/vol, 0.5% NP40 wt/vol, 1mM EDTA, 5mM DTT, 4M Urea), was added to the lysate

and incubated at room temperature for an hour. Beads were collected with the magnet, and the supernatant (“flowthrough”) was transferred to a new tube and stored at 4°C for the additional capture (see below). The collected beads were washed once with lysis/binding buffer followed by two washes with wash buffer 1 (20 mM Tris-HCl pH 7.5, 500 mM LiCl, 0.1% LiDS wt/vol, 0.5% NP40 wt/vol, 1 mM EDTA, and 5 mM DTT), wash buffer 2 (20 mM Tris-HCl pH 7.5, 500 mM LiCl, 0.5% NP40 wt/vol, 1 mM EDTA, and 5 mM DTT), and wash buffer 3 (20 mM Tris-HCl pH 7.5, 200 mM LiCl, 1 mM EDTA and 5 mM DTT). For elution, beads were resuspended in 300 μ l of elution buffer (20 mM Tris-HCl pH 7.5, 1 mM EDTA) and incubated for 3 min at 65°C with agitation before the supernatant containing eluted proteins was transferred to a fresh tube and stored. The elution step was repeated. The beads and the flowthrough from the first capture step were mixed to capture the residual RNPs remaining in the flowthrough. The incubation, wash, and elution steps were repeated, and the eluted proteins were combined with the eluted proteins from the first round.

Peptide sample preparation and TMT labeling for quantitative proteomics analysis

RNA-binding proteome samples collected via oligo(dT) bead pull down were first concentrated to 80 μ l using speed-vac (Concentrator plus, Eppendorf) and then reduced with 20 mM dithiothreitol (DTT) (Sigma-Aldrich) at 37°C for 1h. The samples were placed onto 30kDa molecular weight cut off (MWCO) filter (Amicon 30kDa, Merck Millipore) along with the 200 μ l of urea buffer (8 M urea in 25 mM HEPES buffer, pH 8.5), followed by centrifugation at 15,000 \times g for 15 min at 24°C. Each sample was then reconstituted with 200 μ l of the urea buffer and centrifuged again (twice). The samples were then alkylated with 200 μ l of 80mM iodoacetamide (Sigma-Aldrich) in the urea buffer and incubated at 37°C for 1 hour in the dark, followed by centrifugation. Each sample was then washed with 200 μ l of the urea buffer twice and with 200 μ l of 25 mM HEPES buffer (pH 8.5) twice. 100 ng of trypsin (~1:50 w/w, based on the estimation from TIC area) in 200 μ l of HEPES buffer was added to each sample and incubated at 37°C for

overnight. Samples were then centrifuged and the collected flow-throughs were concentrated to 40 μ l using the speed-vac. Total of 11 samples were labeled with the TMT11plex reagents following the protocol provided by the manufacturer (Thermo Fisher). TMT labeled samples were combined and desalted using the C18 SPE cartridge (Supelco) and the elute from the cartridge was completely dried using the speed-vac and reconstituted with 50 μ l of 10 mM ammonium bicarbonate (ABC) buffer.

A concatenated mid-pH (pH 8) RPLC off-line fractionation was carried out at micro-scale for multidimensional LC-MS3 analysis to improve the quantitative profiling depth. For micro-scale fractionation, a RPLC capillary column (320 μ m i.d. x 55 cm) was in-house packed with Jupiter C18 beads (Phenomenex, 3 μ m). The 50 μ l of combined TMT11-labeled peptide sample was loaded onto the capillary column. A linear gradient of solvent A (10 mM ABC in water, pH 8) and solvent B (10 mM ABC in 90% acetonitrile) was applied on nanoAcquity (Waters) at a flow rate of 7 μ L/min; 2% solvent B isocratic for initial 14 min, 2 to 10% solvent B for following 2 min, 10 to 40% solvent B for next 56 min. The eluent was automatically concatenated into 6 fractions using TriVersa NanoMate (Advion) and reconstituted with 25 mM ABC buffer for further LC-MS3 analysis.

Liquid chromatography and tandem mass spectrometry (LC-MS3) analysis

The TMT11-labeled 6 fractions were analyzed using an Orbitrap Eclipse via MS3 mode (Thermo Fisher Scientific) coupled with nanoAcquity UPLC system (Waters), which was equipped with an in-house packed trap (150 μ m i.d. x 3 cm) and analytical column (75 μ m i.d. x 100 cm) using 3 μ m of Jupiter C18 particle (Phenomenex). During the analysis, the analytical capillary column was heated at 45°C with the column heater (Analytical Sales and Services). A linear gradient of solvent A (water with 0.1% formic acid) and solvent B (acetonitrile with 0.1% formic acid) was applied at a flow rate of 300 nl/min as follows: 5 to 8% solvent B for initial 10 min, 8 to 35% solvent B for next 195 min. Total run time for the SPS-MS3 analysis were 220 min with the following set up for MS acquisition; Full

MS scans (m/z 400–1600) were acquired at a resolution of 120k (at m/z 200) with $4E5$ of AGC target value and 50 ms of ITmax. Selected precursor ions were first isolated at 0.7 Th of isolation window and subjected to HCD fragmentation for MS2 scans in orbitrap at a resolution of 15k (ITmax 60 ms, AGC $5E4$ and NCE 30%). The 10 most intense MS2 fragment ions were synchronously isolated in ion trap for final HCD MS3 scans at a resolution of 50k and 0.4 Th of isolation width (AGC $13E5$, ITmax 150 ms, and NCE 65%). Overall 3 s of cycle time was applied. The mass spectrometry proteomics data have been deposited to the ProteomeXchange Consortium via the PRIDE (58) partner repository with the dataset identifier PXD039054.

LC-MS3 data processing for peptide identification

For all proteome data analysis, canonical protein sequences (SwissProt) of UniProt human reference proteome UP000005640 (last modified on Dec 3th, 2018, 20303 proteins were included) was used. Pig trypsin (UniProt accession P00761) and the cRAP (common Repository of Adventitious Proteins) protein sequences version 2012.01.01 (<http://www.thegpm.org/crap/index.html>) were appended to the search space, to mark the peptides from the common contaminant proteins. To estimate peptide level FDR, decoy sequences were generated by reversing target protein sequences. The RAW format LC-MS3 data file was first converted into mzXML format using msconvert (ProteoWizard version 3.0.1908, (1)) with the following parameters: `--ignoreUnknownInstrumentError --mzXML --filter "peakPicking true [1,2]" --filter "msLevel 1-2"`. Then, peak count filtering (≥ 20 peaks), charge suggestion (within range +1 - +7) and mzXML to MGF conversion was done by MzXML2Search (v5.2.0) with the following parameters: `-mgf -B0 -T20000 -c1-7 -P20`. Resulting MGF files were subjected to the MS-GF+ (v2020.07.02, (40)) for peptide identification at the search tolerance 10ppm. For MS-GF+ search, we set carbamidomethylation of cysteine and TMT labeling of peptide N-terminus/Lysine as static modification, and oxidation of methionine and acetylation of protein N-terminus as variable modification. Also, `-m 3` option was set for the HCD fragmentation.

Total RNA analysis

For comparison between conventional RIC and our modified RIC method described above, one 150mm dish of HeLa cells were harvested and lysed with RIC lysis/binding buffer (20mM Tris-HCl pH 7.5, 500mM LiCl, 0.5% LiDS wt/vol, 0.5% NP40 wt/vol, 1mM EDTA, 5mM DTT). After the RIC procedure described above, RNA was isolated from the elution. For total RNA isolation from inputs, 1 ml of TRIzol (Invitrogen) was added to 2.5% of input lysates (which is about 50 ul). The rRNA ratio was estimated by using TapeStation RNA screen tape.

Measuring 4sU labeling efficiency

HeLa cells were pulse-labeled with 0.5 mM 4sU for 10 min and used directly for RNA purification to obtain total RNA population or used for oligo(dT) enrichment. During RNA purification with TRIzol, DTT was added to aqueous phase in the final 0.1 mM and total RNA was eluted in 1 mM DTT solution to prevent oxidation of the 4sU labeled RNA. For oligo(dT) enriched RNA samples, 5 mM DTT was added to the elution buffer after RIC. Single nucleoside digestion was performed as previously described (29). Nucleoside samples prepared from each experimental condition was reconstituted in 50 μ l of solvent A (200 mM triethylammonium acetate) and loaded onto a BEH C18 column (2.1 mm i.d. x 300 mm, 1.7 μ m particle) (Waters) coupled with the 1290 Infinity UHPLC system (Agilent) and the column heater was set at 25°C. A linear gradient of solvent A and solvent B (90 % methanol) was applied at a flow rate of 100 μ l/min as follows: 100% isocratic solvent A for initial 5 min, 0 to 20% solvent B for 20 min, 20 to 30% solvent B for 20 min, 30 to 90% solvent B for 10min, and 90 to 0% solvent B for 2 min, followed by isocratic 100% solvent A for 33 min. UV absorbance at 260 nm and 330 nm were monitored. U and 4sU standards were separately analyzed or mixed 1:1 ratio, each diluted with equal amount of 400 mM triethylammonium acetate to make final concentration as 200 mM, and analyzed to determine the respective elution time based on the UV signal detection at 260 nm and 330 nm. Relative amount of U and 4sU nucleoside in each sample was estimated based

on the UV signal, area under the curve, obtained by 260 nm and 330 nm UV detection at the respective elution time point.

Pulse-labeled RNA sequencing and data processing

One 150 mm culture dish of HeLa cell for each time point was used for the experiment. Followed by 10 min of 4-thiouridine labeling, cells were harvested after incubation for 0 min, 30 min, and 5 hrs of uridine supplemented media. As a negative control, a no-4sU-labeled sample was also prepared. Cells were harvested without UV crosslinking and then treated with DNaseI. For spike-in RNAs, in vitro transcribed non-human RNAs were prepared with or without 4sU and then polyadenylated with ePAP (NEB). After adding spike-in RNAs to the same amount of lysate, the RIC protocol described above was used to enrich poly(A) RNA in the lysate except elution buffer (20 mM Tris-HCl pH 7.5, 1 mM EDTA, and 1mM DTT). The eluted samples were precipitated with ethanol. Enrichment of 4sU labeled RNA was performed based on the previously described protocol (17) with the following alterations. 50ug of poly(A) enriched RNAs were used for MTS-pulldown. MTS-biotin was diluted in N,N-Dimethylformamide (Sigma, cat#227056). RNAs were incubated with diluted MTS-biotin at room temperature for 2 hrs and purified with RNAClean XP (Beckman, cat#A63987). Dynabeads MyOne Streptavidin C1 (Invitrogen, cat#65002) were washed with nuclease-free water and high salt buffer (10 mM Tris, 1 mM EDTA, 100 mM NaCl, 0.05 % Tween-20 wt/vol) and then blocked with blocking buffer (10 mM Tris, 1 mM EDTA, 100 mM NaCl, 0.05 % Tween-20 wt/vol, 5 ug/ul glycogen) for an hour at room temperature. Biotinylated RNAs were heated at 65°C for 10 min and placed on ice. 10X High salt buffer was added to RNA solution to make it 1X concentration, and pre-washed beads were added to RNAs. Biotinylated RNA and streptavidin beads were incubated in dark for 15 min. The first supernatants were kept as flow-through. After washing beads with high salt buffer three times, 4-thiouridine labeled RNAs were eluted from beads with elution buffer (100 mM DTT, 5% 2-Mercaptoethanol, 20 mM HEPES pH 7.6, 1 mM EDTA, 100 mM NaCl, 0.05% Tween-20 wt/vol). RNA-seq libraries were constructed using MGIEasy

RNA Directional Library Prep Kit V2.0 (MGI, cat#1000006385) and sequenced by paired-end run on MGI sequencer.

The initial parts of sequence analysis were done by using Cutadapt version 3.0 (Martin). For 5' and 3' end of each read, the low-quality bases below Phred quality of 30 were trimmed. After trimming, 3' adaptor sequences of both the first and second read of each pair were removed (Table 2.7). Read pairs with any read shorter than 70 bases were removed after trimming and adaptor clipping. To get the readcount for each gene and spike-in, a transcript reference was build based on spike-in sequences (Table 2.7), UCSC Genome Browser hg38 RefGene annotation (downloaded on February 20, 2020), and hg 38 genome, by RSEM (v1.3.1) (47). Pre-mRNA transcript models were also generated and added to the transcript reference by in-house software, since un-spliced mRNAs might be included in the early stage mRNPs. The read pairs were aligned to the above transcript reference by STAR version 2.7.6a (14). The read count of each gene and spike-in was calculated and normalized to TPM (transcript per million) by RSEM (v 1.3.1) (47). Spike-in normalization was done by the ratio of geometric mean of spike-in TPMs.

Conventional protein analyses

RIC samples were resolved on SDS-PAGE and analyzed by silver staining using EzWay Protein-Silver Staining Kit (KOMABIOTECH, cat#K14040D). For western blot analysis, the eluates of RIC were first concentrated with Amicon 30K Ultra-0.5 (Millipore) and treated with RNase A (Thermo Scientific, cat#EN0531) and Benzonase (Sigma-Aldrich, cat#E1014). The concentrated samples were then loaded on 10% Novex WedgeWell Tris-Glycine Mini Gel (Invitrogen). After transferring to a methanol-activated PVDF membrane (Millipore), the membrane was blocked in PBS-T containing 5% milk, probed with primary antibodies, and washed three times. Anti-mouse or anti-rabbit HRP-conjugated secondary antibodies (Jackson ImmunoResearch Laboratories) were incubated and washed three times again. Chemiluminescence was performed with West Pico Luminol reagents (Thermo), and the signals were detected by ChemiDoc XRS+ System (BioRad).

In detail, LARP1 (Bethyl, A302-087A), ALYREF (Bethyl, A302-892A), TDP-43 (ProteinTech, 10782-2-AP) and G3BP1 (BD Bioscience, 611126) were first detected, then the membrane was stripped with WSE-7240 EzReprobe (2332530) and restained with antibodies against hnRNPA1 (gift from Gideon Dreyfuss), SRSF7 (MBL, RN079PW) and FMR1 (MBL, RN016P). PABPN (Abcam, ab75855), PABPC4 (Bethyl, A301-466A), POLR2 (Santa Cruz, sc-56767), eIF4G2 (MBL, RN003P) were first detected, then the membrane was stripped and restained with IGF2BP3 (Santa Cruz, sc-365640).

Immunofluorescence and confocal microscopy

HeLa cells were cultured on 8-chamber slide glass (Thermo, 154461PK). The cells were labeled for 10 min with 4sU, followed by a 5 hrs chase with uridine-supplemented media, as previously described. To induce cellular stress, cells were treated with 0.5mM sodium arsenite for 1 hour. Subsequently, the cells were fixed using 4% paraformaldehyde for 10 min and permeabilized with 0.1% Triton X-100. After blocking with a 5% BSA buffer, the cells were incubated with anti-G3BP1 antibody (BD, 611127, mouse) for 2 hours at room temperature. Following washing steps, the cells were incubated with an anti-mouse Alexa Fluor 488-conjugated secondary antibody and DAPI (D9542) for 1 hour. Images were captured using a Nikon ECLIPSE Ti2 microscope.

Protein quantity processing and contaminant filtering

Following procedures were done to generate each protein's quantity dynamics from the triplicate experiments. First, protein quantities were divided by the pig trypsin (UniProt accession P00761) quantity of the regarding sample, to reduce the quantification bias from peptide sample preparation. Then, to remove the effect of non-specific binders, the intensity of no 4sU negative control was subtracted from the other channel's intensities. Pseudo intensity was set as the bottom 5% quantity of each replicate and added to all peptides' intensities to avoid division by zero. Protein intensities of each replicate were normalized so that the intensity sum of protein in each replicate is the same with median of summed

intensity. Normalized and log-transformed replicate quantities were merged and smoothed by univariate quadratic spline (from SciPy(<https://scipy.org/>)), using time points as independent variables and quantities as dependent variables. The univariate spline was unsuccessful on 18 proteins with very high variance among replicates, so those proteins were discarded. The peak binding time of RBP was found from the fitted spline line, interpolated at 0.1 min interval. Protein quantification quality was defined as the ratio between per replicate variation and per time-point variation. In practice, it was calculated as root mean squared error (RMSE) between measured quantities and merged protein quantity spline (per replicate variation) divided by standard deviation (std) of merged protein quantities (per time-point variation). Proteins with RMSE / std ratio above 1 were discarded. Before further analyzing data, proteins marked as common lab contaminants by cRAP database were discarded. Also, human keratin and histone proteins were removed before the analysis, because those proteins are less likely to act as real RBP, and show high variance between replicates.

To identify mRNA interacting proteins from one non-labeled (No4sU) and 10 crosslinked (CL) samples, we compared all 10 No4sU versus CL sample pairs and combined the results. For each pair, normalized and log-transformed triplicate quantities were tested for differential expression by the DEqMS package, which uses a moderated ANOVA test considering the number of quantified PSMs per protein group (89). P-values of all 10 NoCL versus CL differential expression tests were merged into one p-value by the empirical Brown's method (59). Resulting p-values of all protein groups were adjusted for multiple test correction by Benjamini-Hochberg method.

Previously identified mRNP list from RBP2GO

We adopted previously identified mRNP list from the meta analysis database, RBP2GO (11). All human RBP datasets were taken, except for in vitro experiments, in silico prediction, review or meta analysis, and non-poly(A) enrichment datasets. The RBP2GO identifiers of used datasets are following: Baltz_HEK293_2012, Castello_HeLa-S3_2012, Beckmann_HuH-7_2015, Castello_HeLa-

S3_2016, Conrad_K562_2016, Milek_MCF7_2017, Perez-Perri_Jurkat_RIC_2018, Perez-Perri_Jurkat_eRIC_2018, Garcia-Moreno_HEK293_2019, Backlund_HuH-7_Cytoplasmic_2020, Backlund_HuH-7_Nuclear_2020, Kramer_HeLa_2014, Panhale_HEK293_2019, Mullari_HEK293_2017.

Protein domain enrichment analysis

Taxon 9606 (human) protein domain annotations in Pfam database (version 32.0) was used for protein domain enrichment analysis. One-sided Fisher's exact test was applied to estimate the statistical enrichment of a particular domain among the quantified RBPs. Benjamini-Hochberg method was applied to the p-values for the multiple test correction.

Clustering analysis on temporal dynamics of RBPs

For the feature standardization, log-transformed quantities were z-score transformed for protein-wise direction, by the mean and standard deviation of all time points for each protein. Also, the maximal time of protein quantities were z-score transformed for feature-wise direction. K-means clustering using above normalized features were done by scipy version 1.4.1 (<https://scipy.org/>). The mean distortion of clustering result was calculated as the mean Euclidean distance between the feature values and the cluster centroids. The number of clusters were manually set to 7 after testing several cluster numbers ($5 \leq K \leq 10$), based on the mean distortion of clustering results.

Filtering out non-protein coding RNA binders and mitochondrial mRNA binders

Several RBPs in our data are primarily known as non-coding RNA or mitochondria-coded mRNA binders, even after we filtered RBPs with previously reported mRNP list. Thus, we defined annotation and knowledge based blacklist for the further analyses. First of all, mitochondrial mRNA binders were defined as genes annotated with GO "mitochondrial matrix" but not with GO "cytosol". Then, we added ribosomal proteins and mitochondrial ribosome proteins to the blacklist.

Next, GO “pre-snoRNP complex”, “sno(s)RNA-containing ribonucleoprotein complex”, and “preribosome” annotated genes were added to the blacklist. Lastly, three proteins (DCAF13, FTSJ3, NGDN) were removed from the blacklist and re-included to the mRNP list, as there are literatures supporting their binding on nuclear-coded mRNAs.

Gene Ontology (GO) and subcellular localization analysis

As previously described, ribosomal proteins, snoRNA related factors, and RBPs exclusively localized to the mitochondrial matrix were removed in this analysis. All GO gene annotations used in this study were obtained from the org.Hs.eg.db R package (version 3.14.0). To gain functional insights to each cluster, GO term enrichment analysis was done by Fisher’s exact test, by setting all 1035 proteins identified by MS as the statistical background. P-values were adjusted for GO hierarchy and local dependencies by weight01 algorithm in topGO R package (2). To test GO terms enriched at a specific time point, we utilized pairwise distances between RBPs used in prior clustering analysis. Per each GO term, pairwise distances within RBPs annotated with GO term and not annotated with GO term were compared by Mann-Whitney U test. To remove redundantly enriched parent-child GO terms, the elim algorithm (described in (2)) was applied to adjusted p-values. We downloaded Human cell map database v1 (26) for deeper analysis of subcellular localizations and polished their data as described in (45).

Binding site mapping of RBPs

As previously described, ribosomal proteins, snoRNA related factors, and RBPs exclusively localized to the mitochondrial matrix were removed in this analysis. The binding locations of RNA-binding proteins (RBPs) were determined based on eCLIP peak locations provided by the ENCODE project (80; 79; 81). To generate non-redundant transcript annotations, we initially calculated read counts for duplicated RNA-seq data from HepG2 and K562 cell lines using RSEM, as previously described (ENCODE data accession: ENCFF002DKZ, ENCFF002DLC, ENCFF002DLE, ENCFF002DLG for HepG2; ENCFF001RDE, ENCFF001RCW,

ENCFF001RDD, ENCFF001RCV for K562). Subsequently, we selected the most abundant transcript for each protein-coding gene, based on TPM values calculated by RSEM. The transcript regions were then divided into subregions, including introns, 5' UTRs, CDS, and 3' UTRs. Finally, for all overlapping subregions, we selected the subregion from the most abundant transcript. In cases where TPM values were tied, which was very rare, we prioritized genes with the smallest RefSeq accession number. The overlap between eCLIP peaks and transcript annotations was determined using the intersectBed tool in Bedtools, with a minimum requirement of $\geq 50\%$ overlap relative to the span of the eCLIP peak (61).

Protein-protein interaction (PPI) network and protein complex analysis

As previously described, ribosomal proteins, snoRNA related factors, and RBPs exclusively localized to the mitochondrial matrix were removed in this analysis. We downloaded PPI data from the BioGRID database (release 4.2.191, (67)). Also, we considered only human PPIs (1) classified as physical interaction and (2) found from at least two different types of experiments, and (3) supported by at least two publications. The networkx python package was used for graph visualization. For the protein complex annotation, we utilized the CORUM database (release 3.0_03.09.2018_coreComplexes). To quantitatively measure the differences among the mRNA binding dynamics of protein within PPI pairs or protein complexes, we calculated Euclidean distances between mRNA binding dynamics vectors, defined as [log₂ protein intensity at 0 min, log₂ protein intensity at 15 min, . . . , log₂ protein intensity at 300 min, peak binding time]. Before calculating Euclidean distances, protein intensities and peak binding times were normalized as described in “Clustering analysis on temporal dynamics of RBPs” section.

mRNA binding dynamics prediction from GO annotations

As previously described, ribosomal proteins, snoRNA related factors, and RBPs exclusively localized to the mitochondrial matrix were removed in this analysis.

To generate a boolean table of RBPs versus GO, we utilized the org.Hs.eg.db R package (v3.14.0). Each cell in this table was marked as "true" if an RBP was annotated with a GO term, and "false" otherwise. To remove less informative annotations, we excluded GO terms with fewer than 7 annotated or unannotated RBPs. Subsequently, we performed multiple correspondence analysis (MCA) to convert the boolean table into numeric values and reduce its dimensionality. From the MCA transformed features, we selected the top 30% (323 features), which retained approximately 98% of the original boolean table's information. As the presence of imbalanced numbers of early and late binder RBPs could introduce prediction accuracy bias, we mitigated this bias by oversampling RBPs. This involved duplicating certain RBPs in clusters with fewer members, ensuring that all clusters contained an equal number of RBPs (200). For each time point, we trained a ridge regression model to predict the z-scores of individual RBPs using the MCA transformed features. To determine the optimal model parameters, we performed 5-fold cross-validation. The scikit-learn python package (v0.23.2, <https://scikit-learn.org>) was utilized for fitting the regression models and conducting cross-validation.

Cell fractionation RNA immunoprecipitation and qPCR

HeLa cell was washed with cold PBS and detached from the plate by scraping with a cell scraper. Cells were resuspended in cytosol fractionation buffer (50mM HEPES pH 7.6, 150mM NaCl, 0.1mM EDTA, 200ug/ml digitonin, 1mM DTT, SupraseIn, proteinase inhibitor and phosphatase inhibitor). After incubation at ice for 10 min, lysate was centrifuged at 2000 g for 10 min at 4°C and supernatant was used for RNA immunoprecipitation. For membrane and nuclear fractionation, subcellular protein fractionation kit for cultured cells (Thermo, 78840) was performed following manufacturer's instruction. Protein A sepharose bead were incubated with salmon sperm DNA overnight at 4°C and washed with cytosol fractionation buffer. 10ug Ab (Bethyl, A302-481A) was added to bead and incubated for 1 hr at 4°C for bead conjugation. Then the lysate and the Ab conjugated bead were subjected to

IP for 3 hrs at 4°C. After IP, the beads were washed with cytosol fractionation buffer.

After immunoprecipitation (IP) of CCDC86 from the cytoplasmic fraction, one-fourth of the sample was used for Western blot analysis, while the remaining sample was subjected to RNA isolation using TRIzol for subsequent qPCR analysis. The list of used oligos is shown in Table 2.7.

Knockdown RNA-seq

HeLa cell was plated in 60 mm dish and final 50 nM siRNAs were reverse-transfected using Lipofectamine 3000 (Invitrogen) and ON-TARGETplus SMART-pool siRNAs (Horizon Discovery) for 48 hrs. Total RNA was purified with TRIzol. RNA-seq reads were processed the same as the pulse-labeled RNA-seq, but without Pre-mRNA transcript models. From ENCODE shRNA-seq dataset, we downloaded fastq files with accession ENCFF541QLM, ENCFF791QXP, ENCFF232RVX, and ENCFF238SIB for shFAM120A of K562 cell line, ENCFF539FEL, ENCFF276RDY, ENCFF454RKS, and ENCFF224TRL for shFAM120A of K562 cell line. Also, ENCFF844XSA, ENCFF327PBI, ENCFF845TFX, and ENCFF841SLY were downloaded for HepG2 cell line shFAM120A, and ENCFF793WXG, ENCFF201DSF, ENCFF344ITC, and ENCFF314EUX were used for shNC of HepG2 cell line. To map spike-in sequences, ENCFF001RTP.fasta was also downloaded. Read counts calculated by RSEM (v1.3.1) were loaded to DESeq2 (v1.34.0) via tximport (v1.22.0). Differential gene expression was tested by DESeq2 with default parameters.

SUnSET assay

HeLa cell was plated in 6 well plate and final 50 nM siRNAs were reverse-transfected using Lipofectamine 3000 (Invitrogen) and ON-TARGETplus SMART-pool siRNAs (Horizon Discovery) for 72 hrs. Cells were incubated in final 0.54ug/ml puromycin for 30 min and then lysed with RIPA buffer (with proteinase inhibitor and phosphatase inhibitor). After BCA assay, same amount of lysate were loaded on 10% Novex WedgeWell Tris-Glycine Mini Gel (Invitrogen). After

transferring to a methanol-activated PVDF membrane (Millipore), the membrane was blocked in PBS-T containing 5% milk, probed with primary antibodies, and washed three times. Anti-mouse or anti-rabbit HRP-conjugated secondary antibodies (Jackson ImmunoResearch Laboratories) were incubated and washed three times again. Chemiluminescence was performed with West Pico Luminol reagents (Thermo), and the signals were detected by ChemiDoc XRS+ System (BioRad). Primary antibodies against puromycin (Sigma-Aldrich, MABE343), α -tubulin (Abcam, ab52866), GAPDH (Santa Cruz, sc-32233) were used.

2.5 Tables

Pfam domain	p-value	q-value	Quantified w/ domain	Quantified w/o domain	Not quantified w/ domain	Not quantified w/o domain
RRM_1	38.117	2E-114	121	83	680	19419
Helicase_C	25.36	7E-34	46	60	755	19442
DEAD	25.34	4E-32	37	30	764	19472
KH_1	48.18	7E-19	19	16	782	19486
zf-CCCH_1	35.14	5E-12	16	18	785	19484
OE_NTP_bind	36.12	4E-10	11	6	790	19496
SAP	36.12	4E-10	11	6	790	19496
HA2	88.12	8E-10	11	7	790	19495
dsm	66.11	5E-09	10	6	791	19496
ST	16.09	8E-08	12	1	794	19501
Ic_path	35.09	2E-07	12	22	789	19480
RRM_5	46.09	2E-07	6	0	795	19502
PW1	96.08	4E-06	5	0	796	19502
Bra	96.08	4E-06	5	0	796	19502
YTH	96.08	4E-06	5	0	796	19502
zf-LHC	96.08	4E-06	10	19	791	19483
SPKC	56.07	2E-05	5	1	796	19501
Surp	56.07	2E-05	5	1	796	19501
La	25.06	7E-05	5	2	796	19500
WD40	25.06	7E-05	25	193	776	19399
PAP_assoc	25.06	7E-05	5	2	796	19500
DUF417	25.06	8E-05	4	0	797	19502
Toprim	25.06	8E-05	4	0	797	19502
RRM_8	25.06	8E-05	4	0	797	19502
DZF	16.05	4E-04	4	1	797	19501
zf-CCCH_4	25.05	6E-04	5	5	796	19497
zf-RanBP	25.05	6E-04	6	10	795	19492
AAA_12	46.05	1E-03	5	6	796	19496
S4	66.05	1E-03	3	0	798	19502
KH_9	66.05	1E-03	3	0	798	19502
NOFS	66.05	1E-03	3	0	798	19502
Nop	66.05	1E-03	3	0	798	19502
zf-RNP4	66.05	1E-03	3	0	798	19502
CB	66.05	1E-03	3	0	798	19502
Ribosomal_L1	66.05	1E-03	3	0	798	19502
BAT2_N	66.05	1E-03	3	0	798	19502
DXRBP_C_core	66.05	1E-03	3	0	798	19502
Lus7	66.05	1E-03	3	0	798	19502
AKAP35	66.05	1E-03	3	0	798	19502
THRAP3_BCLAF	66.05	1E-03	3	0	798	19502
Agonet	66.05	1E-03	3	0	798	19502
Tudor_FRK1	66.05	1E-03	3	0	798	19502
Utp12	66.05	1E-03	3	0	798	19502
C/D_58	86.05	1E-03	4	3	797	19499
zf-C2H2_jaz	16.04	2E-03	5	9	796	19493
SNF2_N	25.04	3E-03	7	25	794	19477
RRM_7	25.04	4E-03	3	1	798	19501
OCRE	25.04	4E-03	3	1	798	19501
CEBP_ZZ	25.04	4E-03	3	1	798	19501
Pho	25.04	4E-03	9	45	792	19457
KOW	36.04	4E-03	4	5	797	19497
AAA_33	36.04	4E-03	4	5	797	19497
MIR_HSR1	46.04	6E-03	5	12	796	19490
zf-HCSAK2H	46.04	6E-03	4	6	797	19496
RNase_T	46.04	6E-03	4	6	797	19496
AAA_11	46.04	6E-03	4	6	797	19496
AWS	66.04	8E-03	3	2	798	19500
Ribosomal_L7Ae	66.04	8E-03	4	7	797	19495
Rit16	25.03	1E-02	2	0	799	19500
Ribosomal_S9	25.03	1E-02	2	0	799	19502
Ribosomal_S8e	25.03	1E-02	2	0	799	19502
Ribosomal_S7	25.03	1E-02	2	0	799	19502
Ribosomal_S5_C	25.03	1E-02	2	0	799	19502
Ribosomal_S5_S	25.03	1E-02	2	0	799	19502
Ribosomal_S4	25.03	1E-02	2	0	799	19502
Ku_C	25.03	1E-02	2	0	799	19502
Ribosomal_L44	25.03	1E-02	2	0	799	19502
Ribosomal_L35	25.03	1E-02	2	0	799	19502
Ribosomal_L28e	25.03	1E-02	2	0	799	19502
Ribosomal_L27A	25.03	1E-02	2	0	799	19502
Ribosomal_L34e	25.03	1E-02	2	0	799	19502
Ribosomal_L22e	25.03	1E-02	2	0	799	19502
Eft1	25.03	1E-02	2	0	799	19502
FXR_C1	25.03	1E-02	2	0	799	19502
SMA-ATX	25.03	1E-02	2	0	799	19502
Suf	25.03	1E-02	2	0	799	19502
zf-RASP	25.03	1E-02	2	0	799	19502
DNA_gyraseB	25.03	1E-02	2	0	799	19502
DNA_topoisomV	25.03	1E-02	2	0	799	19502
DHCT	25.03	1E-02	2	0	799	19502
zf-CCCH_2	16.03	1E-02	3	3	798	19499
AARPC9N	25.03	1E-02	2	0	799	19502
Fcd duplication	25.03	1E-02	2	0	799	19502
RNA_US_meth_1	25.03	1E-02	2	0	799	19502
A_dbsmin	16.03	1E-02	3	3	798	19499
DUF1887	25.03	1E-02	2	0	799	19502
DUF3697	25.03	1E-02	2	0	799	19502
Topoisom_bac	25.03	1E-02	2	0	799	19502
RIM	25.03	1E-02	2	0	799	19502
TOPRM_C	25.03	1E-02	2	0	799	19502
ImrNP_Q_Acd	25.03	1E-02	2	0	799	19502
CS17_C	25.03	1E-02	2	0	799	19502
Ku_N	25.03	1E-02	2	0	799	19502
CDMT_2_SANT_H	25.03	1E-02	2	0	799	19502
INCPMT	25.03	1E-02	2	0	799	19502
MA3	1E-03	1E-02	3	3	798	19499
Gar1	25.03	1E-02	2	0	799	19502
PP5	25.03	1E-02	2	0	799	19502
PSP	25.03	1E-02	2	0	799	19502
Puf	25.03	1E-02	2	0	799	19502
GUCT	25.03	1E-02	2	0	799	19502
CS17F_hinge	25.03	1E-02	2	0	799	19502
LsmAD	25.03	1E-02	2	0	799	19502
RIBOP_C	25.03	1E-02	2	0	799	19502
Ku	25.03	1E-02	2	0	799	19502
NUC153	25.03	1E-02	2	0	799	19502
Rhase_PH_C	1E-03	1E-02	3	3	798	19499
DBC1	25.03	1E-02	2	0	799	19502
CBNT	25.03	1E-02	2	0	799	19502
RRM_3	25.03	1E-02	2	0	799	19502
Nop52	25.03	1E-02	2	0	799	19502
HHH_9	25.03	1E-02	2	0	799	19502
Rhase_PH	25.03	1E-02	3	4	798	19498
Chromo	25.03	1E-02	5	19	796	19483
PAPF	36.03	2E-02	4	12	797	19490
HATPase_c	36.03	2E-02	4	12	797	19490
NTF2	36.03	2E-02	3	5	798	19497
PAM2	36.03	2E-02	3	5	798	19497
CSO	36.03	2E-02	3	5	798	19497
Methyltr_RanB1	46.03	2E-02	3	6	798	19496
DUF1087	56.03	2E-02	2	1	799	19501
Cwf1	56.03	2E-02	2	1	799	19501
RNA_mYG_MT	56.03	2E-02	2	1	799	19501
DUF1086	56.03	2E-02	2	1	799	19501
MEF4c	46.03	2E-02	3	6	798	19496
CHEK12	56.03	2E-02	2	1	799	19501
WGR	56.03	2E-02	2	1	799	19501
LSM14	56.03	2E-02	2	1	799	19501
CHDNT	56.03	2E-02	2	1	799	19501
CSHCH	56.03	2E-02	2	1	799	19501
Staufen_C	56.03	2E-02	2	1	799	19501
Tuba_N	56.03	2E-02	2	1	799	19501
Ribosomal_L3	56.03	2E-02	2	1	799	19501
Ribosomal_S9	56.03	2E-02	2	1	799	19501
PurA	56.03	2E-02	2	1	799	19501
PAPF_req	56.03	2E-02	2	1	799	19501
RnaM2	56.03	2E-02	2	1	799	19501
St-like	56.03	2E-02	2	1	799	19501
STG_glectin	56.03	2E-02	2	1	799	19501
Sac11_inhB	56.03	2E-02	2	1	799	19501
DUF4208	56.03	2E-02	2	1	799	19501
HIF	56.03	2E-02	2	1	799	19501
Cic_N	56.03	2E-02	2	1	799	19501
mWG_box_2	66.03	3E-02	3	7	798	19495
NTP_strand_2	86.03	4E-02	3	8	798	19494
Rim	86.03	4E-02	3	8	798	19494
ArgoN	96.03	4E-02	2	2	799	19500
ArgoMid	96.03	4E-02	2	2	799	19500
ArgoL2	96.03	4E-02	2	2	799	19500
zf-CCCH_3	96.03	4E-02	2	2	799	19500
Whm1	96.03	4E-02	2	2	799	19500

Table 2.1 Pfam protein domains enriched in mRNPs.

Cluster	Primary gene name	Cluster membership (fold)	0m score	15m score	30m score	45m score	1h score	2h score	3h score	4h score	5h score	Maximal binding time	Cluster	Primary gene name	Cluster membership (fold)	0m score	15m score	30m score	45m score	1h score	2h score	3h score	4h score	5h score	Maximal binding time		
I	GAR1	0.99393153	1.225	0.953	0.729	0.544	0.386	0.12	-0.124	-0.67	-1.321	-1.841	7.11E-13	II	RBM6	0.99947865	0.468	0.683	0.78	0.784	0.717	0.443	0.08	-0.619	-2.02	-2.133	38.1
I	RIL	0.9994725	1.076	0.904	0.744	0.593	0.45	0.178	-0.086	-0.63	-1.25	-1.979	7.11E-13	II	DDX46	0.99942461	0.476	0.684	0.778	0.782	0.717	0.447	0.086	-0.627	-2.27	-2.114	38.1
I	SLU15H	0.9925156	1.266	0.939	0.683	0.488	0.335	0.109	-0.07	-0.63	-1.241	-1.96	7.11E-13	II	UTP53	0.99929845	0.454	0.705	0.818	0.823	0.746	0.432	0.023	-0.724	-2.485	-2.033	38.2
I	NOP56	0.99948637	0.975	0.882	0.771	0.647	0.512	0.222	-0.082	-0.689	-1.287	-1.951	7.11E-13	II	SF3B4	0.99879434	0.484	0.694	0.791	0.796	0.73	0.451	0.072	-0.697	-2.207	-2.031	38.3
I	CD3EAP	0.9933385	0.859	0.806	0.743	0.666	0.575	0.343	0.047	-0.695	-1.458	-1.886	7.11E-13	II	ACOT7	0.99604021	0.412	0.726	0.867	0.875	0.781	0.408	-0.061	-0.828	-2.26	-1.954	38.3
I	DKC1	0.99628987	0.882	0.821	0.736	0.634	0.519	0.266	-0.04	-0.543	-1.17	-2.144	7.11E-13	II	KNCP1	0.99936221	0.41	0.69	0.816	0.824	0.743	0.419	0.014	-0.656	-2.11	-2.149	38.4
I	SCAF4	0.99936634	0.988	0.893	0.775	0.64	0.494	0.18	-0.112	-0.654	-1.192	-2.019	7.11E-13	II	SURF4	0.9931107	0.309	0.708	0.887	0.899	0.79	0.37	-0.119	-0.75	-0.961	-2.132	38.5
I	POLR2A	0.99259624	1.238	0.91	0.663	0.479	0.34	0.144	-0.022	-0.495	-1.255	-2.003	7.11E-13	II	PQB81	0.9953139	0.327	0.702	0.872	0.884	0.784	0.386	-0.085	-0.734	-2.07	-2.13	38.7
I	POLR2B	0.98553	1.388	0.956	0.653	0.436	0.282	0.085	-0.067	-0.534	-1.301	-1.879	7.11E-13	II	UBT1	0.99215086	0.565	0.657	0.704	0.708	0.673	0.5	0.216	-0.564	-1.41	-2.049	38.9
I	DDX21	0.9978904	0.866	0.836	0.768	0.67	0.55	0.267	-0.038	-0.655	-1.228	-2.056	7.11E-13	II	NPL30	0.99272555	0.445	0.66	0.759	0.768	0.707	0.45	0.11	-0.548	-1.14	-2.211	38.9
I	SRP1	0.99730611	0.889	0.91	0.801	0.669	0.519	0.192	-0.146	-0.766	-1.294	-1.875	7.11E-13	II	NHR2	0.99864663	0.369	0.693	0.841	0.854	0.767	0.413	-0.033	-0.702	-1.089	-2.123	39
I	TCOF1	0.98317017	1.238	0.966	0.746	0.564	0.407	0.13	-0.147	-0.806	-1.48	-1.67	7.11E-13	II	DDX17	0.99888288	0.45	0.665	0.766	0.776	0.716	0.457	0.108	-0.584	-1.19	-2.162	39.2
I	NOLC1	0.99944288	1.283	0.995	0.753	0.548	0.37	0.069	-0.202	-0.758	-1.342	-1.714	7.11E-13	II	HNRNP33	0.99143244	0.323	0.654	0.806	0.822	0.739	0.405	0.01	-0.549	-0.903	-2.306	39.3
I	SPOU11	0.99990032	0.918	0.865	0.778	0.665	0.533	0.237	-0.076	-0.671	-1.242	-2.006	7.11E-13	II	PATZ1	0.99642569	0.383	0.71	0.863	0.879	0.792	0.425	-0.043	-0.82	-1.23	-1.959	39.3
I	VRMA	0.99474627	0.782	0.756	0.708	0.64	0.556	0.348	0.099	-0.483	-1.221	-2.175	7.11E-13	II	SRRM1	0.99900227	0.416	0.695	0.827	0.841	0.756	0.443	0.019	-0.744	-1.246	-2.016	39.4
I	SLU16H	0.9891466	1.335	0.934	0.641	0.432	0.285	0.102	-0.034	-0.474	-1.255	-1.964	7.11E-13	II	TCF20	0.9489876	0.183	0.59	0.773	0.793	0.699	0.344	-0.027	-0.342	-0.474	-2.538	39.4
I	PHF3	0.98673369	1.169	0.82	0.587	0.439	0.351	0.259	0.163	-0.373	-1.363	-2.052	7.11E-13	II	SART1	0.99884082	0.357	0.692	0.848	0.866	0.781	0.423	-0.025	-0.736	-1.129	-2.078	39.6
I	PNK1	0.997316	0.988	0.858	0.739	0.625	0.511	0.27	-0.006	-0.685	-1.42	-1.879	7.11E-13	II	PRPF6	0.9995211	0.385	0.676	0.812	0.828	0.753	0.437	0.033	-0.654	-1.126	-2.143	39.6
I	PPP1R10	0.99597572	1.026	0.881	0.74	0.601	0.465	0.2	-0.061	-0.594	-1.215	-2.043	7.11E-13	II	PRM4	0.99989785	0.404	0.668	0.796	0.814	0.75	0.46	0.071	-0.653	-2.019	-2.089	40.3
I	SCAF11	0.99155598	1.288	0.952	0.693	0.492	0.336	0.102	-0.095	-0.589	-1.289	-1.89	7.11E-13	II	PRPF40A	0.99861018	0.384	0.694	0.841	0.859	0.78	0.44	-0.002	-0.762	-1.219	-2.014	39.8
I	FAM208A	0.99578231	0.886	0.804	0.709	0.606	0.497	0.268	0.033	-0.467	-1.123	-2.214	7.11E-13	II	AKAP8L	0.99871705	0.496	0.697	0.814	0.824	0.777	0.419	0.462	-0.157	-1.182	-2.171	39.8
I	SCAF8	0.99854006	0.997	0.912	0.795	0.656	0.501	0.171	-0.153	-0.71	-1.205	-1.963	7.11E-13	II	RBM20	0.99962911	0.428	0.672	0.788	0.803	0.739	0.458	0.08	-0.645	-2.126	-2.107	39.8
I	NCP58	0.99841456	0.887	0.855	0.781	0.674	0.544	0.244	-0.073	-0.662	-1.217	-2.034	7.11E-13	II	SNRP1	0.99718621	0.322	0.717	0.951	0.961	0.901	0.81	-0.06	-0.863	-2.126	-2.124	40.5
I	URB2	0.99732753	0.685	0.677	0.605	0.554	0.481	0.314	0.124	-0.724	-1.361	-1.981	7.11E-13	II	DDX5	0.99917725	0.421	0.661	0.775	0.79	0.729	0.459	0.098	-0.596	-1.214	-2.163	40
I	PRRD2	0.99455883	0.791	0.794	0.757	0.688	0.591	0.337	0.029	-0.647	-1.322	-2.017	8.3	II	GPATCH4	0.99944383	0.443	0.669	0.778	0.793	0.734	0.468	0.1	-0.64	-1.235	-2.092	40
I	URB1	0.99832874	0.857	0.865	0.813	0.713	0.578	0.247	-0.113	-0.754	-1.265	-1.942	9.2	II	RBM42	0.99848663	0.407	0.69	0.825	0.841	0.772	0.454	0.029	-0.754	-1.277	-1.994	40.1
I	CSTF3	0.99625602	0.815	0.823	0.78	0.697	0.584	0.295	-0.032	-0.676	-1.271	-2.016	9.6	II	CXK4	0.99982024	0.454	0.656	0.782	0.803	0.733	0.477	0.139	-0.682	-1.363	-2.102	40.2
I	ZNF579	0.99575734	0.695	0.786	0.684	0.574	0.459	0.179	-0.148	-0.573	-0.931	-2.224	11.3	II	ZCCHC1	0.99771555	0.344	0.661	0.801	0.811	0.832	0.757	0.431	-0.618	-1.049	-2.202	40.2
I	SLU16H	0.99526101	0.822	0.843	0.801	0.712	0.587	0.272	-0.077	-0.717	-1.254	-1.988	12	II	UTP11	0.99946262	0.363	0.67	0.817	0.838	0.765	0.444	0.032	-0.666	-1.13	-2.132	40.3
I	CSTF2	0.9961948	0.801	0.833	0.797	0.711	0.586	0.272	-0.071	-0.679	-1.12	-2.049	14	II	MSN	0.98501699	0.182	0.668	0.896	0.928	0.821	0.377	-0.133	-0.718	-0.824	-2.197	40.3
I	FIP1L1	0.99221419	0.742	0.808	0.793	0.718	0.599	0.287	-0.054	-0.634	-1.135	-2.125	19.3	II	RAB10	0.9923318	0.354	0.707	0.876	0.901	0.816	0.438	-0.054	-0.882	-2.285	-1.873	40.3
I	CSTF1	0.99530975	0.695	0.757	0.757	0.708	0.62	0.366	0.053	-0.602	-1.25	-2.103	22.4	II	SRBP1	0.99939022	0.354	0.673	0.828	0.853	0.78	0.452	0.023	-0.711	-1.174	-2.077	40.3
I	CHERP	0.99126541	0.71	0.81	0.815	0.747	0.627	0.295	-0.074	-0.662	-1.166	-2.072	23.2	II	DUSP11	0.9984914	0.458	0.658	0.756	0.772	0.721	0.481	0.137	-0.604	-1.274	-2.105	40.5
I	DDX50	0.99315444	0.899	0.779	0.783	0.728	0.628	0.341	0.002	-0.653	-1.235	-2.074	23.3	II	SRBP1	0.99939022	0.354	0.673	0.828	0.853	0.78	0.452	0.023	-0.711	-1.174	-2.077	40.3
I	CSTF2	0.99294507	0.693	0.784	0.791	0.732	0.625	0.323	-0.022	-0.639	-1.172	-2.114	23.7	II	HNRNP11	0.99788044	0.376	0.646	0.776	0.798	0.737	0.459	0.093	-0.588	-1.103	-2.214	40.8
I	CHD2	0.99170695	0.657	0.706	0.71	0.678	0.613	0.413	0.145	-0.501	-1.245	-2.177	24.1	II	TCERG1	0.99616758	0.293	0.653	0.825	0.854	0.777	0.435	0.01	-0.632	-1.007	-2.207	40.9
I	WDR33	0.99489234	0.678	0.758	0.763	0.722	0.632	0.365	0.038	-0.622	-1.244	-2.094	24.7	II	SF1	0.99881868	0.439	0.655	0.761	0.779	0.727	0.481	0.131	-0.602	-1.251	-2.119	40.9
I	NOL11	0.98343056	0.72	0.847	0.863	0.793	0.66	0.279	-0.153	-0.867	-1.283	-1.859	24.9	II	SF3B1	0.99505318	0.371	0.649	0.784	0.806	0.744	0.46	0.085	-0.589	-1.116	-2.194	40.9
I	LYAR	0.99413851	0.66	0.734	0.746	0.708	0.629	0.389	0.084	-0.575	-1.246	-2.129	25.6	II	RIF1	0.9962013	0.312	0.687	0.868	0.898	0.816	0.442	-0.039	-0.811	-1.187	-1.986	40.9

BMX	0.9993053	0.31	0.614	0.774	0.819	0.775	0.511	0.133	-0.602	-1.187	-2.146	44.4
ZCCX17	0.99956945	0.264	0.64	0.839	0.894	0.84	0.513	0.048	-0.81	-1.312	-1.915	44.4
RPLD	0.9876235	0.258	0.573	0.737	0.784	0.742	0.496	0.116	-0.436	-0.972	-1.243	44.6
APBCE3B	0.99970653	0.285	0.612	0.785	0.834	0.79	0.515	0.122	-0.626	-1.189	-2.127	44.7
SLC25A3	0.99973052	0.255	0.611	0.797	0.851	0.803	0.511	0.102	-0.642	-1.161	-2.127	44.7
SRRT	0.99807098	0.315	0.616	0.775	0.821	0.779	0.518	0.137	-0.722	-1.225	-2.114	44.7
SUGR2	0.99756222	0.277	0.609	0.785	0.835	0.791	0.514	0.121	-0.619	-1.174	-2.139	44.8
PSPC1	0.9976324	0.27	0.614	0.797	0.851	0.805	0.519	0.109	-0.666	-1.155	-2.084	44.9
PWP1	0.99541906	0.393	0.632	0.762	0.801	0.767	0.533	0.165	-0.678	-1.194	-1.58	44.9
SAFB	0.99978545	0.296	0.612	0.78	0.83	0.788	0.521	0.132	-0.632	-1.22	-2.108	45
SFPC	0.99727431	0.264	0.604	0.785	0.84	0.797	0.521	0.125	-0.627	-1.184	-2.127	45.2
PARP1	0.99720864	0.266	0.603	0.783	0.837	0.796	0.523	0.129	-0.621	-1.185	-2.13	45.3
NAF1	0.99976578	0.314	0.612	0.772	0.821	0.783	0.528	0.148	-0.632	-1.257	-2.089	45.3
SLC16A3	0.99717239	0.264	0.602	0.783	0.839	0.798	0.525	0.13	-0.626	-1.192	-2.124	45.4
DEK	0.9997481	0.311	0.612	0.774	0.825	0.787	0.531	0.147	-0.644	-1.272	-2.072	45.5
TALS	0.99719447	0.293	0.602	0.77	0.825	0.791	0.539	0.157	-0.631	-1.262	-2.084	46.1
SRSF6	0.99692183	0.268	0.597	0.775	0.832	0.794	0.532	0.146	-0.615	-1.206	-2.124	45.9
WDR74	0.99997701	0.291	0.599	0.767	0.823	0.791	0.542	0.163	-0.626	-1.203	-2.087	46.3
RPL29	0.9869192	0.393	0.556	0.655	0.7	0.696	0.568	0.32	-0.398	-1.264	-2.225	51
END1	0.9907395	-0.134	0.769	1.141	1.127	0.852	-0.056	-0.912	-1.143	0.073	-1.717	36.6
SRBD1	0.94734003	0.069	0.675	0.941	0.958	0.804	0.433	-0.234	-0.679	-0.302	-2.306	36.5
CHOCRD1	0.92440022	0.112	0.775	1.076	1.102	0.931	0.261	-0.499	-1.288	-0.985	-1.475	39
NSD2	0.9881745	0.17	0.681	0.931	0.98	0.881	0.422	-0.145	-0.918	-1.02	-1.921	41.7
GAPDH	0.97943686	0.072	0.68	0.978	1.038	0.926	0.402	-0.232	-1.011	-1.004	-1.837	42
MRP43	0.87280553	-0.225	0.67	1.11	1.203	1.045	0.303	-0.573	-1.464	-0.921	-1.147	42.2
CEM45	0.93988085	0.234	0.591	0.825	0.868	0.824	0.513	-0.088	-0.46	-1.149	-1.940	42.8
SRM2	0.99550816	0.216	0.601	0.883	0.933	0.854	0.46	-0.05	-0.832	-1.148	-1.978	42.5
MCMS	0.9951905	0.207	0.65	0.873	0.924	0.849	0.465	-0.032	-0.791	-1.116	-2.028	42.8
EEF1A1	0.97902278	0.152	0.677	0.942	1.003	0.913	0.452	-0.145	-1.033	-1.228	-1.723	42.8
FRG1	0.99828453	0.295	0.674	0.862	0.902	0.851	0.481	0.132	-0.688	-1.151	-1.940	42.8
FAM50A	0.98740403	0.04	0.647	0.95	1.02	0.921	0.429	-0.113	-0.918	-0.967	-1.949	42.9
AP3D1	0.8434249	-0.204	0.669	1.019	1.104	0.993	0.419	-0.307	-1.255	-1.185	-1.434	43.2
RACK1	0.9880308	-0.195	0.66	0.897	0.955	0.879	0.476	-0.06	-0.91	-1.23	-1.861	43.3
TCR	0.99728143	0.201	0.654	0.885	0.943	0.87	0.48	-0.039	-0.87	-1.214	-1.909	43.4
PKM	0.9523538	0.183	0.644	0.883	0.947	0.879	0.493	-0.028	-0.877	-1.233	-1.89	44
LDHA	0.9599708	-0.08	0.634	1.003	1.104	1.007	0.457	-0.253	-1.192	-1.159	-1.522	44.4
RUS7	0.9907122	0.231	0.641	0.857	0.918	0.861	0.513	0.021	-0.888	-1.318	-1.866	44.5
MRP43	0.99808197	0.285	0.64	0.87	0.937	0.877	0.513	0.1	-0.807	-1.324	-1.823	44.7
SNRPA	0.99555338	0.152	0.622	0.868	0.942	0.882	0.511	0.002	-0.833	-1.207	-1.939	44.9
YLP1A1	0.99307108	0.223	0.587	0.777	0.832	0.786	0.505	0.12	-0.546	-1.038	-2.246	44.9
RCC2	0.99736824	0.198	0.615	0.835	0.9	0.846	0.513	0.052	-0.739	-1.183	-2.037	44.9
AP2M1	0.99757263	0.07	0.67	0.897	0.957	0.899	0.492	-0.02	-0.778	-1.049	-2.049	45
NCLF	0.99702321	0.095	0.674	0.869	0.909	0.862	0.514	0.088	-0.46	-1.145	-2.118	45
HSR4B	0.9908515	-0.032	0.599	0.928	1.026	0.951	0.493	-0.103	-0.913	-1.042	-1.909	45.1
SSB	0.99676236	0.148	0.615	0.862	0.936	0.878	0.514	0.014	-0.808	-1.19	-1.969	45.1
TCPI	0.9912274	0.104	0.624	0.898	0.979	0.914	0.51	-0.041	-0.917	-1.227	-1.842	45.1
ABR1A	0.98659973	0.11	0.626	0.888	0.979	0.915	0.513	-0.04	-0.924	-1.251	-1.81	45.1
ZNF512	0.9985483	0.118	0.599	0.852	0.926	0.868	0.508	0.023	-0.732	-1.082	-2.079	45.2
XRCC5	0.99625159	0.225	0.598	0.795	0.854	0.808	0.516	0.106	-0.622	-1.125	-2.155	45.2
ADAR2	0.99678421	0.231	0.607	0.806	0.866	0.82	0.52	0.096	-0.672	-1.182	-2.092	45.2
PRM15B	0.99525256	0.234	0.591	0.825	0.868	0.824	0.526	0.075	-0.76	-1.272	-1.977	45.3
RCSHA	0.99402831	0.156	0.574	0.784	0.859	0.811	0.504	0.04	-0.559	-0.977	-2.256	45.3
PRF4B	0.9965477	0.236	0.605	0.801	0.861	0.816	0.523	0.106	-0.662	-1.187	-2.097	45.3
ESF1	0.99978749	0.052	0.581	0.855	0.943	0.884	0.505	0.007	-0.716	-0.996	-2.119	45.4
MHPHOS1	0.99717081	0.198	0.609	0.828	0.896	0.848	0.526	0.07	-0.742	-1.219	-2.015	45.5
AP1	0.99864772	0.095	0.574	0.862	0.901	0.85	0.508	0.033	-0.83	-0.98	-2.195	45.5
PP1A	0.99154371	0.216	0.626	0.847	0.915	0.865	0.53	0.07	-0.844	-1.333	-1.867	45.5
HEATR1	0.99880018	0.093	0.589	0.852	0.932	0.876	0.514	0.025	-0.73	-1.069	-2.084	45.5
HEATR1	0.99878208	0.113	0.595	0.85	0.928	0.873	0.515	0.03	-0.738	-1.099	-2.066	45.5
SCAMP3	0.99868039	0.163	0.599	0.837	0.91	0.859	0.522	0.055	-0.729	-1.15	-2.055	45.6
SRP14	0.99541788	0.253	0.598	0.783	0.84	0.8	0.526	0.13	-0.62	-1.178	-2.134	45.6
USP42	0.99862179	0.121	0.585	0.831	0.907	0.855	0.517	0.056	-0.677	-1.062	-2.131	45.6
XPCS	0.99691999	0.231	0.594	0.787	0.848	0.806	0.525	0.123	-0.616	-1.149	-2.149	45.6
PNR3	0.99616307	0.118	0.563	0.796	0.871	0.823	0.51	0.09	-0.56	-0.951	-2.261	45.7
BRM45	0.99646993	0.221	0.593	0.792	0.855	0.813	0.527	0.118	-0.629	-1.152	-2.137	45.8
RBFCK2	0.99642932	0.232	0.606	0.807	0.87	0.827	0.533	0.105	-0.7	-1.236	-2.043	45.8
NCF2	0.99993351	0.247	0.603	0.795	0.856	0.816	0.533	0.12	-0.671	-1.23	-2.069	45.8
SLC25A6	0.99646970	0.107	0.619	0.895	0.981	0.924	0.531	-0.027	-0.971	-1.332	-1.728	45.8
HMGAT1	0.98813301	-0.007	0.599	0.922	1.023	0.958	0.52	0.075	-0.864	-1.179	-1.999	45.8
SAF2	0.99649492	0.229	0.594	0.791	0.853	0.812	0.529	0.122	-0.635	-1.173	-2.124	45.8
PWP2	0.99747556	0.015	0.569	0.861	0.952	0.894	0.511	0.006	-0.713	-0.971	-2.125	45.8
PLAA	0.99860708	0.117	0.581	0.828	0.905	0.855	0.519	0.062	-0.669	-1.058	-2.139	45.8
SCL1A5	0.98111003	-0.114	0.515	0.844	0.946	0.883	0.481	-0.015	-0.807	-0.961	-2.312	45.9
HSP90A1	0.98431148	-0.054	0.592	0.936	1.045	0.978	0.521	-0.098	-0.999	-1.164	-1.757	46
NACA	0.99013636	-0.085	0.576	0.927	1.038	0.971	0.516	-0.088	-0.919	-1.05	-1.887	46
ZCCX17	0.99753869	0.174	0.602	0.832	0.905	0.859	0.534	0.073	-0.723	-1.222	-2.001	46
DHX8	0.99930248	0.147	0.564	0.786	0.857	0.816	0.522	0.116	-0.557	-1.099	-2.243	46.2
HMGCB3	0.97652913	-0.225	0.484	0.873	0.993	0.928	0.486	-0.058	-0.263	-0.609	-2.258	46.3
ELAVL1	0.99740966	0.204	0.588	0.796	0.864	0.825	0.537	0.12	-0.65	-1.157	-2.107	46.3
PRKDC	0.99952587	0.174	0.566	0.778	0.848	0.81	0.532	0.136	-0.561	-1.063	-2.219	46.3
PRF1	0.99547296	0.227	0.58	0.772	0.836	0.801	0.538	0.112	-0.586	-1.154	-2.165	46.5
TKT	0.99585732	0.023	0.565	0.855	0.95	0.899	0.53	0.028	-0.727	-1.034	-2.088	46.5
DDX49	0.99888296	-0.012	0.549	0.849	0.946	0.894	0.522	0.027	-0.675	-0.94	-2.161	46.5
ZTR	0.99315058	0.243	0.574	0.754	0.814	0.782	0.536	0.173	-0.537	-1.219	-2.221	46.6
PRF31	0.9989192	0.007	0.547	0.836	0.93	0.881	0.525	0.047	-0.645	-0.942	-2.186	46.6
RPSK	0.9962573	0.148	0.568	0.828	0.906	0.867	0.547	0.083	-0.744	-1.219	-2.006	46.7
UTP15	0.99904617	0.119	0.569	0.813	0.894	0.853	0.539	0.096	-0.656	-1.099	-2.129	46.7
RRP36	0.9989575	0.019	0.579	0.873	0.972	0.922	0.544	0.014	-0.834	-1.169	-1.936	46.8
AQR	0.99871406	0.148	0.573	0.804	0.882	0.844	0.544	0.113	-0.651	-1.138	-2.118	46.9
HNR1M	0.9999645	0.203	0.578	0.783	0.853	0.819	0.547	0.143	-0.623	-1.179	-2.125	46.9
NKAP	0.99558667	0.243	0.59	0.781	0.847	0.815	0.551	0.151	-0.654	-1.256	-2.066	47
ARL6P4</												

GRSF	0.99248353	0.085	0.478	0.713	0.82	0.826	0.631	0.283	-0.476	-1.152	-2.207	53.4
PRG1	0.9954737	-0.064	0.446	0.749	0.885	0.893	0.654	0.247	-0.546	-1.11	-1.253	53.4
RPL24	0.9946468	-0.036	0.457	0.752	0.886	0.896	0.66	0.25	-0.584	-1.183	-2.097	53.6
MRT04	0.9965271	0.008	0.473	0.751	0.879	0.887	0.659	0.252	-0.606	-1.243	-2.06	53.6
MEPCE	0.99655015	-0.045	0.456	0.757	0.895	0.905	0.667	0.247	-0.609	-1.21	-2.063	53.8
FRM26	0.98975618	-0.173	0.403	0.743	0.897	0.91	0.662	0.248	-0.491	-0.978	-2.22	53.9
FR3	0.9817433	-0.194	0.381	0.72	0.873	0.887	0.649	0.221	-0.401	-0.861	-2.315	54
ZRANB2	0.9956209	-0.049	0.457	0.762	0.905	0.919	0.679	0.248	-0.654	-1.273	-1.993	54.2
TRMT2A	0.9955487	-0.101	0.436	0.759	0.909	0.925	0.682	0.251	-0.614	-1.196	-2.051	54.3
RPL22L1	0.9932391	0.101	0.482	0.715	0.826	0.838	0.65	0.296	-0.53	-1.257	-2.119	54.4
RPL11	0.98903945	-0.088	0.398	0.687	0.822	0.839	0.644	0.335	-0.344	-0.912	-2.35	54.9
RPL36A	0.9955929	0.113	0.471	0.693	0.803	0.822	0.658	0.328	-0.485	-1.258	-2.146	55.9
TRMT1L	0.9963951	-0.145	0.398	0.735	0.905	0.942	0.732	0.311	-0.617	-1.281	-1.98	57.1
SILC25AS	0.9883739	-0.04	0.434	0.734	0.887	0.921	0.725	0.313	-0.67	-1.415	-1.888	57.3
RPL7	0.9958108	-0.036	0.401	0.674	0.813	0.847	0.689	0.302	-0.399	-1.177	-2.234	57.9
ELAC2	0.93551825	0.097	0.375	0.549	0.641	0.669	0.596	0.427	-0.025	-0.766	-2.562	60.6
AKAP17A	0.98512049	-0.088	0.371	0.669	0.831	0.883	0.745	0.406	-0.499	-1.249	-2.109	60.8
CHD4	0.93365105	0.108	0.424	0.704	0.869	0.928	0.779	0.353	-0.892	-1.834	-1.349	61.8
ZBTB11	0.97909562	-0.101	0.37	0.683	0.861	0.925	0.788	0.413	-0.606	-1.466	-1.867	62.2
PARP12	0.81687545	-0.716	0.205	0.68	0.829	0.758	0.302	-0.144	-0.006	0.615	-2.495	46.6
ERL1	0.9594367	-0.037	0.336	0.664	1.055	1.006	0.513	-0.093	-0.564	-2.224	-2.226	48.7
PCDD11	0.98765157	-0.333	0.409	0.846	1.029	1.021	0.651	0.095	-0.735	-0.967	-1.995	51.6
IK	0.9869971	-0.357	0.408	0.849	1.037	1.032	0.663	0.097	-0.77	-1.019	-1.94	51.9
SRRP1	0.98979528	-0.55	0.321	0.816	1.027	1.024	0.642	0.092	-0.578	-0.638	-2.159	52
IMR4	0.9881969	-0.319	0.389	0.798	0.973	0.973	0.65	0.157	-0.584	-0.876	-2.159	52
CHD3	0.9915779	-0.4	0.368	0.812	1.002	1.003	0.658	0.137	-0.616	-0.846	-2.118	52.4
REX04	0.9912657	-0.389	0.382	0.827	1.019	1.02	0.666	0.125	-0.684	-0.927	-2.038	52.4
LAS1L	0.9997274	-0.389	0.385	0.822	1.01	1.012	0.665	0.133	-0.672	-0.935	-2.052	52.4
NCL5	0.9898873	-0.449	0.318	0.847	1.046	1.048	0.679	0.113	-0.711	-1.011	-1.916	52.9
POLRMT	0.9842161	-0.263	0.39	0.769	0.934	0.938	0.647	0.196	-0.512	-0.877	-2.227	52.8
ATP5F1A	0.9714754	-0.664	0.322	0.897	1.148	1.155	0.71	0.018	-0.985	-1.032	-1.568	52.8
DDX52	0.9966487	-0.393	0.38	0.831	1.028	1.033	0.662	0.113	-0.725	-0.997	-1.971	52.8
NCL3	0.9836496	-0.464	0.363	0.854	1.066	1.068	0.692	0.122	-0.833	-1.013	-1.235	53.1
DIEXF	0.9804655	-0.412	0.385	0.854	1.063	1.073	0.706	0.111	-0.874	-1.163	-1.744	53.2
RPL15	0.9875576	-0.37	0.386	0.831	1.029	1.039	0.697	0.144	-0.767	-1.089	-1.899	53.2
ZCCCH9	0.99188035	-0.608	0.313	0.851	1.09	1.105	0.713	0.098	-0.794	-0.925	-1.843	53.4
NCL2	0.9876916	-0.454	0.368	0.872	1.096	1.098	0.692	0.122	-0.833	-1.013	-1.234	53.4
PNT1	0.9934037	-0.27	0.256	0.812	1.058	1.075	0.694	0.118	-0.609	-0.65	-2.055	53.6
RPS18BP1	0.9945412	-0.58	0.312	0.835	1.07	1.088	0.717	0.126	-0.749	-0.924	-1.896	53.8
AATF	0.9954545	-0.558	0.315	0.828	1.058	1.076	0.712	0.135	-0.727	-0.909	-1.938	53.8
PAD2A	0.9866123	-0.485	0.363	0.836	1.05	1.067	0.719	0.144	-0.812	-1.121	-1.812	53.8
DNTP2	0.9920564	-0.441	0.338	0.796	1.003	1.019	0.697	0.118	-0.617	-0.901	-2.074	53.9
EMG1	0.99669035	-0.559	0.308	0.815	1.043	1.062	0.709	0.149	-0.67	-0.865	-1.998	53.9
H1ATSF1	0.8014798	-1.439	0.016	0.871	1.256	1.29	0.711	-0.186	-1.26	-0.684	-0.575	54
NDOM1	0.9956773	-0.583	0.303	0.826	1.063	1.085	0.724	0.143	-0.726	-0.92	-1.914	54.1
DNXB2	0.9918674	-0.54	0.318	0.827	1.096	1.098	0.692	0.122	-0.833	-1.013	-1.234	54.2
PN01	0.9899217	-0.318	0.383	0.8	0.991	1.01	0.708	0.198	-0.669	-1.114	-1.96	54.2
LARK17	0.9761098	-0.823	0.239	0.867	1.153	1.181	0.754	0.065	-0.92	-0.94	-1.577	54.3
MYBBP1A	0.9916405	-0.32	0.359	0.775	0.966	0.986	0.698	0.219	-0.585	-0.973	-2.103	54.4
RPL16	0.9915328	-0.443	0.333	0.793	1.004	1.027	0.714	0.197	-0.625	-0.955	-2.034	54.5
EXOC5C9	0.9973432	-0.534	0.306	0.803	1.031	1.056	0.723	0.179	-0.657	-0.908	-1.998	54.5
SNRPD1	0.9602028	-0.404	0.371	0.837	1.056	1.081	0.744	0.153	-0.923	-1.311	-1.603	54.6
NOZCL	0.9950943	-0.421	0.332	0.778	0.986	1.01	0.711	0.214	-0.533	-0.936	-2.082	54.7
YTHDC1	0.9898673	-0.347	0.337	0.743	0.931	0.954	0.688	0.248	-0.472	-0.861	-2.222	54.8
SPAN	0.9910435	-0.297	0.368	0.767	0.905	0.982	0.715	0.247	-0.607	-1.077	-2.053	55.2
FRN	0.9914839	-0.356	0.359	0.786	0.986	1.011	0.722	0.219	-0.657	-1.07	-1.957	54.8
UTP3	0.9963958	-0.536	0.305	0.806	1.039	1.069	0.739	0.185	-0.7	-0.98	-1.928	54.9
RPL8	0.99114027	-0.502	0.271	0.725	1.021	1.057	0.681	0.13	-0.357	-0.335	-2.14	54.9
ESRR2	0.9887736	-0.297	0.362	0.758	0.944	0.97	0.709	0.253	-0.586	-1.02	-2.104	55.2
TFEB3	0.9807403	-0.297	0.368	0.767	0.905	0.982	0.715	0.247	-0.607	-1.077	-2.053	55.2
RPL10A	0.9838644	-0.31	0.378	0.794	0.991	1.018	0.732	0.221	-0.738	-1.213	-1.873	55.2
RPL7A	0.9921545	-0.595	0.276	0.798	1.046	1.085	0.76	0.202	-0.698	-0.977	-1.898	55.6
NRGN	0.9976994	-0.526	0.294	0.786	1.02	1.056	0.75	0.22	-0.654	-0.98	-1.966	55.6
SR1	0.98214839	-0.347	0.343	0.759	0.957	0.989	0.725	0.259	-0.579	-1.033	-2.073	55.7
NAT10	0.9978504	-0.505	0.296	0.777	1.005	1.041	0.744	0.23	-0.619	-0.959	-2.012	55.7
RPL1	0.9965557	-0.483	0.302	0.781	1.009	1.047	0.751	0.232	-0.649	-1.011	-1.97	55.9
NRPM1	0.9980632	-0.361	0.347	0.778	0.987	1.023	0.75	0.25	-0.691	-1.171	-1.911	56.1
RBM33	0.9980286	-0.412	0.323	0.795	1.004	1.027	0.74	0.253	-0.549	-0.984	-2.096	56.1
RPL5	0.99530639	-0.365	0.331	0.753	0.957	0.975	0.721	0.271	-0.573	-1.035	-2.068	56.2
RPL18	0.9986063	-0.27	0.213	0.773	1.04	1.087	0.767	0.22	-0.596	-0.797	-1.987	56.2
EIF4AY	0.9871371	-0.72	0.354	0.732	0.916	0.95	0.721	0.297	-0.519	-1.055	-2.13	56.5
DHX30	0.9952847	-0.443	0.286	0.728	0.938	0.977	0.726	0.285	-0.451	-0.846	-2.198	56.5
SURF6	0.9959303	-0.674	0.224	0.763	1.027	1.077	0.731	0.241	-0.59	-0.851	-1.992	56.6
LDHB	0.9782746	-1.051	0.071	0.741	1.061	1.122	0.771	0.195	-0.496	-0.445	-1.969	56.6
UPI14A	0.9983399	-0.686	0.227	0.78	1.048	1.1	0.787	0.232	-0.665	-0.934	-1.89	56.7
RPL11	0.9956822	-0.554	0.272	0.777	1.025	1.076	0.787	0.254	-0.693	-1.08	-1.864	57
RPL19	0.9861351	-0.259	0.347	0.793	0.903	0.941	0.737	0.317	-0.482	-0.955	-2.147	57.1
SUP3L1	0.9953038	-0.701	0.189	0.726	0.987	1.041	0.761	0.273	-0.45	-0.692	-2.134	57.1
NOZCL	0.99790326	-0.51	0.267	0.739	0.97	1.017	0.758	0.286	-0.52	-0.913	-2.094	57.1
RPL5	0.9939977	-0.764	0.185	0.761	1.043	1.102	0.796	0.289	-0.601	-0.833	-1.937	57.2
RPM1	0.9962316	-0.819	0.159	0.752	1.046	1.11	0.804	0.255	-0.585	-0.792	-1.931	57.5
RBM38	0.98299316	-0.625	0.252	0.793	1.063	1.123	0.82	0.239	-0.486	-1.039	-1.613	57.5
NOP2	0.9956532	-0.443	0.285	0.73	0.951	1	0.761	0.308	-0.518	-0.981	-2.093	57.6
BM51	0.9816781	-1.065	0.069	0.756	1.094	1.169	0.826	0.219	-0.625	-0.664	-1.779	57.6
CTH1F1	0.9810884	-0.993	0.105	0.773	1.105	1.179	0.84	0.222	-0.714	-0.831	-1.655	57.7
EXOC5C4	0.9736703	-0.996	0.107	0.781	1.117	1.194	0.85	0.216	-0.776	-0.907	-1.587	57.8
DNX2	0.9957137	-0.606	0.23	0.744	1.001	1.062	0.799	0.297	-0.584	-0.973	-1.97	58
RPM51	0.9961736	-0.591	0.231	0.735	0.987	1.046	0.789	0.302	-0.541	-0.928	-2.03	58
BRK1	0.9984404	-0.469	0.276	0.735	0.965	1.02	0.779	0.312	-0.557	-1.031	-2.029	58
EXOC10	0.9963699	-0.825	0.15	0.747	1.045	1.116	0.822	0.22	-0.495	-0.84	-1.895	58.1
RCL1	0.9817273	-1.055	0.049	0.72	1.052	1.131	0.818	0.259	-0.497	-0.554	-1.922	58.2
DHX37	0.99553043	-0.699	0.192	0.74								

VI	CASC3	0.96404932	-1.99	-0.825	0.007	0.567	0.907	1.115	0.95	0.344	-0.102	-0.971	88.1
VI	UNK	0.99481169	-2.183	-0.972	-0.128	0.424	0.749	0.94	0.82	0.537	0.485	-0.672	88.4
VI	RPS10	0.95668939	-1.904	-0.787	-0.008	0.502	0.802	0.98	0.868	0.561	0.305	-1.319	88.5
VI	TDRD3	0.99083218	-2.103	-0.921	-0.091	0.456	0.783	0.984	0.867	0.534	0.363	-0.873	89.3
VI	PUM2	0.97633841	-1.991	-0.859	-0.048	0.501	0.841	1.074	0.96	0.474	0.064	-1.017	91.4
VI	AGC3	0.99329651	-2.101	-0.937	-0.108	0.45	0.793	0.926	0.921	0.515	0.241	-0.801	91.6
VI	EDF1	0.99069443	-2.169	-1.02	-0.213	0.322	0.646	0.872	0.817	0.672	0.671	-0.599	94.4
VI	RPL34	0.99635468	-2.151	-1.02	-0.191	0.386	0.758	1.055	0.983	0.506	0.141	-0.467	96.3
VI	EIF4A1	0.98313072	-1.989	-0.903	-0.127	0.398	0.726	0.977	0.929	0.665	0.383	-1.059	96.8
VI	RPL21	0.99174732	-2.066	-0.963	-0.152	0.418	0.789	1.091	1.024	0.513	0.041	-0.695	97
VI	CCDC86	0.98600992	-2.232	-1.11	-0.291	0.278	0.646	0.948	0.906	0.567	0.393	-0.104	98.8
VI	EIF251	0.99866883	-2.108	-1.007	-0.2	0.365	0.733	1.041	0.997	0.583	0.206	-0.611	98.9
VI	OTUD4	0.986443	-1.993	-0.932	-0.145	0.412	0.781	1.097	1.053	0.56	0.023	-0.855	99.3
VI	RPL5	0.95489896	-1.814	-0.842	-0.103	0.438	0.81	1.158	1.133	0.538	-0.234	-1.083	101.8
VI	AGC2	0.99461085	-2.16	-1.078	-0.29	0.258	0.615	0.924	0.923	0.702	0.521	-0.414	103.6
VI	SDAD1	0.96378868	-1.841	-0.873	-0.134	0.409	0.784	1.144	1.137	0.581	-0.168	-1.04	103.6
VI	PUM1	0.98437152	-2.167	-1.091	-0.302	0.253	0.618	0.943	0.945	0.683	0.46	-0.34	104.1
VI	OASL	0.99801119	-2.085	-1.023	-0.243	0.299	0.657	0.973	0.975	0.711	0.412	-0.674	104.1
VI	EIF4G1	0.99100378	-2.138	-1.064	-0.289	0.245	0.589	0.885	0.883	0.753	0.624	-0.598	105
VI	CNBP	0.94624407	-1.743	-0.801	-0.102	0.395	0.729	1.038	1.047	0.708	0.119	-1.391	105.4
VI	EIF3G	0.93292685	-2.227	-1.178	-0.415	0.115	0.46	0.764	0.777	0.657	0.73	0.318	105.9
VI	PRRC2A	0.9890395	-2.17	-1.11	-0.332	0.216	0.579	0.909	0.928	0.718	0.538	-0.275	106.7
VI	CPEB3	0.9684972	-2.21	-1.161	-0.385	0.164	0.532	0.871	0.892	0.67	0.546	-0.081	107
VI	FBMS1	0.98845667	-2.172	-1.117	-0.339	0.212	0.58	0.92	0.942	0.708	0.5	-0.233	107.1
VI	STAU1	0.87150666	-1.607	-0.903	-0.265	0.287	0.738	1.301	1.394	0.42	-0.969	-0.397	111
VI	YTHDF2	0.99354776	-2.113	-1.091	-0.331	0.212	0.581	0.938	0.983	0.767	0.485	-0.43	111
VI	YTHDF3	0.97700796	-2.17	-1.136	-0.375	0.16	0.518	0.855	0.888	0.762	0.649	-0.161	111.3
VI	CPEB2	0.95397708	-2.192	-1.182	-0.427	0.115	0.484	0.844	0.892	0.701	0.577	0.187	111.4
VI	GNL2	0.98140848	-1.895	-0.979	-0.259	0.288	0.685	1.117	1.187	0.715	-0.043	-0.816	111.9
VI	EIF4H	0.98239607	-2.118	-1.1	-0.355	0.169	0.519	0.853	0.91	0.826	0.696	-0.4	115.6
VI	ATXN2	0.95296167	-2.152	-1.193	-0.46	0.083	0.467	0.873	0.959	0.738	0.495	0.19	116.5
VI	ATXN2L	0.96975946	-2.145	-1.166	-0.429	0.11	0.484	0.871	0.952	0.785	0.572	-0.036	117.4
VI	CSDE1	0.95623348	-2.14	-1.179	-0.456	0.07	0.436	0.818	0.912	0.816	0.679	0.044	122.4
VI	PABPC1	0.95072827	-2.12	-1.196	-0.487	0.041	0.419	0.836	0.954	0.822	0.603	0.127	124.3
VI	NUFIP2	0.96121103	-2.135	-1.151	-0.425	0.091	0.441	0.792	0.875	0.844	0.784	-0.116	124.8
VI	LARP4	0.93326252	-2.135	-1.158	-0.498	0.074	0.374	0.761	0.875	0.835	0.716	0.203	130.6
VI	GNL3L	0.83520912	-1.148	-0.749	-0.334	0.073	0.453	1.063	1.395	1.082	-0.259	-1.577	135.5
VI	YBX3	0.99765936	-2.107	-1.211	-0.53	-0.028	0.33	0.725	0.855	0.842	0.792	0.332	137.7
VI	LSM14A	0.99778606	-2.118	-1.202	-0.512	-0.009	0.344	0.725	0.844	0.843	0.818	0.267	138.4
VI	STAU2	0.99140719	-2.094	-1.173	-0.478	0.029	0.387	0.778	0.906	0.901	0.788	-0.043	140.6
VI	RPS26	0.98857679	-2.054	-1.174	-0.498	0.008	0.375	0.8	0.959	0.947	0.741	-0.105	142.9
VI	IGFBP1	0.99033965	-2.034	-1.185	-0.524	-0.02	0.353	0.801	0.982	0.967	0.718	-0.057	143.9
VI	PURB	0.99848025	-2.076	-1.217	-0.555	-0.057	0.306	0.727	0.885	0.884	0.782	0.32	143.9
VI	DDX3X	0.99838292	-2.068	-1.208	-0.545	-0.046	0.319	0.744	0.908	0.913	0.782	0.199	146.2
VI	PRRC2C	0.99762883	-2.084	-1.197	-0.522	-0.021	0.338	0.745	0.893	0.904	0.865	0.138	147.3
VI	PABPC4	0.99716377	-2.074	-1.222	-0.567	-0.076	0.281	0.693	0.847	0.861	0.813	0.444	147.7
VI	YBX1	0.99785058	-2.085	-1.217	-0.554	-0.061	0.293	0.696	0.841	0.858	0.825	0.405	148.5
VI	GBP2	0.99897331	-2.094	-1.234	-0.616	-0.13	0.243	0.72	0.937	0.949	0.746	0.39	148.8
VI	IGFBP3	0.99552883	-1.967	-1.224	-0.619	-0.131	0.251	0.758	1.005	1.021	0.714	0.191	149.8
VI	FAM120A	0.99878551	-1.998	-1.225	-0.61	-0.131	0.235	0.702	0.921	0.98	0.814	0.312	158.5
VI	URP1	0.99699548	-1.967	-1.215	-0.61	-0.132	0.24	0.728	0.97	1.039	0.8	0.147	158.9
VI	IGFBP2	0.99650628	-2.033	-1.194	-0.545	-0.053	0.309	0.745	0.93	0.976	0.818	0.048	159.3
VI	EIF3C1	0.99345484	-2.009	-1.221	-0.603	-0.126	0.232	0.68	0.887	0.97	0.865	0.323	170.8
VI	YTHDC2	0.98196729	-1.867	-1.171	-0.605	-0.147	0.217	0.724	1.013	1.17	0.866	-0.2	171
VI	FXR2	0.99367822	-2.071	-1.176	-0.499	-0.001	0.353	0.751	0.898	0.938	0.839	-0.032	171.1
VI	PURA	0.99454185	-1.905	-1.23	-0.674	-0.222	0.14	0.644	0.925	1.071	0.886	0.365	171.5
VI	HULBP	0.98898884	-1.836	-1.237	-0.724	-0.29	0.071	0.606	0.928	1.107	0.894	0.482	171.5
VI	RPS2	0.9992086	-2.025	-1.221	-0.594	-0.116	0.24	0.676	0.87	0.945	0.866	0.359	172.4
VI	FXR1	0.99660438	-1.943	-1.228	-0.651	-0.191	0.168	0.651	0.905	1.033	0.885	0.37	172.6
VI	FMR1	0.99142892	-1.855	-1.223	-0.695	-0.256	0.103	0.623	0.935	1.133	0.93	0.306	176.8
VI	USP10	0.99573582	-2.015	-1.203	-0.575	-0.099	0.253	0.683	0.881	0.992	0.912	0.171	192.3
VI	EIF3	0.9867554	-2.035	-1.197	-0.464	0.027	0.373	0.761	0.991	0.983	0.871	-0.288	193.3
VI	EIF3A	0.99635246	-2.05	-1.182	-0.524	-0.036	0.314	0.717	0.881	0.965	0.896	0.02	198.2
VI	EIF4G2	0.99130015	-1.927	-1.176	-0.59	-0.138	0.204	0.65	0.895	1.112	1.015	-0.045	200
VI	RPS3	0.99996645	-2.051	-1.209	-0.564	-0.081	0.27	0.683	0.855	0.933	0.892	0.273	200.3
VI	EIF3D	0.99959557	-2.077	-1.203	-0.539	-0.05	0.3	0.697	0.848	0.906	0.879	0.237	206.1
VI	UBAP2	0.99036072	-1.927	-1.224	-0.664	-0.224	0.116	0.568	0.814	1.007	0.996	0.54	209.7
VI	ZC3HAV1	0.9953308	-2.117	-1.179	-0.48	0.024	0.372	0.74	0.853	0.871	0.847	0.069	211.8
VI	UBAP2L	0.99473191	-2.004	-1.225	-0.618	-0.155	0.191	0.618	0.816	0.929	0.922	0.527	212.4
VI	SRRBP1	0.98323827	-1.916	-1.229	-0.678	-0.243	0.095	0.547	0.911	0.968	0.972	0.693	213.4
VI	EIF4E	0.99863677	-2.038	-1.217	-0.585	-0.111	0.236	0.649	0.827	0.924	0.917	0.397	213.8
VI	G3BP1	0.99932885	-1.988	-1.222	-0.625	-0.17	0.171	0.595	0.801	0.948	0.968	0.522	220.8
VI	MOV10	0.91766268	-1.536	-1.167	-0.825	-0.511	-0.223	0.277	0.68	1.192	1.274	0.838	221
VI	YTHDF1	0.98118312	-2.09	-1.124	-0.422	0.089	0.396	0.721	0.819	0.919	0.866	-0.252	222.1
VI	CAPRIN1	0.99557979	-2.063	-1.22	-0.583	-0.107	0.237	0.636	0.797	0.874	0.905	0.514	229.7
VI	LSM14B	0.98383848	-1.929	-1.222	-0.664	-0.231	0.1	0.532	0.762	0.962	1.02	0.672	230.1
VI	ZNFY1	0.97473109	-2.21	-1.118	-0.34	0.185	0.515	0.782	0.78	0.728	0.824	-0.146	233
VI	FAM120C	0.99833869	-2.103	-1.193	-0.517	-0.033	0.301	0.656	0.775	0.868	0.964	0.281	233.5
VI	LARP4B	0.99426666	-2.069	-1.222	-0.575	-0.094	0.252	0.648	0.786	0.844	0.87	0.549	233.7
VI	RPS28	0.98800544	-1.977	-1.22	-0.633	-0.188	0.144	0.555	0.755	0.925	1.005	0.634	235.8
VI	LSG1	0.91636356	-2.217	-1.088	-0.154	0.372	0.663	0.801	0.68	0.602	0.832	-0.591	236.8
VI	SND1	0.993483	-2.138	-1.207	-0.515	-0.018	0.322	0.671	0.763	0.769	0.86	0.492	245.8
VI	PRM1	0.95229574	-1.84	-1.153	-0.644	-0.276	-0.012	0.317	0.527	0.882	1.404	0.695	247.2
VI	LARP1	0.96069278	-2.338	-1.104	-0.262	0.278	0.586	0.747	0.625	0.489	0.813	0.155	253.4

Table 2.2 Clustering analysis of mRNA binding dynamics of RBPs

Seed gene	Mean Euclidean distance to protein interactors	p-value	Seed gene	Mean Euclidean distance to protein interactors	p-value	Seed gene	Mean Euclidean distance to protein interactors	p-value	Seed gene	Mean Euclidean distance to protein interactors	p-value
STAU1	3.514936384	5E-17	LARP1	3.092452397	0.09387	SETD2	1.107947363	0.30923	EXOSC9	0.578753513	0.57393
RC3H1	3.570607772	4.2E-10	DDX21	1.601006949	0.09486	SRSF8	1.068772218	0.31646	SNW1	1.247394847	0.57657
MOV10	4.814208015	3E-09	TOP3B	2.314485577	0.09682	PINX1	1.068653422	0.31767	SRRT	0.661056421	0.57777
PABPC1	3.099038955	1.2E-07	EIF3CL	2.966175169	0.09723	CHTOP	1.048182439	0.32497	RRP12	0.506718378	0.58015
SYNCRIP	2.649187933	3.9E-07	APEX1	2.203834876	0.09846	ISY1	1.095911072	0.32775	SRSF11	0.696557295	0.59319
G3BP1	2.25667873	6E-07	EIF4G2	2.942729847	0.09851	ARL6IP4	1.038269713	0.32988	IK	0.646189627	0.60015
CDC5L	1.668116532	9.6E-07	MSI2	2.886789892	0.10089	NOLB	1.037388399	0.33111	GAPDH	0.623693374	0.60041
YBX1	4.571605013	8.3E-06	WDR43	2.707007892	0.10186	TRA2A	2.205720609	0.33315	PIPG	0.829436104	0.60293
EIF3H	4.926631762	7.1E-05	RPF2	1.911400538	0.10358	SMARCA5	0.89592401	0.33458	RBMX2	0.464307453	0.6039
TDRD3	2.580645656	0.00017	USP10	1.320298686	0.10401	NKRF	2.186889005	0.33561	SRSF10	0.871557065	0.607
IGF2BP3	4.183604071	0.00022	YTHDC2	2.77297194	0.10454	ZCCHC8	1.445389592	0.33601	ACIN1	0.752083209	0.61288
EIF4A3	1.805746514	0.00031	EIF3D	2.06807543	0.10484	ZKRN82	1.01610221	0.33606	CPSF4	0.500957342	0.63228
DDX3X	2.864823708	0.00078	NOP53	1.73596523	0.10592	MEPCE	0.938156676	0.33648	SRRM2	0.858016306	0.63876
ZC3HAV1	2.740612715	0.0014	ATXN2	1.866233507	0.1064	YTHDC1	1.0112864	0.33979	PHF3	0.433227004	0.6388
UPF1	2.667313093	0.00165	DDX27	1.595337351	0.10873	EEF1A1	1.166262111	0.34453	AGO3	0.542754064	0.6431
AGO2	2.76530979	0.00323	SSRP1	1.30491813	0.10924	ZC3H13	0.991089751	0.34478	NKAP	0.511726884	0.66964
NFX1	3.472777146	0.00331	MAP4	2.689837347	0.10955	RBM47	0.986780009	0.34604	HNRNPJ	1.271265553	0.69321
IGF2BP2	3.38234806	0.00504	ZNFK1	2.604718263	0.11473	RBM33	0.978822379	0.34981	ADARB1	0.390409967	0.69673
FAM120A	3.867572707	0.00736	POLDIP3	1.853812975	0.11575	SURF6	0.962460824	0.35612	STRBP	0.390409967	0.69673
ALYREF	2.686071455	0.00777	EIF3A	1.827277643	0.11751	USP36	0.959774	0.35739	NCOA5	0.386028079	0.70382
EIF3G	2.765964815	0.00806	RACK1	3.798786925	0.11907	SMARCA4	0.888030916	0.36332	DHX15	0.596651302	0.71949
LSM14A	3.859641045	0.00993	DHX30	1.771116672	0.12003	DROSHA	0.94401025	0.36375	CHERP	0.537019606	0.72712
EIF4B	2.843241499	0.01019	NOL9	2.436533216	0.12283	TPR	0.845635215	0.365	SUPT5H	0.892681262	0.73254
LARP4B	5.951179865	0.01078	TEX10	2.436533216	0.12283	ATXN2L	1.461436056	0.36591	NOP2	0.620324142	0.73362
PABPC4	3.647435152	0.01176	HSPA5	1.21975002	0.1251	XRN2	1.971744912	0.3679	TOP2A	0.803829171	0.73372
PRRC2A	3.03863048	0.01208	SCAF8	2.390694083	0.12633	CHORDC1	0.842305371	0.36862	PRPF3	0.612804654	0.73497
PNN	1.609045357	0.01445	UBAP2L	1.810216474	0.13424	SPATCH8	0.933614759	0.37015	ESF1	0.356999338	0.73696
EIF4A1	2.29948521	0.01472	FYTD1	2.245316565	0.13572	PNO1	0.907763753	0.38047	RBM39	0.88779892	0.73718
RBM34	3.068570891	0.01478	NPM1	1.302022095	0.13899	NXF1	0.895984528	0.38073	SUGP1	0.404356951	0.74156
RBMA8	2.165362641	0.01507	NUFIP2	1.585532943	0.14062	DCAF13	2.108021674	0.38875	UZSURP	0.339707277	0.7501
DDX1	2.491991432	0.01864	PUM3	1.80639242	0.14079	HMG81	0.904620366	0.38875	CSTF2	1.135342765	0.75819
RNP51	1.21840251	0.0191	DIMT1	2.486259303	0.14194	SARNP	0.870893323	0.39479	WBP11	0.425054183	0.75912
FXR1	2.272034676	0.0205	GTPBP4	1.483747494	0.14325	ZC3H11A	0.870893323	0.39479	PABPN1	0.327528494	0.76183
TRIM56	4.082956083	0.021	EIF3L	1.820493274	0.14331	HP1BP3	0.803034606	0.39521	GTI2	0.327281993	0.76393
SND1	4.896067529	0.02156	DDX398	1.417595783	0.14414	LUC7L2	1.578849713	0.40254	PCBP2	1.822085707	0.76666
FTSJ3	2.150053372	0.02282	SRSF5	2.104416004	0.14793	CDK11B	0.819904857	0.4119	RBM3	2.466878109	0.76786
FUBP3	2.9202038782	0.02422	SLIRP	2.094455977	0.1503	PRPF48	1.577044155	0.42062	PRPF31	0.536501171	0.76892
EIF4G1	2.321955574	0.02519	LARP7	1.292984667	0.15794	SUPT16H	0.874125952	0.42097	DDX18	0.425419424	0.76948
UPF3B	1.941961505	0.02713	ZCCHC17	1.962117968	0.16588	BAZZA	0.794842402	0.42384	THRAP3	0.751978243	0.77021
PXR2	1.690211087	0.02929	AP3D1	1.936327479	0.16529	SNRPA	0.767517599	0.42462	SRSF4	0.320353116	0.77222
CASC3	2.461838822	0.02958	RBM28	1.814995248	0.17008	FAM98B	0.789965385	0.42918	WDR33	0.482842143	0.77441
WRMA	1.612137369	0.03013	RBM15	1.585165316	0.1746	LUC7L	0.824214014	0.43647	MBNL1	0.313926259	0.77733
RBMS1	3.183959018	0.03058	SNIP1	1.129520845	0.17575	CLTC	0.765863525	0.43854	AATF	0.50720221	0.78455
PUM1	3.176821126	0.03075	MKRN2	1.822026798	0.1789	ZNF106	0.758189596	0.44122	DDX42	0.29727783	0.79028
LARP4	3.568905553	0.03125	PARP12	1.822026798	0.1789	RAMAC	0.75128889	0.44659	HNRNP3H	0.508195099	0.79075
YTHDF2	3.13967693	0.03125	AQR	1.814987273	0.17979	RNMT	0.75128889	0.44659	RBMS	0.477326506	0.79563
NCPB3	2.99349739	0.03424	PRRC2C	1.801018942	0.18248	TUBB	0.736160684	0.45197	SRSF7	0.547935498	0.79829
YTHDF3	2.693486365	0.04051	LDHA	1.797975521	0.18338	RPRD2	0.726596075	0.45871	XPOS	0.376351201	0.8174
MTRX	2.793425759	0.04308	LDHB	1.797975521	0.18338	RBM7	0.820805814	0.46778	DDX24	0.273235057	0.81752
CHD3	1.525909136	0.04314	PRRC2B	1.796064882	0.18428	HSPA8	1.124302209	0.47181	PARP1	0.562045401	0.81984
CSD2	2.516511005	0.04743	UNK	1.796064882	0.18428	PTBP3	0.695159219	0.47493	NIFK	0.665930299	0.82205
FMR1	2.256762362	0.04841	YBX3	1.752982118	0.19069	HMGAI	0.685915363	0.47763	PQB1	0.269137247	0.82375
CHD4	1.360576088	0.04854	BCLAF1	3.33225379	0.20524	RBM15B	0.683492881	0.4817	KHSRP	0.463922623	0.82389
YTHDF1	2.135125606	0.05159	RTF1	1.637479679	0.20777	MFPA1	0.662814402	0.48983	HNRNPUL1	0.448891151	0.83373
STAU2	2.423407131	0.05187	PA2G4	2.376691053	0.21857	HSP90AA1	1.067087477	0.49014	UBAP2	0.465412726	0.84629
PRM1	5.399110504	0.05411	SAP1B	1.286052711	0.22245	RBM6	0.63042647	0.50475	SRRM1	0.686966268	0.86448
IGF2BP1	2.189016861	0.05442	DDX47	1.533719343	0.22675	BAZ1B	0.626729363	0.50746	AKAP8	0.219487486	0.87297
EIF4H	5.186179758	0.05755	SCAF4	1.527185316	0.2288	ILF2	1.740848989	0.51003	ADAR	0.219120732	0.87367
SNRPD1	1.392042097	0.06017	ELOA	1.504264523	0.24134	PHF10	0.589908618	0.52101	HSP90AB1	0.431722817	0.87697
OTUD4	2.211018098	0.0614	POLR2A	1.386629554	0.24194	DHX8	0.770959394	0.52358	YLFM1	0.214824176	0.87717
NCL	1.439160666	0.0625	RTC8	1.194681123	0.2454	APIS	0.582656924	0.52507	SFA1	0.546389459	0.87887
NOL11	4.826023079	0.06283	CAPRIN1	1.262149697	0.25311	RBM12	0.580235673	0.52778	RBM10	0.212079155	0.88059
GNL2	4.815482738	0.06325	EXOSC10	1.217937382	0.25584	PTCD3	0.573555913	0.52913	SMND1	0.210850084	0.88261
LYAR	1.815482738	0.06325	ELAC2	1.407706646	0.25862	DAZAP1	0.640799704	0.52924	CSTF1	0.440911153	0.88741
SRPK1	4.150486903	0.06888	SCAF11	1.406765665	0.25972	PPLHL1	0.605938658	0.53402	ILF3	1.056253094	0.89079
RRP8	4.24947421	0.07074	GEMIN5	1.403987405	0.26082	BRIX1	1.267944515	0.54101	PCBP4	0.203161623	0.89109
PWP1	4.190485099	0.0726	MAGOH	1.115913676	0.26317	AKAPBL	0.561770277	0.54129	HNRNPIL	0.289152497	0.89158
UTP15	4.102663372	0.07546	CHD1	1.397661214	0.26526	ZC3H18	1.015129272	0.54874	CELF1	1.357129245	0.89588
EIF251	4.075495337	0.07643	TCP1	1.082414807	0.27027	NSUN2	0.537667495	0.55207	SNRNP70	0.677524663	0.8961
EIF253	4.075495337	0.07643	LUC7L3	1.11341146	0.28475	EXOSC4	0.590996632	0.55309	DHX9	0.708298018	0.90929
DHX36	3.900759525	0.08143	SSB	1.059519141	0.28639	GRWD1	0.56244969	0.55499	NGDN	0.16825777	0.9117
SERBP1	3.579440328	0.0896	CRNL1	1.229624097	0.29266	MCM5	0.746111452	0.55635	SRSF2	0.51553168	0.91254
G3BP2	1.222965774	0.09166	GNL3	1.198690028	0.29735	RAN	0.53125838	0.56012	CCAR1	0.153581553	0.91754
HTATSF1	3.124179642	0.0933	CLK3	0.887027857	0.30519	RPA1	0.865115401	0.5667	RBM14	0.257418549	0.91902

PRPF6	0.50412963	0.92045
SF3A2	0.608031844	0.92295
RAVER1	0.135499182	0.92454
EFTUD2	0.584631622	0.92588
CSTF3	0.378002757	0.92618
PSPC1	0.250149171	0.92767
FUBP1	0.418184548	0.92787
SRSF6	0.453248829	0.92874
DDX46	0.242909065	0.92996
TAF15	0.352723674	0.93075
SAFB2	0.242125095	0.93092
PTBP2	0.11597408	0.93331
TOP1	0.497167251	0.93437
NUDT21	0.285190036	0.93813
PCBP1	1.160627775	0.94171
TCERG1	0.481044858	0.94407
PRPF40A	0.511651547	0.94483
FIP1L1	0.330014232	0.94493
SRSF1	0.675797376	0.94589
TOP2B	0.084812686	0.94664
DDX5	0.929944691	0.94799
HNRNPC	0.795398226	0.94816
PHF5A	0.337157769	0.94898
SF3B6	0.505876188	0.94935
NCBP2	0.208096665	0.94939
HNRNPR	0.67870596	0.95586
POLR2B	0.204600852	0.95603
MATR3	0.963943455	0.95862
SF3B3	0.462652214	0.95898
PUF60	0.4834033	0.9591
SAFB	0.377408637	0.96068
TARDBP	0.814348659	0.96202
KHDRBS1	0.285139423	0.96553
ZFR	0.17596801	0.96858
RBM25	0.232554976	0.96908
SF3B2	0.474878748	0.97079
DDX23	0.297048068	0.97114
XRCC6	0.570083431	0.97162
SRSF9	0.50368231	0.97172
SART1	0.329033517	0.97436
SF3A3	0.2882199	0.97445
RBMX	0.565716565	0.97615
SF1	0.296316992	0.97638
SUPT6H	0.146991711	0.97671
RBFOX2	0.214872709	0.97793
HNRNPM	0.319181125	0.97858
CPSF7	0.29271725	0.97899
ZNF326	0.124942302	0.98052
SF3B4	0.342838589	0.98383
CPSF6	0.18571139	0.98462
CSTF2T	0.23235951	0.98465
TRA2B	0.582997878	0.98729
SRSF3	0.4580724	0.98762
SF3B1	0.437802929	0.98766
HNRNPH2	0.264697581	0.99013
SNRNP200	0.457151704	0.99235
EMSR1	0.62701859	0.99434
HNRNPAB	0.111087051	0.99563
RALY	0.233788581	0.99594
SFPQ	0.398811072	0.99689
FUS	0.78408873	0.99743
QKI	0.184016756	0.99766
PTBP1	0.847172762	0.99806
HNRNPDL	0.220319836	0.99851
DDX17	0.224824254	0.99932
HNRNPA3	0.262728168	0.99948
HNRNPL	0.673796126	0.9995
NONO	0.208977205	0.99955
ELAVL1	0.998787522	0.99958
HNRNPF	0.202524499	0.99982
HNRNPK	0.603109362	0.99988
HNRNPA2B1	0.628277453	0.99991
HNRNPA0	0.164643759	0.99991
HNRNPD	0.852686553	0.99998
U2AF2	0.517041145	1
HNRNPH1	0.445753745	1
HNRNPA1	0.564881052	1

Table 2.3 Mean Euclidean distance to protein interactors

Name of GO term	Contribution to										Name of GO term	Contribution to									
	0 min	15 min	30 min	45 min	60 min	90 min	120 min	180 min	240 min	300 min		0 min	15 min	30 min	45 min	60 min	90 min	120 min	180 min	240 min	300 min
transcription elongation factor complex	16.54	8.058	2.196	-1.575	-3.733	-4.865	-3.969	-2.923	-3.747	-3.086	histone binding	5.186	2.01	-0.044	-1.219	-1.737	-1.551	-0.729	-0.11	-1.565	-0.251
nucleoside diphosphate kinase activity	12.88	6.222	1.642	-1.272	-2.895	-3.556	-2.538	-1.136	-1.779	-5.567	cellular response to growth factor stimulus	5.107	3.714	2.547	1.559	0.71	-0.702	-1.884	-3.844	-4.727	-2.481
mRNA cleavage and polyadenylation specificity factor complex	12.62	6.859	2.678	-0.214	-2.084	-3.689	-3.722	-3.235	-4.565	-4.633	protein localization to chromosome	5.128	2.604	0.951	-0.028	-0.506	-0.557	-0.194	-0.559	-3.025	-3.814
kinetochore	12.56	6.382	2.054	-0.796	-2.5	-3.609	-3.2	-2.629	-4.601	-3.657	cellular homeostasis	5.107	3.714	2.547	1.559	0.71	-0.702	-1.884	-3.844	-4.727	-2.481
transporter activity	12.04	7.142	3.017	0.914	0.891	-2.884	-3.746	-5.109	-4.651	-4.133	histone H1-nucleosome	5.086	3.605	2.019	1.025	0.249	-0.834	-1.604	-3.074	-4.043	-2.601
mRNA cleavage factor complex	12.01	6.664	2.766	0.043	-1.748	-3.385	-3.588	-3.446	-4.773	-4.541	intracellular organelle lumen	5.05	4.303	3.469	2.585	1.683	-0.074	-1.636	-3.863	-5.071	-6.448
nucleoside binding	11.61	6.805	3.282	0.785	-0.918	-2.734	-3.479	-4.82	-6.691	-6.845	leukocyte mediated immunity	4.988	2.999	1.427	0.308	-0.476	-1.313	-1.557	-1.592	-2.078	-2.666
pre-mRNA cleavage required for polyadenylation	10.22	5.624	2.178	-0.009	-1.564	-3.086	-2.937	-2.544	-2.708	-4.421	nitrate activity	4.951	3.797	2.505	1.688	0.755	-0.833	-2.038	-3.212	-3.623	-4.1
viral RNA genome replication	9.86	5.421	2.226	0.122	-1.147	-2.025	-1.948	-2.325	-4.963	-5.322	cellular chemical homeostasis	4.949	3.479	2.259	1.417	-0.912	-1.543	-3.053	-4.08	-4.931	
transferase complex, transferring phosphorus-containing groups	9.877	2.651	1.856	-4.264	-1.308	-3.908	-1.287	1.253	-1.227	3.86	N-methyltransferase activity	4.927	3.138	1.781	0.777	0.049	0.836	-1.305	-2.081	-3.149	-3.301
transcription by RNA polymerase I	9.5	4.799	1.601	-0.297	-1.36	-1.893	-1.679	-2.773	-3.865	-2.084	enzyme regulator activity	4.909	2.576	0.893	0.273	-1.037	-1.757	-1.919	-2.045	-2.117	-0.771
RNA polymerase II complex binding	9.385	6.659	2.836	0.753	0.739	-2.46	-3.192	-3.898	-4.748	-3.597	membrane protein complex	4.878	3.724	2.606	1.535	0.52	-1.306	-2.786	-4.48	-3.666	-0.714
mRNA 3' end processing	9.311	5.143	2.128	0.046	1.301	-2.476	-2.568	-2.574	-3.841	-3.929	U1 snRNP	4.866	3.715	2.226	1.34	0.643	-0.412	-1.395	-2.233	-4.739	-2.763
mRNA polyadenylation	9.24	4.668	1.437	0.171	-2.011	-2.874	-2.531	-1.762	-2.844	-2.613	positive regulation of mRNA processing	4.866	3.139	1.829	0.853	0.137	-0.768	-1.31	-2.296	-3.474	-3.636
regulation of RNA export from nucleus	8.998	4.728	1.723	-0.262	-1.455	-2.253	-2	-1.728	-3.55	-4.198	cis-regulatory region sequence-specific DNA binding	4.825	3.456	2.358	1.473	0.749	-0.382	-1.305	-2.055	-4.449	-3.671
actin cytoskeleton	8.871	6.203	4.086	2.406	1.067	-0.928	-2.441	-5.187	-7.513	-6.563	molecular function regulator	4.81	2.84	0.533	-0.626	-1.279	-1.725	-1.615	-1.559	-1.915	-1.073
cytoskeleton, centrosomal region	8.822	4.795	1.944	0.033	-1.151	-2.07	-2.847	-2.227	-4.094	-3.984	biological process	4.791	2.744	1.287	0.295	-0.332	-0.897	-1.034	-1.527	-2.785	-2.546
mRNA cleavage	8.692	3.669	0.253	-1.876	-3.004	-3.261	-2.205	-0.432	-1.304	-0.532	endoplasmic reticulum membrane	4.773	4.32	3.429	2.261	0.957	-1.594	-3.512	-4.278	-2.333	-4.04
transferase activity, transferring phosphorus-containing groups	8.544	4.938	2.271	0.396	0.857	-0.055	2.283	-2.391	-3.743	4.809	negative regulation of immune response	4.704	3.876	3.059	2.257	1.476	0.007	-1.356	-3.553	-4.966	5.601
cytoplasmic vesicle membrane	8.41	5.843	3.694	1.901	0.409	-1.867	-3.457	-5.337	-8.824	-3.752	regulation of mRNA 3' end processing	4.686	2.52	0.999	0.006	-0.611	-1.027	-0.93	-0.926	-2.065	-3.639
ribilic acid	8.346	4.648	1.998	0.179	-0.999	-2.087	-2.354	-2.976	-4.386	-2.37	response to radiation	4.678	3.029	1.762	0.804	0.092	-0.82	-1.348	-2.174	-3.033	-2.594
regulation of circadian rhythm	8.16	5.524	3.406	1.73	0.419	-1.366	-2.417	-3.675	-5.069	-4.71	DNA-templated transcription, initiation	4.656	3	2.221	1.359	0.659	-0.48	-1.317	-2.021	-4.304	-3.124
transcription elongation from RNA polymerase II promoter	8.123	4.472	1.843	0.032	-1.142	-2.203	-2.385	-2.657	-3.773	-2.311	precatalytic spliceosome	4.652	3.132	1.893	0.886	0.073	-1.118	-1.913	-2.861	-3.085	-1.659
positive regulation of RNA splicing	8.043	4.143	1.477	-0.22	-1.184	-1.723	-1.481	-1.816	-4.092	-3.147	exonuclease activity, active with either ribo- or deoxyribonucleic acid and producing 5'-phosphonucleotides	4.65	4.04	4.231	3.37	2.248	0.351	-2.848	-4.821	-5.555	-4.63
mRNA csa splicing via spliceosome	7.84	4.603	2.261	0.633	0.446	-1.515	-1.879	-2.749	-4.586	-4.163	protein methylation	4.638	2.407	0.846	-0.222	-0.882	-1.35	-1.995	-2.747	-1.348	-2.166
ion transmembrane transport	7.729	4.939	2.734	0.993	-0.336	-2.076	-2.997	-3.736	-4.006	-3.255	T cell activation	4.626	4.057	3.253	2.302	1.276	1.75	-2.437	-4.06	-3.779	-4.477
positive regulation of transcription by RNA polymerase I	7.432	4.468	2.332	0.844	-0.155	-2.127	-1.783	-3.255	-2.555	-3.399	histone modification	4.6	2.136	0.484	-0.997	-1.037	-0.642	-0.628	-2.028	-2.128	-1.332
U2-type small spliceosome	7.388	2.733	1.218	-0.405	-1.343	-2.877	-1.576	-1.665	-2.014	-2.088	lymphocyte differentiation	4.597	3.687	2.355	1.82	0.944	0.096	-2.035	-3.557	-3.766	-3.801
pre-mRNA binding	7.357	4.363	2.206	0.714	-0.27	-1.241	-1.591	-2.55	-4.548	-4.44	intracellular organelle	4.566	3.145	2.035	1.172	0.497	-0.479	-1.206	-2.991	-3.844	-2.395
lysosome	7.279	5.799	4.207	2.577	0.776	-1.193	-4.172	-6.069	-6.006	-3.661	metal ion binding	4.555	2.988	1.743	0.775	0.041	-0.882	-1.31	-1.651	-2.295	-3.979
mRNA splice site selection	7.263	4.107	1.855	0.35	-0.702	-1.643	-1.887	-2.48	-3.913	-2.884	organelle subcompartment	4.548	3.558	2.501	1.436	0.472	-1.356	-2.577	-3.159	-2.279	-3.883
integral component of membrane	7.225	4.759	2.897	1.407	0.311	-1.154	-2.093	-3.691	-5.274	-4.409	cellular metabolic process	4.538	3.078	1.873	0.899	0.096	-1.038	-1.609	-2.201	-2.587	-2.808
ion transport	7.183	4.644	2.593	0.96	-0.318	-2.041	-2.976	-3.617	-3.602	-2.825	protein complex oligomerization	4.537	2.807	1.442	0.932	-0.391	-1.256	-1.675	-1.614	-1.675	-2.407
monocarboxylic acid metabolic process	7.173	6.224	4.782	3.038	1.151	-2.489	-5.294	-6.798	-4.059	-3.736	activation of immune response	4.536	3.51	2.558	1.679	0.874	-0.523	-1.646	-3.145	-3.834	-4.009
catalytic activity, acting on a RNA	7.158	4.742	2.902	1.512	0.462	-0.987	-2.036	-4.35	-5.91	-3.707	DNA splicing	4.528	3.196	2.088	1.17	0.413	0.725	-1.51	-2.531	-3.218	-3.412
negative regulation of cell population proliferation	7.085	5.483	3.981	2.578	1.278	-1.012	-2.882	-5.336	-6.068	-5.107	negative regulation of protein modification process	4.528	2.382	0.901	-0.056	-0.612	-0.952	-0.832	-0.951	-2.197	-2.209
RNA binding	7.034	5.323	3.839	2.534	1.371	-0.656	-2.477	-5.403	-6.526	-4.689	ribose phosphate metabolic process	4.528	4.159	3.329	2.192	0.89	-1.75	-3.852	-4.995	-2.648	-1.832
animal organ morphogenesis	7.01	5.242	3.623	2.622	0.86	-0.264	-2.714	-4.274	-4.716	-5.869	nuclear chromosome segregation	4.528	2.962	1.807	0.88	0.188	-0.765	-1.369	-2.298	-3.122	-2.823
chromatin DNA binding	6.959	5.317	3.867	2.571	1.393	-0.711	-2.587	-5.71	-7.055	-4.044	nuclear lumen	4.499	3.748	2.979	2.207	1.444	-0.01	-1.312	-3.333	-4.613	-3.632
positive regulation of chromosome organization	6.831	4.531	2.718	1.309	0.322	-1.195	-2.016	-3.077	-4.269	-3.063	secretory granule	4.497	3.433	2.475	1.608	0.817	-0.811	-1.777	-3.588	-4.235	-2.648
cell cycle G2/M phase transition	6.809	4.501	3.207	1.057	0.793	-1.147	-0.99	-1.86	-3.58	-2.425	cellular response to insulin stimulus	4.428	3.237	0.854	0.146	-0.776	-1.309	-1.379	-1.581	-2.127	-2.3
RNA polymerase binding	6.793	3.295	0.881	-0.67	-1.554	-2.006	-1.618	-1.153	-2.313	-1.653	kinase binding	4.429	2.923	1.71	0.748	-1.103	-0.998	-1.528	-1.949	-2.331	-3.004
mRNA processing	6.778	4.539	2.758	1.359	0.27	-1.225	-1.428	-3.375	-4.442	-4.514	3'-5' exonuclease activity	4.416	4.635	4.207	3.318	2.134	0.517	-3.014	-2.666	-3.555	-5.006
positive regulation of mRNA splicing via spliceosome	6.73	3.937	1.925	0.532	-0.384	-1.275	-1.569	-2.327	-3.966	-3.603	intracellular protein transport	4.399	3.52	2.55	1.547	0.558	-1.217	-2.538	-3.452	-2.689	-2.678
nucleoside-containing small molecule metabolic process	6.729	5.251	3.67	2.066	0.509	-2.24	-4.234	-5.435	-5.732	-2.565	response to growth factor	4.391	3.271	2.203	1.231	0.347	-1.02	-1.843	-2.121	-1.985	-4.488
negative regulation of transferase activity	6.72	5.14	3.533	1.961	0.476	-2.072	-3.872	-4.969	-3.705	-3.211	chromosome, telomeric region	4.391	1.639	-0.167	-1.231	-1.738	-1.705	-1.103	-0.534	-1.159	-1.603
protein-containing complex disassembly	6.665	2.242	0.74	-2.568	-1.466	-4.426	-3.12	0.483	0.811	2.163	chromatin remodeling	4.385	2.89	1.653	0.846	0.246	-1.407	-2.063	-2.101	-1.725	-2.01
regulation of nucleocytoplasmic transport	6.657	3.714	1.61	0.176	-0.739	-1.535	-1.165	-1.983	-3.323	-3.928	response to lipopolysaccharide	4.362	2.015	0.486	-0.41	-0.836	-0.838	-0.439	-0.548	-2.237	-1.554
nucleoside organization	6.613	4.015	2.075	0.666	-0.326	-1.445	-1.939	-2.671	-3.758	-3.229	positive regulation of innate immune response	4.35	2.748	1.494	0.53	-0.19					

U2-type precatytic spliceosome	5.271	3.487	2.075	0.967	0.11	-1.116	-1.915	-3.038	-3.839	-2.192
ubiquitin protein ligase binding	5.245	3.897	2.672	1.591	0.634	-0.943	-1.234	-2.518	-3.91	-3.535
T cell differentiation	5.208	4.361	3.394	2.358	1.302	-0.716	-2.412	-4.346	-4.51	-4.619
nucleic acid metabolic process	5.2	3.354	1.926	0.841	0.029	-1.074	-1.607	-2.444	-3.286	-3.007
embryonic morphogenesis	5.198	2.436	1.596	0.518	1.062	-1.164	-0.663	-0.386	-2.042	-2.374
organophosphate metabolic process	5.195	4.483	3.423	2.15	0.782	-1.853	-3.873	-4.959	-2.916	-2.431
unfolded protein binding	3.712	4.052	3.782	3.062	2.034	-0.454	-2.866	-5.516	-4.641	-3.164
response to lipid	3.709	2.141	1.045	0.32	-0.126	-0.49	-0.566	-1.074	-2.396	-2.562
regulation of leukocyte mediated immunity	3.69	1.572	0.782	0.009	-0.486	-0.743	-0.676	-0.83	-1.87	-1.889
transferase complex	3.664	0.803	-0.876	-1.652	-1.78	-0.942	0.252	0.794	-1.31	1.199
regulation of cellular localization	3.644	2.316	1.3	0.536	-0.026	-0.73	-1.115	-1.675	-2.271	-1.979
supramolecular fiber organization	3.628	3.807	3.429	2.658	1.638	-0.663	-2.697	-4.378	-3.278	-4.144
cellular response to basic stimulus	3.621	1.296	0.218	-1.069	1.425	-1.201	-0.461	0.363	-0.951	-0.728
lysosomal vesicle	3.604	2.589	1.692	0.9	0.204	-0.54	-1.794	-2.736	-2.581	-0.933
Golgi vesicle transport	3.6	2.66	1.858	1.168	0.57	-0.43	-1.256	-2.579	-2.362	-2.249
organonitrogen compound catabolic process	3.565	2.895	2.005	1.207	1.603	-0.621	-1.586	-2.678	-2.923	-2.623
lysophosphine activation	3.59	1.165	1.07	0.25	-0.349	-1.06	-1.37	-1.578	-1.688	-1.03
regulation of intrate activity	3.583	2.78	1.96	1.15	0.373	-1	-2.039	-2.909	-2.386	-1.512
negative regulation of transcription by RNA polymerase II	3.579	1.372	0.859	0.43	0.076	-0.445	-0.772	-1.067	-1.163	-1.268
positive regulation of DNA metabolic process	3.507	2.342	1.418	0.692	0.127	-0.654	-1.146	-1.82	-2.346	-2.118
positive regulation of intracellular transport	3.505	2.702	1.93	1.203	0.534	-0.59	-1.402	-2.157	-2.352	-3.373
protein import	3.504	3.083	2.294	1.467	0.999	-0.908	-2.153	-2.566	-1.616	-3.324
protein heterodimerization activity	3.498	0.255	-2.402	-3.214	3.304	-1.765	0.42	2.487	0.888	0.839
monocuclear cell differentiation	3.487	2.902	2.266	1.601	0.928	-0.368	-1.503	-2.998	-3.352	-2.962
tube morphogenesis	3.487	2.191	1.211	0.482	-0.035	-0.715	-1.097	-1.728	-2.304	-1.477
positive regulation of neurotropic transport	3.472	2.75	2.074	1.447	0.65	0.071	-1.337	-2.448	-3.396	-2.362
carbohydrate derivative metabolic process	3.465	3.451	2.957	2.118	1.173	-1.084	-3.09	-4.354	-2.529	-1.912
import into nucleus	3.438	2.692	1.889	1.085	0.324	-0.931	-1.693	-1.728	-2.208	-3.888
3'-UTR mediated mRNA stabilization	3.428	2.169	1.29	0.622	0.241	-0.388	-0.718	-1.069	-2.008	-1.544
cellular response to lipid	3.393	1.857	0.877	0.085	-0.336	-0.636	-0.610	-1.183	-1.884	-1.884
negative regulation of phosphorylation	3.376	3.063	2.506	1.79	0.985	-0.645	-2.002	-3.173	-2.676	-2.234
transmembrane receptor protein serine/threonine kinase signaling pathway	3.37	2.317	1.472	0.796	0.256	-0.537	-1.099	-1.967	-2.564	-2.043
regulatory regulation of telomere maintenance via telomerase	3.36	1.458	0.31	-0.266	-0.42	-0.807	-0.5	0.215	-2.34	-2.838
regulation of localization	3.351	2.116	1.164	0.443	-0.096	-0.785	-1.173	-1.688	-2.052	-1.729
leukocyte differentiation	3.332	2.577	1.886	1.252	0.67	-0.356	-1.219	-2.488	-3.055	-2.598
microtubule organizing center	3.3	2.68	2.075	1.482	0.899	-0.234	-1.303	-3.047	-3.681	-2.148
head development	3.29	2.322	1.531	0.894	0.374	-0.388	-0.904	-1.617	-2.366	-1.188
negative regulation of mitotic cell cycle	3.257	0.896	-0.532	-1.237	-1.41	-0.803	0.219	0.973	-0.687	-0.676
negative regulation of phosphate metabolic process	3.243	2.751	2.138	1.454	0.744	-0.611	-1.701	-2.691	-2.459	-2.87
regulation of immune effector process	3.242	2.37	1.429	0.802	0.424	-0.367	-0.939	-1.76	-2.46	-3.211
U4L5-U5 snRNP complex	3.219	2.669	2.081	1.469	0.845	-0.387	-1.521	-3.15	-3.471	-1.809
brain development	3.218	2.428	1.746	1.158	0.649	-0.185	-0.845	-1.892	-2.788	-3.488
regulation of vesicle-mediated transport	3.204	1.523	0.374	-0.378	-0.819	-1.091	-0.803	-0.875	-1.199	-0.237
proteasomal protein catabolic process	3.202	2.35	1.7	1.199	0.8	0.154	-0.473	-2.065	-3.663	-3.202
DNA binding	3.197	1.902	0.937	0.242	-0.236	-0.735	-0.886	-1.018	-1.516	-1.887
mRNA transcription	3.192	1.985	1.171	0.64	0.301	-0.113	-0.537	-1.246	-2.173	-0.781
negative regulation of telomere maintenance via telomere lengthening	3.182	1.271	0.059	-0.488	-0.586	-0.085	0.628	0.486	-0.921	-2.406
protein homodimerization activity	3.167	2.1	1.16	0.349	0.334	-1.325	-1.847	-1.766	-0.922	-1.581
nuclear protein-containing complex	3.152	2.102	1.287	0.659	0.178	-0.469	-0.947	-1.742	-2.402	-1.786
negative regulation of cell cycle process	3.151	1.757	0.813	0.223	-0.097	-0.228	-0.085	-0.266	-1.781	-1.48
cell surface receptor signaling pathway involved in cell-cell signaling	3.101	1.291	0.051	-0.739	-1.187	-1.418	-2.325	-0.942	-0.838	1.916
tube development	3.085	1.855	0.488	0.297	-0.157	-0.682	-0.956	-1.484	-2.01	-0.896
positive regulation of immune system process	3.075	2.528	1.943	1.341	0.74	-0.396	-1.366	-2.576	-2.793	-2.434
transcription by RNA polymerase II	3.06	1.816	0.88	0.198	-0.281	-0.806	-0.993	-1.311	-1.432	-1.311
nucleobase-containing compound biosynthetic process	3.043	1.783	0.857	0.2	-0.247	-0.716	-0.888	-1.163	-1.163	-0.621
regulation of telomere maintenance via telomerase	3.023	1.438	0.055	-0.604	-0.251	-0.08	0.239	-0.272	-2.116	-2.18
establishment of protein localization to organelle	3.022	2.451	1.915	1.27	0.472	-0.920	-1.909	-2.375	-3.051	-0.481
protein kinase activity	3.007	2.792	2.369	1.803	1.15	-0.227	-1.457	-2.853	-3.617	-3.617
transcription regulator complex	2.989	2.388	1.801	1.225	0.66	-0.422	-1.415	-2.904	-3.15	-1.174
regulation of T cell differentiation	2.964	3.339	3.164	2.466	1.879	-0.067	-1.961	-4.063	-3.795	-4.162
response to peptide hormone	2.963	1.917	1.06	0.374	-0.16	-0.845	-1.139	-1.096	-1.607	-2.007
cellular response to peptide hormone stimulus	2.951	1.644	0.673	-0.019	-0.483	-0.915	-0.943	-0.704	-0.864	-1.341
response to organic cyclic compound	2.949	2.58	1.821	1.366	0.647	-0.868	-2.203	-3.462	-2.548	-1.644
negative regulation of mRNA processing	2.929	2.25	1.702	1.251	0.865	-0.197	-0.452	-1.939	-1.38	-3.425
animal organ development	2.909	1.808	0.979	0.37	-0.066	-0.579	-0.835	-1.236	-1.767	-1.583
regulation of protein transport	2.863	2.222	1.624	1.069	0.556	-0.342	-1.076	-2.071	-2.479	-2.386
embryo development	2.857	1.636	0.749	0.328	-0.292	-0.712	-0.869	-1.173	-1.61	-0.72
peptidyl-lysine modification	2.854	0.403	-0.902	-1.35	-1.198	-0.047	1.426	1.552	-1.737	-1.095
protein folding	2.847	2.594	2.025	1.249	0.366	-1.404	-2.769	-3.287	-3.303	-3.919
transcription-DNA-templated	2.814	1.446	0.79	0.183	-0.228	-0.652	-0.8	-1.035	-1.504	-1.24
regulation of chromosome organization	2.789	1.435	0.518	-0.057	-0.371	-0.505	-0.361	-0.411	-1.364	-1.673
chromosome	2.769	2.389	1.952	1.474	0.972	-0.052	-1.024	-2.521	-3.139	-2.818
magnesium ion binding	2.765	3.316	3.114	2.382	1.318	-1.152	-3.25	-4.245	-1.73	-2.518
regulation of cellular component size	2.749	1.727	1.008	0.522	0.209	-0.107	-0.284	-0.991	-2.267	-2.566
intrinsic apoptotic signaling pathway	2.733	1.631	0.726	0.202	-0.544	-1.274	-1.979	-0.801	-1.42	-0.998
positive regulation of catalytic activity	2.73	2.312	1.832	1.313	0.773	-0.296	-1.255	-2.531	-2.75	-2.127
negative regulation of DNA metabolic process	2.727	1.317	0.46	0.02	-0.121	-0.086	-0.417	-0.028	-2.136	-2.742
DNA-templated transcription, elongation	2.713	2.454	1.962	1.366	0.647	-0.868	-2.203	-3.462	-2.548	-1.644
nuclear chromosome	2.708	2.369	1.931	1.423	0.872	-0.266	-1.322	-2.748	-2.929	-2.038
cellular response to inorganic substance	2.692	2.023	1.49	1.064	0.722	-0.2	-0.225	-1.186	-2.579	-2.01
tissue development	2.687	1.687	0.873	0.224	-0.282	-0.939	-1.24	-1.234	-0.467	-0.809
meiosis	2.677	1.432	0.549	-0.308	-0.392	-0.615	-0.497	-0.271	-0.872	-1.973
regulation of catalytic activity	2.664	1.96	1.315	0.729	0.203	-0.671	-1.31	-1.927	-1.798	-1.167
DNA helicase activity	2.663	1.076	0.037	-0.576	-0.874	-0.897	-0.638	-0.584	-1.117	0.908
U2-type spliceosomal complex	2.665	2.244	1.711	1.271	0.751	-0.294	-1.261	-2.463	-2.843	-1.644
neuron apoptotic process	2.655	2.446	2.403	1.866	1.391	0.073	-1.022	-2.919	-3.263	-3.055
plasma membrane region	2.605	2.547	2.051	1.279	0.37	-1.404	-2.587	-2.178	-1.039	-2.792
cell surface receptor signaling pathway	2.594	1.491	0.724	0.216	0.102	-0.401	-0.543	-1.129	-1.369	-0.88
protein import into nucleus	2.589	2.154	1.546	0.851	0.147	-1.062	-1.147	-1.294	-0.07	-3.323
small molecule metabolic process	2.565	1.894	1.184	0.474	-0.206	-1.367	-2.139	-2.556	-0.819	-0.67
regulation of cytoskeleton organization	2.564	1.904	1.343	0.869	0.47	-0.146	-0.587	-1.236	-1.982	-1.399
autophagy	2.551	0.851	-0.343	-1.12	-1.561	-1.719	-1.303	-0.065	-0.788	-1.92
regulation of lymphocyte differentiation	2.532	2.706	2.511	2.047	1.403	-0.124	-1.581	-3.188	-2.983	-3.324
regulation of protein catabolic process	2.511	2.042	1.595	1.164	0.745	-0.064	-0.836	-2.171	-2.855	-2.313
alternative mRNA splicing, via spliceosome	2.473	1.694	1.101	0.656	0.325	-0.112	-0.407	-1.059	-2.007	-2.665
regulation of DNA repair	2.472	1.635	0.952	0.402	0.035	-0.646	-1.005	-1.317	-1.37	-1.087
endosome	2.457	1.494	0.716	0.206	0.12	-0.784	-1.178	-1.798	-1.778	-0.834
response to lv	2.442	1.166	1.146	0.823	0.621	-0.327	-0.911	-1.48	-2.305	-2.271
telomere maintenance	2.438	1.258	0.488	0.027	-0.132	-0.324	-0.319	-0.905	-1.969	-0.482
vesicle	2.427	1.876	1.352	0.855	0.388	-0.448	-1.137	-2.005	-2.081	-1.227
regulation of establishment of protein localization	2.414	1.768	1.197	0.683	0.246	-0.499	-1.818	-1.914	-1.007	-1.007
microtubule cytoskeleton	2.41	1.581	0.956	0.487	0.13	-0.385	-0.803	-1.697	-2.23	-0.449
RNA modification	2.38	2.402	2.229	1.601	1.493	0.37	-1.980	-2.711	-3.576	-3.658
3'-5' exonuclease activity	2.365	3.214	3.353	2.962	2.011	0.113	-2.015	-4.337	-3.74	-4.116
ion binding	2.364	1.662	1.066	0.572	0.172	-0.378	-0.657	-0.783	-1.131	-2.887
negative regulation of mRNA metabolic process	2.332	1.296	0.587	0.132	-0.135	-0.321	-0.336	-0.674	-1.541	-1.337
regulation of cell migration	2.239	1.946	1.561	1.116	0.637	-0.329	-1.185	-2.219	-2.157	-1.634
positive regulation of response to DNA damage stimulus	2.235	0.482	-0.613	-1.188	-1.365	-0.956	-0.111	1.038	-0.885	-0.605
positive										

kappaB kinase/NF-kappaB signaling	2.299	0.667	-0.408	-1.036	-1.315	-1.173	-0.57	0.492	0.465	0.578
holonemic DNA binding	2.293	-0.094	-1.515	-2.188	-2.264	-1.527	-0.86	1.226	0.914	3.463
immune effector process	0.291	0.231	0.051	1.565	0.839	1.404	-0.216	-1.51	1.031	3.388
embryo development ending in birth or egg hatching	2.291	0.925	0.026	-0.51	-0.773	-0.795	-0.547	-0.388	-0.799	0.57
response to oxygen-containing compound	2.29	1.817	1.31	0.797	0.31	-0.574	-1.209	1.644	-1.37	1.718
signal transduction	2.288	2.193	1.884	1.435	0.908	-0.173	-1.047	-1.707	-1.688	-4.094
response to hormone	2.281	1.39	0.737	0.273	0.045	-0.392	-0.551	-0.895	-1.456	-1.343
regulation of stem cell differentiation	2.281	1.768	1.366	1.043	0.723	0.301	-0.184	-1.424	-2.291	-3.152
methyltransferase complex	1.196	0.481	0.197	0.213	0.414	0.99	1.329	0.198	2.575	-2.443
heterochromatin organization	1.194	0.674	0.243	-0.097	0.345	-0.582	-0.516	0.144	0.494	-1.208
enzymatic activity	1.182	2.437	2.915	1.28	2.263	0.481	-1.484	3.748	3.228	3.618
positive regulation of cell migration	1.178	1.355	1.292	1.053	0.694	-0.188	-1.03	-1.86	-1.418	-1.077
RNA metabolic process	1.176	1.611	1.69	1.502	1.129	0.102	-0.941	-2.073	-1.84	-2.355
DNA biosynthetic process	1.13	0.481	0.062	-0.181	-0.293	-0.285	-0.169	-0.184	-0.551	-0.011
mitotic cell cycle	1.125	0.931	0.683	0.407	0.321	0.391	-0.758	-0.886	-0.954	-0.731
protein-DNA complex	1.121	1.109	1.002	0.817	0.568	-0.054	-0.741	-1.849	-1.89	-0.894
leukocyte cell-cell adhesion	1.087	2.291	2.683	2.462	1.899	0.045	-1.855	-3.597	2.348	-2.677
posttranscriptional gene silencing	1.081	0.208	-0.314	-0.561	-0.604	-0.317	0.144	0.598	0.036	-0.271
transition metal ion binding	1.076	0.876	0.691	0.523	0.371	0.116	-0.088	-0.438	-0.974	-2.152
immune system development	1.053	0.495	0.115	-0.125	-0.258	-0.32	-0.258	-0.273	-0.398	-0.092
regulation of RNA processing	1.044	0.925	0.793	0.644	0.475	0.083	-0.369	-1.281	-1.683	-0.63
extracellular space	1.04	0.618	0.292	0.041	-0.15	-0.414	-0.588	-0.804	-0.664	0.629
regulation of protein localization	1.033	0.572	0.845	0.669	0.458	-0.023	-0.507	-1.227	-1.36	-0.86
negative regulation of cell cycle	1.017	0.222	-0.883	-1.097	-0.986	-0.173	0.855	1.844	0.603	-0.961
cellular protein-containing complex assembly	1.001	0.476	0.097	-0.162	-0.325	-0.446	-0.405	-0.216	-0.126	0.106
cellular response to stimulus	1.001	0.78	0.57	0.373	0.187	-0.147	-0.429	-0.811	-0.922	-0.622
mechanoresponse activity	0.995	0.495	0.299	0.163	0.269	0.223	-0.425	-0.908	-2.391	-3.065
DNA packaging	0.996	1.361	1.434	1.289	0.991	0.162	-0.69	-1.657	-1.6	-2.288
protein localization to organelle	0.994	0.947	0.816	0.628	0.407	-0.058	-0.459	-0.856	-0.892	-1.528
RNA processing	0.94	1.462	1.606	1.487	1.138	0.139	-0.891	-2.009	-1.719	-2.122
cell division	0.936	1.006	0.907	0.689	0.395	-0.272	-0.856	-1.278	-0.785	-0.741
response to temperature stimulus	0.935	2.266	2.76	2.623	2.04	0.161	-1.847	-3.821	3.699	-2.515
transcription regulatory region nucleic acid binding	0.935	0.271	-0.137	-0.343	-0.397	-0.215	0.118	0.484	0.003	-0.719
regulation of alternative mRNA splicing, via spliceosome	0.932	0.625	0.468	0.328	0.182	0.077	-0.182	-0.726	-1.524	-2.500
posttranscriptional gene silencing by RNA	0.929	0.444	-0.615	-0.871	-0.89	-0.484	0.15	0.961	0.599	0.265
spindle organization	0.923	1.419	1.446	1.139	0.617	-0.677	-1.798	-2.206	-0.463	0.402
methyltransferase activity	0.906	0.941	0.877	0.74	0.551	0.092	-0.373	-1.029	-1.235	-1.47
positive regulation of protein localization to nucleus	0.881	1	0.963	0.801	0.543	-0.154	-0.928	-2.044	-1.731	0.67
regulation of cell population proliferation	0.869	1.271	1.444	1.434	1.28	0.683	-0.1	-1.563	-2.402	-2.915
sequence-specific double-stranded DNA binding	0.862	0.25	-0.145	-0.364	-0.445	-0.328	-0.031	0.449	0.244	-0.493
phosphate-containing compound metabolic process	0.858	0.881	0.903	0.685	0.379	-0.313	-0.891	-1.161	-0.517	-0.925
catabolic process	0.858	0.61	0.351	0.188	0.307	0.188	0.168	0.307	0.188	0.307
5mC-like protein family complex	0.831	1.546	1.728	1.509	1.029	-0.429	-1.897	-3.224	-1.619	-0.616
rRNA 3'-end processing	0.831	1.994	2.488	2.465	2.063	0.595	-1.125	-3.354	-3.127	-2.829
system process	0.815	0.496	0.255	0.079	-0.044	-0.181	-0.233	-0.29	-0.416	-0.481
small nuclear ribonucleoprotein complex	0.801	1.554	1.782	1.609	1.148	-0.248	-1.744	-3.327	-2.078	-0.505
positive regulation of signal transduction	0.784	0.756	0.662	0.524	0.306	-0.013	-0.287	-0.679	-0.719	-0.493
regulation of response to external stimulus	0.775	0.485	0.299	0.163	0.144	0.161	-0.023	0.694	0.483	0.493
regulation of organelle organization	0.775	0.331	0.049	-0.111	-0.183	-0.179	-0.122	-0.245	-0.51	0.174
regulation of DNA-templated transcription, elongation	0.769	1.348	1.468	1.241	0.773	-0.326	-1.825	-2.924	-1.369	-1.044
heart development	0.762	0.723	0.573	0.365	0.142	-0.211	-0.306	-0.299	-0.608	-2.955
regulation of RNA metabolic process	0.76	0.472	0.265	0.122	0.027	-0.071	-0.114	-0.231	-0.336	-0.675
cellular macromolecule localization	0.758	1.142	1.236	1.113	0.841	0.07	-0.715	-1.516	-1.248	-1.681
positive regulation of protein-containing complex assembly	0.755	0.119	-0.247	-0.401	-0.392	-0.071	0.4	0.936	0.244	-1.333
DNA recombination	0.755	1.239	1.365	1.23	0.919	0.053	-0.778	-1.477	-0.986	-2.38
condensed chromosome	0.746	0.896	1.204	1.15	0.964	0.341	-0.483	-1.181	-1.901	-1.565
regulation of mitotic cell cycle phase transition	0.743	0.84	0.874	0.848	0.767	0.457	-0.007	-1.129	-1.291	-1.575
intracellular anatomical structure	0.739	-0.053	-0.468	-0.602	-0.536	-0.088	0.419	0.62	0.241	0.209
system process	0.728	1.751	2.139	2.028	1.654	0.367	-0.939	-2.018	-1.492	-2.344
muscle structural development	0.726	0.439	-1.077	-1.313	-1.254	-0.628	-0.193	1.042	0.71	2.041
positive regulation of transcription by RNA polymerase II	0.714	0.464	0.277	0.146	0.062	-0.04	0.024	0.078	-0.272	-1.493
transcription co-regulatory region involved in reproduction	0.711	0.224	-0.081	-0.241	-0.289	-0.168	0.079	0.393	0.193	-0.263
regulation of cell death	0.71	1.133	1.286	1.206	1.014	0.328	-0.444	-1.48	-1.629	-1.48
circulatory system development	0.704	0.62	0.481	0.312	0.176	-0.172	-0.551	-0.257	-0.091	-1.38
DNA repair	0.699	0.241	-0.044	-0.225	-0.299	-0.256	-0.297	-0.129	-0.014	-0.128
cytoskeletal protein binding	0.695	1.496	1.749	1.603	1.188	-0.011	-1.148	-1.845	-0.909	-2.819
sequence-specific DNA binding	0.694	0.213	-0.083	-0.235	-0.278	-0.159	0.066	0.296	-0.049	-0.465
regulation of microtubule-based process	0.694	1.359	1.489	1.234	0.727	-0.596	-1.713	-2.161	-0.338	-0.646
response to chemical	0.691	0.46	0.293	0.176	0.095	-0.002	-0.07	-0.281	-0.615	-0.747
homeostatic process	0.681	0.782	0.883	0.599	0.993	0.885	0.497	-0.998	-0.557	-2.125
regulation of biological process	0.671	0.373	0.162	0.016	-0.084	-0.204	-0.288	-0.495	-0.553	0.401
regulation of kinase activity	0.663	0.977	1.005	0.824	0.501	-0.339	-1.134	-1.713	-0.789	0.004
establishment of localization in cell	0.653	0.512	0.553	0.484	0.618	0.174	0.376	-1.127	-0.891	-1.39
regulation of posttranscriptional gene silencing	0.652	0.432	0.275	0.163	0.083	-0.034	-0.15	-0.482	-0.749	-0.188
negative regulation of multicellular organismal process	0.648	0.559	0.07	0.018	0.046	0.185	0.158	-0.579	-1.45	0.645
negative regulation of molecular function	0.648	0.171	-0.614	-0.773	-0.731	-0.375	0.187	0.511	0.313	0.263
regulation of protein stability	0.647	0.216	0.033	0.022	0.114	0.362	0.53	-0.165	-1.469	-0.318
chromosome organization	0.641	0.406	0.224	0.085	-0.022	-0.171	-0.274	-0.432	-0.466	0.01
positive regulation of cell cycle process	0.627	0.325	0.158	0.092	0.094	0.179	0.224	0.47	0.906	0.654
positive regulation of apoptotic process	0.636	1.278	1.536	1.501	1.251	0.883	-0.613	-1.895	-1.88	-2.198
biological regulation	0.624	0.307	0.103	-0.03	0.113	-0.197	-0.251	-0.434	-0.498	0.508
regulation of anatomical structure morphogenesis	0.576	0.473	0.115	-0.141	-0.189	-0.116	-0.408	-0.928	-1.441	-2.894
regulation of protein ubiquitination	0.562	0.572	-1.076	-1.119	-0.848	0.129	1.063	1.199	0.464	1.127
nucleolus	0.561	0.984	1.181	1.196	1.067	0.518	-0.221	-1.554	-2.247	-1.844
positive regulation of intracellular signal transduction	0.558	0.955	1.111	1.069	0.888	0.301	-0.329	-1.063	-1.152	-2.32
negative regulation of catabolic process	0.519	0.213	0.067	0.011	0.04	0.205	0.399	0.21	0.572	0.184
regulation of cell differentiation	0.517	0.343	0.2	0.083	0.102	-0.149	-0.234	-0.307	-0.291	-0.15
cellular component organization or biogenesis	0.505	0.13	-0.143	-0.332	-0.451	-0.534	-0.479	-0.175	-0.293	-1.187
cell migration	0.503	0.021	1.213	1.159	0.928	0.188	-0.014	-1.487	-1.25	-1.662
regulation of cell cycle	0.502	0.406	0.296	0.18	0.064	-0.144	-0.297	-0.39	-0.881	-0.329
positive regulation of biological process	0.501	0.237	0.055	-0.061	0.125	-0.142	-0.084	-0.023	0.076	-0.329
regulation of cellular protein localization	0.499	0.718	0.791	0.749	0.62	0.194	-0.315	-1.115	-1.258	-0.884
intracellular protein-containing complex	0.488	0.539	-1.145	-1.417	-1.431	-0.96	-1.132	-1.598	-2.46	-3.004
protein localization to nucleus	0.487	0.804	0.876	0.766	0.533	-0.113	-0.745	-1.26	-0.72	-0.628
regulation of muscle cell differentiation	0.48	0.296	-0.689	-0.793	-0.871	-0.276	-0.288	-0.844	-0.115	-1.546
DNA modification	0.479	0.903	1.204	1.374	1.411	1.096	0.326	-1.964	-3.225	-3.301
RNA stem-loop binding	0.465	0.046	-0.191	-0.296	-0.311	-0.209	-0.101	-0.246	-0.407	1.

regulation of developmental process	0.359	0.275	0.192	0.107	0.02	-0.159	-0.34	-0.666	-0.462	0.614	Signal transduction by p53 class mediator	-1.478	-1.144	-0.765	-0.369	0.018	0.684	1.112	1.112	0.4	-0.431	
muscle organ development	0.358	0.774	-1.383	-1.587	-1.496	-0.791	0.133	1.28	3.15	2.946	location	-1.482	-0.737	-0.193	0.187	0.444	0.84	0.677	0.891	0.256	-0.172	
hemopoiesis	0.349	0.19	0.078	0.005	-0.04	-0.073	-0.072	-0.092	0.186	-0.164	2-UTR-mediated mRNA destabilization	-1.486	-2.026	-2.183	-2.056	-1.728	-0.771	0.289	1.601	2.459	5.947	
gene silencing by miRNA	0.334	-0.461	-0.889	-1.03	-0.956	-0.413	0.322	1.3	1.076	0.717	negative regulation of metabolic process	-1.491	-1.203	-0.909	-0.617	-0.334	0.183	0.604	1.109	1.256	1.403	
positive regulation of cytokine production	0.299	0.104	-0.086	-0.257	-0.398	-0.556	-0.532	0.065	0.822	0.527	nervous system process	-1.499	0.289	1.345	1.832	1.893	1.33	0.181	-1.193	-1.143	-2.938	
cellular response to radiation	0.288	0.144	-0.157	-0.401	-0.324	0.038	0.458	0.807	0.201	-0.568	catalytic activity, acting on a nucleic acid	-1.515	-0.704	-0.138	0.233	0.454	0.595	0.57	0.471	0.652	3.1	
regulation of cell cycle	0.287	0.204	0.142	0.092	0.049	-0.034	-0.13	-0.358	-0.425	0.176	nervous system development	-1.521	-1.321	-1.071	-0.788	-0.488	0.113	0.646	1.327	1.5	1.603	
biological process involved in interaction with symbiont	-0.505	-1.68	-2.185	-2.179	-1.803	-0.435	1.113	2.849	2.278	2.547	muscle cell differentiation	-1.53	-0.908	-0.477	-0.192	0.076	0.15	0.22	0.576	0.199	0.982	
regulation of mitotic cell cycle	-0.507	-0.145	0.111	0.278	0.37	0.386	0.258	-0.129	-0.355	-0.268	regulation of macromolecule biosynthetic process	-1.53	-0.98	-0.556	-0.235	0.020	0.296	0.455	0.666	0.922	0.36	
negative regulation of transcription, DNA templated	-0.517	-0.3	-0.137	-0.017	0.067	0.159	0.189	0.197	0.215	0.144	myeloid cell differentiation	-1.541	-1.404	-1.194	-0.938	-0.651	-0.407	0.523	1.355	1.753	2.153	
negative regulation of nitrogen compound metabolic process	-0.519	-0.297	-0.119	0.021	0.127	0.256	0.301	0.235	0.082	-0.086	sexual reproduction	-1.552	-0.876	-0.382	-0.202	0.208	0.467	0.578	0.754	0.865	-0.029	
establishment of localization	-0.527	-0.351	-0.198	-0.07	0.033	0.172	0.23	0.182	0.125	0.404	presynapse	-1.553	-1.695	-1.691	-1.565	-1.342	-0.688	0.12	1.752	2.072	3.689	
endoplasmic reticulum	-0.543	0.094	0.476	0.658	0.691	0.482	0.132	-0.342	-0.398	-1.25	negative regulation of biological process	-1.554	-1.442	-1.085	-0.798	-0.497	0.098	0.623	1.296	1.51	1.749	
developmental growth	-0.564	0.308	0.819	1.047	1.062	0.694	0.113	-0.74	-0.898	-1.842	regulation of cellular macromolecule biosynthetic process	-1.562	-0.999	-0.568	-0.241	0.031	0.311	0.475	0.686	0.928	0.961	
maturation of 5.8S rRNA	-0.574	0.841	1.518	1.625	1.336	0.138	-1.153	-1.994	-0.483	-1.239	transcription compressor activity	-1.574	-0.104	0.819	1.394	1.441	1.049	0.213	1.206	-1.222	-0.725	
regulation of metabolic process	-0.575	-0.464	-0.368	-0.204	-0.299	-0.073	0.057	0.341	0.651	0.918	microRNA catabolic process	-1.578	-0.815	-0.348	-0.065	0.011	0.019	0.036	0.731	1.773	2.263	
regulation of protein modification process	-0.584	-0.502	-0.347	-0.151	0.061	0.441	0.661	0.565	0.467	-0.189	0.139	protein stabilization	-1.582	-0.698	-0.407	0.401	0.675	0.806	0.502	0.331	0.616	0.831
regulation of cell death	-0.601	0.073	0.47	0.649	0.661	0.37	-0.091	-0.727	0.544	-0.26	response to stress	-1.619	-1.031	-0.588	-0.262	-0.029	0.242	0.371	0.586	0.992	1.338	
cytoskeleton organization	-0.611	0.088	0.424	0.646	0.384	0.116	-0.24	-0.705	0.398	0.269	proteolysis	-1.619	-0.483	-0.23	0.634	0.779	0.553	0.135	0.449	-0.025	0.198	
DNA replication	-0.62	-0.735	-0.715	-0.605	-0.444	-0.092	0.158	0.16	0.218	2.676	regulation of protein phosphorylation	-1.623	-1.041	-0.605	-0.286	-0.006	0.207	0.345	0.611	0.983	1.361	
locomotion	-0.62	0.319	0.842	1.046	1.077	0.552	-0.076	-0.763	0.561	-1.761	hydrolase activity	-1.642	-0.791	-0.202	0.179	0.403	0.545	0.501	0.401	0.675	-0.159	
ATP-dependent activity, acting on DNA	-0.621	-0.164	0.154	0.349	0.446	0.432	0.281	-0.136	-0.304	-0.407	catalytic activity, acting on DNA	-1.645	-0.466	0.308	0.747	0.927	0.753	0.219	0.127	-0.55	0.436	
local adhesion	-0.644	-0.261	-0.169	-0.105	0.153	0.495	-0.091	-0.231	1.163	1.507	positive regulation of response to biotic stimulus	-1.647	-1.194	-0.798	-0.452	-0.152	0.334	0.952	1.136	1.004	0.836	
regulation of DNA metabolic process	-0.65	-0.125	0.21	0.396	0.47	0.404	0.216	-0.053	0.094	-0.774	regulation of gene silencing by miRNA	-1.659	-1.582	-1.348	-1.003	-0.591	0.296	1.083	1.858	1.563	1.388	
RNA polymerase II transcription regulatory region sequence-specific DNA binding	-0.653	-0.483	-0.663	-0.94	-0.48	-0.136	0.319	1.259	1.542	0.802	RNA helicase activity	-1.668	-1.253	-0.877	-0.540	-0.243	0.301	0.796	1.616	1.76	1.131	
negative regulation of cellular metabolic process	-0.654	-0.545	-0.398	-0.23	0.055	0.269	0.504	0.582	0.281	0.245	modulation by host of symbiont process	-1.68	-0.759	-0.387	-0.134	-0.213	0.226	2.083	3.539	3.651	1.457	
growth	-0.677	0.53	1.127	1.267	1.086	0.217	-1.74	-1.319	-0.195	-1.296	organelle organization	-1.699	-1.068	-0.597	-0.254	-0.014	0.233	0.367	0.566	1.01	1.437	
DNA-binding transcription factor binding	-0.685	-0.56	-0.404	-0.245	-0.093	0.159	0.351	0.321	0.955	0.951	protein phosphorylation	-1.699	-0.802	-0.334	0.165	0.326	0.465	0.521	0.638	0.428	0.638	
ATP hydrolysis activity	-0.701	-0.293	-0.007	0.182	0.298	0.382	0.369	0.31	0.176	0.215	miRNA binding	-1.72	-1.119	-0.643	-0.267	0.033	0.475	0.797	1.269	1.296	-1.122	
cell cycle process	-0.704	-0.585	-0.469	-0.358	-0.252	-0.059	0.11	0.396	0.704	1.217	cell part morphogenesis	-1.735	-1.206	-0.865	-0.469	-0.505	-0.269	0.092	1.466	2.771	0.899	
negative regulation of apoptotic process	-0.715	0.164	0.63	0.779	0.698	0.143	-0.543	-1.124	-0.274	0.241	response to biotic stimulus	-1.761	-1.317	-0.942	-0.621	-0.343	0.129	0.535	1.253	1.76	1.31	
transport	-0.727	-0.515	-0.322	-0.147	0.005	0.241	0.383	0.425	0.305	0.353	cellular process involved in reproduction in multicellular organism	-1.766	-0.771	-0.059	0.436	0.767	1.121	1.277	1.473	-3.236	-3.236	
response to abiotic stimulus	-0.729	0.19	0.657	0.78	0.656	0.003	-0.75	-1.264	-0.111	0.569	microtubule cytoskeleton organization involved in mitosis	-1.769	-0.708	-0.098	0.174	0.208	-0.103	-0.481	0.234	1.382	1.163	
response to external stimulus	-0.75	-0.358	-0.13	-0.021	0.009	-0.041	0.077	0.258	0.077	0.232	response to other organism	-1.775	-1.347	-0.974	-0.646	-0.355	0.147	0.577	1.289	1.689	1.385	
protein localization to nucleus	-0.776	0.014	0.531	0.825	0.93	0.696	0.071	-1.409	-1.711	0.815	nervous compound transport	-1.79	-0.973	-0.356	0.093	0.402	0.703	0.749	0.481	0.349	0.534	
regulation of cellular response to stress	-0.784	-0.614	-0.58	-0.615	-0.677	-0.575	-0.623	0.507	1.734	1.987	immune process	-1.829	-1.23	-0.746	-0.365	-0.062	0.366	0.629	0.988	1.298	1.032	
positive regulation of macromolecule biosynthetic process	-0.783	-0.568	-0.397	-0.257	-0.141	0.051	0.225	0.581	0.821	0.468	regulation of neuron death	-1.834	-0.346	0.641	1.223	1.49	1.376	0.811	0.365	-0.912	-2.084	
DNA metabolic process	-0.786	-0.341	-0.032	0.176	0.323	0.383	0.339	0.189	0.095	-0.321	UDP-ATPase	-1.834	-0.029	1.566	1.711	1.825	1.139	-0.298	-2.064	-1.763	-1.122	
RNA methyltransferase activity	-0.788	0.072	0.655	1.001	1.148	0.993	0.452	-0.526	-1.643	-0.964	catalytic activity, acting on a protein	-1.847	-0.607	0.957	1.409	1.455	0.873	0.022	0.277	0.427	-0.686	
catalytic activity	-0.796	0.126	0.633	0.827	0.799	0.38	-0.135	-0.432	0.069	-1.473	helicase activity	-1.848	-1.277	-0.81	-0.426	-0.107	0.396	0.788	1.385	1.53	0.368	
peptidyl-serine modification	-0.802	0.163	0.723	0.961	0.952	0.447	-0.388	-1.493	-1.101	0.488	endonuclease activity, producing 5'-phosphonucleotides	-1.848	-1.03	-0.268	0.394	0.934	1.594	1.667	3.591	-1.389	-0.935	
S-adenosylmethionine-dependent methyltransferase activity	-0.805	0.024	0.563	0.864	0.874	0.789	0.301	-0.736	-1.111	-0.863	movement of cell or subcellular component	-1.865	-0.491	0.387	0.808	0.805	0.896	1.143	-0.452	0.124	-0.322	
regulation of nitrogen compound metabolic process	-0.821	-0.346	-0.039	0.145	0.232	0.239	0.143	0.06	0.11	0.669	neurite receptor binding	-1.883	-0.669	-0.341	0.144	0.446	0.52	0.716	1.307	0.807	0.449	
modification-dependent macromolecule catabolic process	-0.814	0.502	1.224	1.494	1.429	0.775	-0.079	-0.889	-0.623	-3.027	regulation of cell communication	-1.887	-1.405	-0.94	-0.504	-0.168	0.532	0.945	1.13	0.905	1.331	
generation of precursor metabolites and energy	-0.825	-1.584	-2.46	-2.749	-2.162	-0.908	-2.183	-3.49	-0.06	-2.869	plasma membrane bounded cell projection organization	-1.893	-1.711	-1.514	-1.301	-1.068	-0.541	0.608	1.457	2.825	3.677	
cellular developmental process	-0.834	-0.476	-0.49	-0.292	-0.029	0.257	0.495	0.569	0.362	0.699	organization	-1.893	-1.711	-1.514	-1.301	-1.068	-0.541	0.608	1.457	2.825	3.677	
osteoblast differentiation	-0.836	-0.575	-0.279	0.033	0.391	0.761	0.971	0.73	0.424	-0.524	UDP-ATPase	-1.897	-0.468	1.713	2.088	1.818	1.312	-2.005	-4.551	-1.447	-3.284	
positive regulation of cellular biosynthetic process	-0.836	-0.564	-0.372	-0.239	-0.146	-0.014	0.121	0.556	0.9	0.504	organic substance transport	-1.941	-1.294	-0.744	-0.286	0.063	0.864	0.884	0.884	0.733	0.195	
cell differentiation	-0.838	-0.798	-0.654	-0.458	-0.228	0.229	0.588	0.787	0.515	0.874	protein C-terminus binding	-1.948	-2.58	-2.698	-2.431	-1.898	-0.421	1.095	2.873	3.04	4.968	
macromolecule modification	-0.865	-0.803	-0.528	-0.296	-0.066	0.447	0.229	-0.348	-0.402	-1.452	postprandial	-1.964	-1.023	-0.594								

fructocyclinase transport	-1.577	-0.377	0.287	0.684	0.875	0.650	0.004	-0.189	-1.338	cellular protein metabolic process	-4.528	-2.977	-1.758	-0.836	-0.116	0.859	1.481	2.367	3.127	2.624
cellular response to nutrient levels	-1.379	-0.464	0.768	1.196	1.336	1.061	0.463	-0.468	-0.868	-2.454	-3.054	-1.853	-0.895	-0.341	0.912	1.557	2.371	2.849	2.493	
heterochromatin assembly	-1.417	-1.353	-1.297	-1.217	-1.091	-0.639	0.117	2.246	3.649	1.002	-4.507	-1.919	-1.066	-0.444	0.366	0.808	1.813	3.426	4.706	
cellular macromolecule metabolic process	-1.432	-0.872	-0.464	-0.176	0.022	0.245	0.365	0.653	1.031	0.646	-4.637	-2.678	-1.148	0.016	0.872	1.861	2.182	1.871	1.256	0.406
positive regulation of cell growth	-1.438	-0.514	0.088	0.429	0.660	0.931	0.403	0.265	0.441	-0.978	-4.447	-3.448	-2.251	1.286	-0.31	1.305	2.405	3.077	2.518	2.771
hematopoietic progenitor cell differentiation	-1.45	-0.706	-0.155	0.235	0.492	0.712	0.681	0.364	0.095	-0.267	-4.791	-2.718	-1.128	0.056	0.907	1.864	2.173	2.003	1.543	0.092
mRNA metabolic process	-1.452	-0.326	0.329	0.632	0.687	0.405	0.036	0.133	0.900	-1.344	-4.797	-4.766	-4.279	-3.462	-2.423	-0.055	2.21	5.08	5.645	6.847
negative regulation of macromolecule metabolic process	-1.456	-1.126	-0.816	-0.528	0.263	0.191	0.543	0.964	1.142	1.35	-4.85	-3.663	-2.599	-1.647	0.784	0.651	1.799	3.274	4.056	3.675
chromosome segregation	-2.686	-0.922	0.211	0.844	1.097	0.873	0.231	0.552	0.207	0.697	-4.868	-3.326	-2.128	-1.204	-0.489	0.536	1.266	2.682	4.021	3.52
tRNA modification	-2.686	-0.922	0.211	0.844	1.097	0.873	0.231	0.552	0.207	0.697	-4.868	-3.326	-2.128	-1.204	-0.489	0.536	1.266	2.682	4.021	3.52
cell junction	-2.693	-0.703	-2.475	-2.07	-1.54	-4.287	0.981	2.844	3.594	4.349	-4.87	-3.338	-0.611	0.423	0.985	1.177	0.848	0.774	2.144	1.517
regulation of gene expression, epigenetic	-2.719	-2.213	-1.769	-1.361	-0.964	-0.144	0.769	2.753	3.897	1.752	-4.881	-1.904	-0.038	0.967	1.333	0.913	-0.031	-0.484	1.857	2.27
transcription regulator activity	-2.721	-1.325	-0.393	0.182	0.495	0.651	0.599	0.894	1.646	-0.018	-4.909	-4.593	-4.047	-3.32	-2.454	-0.666	1.628	5.197	6.886	6.08
negative regulation of macromolecule biosynthetic process	-2.727	-2.043	-1.422	-0.864	-0.367	0.458	0.173	1.785	2.02	2.086	-4.987	-3.687	-2.698	-1.558	-0.481	1.361	2.645	3.404	2.723	3.447
maturation of LSU-RNA from tricornic RNA transcript (SSU-RNA, S45 RNA, LSU-rRNA)	-2.731	-1.513	-0.589	0.079	0.172	1.3	1.237	0.917	-0.413	-0.617	-5.077	-4.202	-3.192	-2.106	-1.005	1.079	2.773	4.423	3.976	3.334
organic substance catabolic process	-2.735	-1.646	-0.858	-0.309	0.056	0.429	0.579	0.974	1.747	1.763	-5.127	-2.981	-1.402	-0.278	0.49	1.304	1.612	2.07	2.745	1.566
ambedoid-type cell migration	-2.75	-1.199	-0.19	0.394	0.659	0.593	0.214	-0.012	1.031	1.279	-5.142	-3.326	-1.915	-0.835	-0.02	1.04	1.65	2.476	3.229	2.843
transcription coactivator activity	-2.753	-1.269	-0.267	0.539	0.71	0.848	0.951	0.666	1.164	-0.144	-5.188	-3.277	-1.899	-0.69	0.315	1.32	0.588	1.501	3.659	5.555
mRNA metabolic process	-2.768	-0.238	0.26	1.934	2.007	1.079	0.316	-1.666	-0.333	-0.968	-5.191	-4.894	-4.222	-3.233	-2.175	0.226	2.446	5.175	5.588	6.331
negative regulation of cellular macromolecule biosynthetic process	-2.782	-0.884	-1.45	-0.878	-0.367	0.48	1.111	1.828	2.042	2.1	-5.213	-3.568	-2.541	-1.111	-0.299	0.813	1.516	2.566	3.602	3.793
biological process involved in symbiotic interaction	-2.789	-1.759	-0.988	-0.424	-0.02	0.468	0.741	1.262	1.901	1.608	-5.213	-4.715	-4.085	-3.355	-2.551	0.822	0.938	4.176	6.884	8.984
regulation of hydrolase activity	-2.839	-1.563	-0.64	-0.009	0.39	0.695	0.636	0.433	0.941	0.955	-5.214	-2.976	-1.258	0.025	0.95	1.995	2.339	2.165	1.701	0.274
transcription coactivator activity	-2.84	-1.249	-0.18	0.467	0.799	0.887	0.676	0.667	1.261	-0.486	-5.226	-2.824	-0.844	0.291	0.94	1.321	1.189	1.413	2.618	0.924
positive regulation of protein modification process	-2.843	-1.897	-1.075	-0.413	0.115	0.82	1.315	1.165	1.098	1.895	-5.24	-2.88	-1.254	0.06	0.966	1.129	0.291	2.038	1.325	
regulation of proteolysis	-2.848	-2.276	-1.816	-1.457	-1.157	-0.607	0.03	1.861	3.951	4.35	-5.261	-3.605	-2.805	-1.747	-0.817	0.708	1.865	3.76	4.195	4.951
supramolecular fiber	-2.886	-1.257	-0.319	0.11	0.189	-0.175	-0.56	0.317	2.864	1.717	-5.266	-3.734	-2.321	-1.199	-0.177	1.339	2.167	2.555	2.544	3.674
regulation of response to cytokine stimulus	-2.914	-1.924	-1.077	-0.271	0.201	0.972	1.317	1.36	0.81	1.808	-5.268	-3.33	-1.787	-0.711	0.01	0.765	1.107	2.091	3.703	3.666
maturation of SSU-RNA	-2.935	-0.656	2.579	3.233	2.973	0.626	-1.576	-3.449	-0.556	-1.851	-5.285	-3.362	-1.821	-0.742	0.014	0.762	1.13	2.17	3.759	3.676
regulation of mRNA stability	-2.941	-2.359	-1.78	-1.218	-0.682	0.28	1.06	2.042	2.493	3.107	-5.291	-4.196	-3.096	-2.151	-1.315	0.165	1.548	4.247	6.035	4.263
regulation of viral genome replication	-2.944	-2.703	-2.225	-1.595	-0.868	-0.531	1.657	2.427	2.007	3.221	-5.294	-4.766	-3.624	-2.325	-0.964	1.519	3.23	3.682	7.23	6.53
single-stranded DNA binding	-2.958	-2.033	-1.266	-0.635	-0.117	0.654	1.175	1.787	1.98	1.412	-5.295	-3.88	-2.474	-1.338	-0.397	0.974	1.904	3.127	3.919	3.752
cellular response to extracellular stimulus	-2.963	-0.831	0.617	1.529	1.407	0.538	-0.33	0.197	-0.442	-1.483	-5.65	-4.235	-2.861	-1.458	-0.214	1.779	2.966	3.204	3.961	4.643
positive regulation of viral process	-2.985	-1.78	-0.874	-0.212	0.253	0.764	0.947	1.09	1.413	1.383	-5.655	-3.431	-1.692	-0.359	0.638	1.878	2.433	2.721	2.496	0.95
DNA-binding transcription factor activity, RNA polymerase II-specific	-3.042	-2.231	-1.63	-1.171	-0.795	-0.11	0.683	2.797	4.281	1.213	-5.718	-3.979	-2.535	-1.345	-0.368	1.085	2.061	3.242	3.873	3.683
mRNA export from nucleus	-3.067	-2.142	-0.047	0.9	1.409	1.707	1.468	0.665	0.062	1.971	-5.724	-4.045	-2.614	-1.428	-0.445	1.031	2.035	3.292	3.946	4.031
posttranscriptional regulation of gene expression	-3.149	-2.314	-1.586	-0.955	-0.409	0.469	1.12	1.957	2.39	2.478	-5.769	-4.031	-2.609	-1.452	-0.511	0.879	1.838	3.181	4.189	4.283
GTPase activity	-3.149	-2.832	-2.46	-2.04	-1.582	-0.578	0.489	2.591	4.303	5.257	-5.78	-3.696	-2.105	-0.92	-0.064	0.942	1.393	1.989	3.276	4.966
glutaminase synthesis	-3.15	-2.019	-1.102	-0.376	0.181	0.874	1.148	1.058	1.093	2.264	-5.781	-3.721	-0.393	0.78	1.557	1.881	1.844	0.281	1.029	2.223
gonad development	-3.156	-2.897	-2.397	-1.744	-1.013	-0.439	0.897	2.408	2.179	4.592	-5.823	-3.241	-1.44	-0.259	0.449	0.946	0.897	1.258	3.149	4.604
neuron development	-3.169	-2.25	-1.56	-1.046	-0.661	0.115	0.342	1.553	3.149	3.356	-5.852	-4.602	-3.416	-2.306	-1.279	0.498	1.898	3.699	4.749	6.654
organelle localization	-3.186	-2.241	-1.478	-0.847	-0.42	0.259	0.309	2.14	1.18	0.806	-5.864	-4.184	-2.64	-1.57	-0.569	0.965	1.407	2.037	3.146	4.116
cell junction	-3.275	-2.076	-1.096	-0.316	0.287	1.043	1.335	1.161	0.984	1.954	-5.878	-5.285	-4.544	-3.698	-2.773	-0.806	1.165	4.653	7.348	9.821
positive regulation of phosphate metabolic process	-3.275	-2.432	-1.788	-1.292	-0.898	-0.261	0.359	1.975	3.76	3.852	-5.893	-3.008	-1.013	0.28	1.042	1.542	1.434	1.609	2.899	1.196
multi-organ process	-3.304	-1.91	-0.921	-0.246	0.116	0.654	0.89	1.592	2.391	0.657	-5.907	-3.97	-2.429	-1.272	-0.252	1.113	2.033	3.377	4.222	3.623
regulation of viral process	-3.329	-2.161	-1.387	-0.42	0.229	0.497	1.01	2.592	2.427	1.49	-5.956	-4.533	-3.092	-1.896	-0.855	1.303	2.205	4.041	5.717	7.197
Golgi apparatus	-3.327	-1.161	0.242	1.05	1.409	1.287	0.71	0.119	0.69	-1.018	-6.161	-4.388	-2.908	-1.655	-0.604	1.409	2.143	3.571	4.405	4.6
neuronal cell body	-3.364	-2.326	-2.764	-2.065	-1.238	-0.476	1.872	2.874	2.439	5.006	-6.204	-4.444	-2.952	-1.691	-0.63	1.009	2.169	3.633	4.647	4.644
cellular response to cytokine stimulus	-3.398	-2.659	-1.964	-1.313	-0.705	0.384	1.301	2.597	3.099	2.659	-6.244	-3.822	-1.982	-0.621	0.357	1.493	1.989	2.516	3.268	3.005
membrane	-3.438	-2.297	-1.398	-0.697	-0.154	0.597	1.084	1.821	2.42	2.064	-6.316	-4.129	-2.459	-1.429	-0.637	0.933	1.223	2.565	3.607	3.807
regulation of protein modification by small protein conjugation or removal	-3.474	-2.756	-1.853	-0.863	0.126	1.833	2.867	2.463	0.286	1.372	-6.328	-4.201	-2.551	-1.284	-0.316	1.008	1.89	3.392	4.693	3.666
regulation of mRNA catabolic process	-3.52	-2.809	-2.115	-1.448	-0.817	0.308	1.225	2.418	3.021	3.737	-6.368	-3.949	-2.155	-0.86	0.404	1.094	1.624	2.473	4.164	3.787
negative regulation of intracellular signal transduction	-3.535	-1.938	-3.844	-3.373	-2.463	-0.687	1.377	4.415	4.598	6.717	-6.424	-4.222	-2.399	-0.907	0.298	2.005	2.999	3.648	3.234	1.767
plasma membrane bounded cell projection	-3.558	-2.263	-1.206																	

cluster	gene name	Expected cluster	Expected peak binding time	Slope of error	RMSE
I	ZNF579	IV	64.1	-0.2074	0.651
I	URB2	IV	59	-0.1487	0.498
I	DDX21	III	56	-0.0995	0.407
I	SCAF11	II	41.1	-0.0445	0.388
I	PHF3	II	45.1	-0.0895	0.359
I	URB1	III	49.8	-0.0979	0.359
I	POLR2B	I	7.11E-13	-0.0653	0.240
I	SSRP1	II	35.3	-0.0706	0.236
I	FAM208A	I	37.1	-0.0782	0.234
I	SCAF4	I	20.6	-0.0733	0.214
I	VRMA	II	47	-0.0367	0.191
I	SPOUT1	II	31.4	-0.0483	0.161
I	POLR2A	I	7.11E-13	-0.0227	0.112
I	TCOF1	I	7.11E-13	-0.0149	0.109
I	CSTF2	II	29.6	-0.0135	0.081
I	SUPT5H	I	7.11E-13	-0.0172	0.068
I	PINK1	I	7.11E-13	-0.0217	0.068
I	CSTF3	II	26.2	-0.0112	0.068
I	FIP1L1	II	21.6	-0.0178	0.054
I	PPP1R10	I	7.11E-13	-0.0131	0.052
I	SUPT6H	I	7.11E-13	0.00211	0.052
I	SCAF8	I	7.11E-13	-0.0135	0.042
I	SUPT16H	I	7.9	-0.0084	0.036
I	CD3EAP	I	7.11E-13	-0.0079	0.028
I	RPRD2	I	7.11E-13	0.00779	0.025
III	DDX50	V	71.9	-0.2701	0.838
III	DDX42	V	73.6	-0.2632	0.806
III	KHSRP	V	74.1	-0.2687	0.805
III	HNRNPD	V	76.8	-0.2673	0.777
III	EPRS	V	65.2	-0.2413	0.737
III	DDX60L	V	67.8	-0.2345	0.722
III	ZNF385A	V	75.3	-0.2302	0.683
III	CMSS1	V	68.9	-0.2271	0.667
III	FAM133B	V	67.8	-0.2253	0.660
III	PPHLN1	V	69.2	-0.2176	0.640
III	DDX31	V	68.1	-0.1958	0.619
III	FSCN1	V	65.2	-0.212	0.614
III	KNOP1	V	66.6	-0.2016	0.606
III	CIRBP	V	71.9	-0.2066	0.600
III	FUBP1	V	65.8	-0.1955	0.586
III	HNRNPUL2	V	66.4	-0.1875	0.553
III	GPATCH4	IV	64.5	-0.1816	0.538
III	EWSR1	IV	66.8	-0.1752	0.532
III	CCDC59	IV	65.5	-0.1779	0.528
III	RBM34	IV	62.9	-0.1682	0.515
III	DHX33	IV	67.6	-0.1683	0.508
III	CHD1	IV	66.9	-0.1723	0.504
III	TTF1	IV	67.3	-0.1717	0.501
III	TRNAU1AP	IV	64.8	-0.1611	0.496
III	HNRNPA3	IV	69.1	-0.1697	0.495
III	APOBEC3B	IV	64.3	-0.1715	0.494
III	SPEN	IV	60.2	-0.1643	0.489
III	CAFAP4	IV	59.9	-0.164	0.484
III	DEK	IV	57.7	-0.1606	0.480
III	ZC3H4	IV	60.4	-0.1536	0.471
III	HNRNPH2	IV	62	-0.1583	0.465
III	ZCCHC17	IV	65.6	-0.1403	0.453
III	PQBP1	IV	50.6	-0.1522	0.443
III	CCAR1	IV	58.2	-0.0983	0.423
III	HNRNPF	IV	62.7	-0.134	0.405
III	TCERG1	IV	60.5	-0.1326	0.397
III	RBM4	IV	62.3	-0.1339	0.389
III	DDX51	IV	54.4	-0.1114	0.387
III	MMTAG2	IV	60	-0.1277	0.386
III	RAB10	IV	51.6	-0.128	0.382
III	HNRNPH1	IV	63.1	-0.128	0.377
III	DDX17	IV	59.2	-0.1159	0.377
III	ANXA7	III	50.2	-0.1153	0.367
III	HNRNPA8	IV	59	-0.1242	0.359
III	PARP1	II	32.5	0.12883	0.356
III	TUBB	III	51.1	-0.1161	0.356
III	CHD2	III	59.6	-0.1182	0.355
III	NOLB	III	52.4	-0.0848	0.354
III	AKAP8	III	59.8	-0.1121	0.347
III	ZC3H18	III	55.8	-0.1094	0.347
III	UZSURP	III	55.6	-0.1024	0.325
III	PRPF6	IV	55.5	-0.0949	0.320
III	USP36	IV	58.3	-0.1061	0.318
III	CUSTOS	III	51.2	-0.0798	0.318
III	NCL	III	50.4	-0.1086	0.316
III	TRA2B	III	32.7	0.10732	0.316
III	PRPF38B	III	52.9	-0.1044	0.313
III	RRP8	IV	54.4	-0.0954	0.312
III	NUDT21	I	7.11E-13	0.09048	0.308
III	HNRNPL1	IV	56.7	-0.098	0.305
III	SLC16A3	IV	55.7	-0.1043	0.304
III	RBMX2	III	51.2	-0.0902	0.303

cluster	gene name	Expected cluster	Expected peak binding time	Slope of error	RMSE
II	SUGP1	III	52.8	-0.0847	0.303
II	NSN	IV	53	-0.1008	0.302
II	DAZAP1	III	56.8	-0.1034	0.300
II	FUS	III	56.3	-0.101	0.299
II	DDX10	IV	54.8	-0.1006	0.295
II	NOL11	III	47.3	-0.0388	0.285
II	SF3B6	III	49.4	-0.0752	0.285
II	SMNDC1	III	53.1	-0.0936	0.284
II	RBBP6	III	51.6	-0.02	0.283
II	ZCCHC8	IV	56.1	-0.0812	0.282
II	SRSF3	IV	57.4	-0.0528	0.280
II	BAZ1B	II	33.7	0.09538	0.279
II	SRSF5	I	14.2	0.08685	0.275
II	RAMAC	III	48.8	-0.0903	0.273
II	RBM12	III	55	-0.0818	0.272
II	CLTC	III	44.6	-0.0821	0.267
II	HNRNPA1	III	45.4	0.07037	0.263
II	ZNF106	III	52.9	-0.0702	0.263
II	TAI15	III	51.8	-0.0784	0.259
II	RBM39	II	32.5	0.07624	0.254
II	RBM10	III	44.3	0.03329	0.248
II	ZCRB1	III	53.6	-0.0792	0.243
II	TCF20	III	48.9	-0.132	0.242
II	CHERP	II	34.7	0.05545	0.240
II	WDR43	II	35.9	0.06771	0.237
II	SNIP1	III	45.6	-0.0395	0.237
II	SF3B2	III	50.5	-0.0511	0.232
II	HNRNPH3	III	52.3	-0.0547	0.232
II	HNRNPA0	III	51.9	-0.0785	0.229
II	PTBP2	III	53.1	-0.0782	0.227
II	SF1	III	55.6	-0.0774	0.227
II	SRRT	III	54.3	-0.0767	0.227
II	RBM42	III	52.9	-0.0683	0.221
II	LYAR	III	31.3	0.06485	0.220
II	RBM3	III	55.7	-0.0696	0.220
II	DUSP11	III	49.3	-0.0388	0.206
II	RTF1	I	8.5	0.01131	0.206
II	SUB1	III	53.8	-0.0438	0.204
II	SART1	III	41.5	0.03754	0.203
II	SURF4	III	35.7	0.05909	0.202
II	SRSF9	III	36	0.06861	0.198
II	UZAF2	III	55.6	-0.0333	0.198
II	RBM5	III	37.5	0.04759	0.192
II	ZNF326	II	35.3	0.0535	0.192
II	DHX15	III	51.7	-0.0417	0.191
II	NONO	III	38.5	0.06239	0.188
II	RBM14	III	52.5	-0.0599	0.187
II	GRWD1	III	47.8	-0.059	0.185
II	ZNF207	III	44.5	-0.0425	0.183
II	KHDRBS1	III	55.1	-0.0616	0.181
II	PABP1	III	46.7	0.04427	0.181
II	RBM25	III	48.5	-0.0289	0.180
II	SRSF10	III	39.4	0.05332	0.176
II	SF3B3	III	47.7	-0.0117	0.176
II	DIDO1	III	38.8	-0.0596	0.174
II	CSTF2	I	13.5	0.06018	0.174
II	RBM19	III	46.3	-0.0273	0.172
II	SFPQ	II	40.2	0.05869	0.172
II	CPSF4	I	15.6	0.05294	0.169
II	RBM4B	II	39.2	0.03654	0.167
II	CSTF1	II	44.1	-0.0266	0.165
II	SRRM1	III	49.8	-0.0333	0.165
II	SON	II	39.1	0.04987	0.164
II	THRAP3	II	37	0.04534	0.164
II	BCLAF1	III	46.6	-0.0306	0.163
II	BLUD1	III	45	-0.0302	0.163
II	SCAF1	II	35.4	-0.0459	0.163
II	SF3B1	III	47.9	-0.0445	0.163
II	SRSF7	III	50.4	0.00816	0.162
II	PUF60	II	39.5	-0.0528	0.161
II	LUC7L	III	47.9	-0.0511	0.161
II	RBMXL1	II	33.5	-0.0135	0.160
II	CPSF7	I	7.3	0.01869	0.159
II	UZAF1L5	II	44	-0.0255	0.157
II	WDR33	II	26.7	0.04669	0.156
II	ELOA	III	33.8	0.03208	0.156
II	SF3A2	II	41.7	-0.0139	0.155
II	RBM7	II	44.3	-0.0311	0.154
II	SMARCA5	III	44.8	-0.0244	0.152
II	RBM6	III	46.2	-0.0509	0.152
II	SAFB	III	31.8	0.0417	0.148
II	SRSF8	III	51.2	-0.0461	0.146
II	ZC3H13	III	50.4	-0.014	0.146
II	HNRNPA2B1	III	49.4	-0.0478	0.145
II	PHF5A	II	39.5	0.02919	0.145
II	CPSF6	I	4.6	0.03707	0.144
II	SF3A3	III	45.2	-0.0151	0.141

cluster	gene name	Expected cluster	Expected peak binding time	Slope of error	RMSE
II	PATZ1	III	32.5	0.02996	0.135
II	LUC7L2	II	42.6	-0.0188	0.132
II	H1FX	III	47.8	-0.0442	0.131
II	TIAL1	III	50.6	-0.0376	0.128
II	SETD2	II	37.5	0.02135	0.127
II	PSPC1	II	39.2	0.04178	0.126
II	SRSF6	II	39	0.0379	0.126
II	DDX46	III	43.4	-0.0238	0.125
II	ACOT7	II	40.4	0.0218	0.125
II	SRSF4	II	41.4	0.03822	0.122
II	XRN2	II	42.2	0.02896	0.121
II	SNRNP70	II	34.3	0.03073	0.120
II	NCOA5	III	49.9	-0.0307	0.119
II	HNRNPK	III	34.2	0.02066	0.112
II	HNRNPU	III	46.8	-0.0334	0.109
II	SNRNP200	III	49.5	-0.0144	0.109
II	PHRF1	II	31.2	-0.0232	0.106
II	RBM15	II	41.7	-0.0291	0.104
II	SRSF1	III	49.9	-0.0029	0.101
II	CDK13	II	34.1	0.03073	0.101
II	WBP11	III	44.5	-0.0318	0.099
II	HNRNPL	III	46.6	-0.0333	0.099
II	SUGP2	III	48.1	-0.0329	0.098
II	SRSF2	III	43.6	0.00969	0.097
II	HNRNPD	II	37.8	0.0141	0.092
II	SF3A1	II	39.9	0.00869	0.086
II	AKAP9L	II	40	0.02105	0.085
II	SF3B4	II	33.9	0.02822	0.081
II	HNRNPA0	III	46.3	0.00922	0.078
II	TRA2A	II	42.1	0.01737	0.076
II	SLC25A3	III	46.5	-0.0153	0.074
II	SLTM	II	44	-0.0034	0.073
II	MFAP1	II	40.2	0.01871	0.073
II	PDCD6	II	41.8	-0.0033	0.069
II	UBTF	II	31.6	0.00505	0.069
II	SLC16A1	II	44.4	-0.008	0.068
II	RBMX	III	49.2	-0.0022	0.067
II	PWP1	III	48.5	0.00221	0.067
II	PRPF40A	II	40	-0.015	0.063
II	LUC7L3	II	41	0.00132	0.063
II	DDX5	II	39.8	-0.01	0.035
III	EIF253	VI	101	-0.4008	1.167
III	ILF3	VI	80.3	-0.3395	0.998
III	NXF1	V	82.5	-0.2943	0.879
III	PNISR	V	79		

III	NBP2	IV	58.5	-0.1088	0.338
III	ER3	II	40.7	0.08882	0.326
III	MTPAP	II	33	0.09146	0.322
III	CHORDC1	IV	47.3	-0.0925	0.321
III	TRMT2A	IV	61.5	-0.1062	0.313
III	RBM15B	IV	58.4	-0.0365	0.312
III	STF2	IV	60.8	-0.0919	0.303
III	CELF1	IV	61.6	-0.1008	0.296
III	STRBP	IV	59.8	-0.0895	0.290
III	DBR1	IV	58.4	-0.0867	0.288
III	RBFOX2	IV	55.5	-0.0751	0.275
III	BAZZA	IV	57.8	-0.0921	0.272
III	ISY1	IV	60	-0.0909	0.269
III	HSPAB	II	33.1	0.07719	0.265
III	RAN	IV	49.8	-0.0888	0.265
III	AP3D1	III	42.4	0.07104	0.260
III	TRMT10A	III	48	0.04401	0.253
III	ADARB1	II	37.6	0.08475	0.252
III	GAPDH	IV	46.8	-0.0856	0.249
III	MBNL1	III	53	-0.0671	0.246
III	NKRF	IV	58	-0.0816	0.241
III	CLK3	III	49.6	0.05123	0.240
III	HNRNPMM	IV	57.4	-0.0776	0.235
III	PHF6	II	30.2	0.02061	0.232
III	AQR	IV	57.2	-0.0609	0.228
III	ZC3H8	II	44	0.07688	0.222
III	HMGAI	III	52.4	-0.0695	0.222
III	BUD23	IV	61	-0.0752	0.221
III	EEF1A1	III	46.3	-0.0525	0.216
III	SUMO3	III	57.1	-0.057	0.215
III	PRPF4B	III	44.3	0.05377	0.215
III	PARP2	III	44.7	0.07387	0.214
III	ZFC3H1	III	49.7	-0.0401	0.213
III	RRP12	IV	57.5	-0.0576	0.211
III	RNMT	III	57.5	-0.0689	0.211
III	FARSA	IV	53.7	-0.0688	0.210
III	ZBTB11	III	47.8	0.01276	0.207
III	DDX47	II	42.2	0.06544	0.202
III	NUMA1	III	42.3	0.05122	0.201
III	PTBP1	IV	56	-0.0452	0.201
III	TARDBP	III	54.3	-0.0676	0.200
III	SLC1A5	III	46.5	-0.0177	0.198
III	ABT1	IV	50.4	-0.0561	0.193
III	DDX56	IV	55	-0.0623	0.190
III	PHF10	III	46.8	-0.0077	0.189
III	SEPRNH1	IV	52.9	-0.0464	0.188
III	XPOS	III	51.6	-0.0572	0.185
III	TRMT1L	III	45.8	0.05315	0.185
III	DDX49	IV	53.4	-0.0627	0.183
III	AP2M1	II	39.7	-0.0245	0.182
III	NSD2	II	44.3	-0.0266	0.181
III	SLC28A6	III	50.5	-0.0317	0.181
III	NVL	IV	55.3	-0.0593	0.180
III	RBM26	III	51.4	-0.023	0.179
III	TRMT1	III	45.3	0.05672	0.178
III	RBM12B	III	55	-0.0593	0.178
III	HSPA5	III	43.7	0.05363	0.174
III	TENT4B	III	46.8	-0.022	0.172
III	REFPN1	III	42.4	0.03407	0.171
III	NKAP	III	52.5	-0.0476	0.169
III	ZNF638	III	50.3	-0.0314	0.166
III	DXH36	III	52.7	-0.0381	0.162
III	CDC5L	III	51.6	0.00094	0.159
III	DUS3L	III	52.2	-0.0346	0.158
III	HSP90AB1	III	46.8	0.03119	0.157
III	DIMT1	IV	56	-0.0486	0.149
III	PPIG	IV	54.9	-0.0459	0.148
III	DROSHA	III	52.8	-0.0498	0.148
III	RBM28	III	52.8	-0.0459	0.147
III	COPB2	III	46	0.0246	0.146
III	ZNFANB2	III	48	-0.0036	0.146
III	FRG1	III	46.6	-0.041	0.146
III	XRCC6	III	50.1	-0.0449	0.145
III	LDHA	II	40.2	0.03267	0.145
III	FAM50A	III	48	-0.0202	0.144
III	DXH8	III	53	-0.0485	0.142
III	PRPF3	III	47	-0.0363	0.141
III	AKAP17A	III	52.4	-0.0119	0.141
III	RPA1	II	40.8	-0.0159	0.141
III	TOE1	III	45.9	0.03763	0.141
III	ADAR	III	45.6	0.04299	0.141
III	ARPC1B	III	54.1	-0.0405	0.136
III	ESF1	III	49.7	-0.0397	0.135
III	DDX23	III	46.5	0.01212	0.134
III	PKM	II	38.9	0.02233	0.129
III	HNRNPC	III	53.9	-0.0136	0.128
III	RAVER1	III	49.5	-0.0391	0.127
III	ZMAT2	III	40.4	0.02507	0.127
III	RAVER2	III	47.7	-0.0347	0.123
III	RACK1	III	46.8	-0.0415	0.122
III	SMARCA4	II	46.7	-0.0209	0.121
III	HSP90AA1	III	45.4	0.02863	0.121
III	APEX1	III	55.2	0.02218	0.120
III	SRRM2	III	47.7	-0.0269	0.118
III	ADARB2	III	50.4	-0.0352	0.110
III	TOP2B	III	53.5	-0.0367	0.109
III	FEN1	III	51.2	0.00734	0.109
III	SRSF11	III	49.6	-0.0119	0.107
III	PRPF31	III	45	0.00283	0.107
III	PLAA	II	39.8	0.01423	0.103
III	DDX18	III	52.4	-0.0194	0.102
III	SCAMP3	III	49.2	-0.0083	0.098
III	ARL6IP4	III	50.4	-0.0224	0.096
III	ISY1	III	46.7	-0.002	0.095
III	MATR3	III	47.1	0.00463	0.094
III	SNW1	II	46.2	0.02973	0.093
III	RCC2	II	40.3	0.01303	0.089
III	UTP15	II	43.4	0.01399	0.085
III	METTL6	III	51	-0.0044	0.083
III	TKT	III	47.3	-0.003	0.082
III	DKH9	III	45.2	0.00702	0.079
III	ISG20L2	III	51.2	-0.0244	0.076
III	SNRPA	III	48.4	-0.0034	0.074
III	NSUN2	III	50.4	0.02175	0.073
III	RBM27	III	48.6	-0.0175	0.071
III	EFTUD2	III	47.5	-0.0179	0.064
III	TCP1	III	47.3	-0.0147	0.061
III	HMG81	III	48.1	-0.0007	0.052
III	ILF2	III	48.4	-0.0017	0.051
III	WDR75	II	44	-0.0003	0.050
III	PCBP2	III	48.4	-0.0055	0.049
III	TECR	III	43.4	-0.0065	0.047
III	DHX16	III	47.4	0.00644	0.040
III	DKH9	III	52.1	-0.004	0.038
III	SAFB2	III	47.2	-0.0026	0.024
III	TOP2A	III	48.1	0.00431	0.023
IV	E1F1AY	VI	87.8	-0.2808	0.815
IV	E1F3H	VI	87.5	-0.2175	0.640
IV	IK	II	32.3	0.18257	0.549
IV	PNO1	V	70	-0.1691	0.495
IV	GPATCH8	V	68.4	-0.1225	0.484
IV	GIGYF2	V	79.3	-0.1652	0.480
IV	PARP12	IV	59.7	0.00253	0.460
IV	RPS19BP1	V	69.5	-0.1408	0.435
IV	RBM33	V	67.8	-0.1457	0.433
IV	DHX30	V	74.3	-0.1479	0.430
IV	ESRP2	III	36.7	0.1292	0.402
IV	H1TASF1	IV	51.6	0.09479	0.384
IV	DDX27	III	53.4	0.09189	0.351
IV	ERAL1	V	60.5	-0.1062	0.347
IV	RBM38	IV	62.6	-0.0648	0.345
IV	C1orf131	V	65.6	-0.0775	0.327
IV	RBM47	IV	66.1	-0.0933	0.323
IV	ZCCHC9	IV	63.3	-0.0771	0.297
IV	RTC8	IV	54.9	0.06601	0.288
IV	NOM1	IV	60	-0.0819	0.273
IV	SAP18	IV	58	0.07634	0.272
IV	CRNKL1	III	50.7	0.06171	0.263
IV	REXO4	IV	61.3	-0.0868	0.255
IV	PNN	IV	58.5	0.0614	0.242
IV	RP9	III	51.1	0.04089	0.238
IV	LDHB	IV	54	0.06568	0.222
IV	ACIN1	IV	59.9	-0.0093	0.216
IV	CHD3	III	49.6	0.06471	0.212
IV	RNPS1	IV	63.3	-0.071	0.211
IV	NOP16	IV	65	-0.0537	0.205
IV	PUM3	IV	64.5	-0.065	0.200
IV	DDX24	IV	60.4	-0.0386	0.191
IV	HMCES	IV	53.8	0.04691	0.183
IV	RCL1	IV	56.8	0.04098	0.182
IV	LARP7	IV	50.9	0.04737	0.178
IV	ZC3H14	IV	64.1	-0.0094	0.177
IV	FAM98B	IV	57.4	0.01062	0.174
IV	ALKBH5	IV	63.3	-0.0519	0.170
IV	PTBP3	III	54.2	-0.0303	0.169
IV	ZC3H11A	V	70.9	-0.049	0.169
IV	SNRPD1	III	54.3	-0.0091	0.165
IV	TRMT6	IV	57.1	0.02474	0.158
IV	EXOSC9	IV	56.6	-0.0435	0.156
IV	EXOSC10	IV	62.3	-0.0485	0.150
IV	TPR	III	48.8	0.04877	0.143
IV	DNTIIP2	III	54.7	-0.0027	0.142
IV	NIKF	IV	57.1	0.0082	0.137
IV	NOL9	III	50.6	0.0056	0.134
IV	PMP11	IV	58.7	-0.0362	0.131
IV	DHX37	IV	54.8	0.04321	0.126
IV	RC3H1	V	64.8	-0.0349	0.118
IV	DHX38	III	53.9	0.02241	0.108
IV	RSL24D1	IV	58.8	0.02089	0.106
IV	SURF6	IV	59.8	-0.0199	0.100
IV	EXOSC4	IV	58.2	0.00264	0.091
IV	NAT10	IV	52.8	0.02655	0.083
IV	NOP2	IV	60.4	-0.026	0.082
IV	MYBBP1A	III	52.7	0.02567	0.077
IV	BRX1	IV	56.4	-0.0086	0.076
IV	YTHDC1	IV	56.6	0.00307	0.073
IV	DDX52	IV	52.3	-0.0072	0.068
IV	AATF	IV	52.3	0.01654	0.064
IV	SRPK1	IV	53.2	0.00297	0.054
IV	NGDN	IV	57.2	-0.0179	0.054
IV	PAZG4	IV	54.3	-0.0098	0.052
IV	NSUN5	IV	57.3	0.00987	0.043
IV	NPM1	IV	56.4	-0.0035	0.018
V	MTREX	IV	55.5	0.24664	0.738
V	TOP3B	V	63.4	0.16881	0.501
V	TEXT10	IV	68.4	0.12074	0.428
V	NOC3L	IV	62.5	0.09964	0.410
V	RPF2	IV	58.3	0.13129	0.405
V	FTSJ3	IV	60.3	0.12641	0.402
V	CCDC9	V	68.9	0.08714	0.360
V	MSI2	V	88.8	-0.0866	0.357
V	TRIM56	V	68.8	0.0936	0.322
V	DDX54	IV	63	0.09625	0.314
V	PRRC2B	V	70.7	0.05724	0.310
V	NOL12	V	68.3	0.08278	0.305
V	SPATS2L	V	69.4	-0.04	0.297
V	CCDC137	IV	62.1	0.01521	0.281
V	POLDIP3	V	82.2	-0.074	0.230
V	UPF3B	V	70.7	-0.0709	0.227
V	NCBP3	V	71.7	0.06355	0.220
V	TUT7	V	67.1	0.05912	0.217
V	DDX55	V	71.1	0.02508	0.213
V	SYNCRIP	V	74.1	-0.035	0.207
V	AP5	V	69.5	0.01042	0.185
V	ALREF	V	66.6	0.05577	0.185
V	MAP4	V	67	-0.0329	0.176
V	HELZ2	V	68	0.03019	0.170
V	SARNP	V	77.6	-0.0487	0.168
V	DDX1	V	71.9	0.03416	0.163
V	PTCD3	V	67	0.02092	0.162
V	NOP53	V	83.6	0.05135	0.151
V	TSNAX	V	75	-0.0438	0.145
V	NFX1	V	72.6	0.03937	0.139
V	MKRN2	V	65.9	0.01986	0.133
V	E1F4A3	V	69.9	-0.0436	0.126

VI	YTHDF2	VI	112.1	0.00278	0.013
VII	LSM14B	V	68.5	0.35314	1.080
VII	FAM120C	V	68.4	0.33196	0.966
VII	PURB	V	75.9	0.29207	0.845
VII	STAU2	V	74.2	0.28439	0.827
VII	UBAP2L	V	86.3	0.23182	0.723
VII	FAM120A	V	82.1	0.23827	0.708
VII	PYMT	VI	87.2	0.21211	0.665
VII	LARP4B	VI	88	0.21476	0.662
VII	ZNF1	V	87.9	0.19828	0.590
VII	USP10	VI	102.6	0.16231	0.471
VII	UBAP2	VI	114.9	0.15809	0.464
VII	EIF4B	VI	116.9	0.1238	0.373
VII	YBX1	VI	105.9	0.1219	0.354
VII	IGF2BP3	VI	107.1	0.1084	0.342
VII	LSG1	VI	83.5	0.10981	0.336
VII	EIF3CL	VI	108.3	0.10442	0.324
VII	ZC3HAV1	VI	98.5	0.10995	0.320
VII	IGF2BP2	VI	106.9	0.10332	0.313
VII	G3BP2	VI	119.6	0.10586	0.307
VII	PRRC2C	VI	107	0.10317	0.302
VII	EIF3L	VI	108.4	0.0848	0.284
VII	FXR1	VI	138.3	0.09015	0.263
VII	MCV10	VII	217.3	0.02518	0.229
VII	SNF1	VI	100.1	0.06515	0.228
VII	EIF3D	VII	235.4	-0.0448	0.224
VII	SERBP1	VII	197.9	0.07631	0.222
VII	PURA	VI	133.8	0.0659	0.222
VII	HDLBP	VII	140.5	0.03487	0.201
VII	YTHDC2	VI	144.4	0.05182	0.183
VII	G3BP1	VII	209.7	0.04701	0.137
VII	FMR1	VII	166.2	0.04163	0.124
VII	FXR2	VII	193.7	0.01564	0.098
VII	PABPC4	VI	130	0.02546	0.097
VII	EIF4G2	VII	200.9	0.02789	0.092
VII	DOX3X	VI	128.3	-0.0066	0.091
VII	EIF3A	VII	213.6	0.02315	0.079
VII	LARP1	VII	249.8	-0.0158	0.064
VII	YBX3	VI	131.6	0.01832	0.054
VII	CAPRIN1	VII	188.6	0.00714	0.047
VII	LSM14A	VI	130.6	0.00994	0.036
VII	UPF1	VII	157.6	0.01131	0.035
VII	YTHDF1	VII	222.7	-0.0094	0.034
VII	IGF2BP1	VII	140.4	-0.0015	0.024

Table 2.6 Accuracy of mRNA binding dynamics prediction using GO annotations

Sequence ID	
IVT_A10	GATGGCTTCCAAGGTGTACGACCCCGAGCAAGCTGACTCATAGATAGCACTACACACTCTGACAGAC AGTGTCTATGCACACGGATCCCTAGATACTGCACTCAGAGTATGTGATGTCTAGATGTAGCTGTACACT CTATGTCTCATGATAGCATGATGCAGATGAGACTCATCTACTGATCTATAGAGCCGG
IVT_A30	GATGGCTTCCAAGGTGTACGACCCCGAGCAAGCTGACTCATAGATAGCACTACACACTCTGACAGAC AGTGTCTATGCACACGGATCCTGCCTACAGAGACAGTAGTGTGAGCAGATATGTATGACTACGTAGCA TACGCTATGACTGACGAGCATATATATGATATGAGACTAGTGTATCACTGTAGCCGG
IVT_A60	GATGGCTTCCAAGGTGTACGACCCCGAGCAAGCTGACTCATAGATAGCACTACACACTCTGACAGAC AGTGTCTATGCACACGGATCCCTCTCGCATAGACATCTCTGTAGTCTGCTCAGAGCGTGTCTCTCATGA GTATATGTGTGTAGAGACTACTGTGCTGATACATATATACATAGACTGAGCGCCGG
IVT_A90	GATGGCTTCCAAGGTGTACGACCCCGAGCAAGCTGACTCATAGATAGCACTACACACTCTGACAGAC AGTGTCTATGCACACGGATCCGACACAGTGTCTATGCTGTCTGTATCTATCTGAGTATAGCTAGTCTAC TCAGAGATCTCATCAGTGCACATATATGACATACAGTCTGATCTCATGTGCCGG
IVT_A120	GATGGCTTCCAAGGTGTACGACCCCGAGCAAGCTGACTCATAGATAGCACTACACACTCTGACAGAC AGTGTCTATGCACACGGATCCGACATGAGTCTATGATCTGTGATGTGCGTGACTATCTGCAGCTCATACT CTGTGTATCATGATCACTCAGCATGAGATCTATGTGTCTGAGAGACAGGCCGG
IVT_A150	GATGGCTTCCAAGGTGTACGACCCCGAGCAAGCTGACTCATAGATAGCACTACACACTCTGACAGAC AGTGTCTATGCACACGGATCCGATGCTCATAGTCACTGTGCACACTATACAGATGTGTGACATGCA GCGTAGAGACATCAGCACAGACATATATCTGAGTATGACTCGTATCATCTGCGCCGG
IVT_A180	GATGGCTTCCAAGGTGTACGACCCCGAGCAAGCTGACTCATAGATAGCACTACACACTCTGACAGAC AGTGTCTATGCACACGGATCCCTCTCGTATCTGTAGTGTACACAGCTCTACTACAGCTCACACTTAGT CTACTACGACAGATCTATGTGTATATGTAGTCTAGCAGTGTCTGAGCCGG

Sequencing adaptors	
Read 1 3' adaptor	AAGTCGGAGGCCAAGCGGTCTTAGGAAGACAA
Read 2 3' adaptor	AAGTCGGATCGTAGCCATGTCGTTCTGTGAGCCAAGGAGTTG

qPCR primer	
18S_fwd	CTCAACACGGGAAACCTCAC
18S_rev	CGCTCCACCAACTAAGAACG
28S_fwd	CTAAATACCGGCACGAGACC
28S_rev	TTCACGCCCTCTTGAACCT
CHAC1_fwd	GTGTGGTGACGCTCCTTGAA
CHAC1_rev	ACTTCAGGGCCTTGCTTACC
CSPG4_fwd	GCTGCAGCTCTACTCTGGAC
CSPG4_rev	GATGGAGTCACTCAGCAGCG
GAPDH_fwd	GTGGAGATTGTTGCCATCAACGA
GAPDH_rev	CCCATTCTCGGCCTTGACTGT
HSPA1A_fwd	CCCCACCATTGAGGAGGTAG
HSPA1A_rev	AGGAAATGCAAAGTCTTGAAGCTC
PCBP1_fwd	GGACAACACACCATTCTCCGC
PCBP1_rev	AGCCTTTCACCTCTGGAGAGCT
PCNA_fwd	GCCAGAGCTCTTCCCTTACG
PCNA_rev	TAGCTGGTTTCGGCTTACAG
PLOD2_fwd	GACAGCGTTCTCTTCGCTCCTCA
PLOD2_rev	CTCCAGCCTTTCTGTGGTACT
SLC7A11_fwd	TGCCCAGATATGCATCGTCC
SLC7A11_rev	GAGGGAAAGGGCAACCATGA
SPINK4_fwd	TGTTGTGGACAGGGAAAGTGC
SPINK4_rev	GCAGACCAGTTGGACATCT

Table 2.7 Oligo and spike-in sequences utilized in this study

3. Conclusion

During the life cycle of mRNA, which includes processes such as transcription, processing, translation, and eventual decay, it interacts with a multitude of RNA-binding proteins (RBPs). These RBPs play a crucial role in determining the fate of mRNA, influencing not only its processing stages but also stability, localization, and functions. Therefore, understanding the mRNA interactome and its remodeling is essential for understanding mRNA.

In this study, a novel method was developed to investigate the mRNA binding dynamics of RBPs by combining metabolic labeling with RNA interactome capture method. mRNA binding dynamics of over 700 RBPs were identified over a 5-hour period following transcription. The sequence of peak binding times of these RBPs aligned with the order of mRNA life cycle, including co-transcriptional processing, splicing, nuclear export, and translation. By introducing a temporal dimension into previous studies on RBPs' localization, functions, and protein-protein interactions, we have significantly expanded understanding of mRNP remodeling and their roles in mRNA regulation. Notably, stress granule proteins exhibited late binding dynamics, suggesting their involvement in the terminal stage of the mRNA life cycle. Some RBPs such as CCDC86 and FAM120A/C displayed unexpected mRNA binding that deviated from their previously suggested functions. The mRNA binding dynamics uncovered in this study provide a critical basis for future investigations into the yet unknown functions and regulatory mechanisms of these proteins.

In conclusion, using a time-resolved mRNP capture method, this study has provided valuable insights into the molecular chronology of mRNP remodeling throughout the mRNA life cycle. It is anticipated that these findings will contribute

to further advancements in our understanding of mRNA regulation and cellular processes.

국문초록

mRNA-단백질 상호작용에 대한 시계열 분석

mRNA는 수많은 RNA 결합 단백질들과 결합하며 mRNA의 일생 동안 결합 단백질 조합은 지속적으로 변경된다. 하지만 이렇게 시간적으로 mRNA 결합 단백질의 종류와 조합이 변하는 것을 알고 있는데도 불구하고 지금까지 mRNA-단백질 복합체 (mRNP)에 대한 연구는 어떤 단백질이 mRNA에 결합하는지에 대한 정보를 위주로 이뤄져 왔고 이러한 단백질들이 어떤 순서로 어떻게 결합하는지에 대해서는 많은 연구가 이뤄지지 않았다.

본 연구에서는 4-thiouridine을 이용한 RNA 표지법과 UVA 크로스링킹, RNA 분리 및 질량 분광법을 결합하여 mRNA의 일생동안 시간대별로 mRNA와 상호작용하는 단백질체에 대한 역학 데이터를 얻었다. 구체적으로는 mRNA가 전사되고 5시간이 지나기까지 10개의 시점 동안 700개 이상의 mRNA 결합 단백질의 변화를 정량적으로 관찰할 수 있었다. 이렇게 확인한 mRNA 결합 단백질들의 mRNA 결합 순서는 기존 연구들을 통해 일반적으로 알려진 단백질의 기능, 세포 내 위치 및 상호작용과 대체적으로 일치하였다. 흥미롭게도 stress granule과 바이러스 RNA에 연관된 단백질들이 오래된 시점까지 mRNA와 결합하는 것으로 발견되었으며 이는 이러한 단백질들이 mRNA 생명주기의 마지막 단계에서 아직 구체적으로 밝혀지지 않은 어떤 역할을 할 수도 있다는 것을 시사한다. 이 연구에서는 또한 기존에 연구되어 왔던 RNA 결합단백질들의 기능연구를 바탕으로 다양한 RNA 결합 단백질들의 mRNA의 결합 역학 예측값을 계산하고 이를 실제 관측한 mRNA 결합 역학값과 비교하였다. 이러한 비교를 통해 밝혀낸 예상치 못한 mRNA 결합 역학을 가진 다수의 RNA 결합 단백질들의 존재는 이 단백질들이 아직 알려지지 않은 기능과 조절 메커니즘을 가지고 있을 수도 있다는 것을 시사한다. 이 연구는 기존의 mRNA 결합 단백질체 데이터에 새롭게 시간적 차원을 도입함으로써 mRNP 리모델링에 대한 독특한 자원과 통찰력을 제공한다.

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감사의 글

박사 학위 과정을 졸업 논문으로 남기며 제 인생에서 짧지도, 길지도 않았던 7년의 지난한 시간들이 비로소 마무리되는 것 같습니다. 때로는 후회하고 좌절하기도 했지만 결국 새로이 알아가는 즐거움과 내가 쌓아온 시간에 대한 뿌듯함 덕분에 이렇게 박사 학위 논문을 작성하는 순간까지 도달할 수 있었던 것 같습니다. 지금까지 많은 사람들의 도움이 있어 미숙했던 제가 한 사람의 박사로서 성장할 수 있었기에 이 자리를 빌려 짧게나마 감사의 마음을 기록하고자 합니다.

먼저 제 연구 생활을 시작했을 때부터 오랫동안 지원해주신 지도교수님이신 김빛내리 교수님과 그 동안 저와 인연을 맺었던 많은 연구실 선후배님들과 대학원 동기들에게도 감사드립니다. 처음 자연대라는 낯선 환경에서 낯선 공부를 시작할 때 이 분들의 조언과 지지가 무엇보다도 큰 힘이 되었습니다. 또한 바쁘신 와중에도 저의 박사 학위 심사를 맡아주신 노유선 교수님, 이현우 교수님, 장혜식 교수님, 김유식 교수님, 김종서 교수님께도 진심으로 감사의 인사를 드립니다.

나보다도 더 나를 믿어주고 응원해준 친구들과 나리, 민영언니, 한결이에게도 감사의 인사를 하고 싶습니다. 훌륭한 이들 곁에서 부끄럽지 않은 친구로 남을 수 있도록 더 열심히 살겠습니다.

연구실 생활에서 때로는 날카로운 비평을 해주는 연구자로 때로는 따뜻한 이해자로서 제 곁을 지켜준 남편, 김동완 박사에게도 감사의 인사를 전합니다. 앞으로도 서로 이해하고 존중하는 동반자로서 함께 살아갈 수 있도록 저도 더 노력하도록 하겠습니다. 남편과 함께 새로운 가족이 되어 응원해주신 시부모님과 가족들에게도 감사드립니다.

마지막으로 사랑하는 저의 가족에게 고맙다는 말을 하고 싶습니다. 제가 세상에서 가장 존경하는 엄훈, 장효순 두 분의 박사님 덕분에 연구를 시작하고 여기까지 올 수 있었습니다. 학위 과정을 겪고 나서야 부모님이 저를 아끼고 사랑하며 길러주셨기에 제가 모든 힘든 과정들을 견뎌내고 이겨낼 수 있었다는 걸 깨달을 수

있었습니다. 학위 과정을 시작할 때만 해도 초등학생이었는데 어느새 자라 제 든든한 지지자가 된 두 동생, 재형이와 재연이에게도 고맙다는 말을 하고 싶습니다. 무엇보다도 저의 대학원 진학을 가장 많이 응원해주셨던 아빠에게 기쁜 마음으로 박사가 되었음을 말하고 가족들 모두 함께 그 사실을 즐길 수 있어 감사합니다.

지금의 제가 있도록 도움을 주신 모든 분들께 감사드리며 이 논문을 마칩니다.

엄부연 올림