IRESbase: a Comprehensive Database of Experimentally Validated Internal Ribosome Entry Sites

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Abstract

Internal Ribosome Entry Sites (IRESs) are functional RNA elements that can directly recruit ribosomes to an internal position of the mRNA in a cap-independent manner to initiate translation. Recently, IRES elements have attracted much attention for their critical roles in various processes including translation initiation of a new type of RNA, circular RNA, with no 5′ cap to support classical cap-dependent translation. Thus, an integrative data resource of IRES elements with experimental evidences will be useful for further studies. In this study, we present a comprehensive database of IRESs (IRESbase) by curating the experimentally validated functional minimal IRES elements from literature and annotating their host linear and circular RNA information. The current version of IRESbase contains 1328 IRESs, including 774 eukaryotic IRESs and 554 viral IRESs from 11 eukaryotic organisms and 198 viruses. As our database collected only IRES of minimal length with functional evidences, the median length of IRESs in IRESbase is 174 nucleotides. By mapping IRESs to human circRNAs and lncRNAs, 2191 circRNAs and 168 lncRNAs were found to contain at least one entire or partial IRES sequences. The IRESbase is available at http://reprod.njmu.edu.cn/iresbase/index.php.

KEYWORDS: IRES; Circular RNA; Long noncoding RNA; Eukaryotic IRES; Viral IRES

Introduction

Translation initiation is a crucial and highly regulated step during protein synthesis in eukaryotes. Generally, eukaryotic mRNAs recruit ribosomes to initiate translation by a canonical cap-dependent scanning mechanism, which requires a methylated cap structure at the 5′ end of mRNAs and is mediated by the eukaryotic translation initiation factors (eIFs). Instead of the cap-dependent manner, a subset of eukaryotic mRNAs can initiate an internal translation through specialized sequences, called internal ribosome entry sites (IRESs), which can directly recruit 40S ribosomal subunits to initiate translation.

The IRES elements were first discovered about 30 years ago in picornaviruses [1], following the discovery of novel IRESs in many other pathogenic viruses (*e.g.*, EMCV, FMDV, and HIV) [2–4]. The IRES elements ensure the efficient viral translation, when canonical eIFs necessary for mRNA recruitment are inhibited in infected cells. Besides the viral mRNAs, IRESs were also found in a subset of eukaryotic mRNAs (*e.g.*, *XIAP*, *p53*, *DAP5*, and *Apaf-1*) [5–8]. The IRESs in eukaryotic mRNAs allow their translation to continue under many physiologically stressful conditions when the cap-dependent translation is suppressed. In addition, for those eukaryotic IRES-containing mRNAs with long and highly structured 5′-UTRs (incompatible with the cap-dependent scanning mechanism), the IRES elements ensure their efficient translation under normal physiological conditions even when cap-dependent translation is fully active [9]. The increasing number of discovered eukaryotic IRESs suggests that IRES-driven translation initiation accounts for a significant proportion of eukaryotic mRNAs. Although the studies of IRESs have been limited, eukaryotic mRNAs bearing IRESs seem to play important roles in diverse processes, including stress responses, cell survival, apoptosis, mitosis, tumorigenesis and progression [10–14].

The two IRES databases, IRESdb and IRESite were built in 2002 and 2005, respectively [15,16]. In addition, the Rfam database collected IRESs as a type of cis-regulatory RNA element [17]. However, they only include IRESs in mRNAs. Recently, the IRES elements were also found in the circular RNAs (circRNAs) and

long noncoding RNAs (lncRNAs) [18]. The circRNAs, *circ-FBXW7*, *circ-ZNF609*, *circ-SHPRH*, *circPINTexon2*, and *circβ-catenin*, were found to be translated into polypeptides mediated by IRES elements [19–23]. The translation of two small open reading frames (120 nucleotides and 141 nucleotides long) within the lncRNA *meloe* was achieved by an IRES-dependent mechanism [24]. Identification of the translation of circRNAs and lncRNAs driven by IRES elements has attracted more attention recently.

The IRESdb database only has 30 viral IRESs and 50 eukaryotic IRESs, and the IRESite database contains 125 IRESs from 43 viruses and 70 eukaryotic mRNAs. The Rfam database built 32 RNA families with about 11 viral IRESs and 21 eukaryotic IRESs. In this study, by manual curation, we developed a novel non-redundant public database and named it IRESbase. This database contains updated experimentally validated IRESs, including 554 viral IRESs, 691 human IRESs, and 83 IRESs from other eukaryotic species.

In order to facilitate development of new IRES-dependent functional regulation studies, we developed a new resource database named IRESbase which is rich with information about human IRESs. This database includes information regarding the genomic positions, sequence conservation, SNPs, nucleotide modifications, targeting microRNAs, host gene, host transcripts (mRNA, circRNA, and lncRNA), GO terms (biological process, molecular function, and cellular component), KEGG pathway annotations, and several critical experimental assay information. In the database, 2191 circRNAs and 168 lncRNAs were found to contain at least one entire or partial IRES element. Among these transcripts, 1012 circRNAs were found to contain an open reading frame (ORF) longer than 300 nucleotides, and all the 166 lncRNAs were found to contain at least two small ORFs (ranging from 60 to 300 nucleotides in length). Our IRESbase database allows users to search, browse, and download as well as to submit experimentally validated IRESs.

Results

Database content

IRESbase is intended to be a comprehensive database that includes both eukaryotic and viral IRESs with experimental evidences and covers not only the IRES sequences and structural information but also the IRES host transcript and gene information. The database currently contains a total 1328 IRES entries, including 774 eukaryotic IRES entries and 554 viral IRES entries. Each eukaryotic IRES entry contains three basic types of records – IRES, gene, and transcript records if available, each viral IRES entry contains only the IRES and transcript records. In total, 1328 IRES records, 725 eukaryotic gene records, 3633 eukaryotic transcript (1274 mRNAs, 168 lncRNAs, and 2191 circRNAs) records, and 588 viral transcript records are included in our established IRESbase. The data sources and the structure of IRESbase are shown in **Figure 1**.

As the available data are different in different species, human IRES records have the largest number of attributes (32 in total, if available); the IRES records for other eukaryotic species and viruses have 20 and 24 attributes, respectively (Figure 1). The 32 attributes of the human IRES record are IRESbase ID, organism, sequence, sequence length, seven critical validation assay information (i.e., bicistronic backbone, positive and negative controls, second cistron expression, tested cell types, methods used to analyse RNA structure, and *in vitro* translation experiments), predicted two-dimensional (2D) structure, minimal free energy (MFE), verified 2D structure, PUBMED ID, reference, host gene ID, host gene symbol, host gene synonym, host mRNA ID and its IRES alignment result, genomic position (location and strand) in hg19, genomic position in hg38, host lncRNA ID and its IRES alignment result, host circRNA and its alignment result, sequence conservation, common single nucleotide polymorphism (SNP), flagged SNP, N6-methyladenosine (m^6A) site, N1-methyladenosine (m^1A) site, pseudouridine modification (ψ) site, 2′-O-methylation (2′-O-Me) site, and predicted microRNA-IRES interaction. The IRES record for other eukaryotic species only has the first 20 attributes, and the first 18 attributes are included in the viral IRES record. The viral IRES record contains six other attributes including viral genome ID (*e.g.*, *NC_006273*), genome shape, virus

type, genomic position (location and strand), coding sequence (CDS) of regulation, and three-dimensional (3D) structure.

As shown in Figure 1, the eukaryotic gene records commonly have nine attributes, which are gene ID, gene symbol, gene synonym, gene note, GO process, GO function, GO component, KEGG pathway, and IRESbase ID. For human, besides the above nine attributes, three other attributes (OMIM ID, OMIM phenotype, and HGNC ID) are included. The eukaryotic transcript records for IRES host mRNA, lncRNA, and circRNA contains 12, 13, and 11 attributes, respectively. The 12 attributes of eukaryotic mRNA record are transcript ID, name, version, sequence, sequence length, IRESbase ID & IRES alignment result, gene symbol, CDS region, protein ID, protein name, CCDS ID, and sequence. For lncRNA record, besides the first seven attributes in the mRNA record, the other six attributes are gene ID, ORF, ORF's coding potential score, ORF's sequence conservation, predicted protein sequence and length. For circRNA record, the 11 attributes are circRNA ID (circBase ID, circRNADb ID, and circAtlas ID) [25–27], genomic location, strand, gene symbol, best transcript, IRESbase ID and the IRES alignment result, ORF, coding potential score, predicted protein sequence, protein length, and reference. The viral transcript record has 21 attributes, including NCBI locus, accession, version, virus name, organism, virus type, virus group, transcript sequence, sequence length, transcript shape, gene name, gene ID, gene tag, gene function, CDS region, protein name, protein ID, protein sequence, IRESbase ID, IRES location, and strand.

Database interface

Simple, advanced, and BLAST search

IRESbase was developed in a user-friendly mode, providing a search engine to find the IRESs of interest. The homepage (Figure S1) offers a search box for querying the IRESbase by IRES ID, gene ID, transcript (*e.g.*, mRNA, lncRNA, and circRNA) ID, protein ID, PubMed ID, chromosomal location, organism name, gene name, protein name or a substring of any of the above keywords. If a keyword (*e.g.*, *FUBP1* or HCMV) is added into the search bar, the results will be shown in a tabular format. By clicking on the IRES ID (*e.g.*, *hsa_ires_00089.1* or *vir_ires_00484.1*), the detailed

information will be shown in three parts: the IRES information, its host gene information, and its host transcript information (**Figures 2 and 3**). Furthermore, the terms in the page are cross-linked to several external databases including NCBI, UCSC, AmiGO, KEGG, HGNC, RMbase, circBase, and circRNADb [25,26,28–32].

In addition, IRESbase provides three additional advanced search options for users, including (1) 'BLAST search', (2) 'Advanced search', and (3) 'Chromosome location'.

(1) BLAST search: this option was designed to find if there was a similar IRES in the RNA sequence of interest. It provides four IRES sequence datasets (*e.g.*, *Homo sapiens*, other eukaryotic organisms, virus, and all organisms) for users. Users can input more than one query sequence in FASTA format. The search results would be summarized in a table containing job title, IRES ID, score, expect, identity, gaps, and strand (**Figure 4**). By clicking the 'Job title,' the alignment detail will be shown at the nucleotide level.

(2) Advanced search: in this option, users can use one or more query fields together to retrieve the IRESs of interest. Different query fields are provided for users to search IRESs of different organisms, including virus, *Homo sapiens*, and other eukaryotic organisms (Figure 1).

(3) Chromosome location: this option was designed for users to find if there was a verified IRES located in the circRNAs of interest through the input of a specific chromosomal region in *Homo sapiens* (hg19 or hg38).

Data browse, download, and submission

Instead of searching for a specific IRES, all entries of IRESbase were grouped by organism, GO & KEGG, chromosome, and transcript type. Users can browse the IRES group of interest by clicking the count on the left of the corresponding page. Unlike other existing IRES databases, IRESbase supports users to download all the IRES records together in a simple tab-delimited format or to download each IRES record separately in a standard PageTab (Page layout Tabulation) format, which only contains several basic IRES information and the validation assay information. In

addition, users can also select those IRES attributes of interest to download in an Excel-compatible format.

IRESbase allows and encourages users to submit novel experimentally validated IRESs. In the submission, several basic IRES information (*e.g.*, IRES sequence, organism, host gene ID, host gene name, and host transcript ID) and validation assay information (*e.g.*, bicistronic backbone, positive and negative controls, second cistron expression, tested cell types, methods to analysis RNA structure, *in vitro* translation experiments, and PubMed ID) should be provided. In addition, users can also submit novel verified IRES by emailing a PageTab format file, in which all the essential information should be assembled. The submitted record will be included in the next release after manual check by our curators.

Comparison with existing IRES databases

The current version of IRESbase contains the largest collection of experimentally validated IRESs in 11 eukaryotic organisms and 198 viruses. When compared with the existing IRES databases, IRESbase contains the largest number of eukaryotic IRESs and viral IRESs, totally including 1328 IRESs, while Rfam, IRESdb and IRESite only contains about 32 IRESs, 80 IRESs, and 135 IRESs in total, respectively (**Figure 5A**). In particular, IRESbase is the first database containing IRESs found in circRNAs and lncRNAs (Figure 5C). Moreover, IRESbase has minimal data redundancy. Unlike the IRESite database which collects all the truncated overlapping 5′ UTR sequences validated to contain IRES activity, IRESbase only stores the shortest functional sequences as the core IRES region. The median length of IRESs in IRESbase is 174 nucleotides, which is much shorter than that in IRESite (Figure 5B).

In addition, IRESbase provides richer information and more useful functions than other IRES databases. Besides the experimentally verified 2D structure of 56 IRESs, IRESbase collected 12 IRES 3D structure and predicted 2D structure for all of the IRESs with Vienna RNA package [33]. It also provides more annotations, including genomic positions, sequence conservation, SNPs, nucleotide modifications, and targeting microRNAs for human IRESs. And apart from the IRES host transcripts collected from literature, IRESbase also provides many other potential IRES host

transcripts (mRNA, lncRNA, and circRNA) predicted by sequence identity. Compared with existing databases, IRESbase provides more query fields (*e.g.*, genomic location, gene synonym) and search methods (fuzzy, advanced, and BLAST search). Additionally, the entire IRES dataset or those matching specific terms can be easily batch downloaded from IRESbase.

Data statistics and analyses

In addition to 5′ UTRs, IRESs were also found in the CDS region. In the 691 human IRESs, 60% IRESs were found to be located only in the 5′ UTR region, 27% IRESs crossed the start codon, and 4% IRESs were only in CDS regions (Figure 5D). To analyse the functions of human IRESs, the gene set enrichment analysis was performed for the human IRES host genes using Metascape (www.metascape.org) [34]. As shown in Figure 5E, the most significant term is 'hsa05200: Pathways in cancer.' The enriched terms indicate that human IRESs may play important roles in cancer, cellular stress response, virus infection, and cell signalling.

As early as 1995, IRESs in mRNAs have been shown to be effective in initiating the protein synthesis of artificial circular RNAs [35], and in recent studies, IRESs found in circRNAs were also proved to be able to initiate the translation of linear transcript (*e.g.*, bicistronic transcript) [19–23]. All of the above-mentioned reasons indicate that the activity of IRES is not specific for the RNA type and IRES can play roles in any kinds of host RNAs. As only nine circRNAs and one lncRNAs have been respectively found to be translated via IRES so far, in order to find more potential coding circRNAs and lncRNAs, mRNA-derived IRESs were mapped to circRNA and lncRNA by using the pairwise sequence alignment. Complete 167 IRES sequences derived from mRNAs were found to be located within 371 circRNAs, and 45 complete IRES sequences derived from mRNAs were found in 83 lncRNAs. In particular, three complete IRES sequences derived from circRNAs were found to be located in eight mRNAs. Moreover, 1777 circRNAs and 77 lncRNAs were found to contain partial sequence (at least 30 nucleotides) of mRNA derived IRESs.

In order to investigate the potential coding circRNAs and lncRNAs, open reading frames (ORFs) were predicted for the circRNAs and lncRNAs containing a full or

partial IRES sequence. Of the 371 circRNAs with an entire mRNA-derived IRES element, 261 were found to contain an ORF (> 300 nucleotides). Further, of the 1777 circRNAs with a partial mRNA-derived IRES element, 722 circRNAs were found to contain an ORF (> 300 nucleotides). The lncRNAs were all predicted to contain small ORFs (longer than 60 nucleotides and shorter than 300 nucleotides). And in 61 lncRNAs, the IRESs were found to be located between two small ORFs, which indicated that these lncRNAs may code multiple small peptides. In addition, the coding potential score was calculated for the circRNAs and lncRNAs, and the results suggested that 779 circRNAs and three lncRNAs were able to code proteins and small peptides, respectively.

Discussion and perspectives

In recent years, as a functional RNA element which recruits ribosome to initiate translation in a cap-independent manner, IRES was found to mediate circRNA and lncRNA translation [18,24]. Although only few peptides coded by the circRNA have been found, these peptides were found to play important roles in various biological processes [19–23]. In addition to the ORF, it was found that the coding ability of circRNA further depends on the IRES element. However, so far only a few IRESs are available in existing IRES databases, and the translation initiation mechanism via IRES is still elusive, especially for cellular IRESs. Therefore, there is an urgent need for a comprehensive curated dataset of all experimentally validated IRES elements, which could be a rich resource for functional studies and provides clues for circRNA and lncRNA protein coding ability.

In the near future, we will collect and update more IRES related information, including regulatory proteins, critical sites or regions for their activity, and experimentally verified biological function. We also plan to expand the database with experimentally validated sequences without IRES activity, which can not only help prevent repeated validations, but also facilitate the development of bioinformatics tools for the identification of IRES elements. Finally, as an open-access IRES

database, we hope researchers can not only use its content but also help us update the database with information on new IRESs and provide us with a feedback.

Materials and methods

IRES dataset

To construct IRESbase with high quality information, the experimentally validated IRES sequences were manually searched from literature published before Oct. 14, 2019 using PubMed with either of the keywords “IRES,”, “IRESs”, “internal ribosome entry site”, “internal ribosome entry sites”, “internal ribosomal entry site”, “internal ribosomal entry sites”, “internal ribosome entry segment”, “internal ribosomal entry segment”, “internal ribosome entry sequence”, and “internal ribosomal entry sequence” in the titles or abstracts (Figure S2). We manually examined the abstracts of the retrieved literature, further examined the corresponding full texts and validated a novel IRES through experiments. As to the literature studying previously discovered IRESs, we further found the original publications through their citations. For published reviews and databases of IRESs, we checked all the citations of their collected IRESs, and located the original publications which discovered and validated these IRESs. The sequences of experimentally validated IRESs together with experiment information essential for the validation, including bicistronic backbone, positive and negative controls, second cistron expression, tested cell types, methods to analyse RNA structure, and *in vitro* translation experiments, were extracted. Instead of collecting all the truncated 5′ UTR sequences experimentally validated to contain IRES activity as IRESite did, only the shortest one was preserved in IRESbase to reduce data redundancy (Figure S3). In total, from 236 literature, 1328 experimentally validated IRES sequences, including 554 viral IRESs, 691 human IRESs, and 83 other eukaryotic (i.e., mouse, fly, yeast, *etc.*) IRESs, were collected.

Collection of IRES sequences

As the available IRES sequence-related information are varied in different literature, we manually extracted the IRES sequence using different methods (Figure S2), which

can be roughly classified into three categories: (a) extracted IRES sequence directly from the figure of its 2D structure, (b) extracted IRES sequence indirectly through the information of its host transcript and position, and (c) extracted IRES sequence by using the NCBI BLAST tool with the forward and reverse primers reported in the literature. Note that if more than one of the overlapping sequences was experimentally validated to contain IRES activity in literature, only the minimal functional one in them was selected (Figure S3). In addition, the IRES sequences derived from different literature were compared pair wise, and if the sequence identity was over 90%, only the shortest one was selected.

Annotation of IRESs

We searched and collected the 2D structures of IRESs (or IRES host 5′ UTRs) from literature. The 3D structures of IRESs were manually searched and collected from the PDB, PDBj, and PDBe databases [36–38]. The sequences in the collected IRES 2D structures were manually extracted from the corresponding figures, and then the IRES-matched regions were calculated by sequence alignment. In addition, for all IRESs, the secondary structure and the minimal free energy (MFE) were also calculated using RNAfold of Vienna RNA package [33].

For human IRESs, genomic position, sequence conservation, single nucleotide polymorphisms (SNPs), RNA modification sites, potential host circular RNA, and microRNA-IRES interaction data were provided. As shown in Figure S4, the IRES genomic positions were obtained by mapping the IRES sequences to their host transcript sequences, and chromosome positions were extracted from NCBI transcript annotation files (GRCh37.p13 and GRCh38.p10) [39]. Based on the genomic positions, the phyloP scores (hg38 phyloP100way) were extracted from the UCSC database [28]. The dbSNP-NCBI database (150 release) was searched for the common SNPs and flagged SNPs within the IRES sequences [40]. The RMBase v2.0 database was searched for RNA modification sites (*e.g.*, N6-methyladenosines, N1-methyladenosines, pseudouridine modifications, and 2′-O-methylations) within human IRES regions [32]. The potential miRNA-IRES interactions were predicted by miRanda (version: aug2010) with a score threshold of 150 [41].

Annotation of IRES host genes and transcripts

The host genes and transcripts of IRESs were collected from the literature, if available. For those IRES sequences without detailed host gene or transcript information in the literature, the nucleotide BLAST in NCBI was used to search for their host genes and transcripts with a sequence identity of at least 95% [42]. For viral IRESs, the closest gene with CDS downstream to the IRES element was regarded as its host gene. For human IRESs, besides mRNAs, we also aligned them to lncRNAs and circRNAs, and only those containing an IRES fragment of at least 30 nucleotides were considered as candidate IRES host transcripts, and 30 nucleotides were derived from the minimum length of known IRES elements.

For each IRES entry, the mRNA and lncRNA information were extracted from the NCBI nucleotide database, and the circRNA information was extracted from circBase, circRNADb, and circAtlas [25–27]. The ORF (< 300 nucleotides) and its corresponding peptide sequence were predicted for each lncRNA, and the ORF (> 300 nucleotides) and its corresponding peptide sequence were predicted for each circRNA. The coding potential score of ORFs was calculated by CPAT [43]. The sequence conservation of ORFs in lncRNA was assessed by conservation score, which was the mean phyloP score [28]. Gene level functional information (i.e., OMIM and Gene Ontology terms of biological process, molecular function, and cellular component) was extracted from the NCBI gene database, and the pathway information was retrieved from the KEGG PATHWAY database [30].

Database construction

The IRESbase database was constructed by the assembly of all curated minimal IRES sequences and structure information, related transcript and gene information, and annotations. IRESbase was configured in a typical XAMPP (X-Windows + Apache + MySQL + PHP + Perl) integrated environment.

Availability

IRESbase is freely accessible at http://reprod.njmu.edu.cn/iresbase/index.php.

Authors' contributions

JZ designed the database structure, extracted IRES related information, constructed IRES datasets, and wrote the manuscript. YL searched and manually collected the IRES sequences from literature. CW and HTZ designed and constructed the website. HZ and BJ joined the study. XJG and XFS conceived the study, supervised the work, manuscript writing and editing. All authors read and approved the final manuscript.

Competing interests

The authors have declared no competing interests.

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Figure legends

Figure 1 Data sources and the IRESbase structure

For record terms, the '*(e)*', '*(v)*', and '*(h)*' tags indicate eukaryotic data, viral data, and human data, respectively. If the tag is located at the end it indicates the tag is shared by all the terms in the line, while the superscript tag indicates that the tag only belongs to the tagged term itself. Terms without tags are commonly used for different species. For query terms, superscript '*e*' is exclusively for the eukaryotic data, superscript '*h*' is exclusively for the human data, while the remaining terms without superscripts are commonly used in different species.

Figure 2 The IRES entry page (Left: *hsa_ires_00089.1*; Right: *vir_ires_484.1*)

The terms shown in the 'miRNA' field of '*hsa_ires_00089.1*' (left) were truncated for easy presentation.

Figure 3 The gene and transcript (mRNA, lncRNA, and circRNA) records in the page of a human IRES entry (*hsa_ires_00089.1*)

The IRES region is marked in red and the boundary codons of the CDS region are highlighted with yellow.

Figure 4 The result page of BLAST search

Figure 5 Statistic and analysis of human IRESs

A. Comparison with other IRES databases based on the number of IRESs curated. **B.** Comparison with IRESite based on the IRES length. **C.** The statistics of human full-IRES host transcripts (mRNA, lncRNA, and circRNA). **D.** The statistics of human IRES location in its host mRNA. **E.** The pathway and biological process enrichment analysis for the human IRES host genes (colored by enriched term).

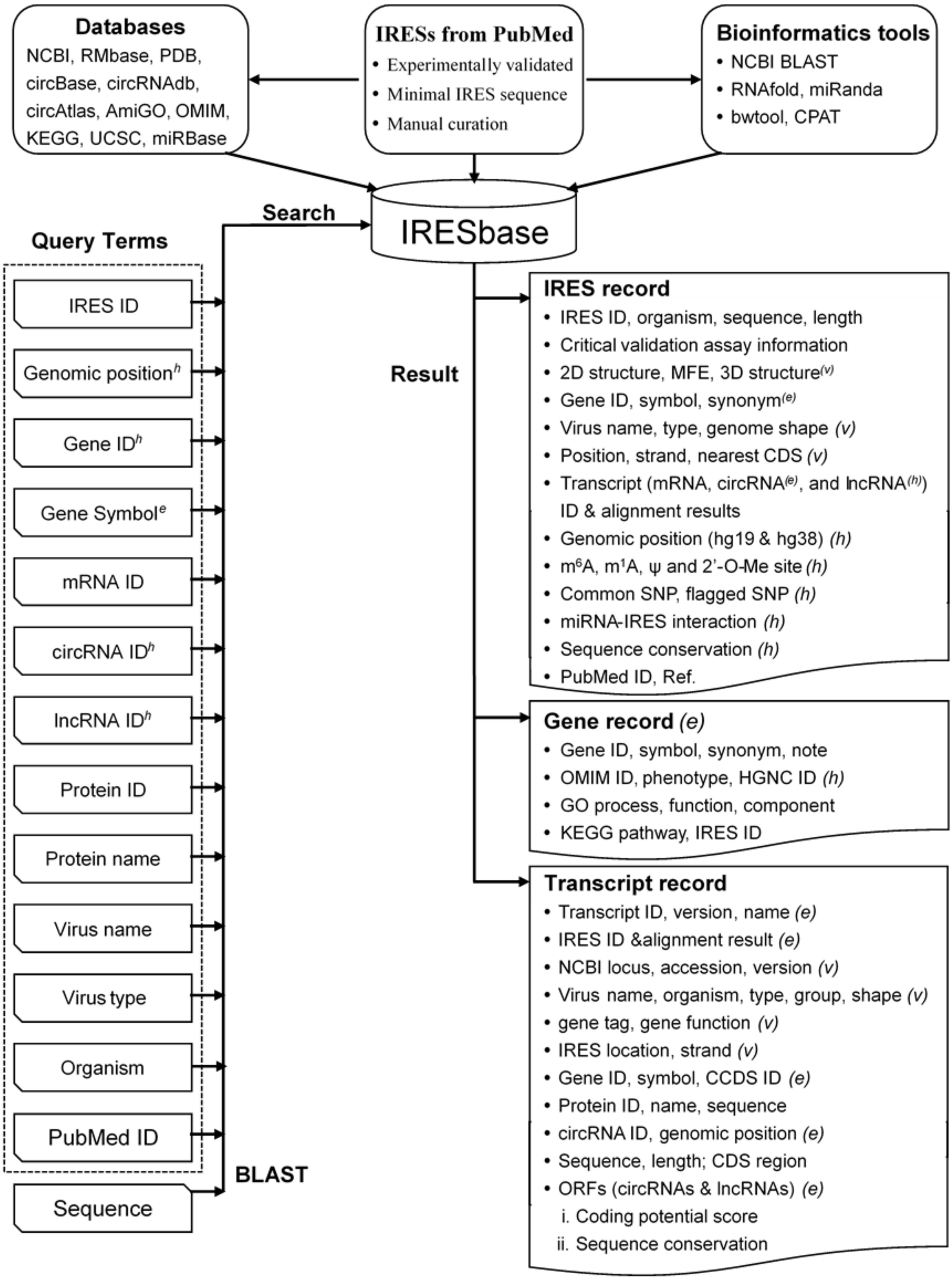
Supplementary material

Figure S1 The homepage of IRESbase

Figure S2 The workflow of collecting experimentally verified IRES elements

Figure S3 The illustration for the selection of the minimal IRES

Figure S4 The illustration for the annotation of human IRESs


Databases
NCBI, RMbase, PDB, circBase, circRNAdb, circAtlas, AmiGO, OMIM, KEGG, UCSC, miRBase
IRESs from PubMed
• Experimentally validated
• Minimal IRES sequence
• Manual curation
Bioinformatics tools
• NCBI BLAST
• RNAfold, miRanda
• bwtool, CPAT
IRESbase
Search
Query Terms
IRES ID
Genomic position[h]
Gene ID[h]
Gene Symbol[e]
mRNA ID
circRNA ID[h]
lncRNA ID[h]
Protein ID
Protein name
Virus name
Virus type
Organism
PubMed ID
Sequence
BLAST
Result
IRES record
• IRES ID, organism, sequence, length
• Critical validation assay information
• 2D structure, MFE, 3D structure[(v)]
• Gene ID, symbol, synonym[(e)]
• Virus name, type, genome shape (v)
• Position, strand, nearest CDS (v)
• Transcript (mRNA, circRNA[(e)], and lncRNA[(h)]) ID & alignment results
• Genomic position (hg19 & hg38) (h)
• m6A, m1A, ψ and 2'-O-Me site (h)
• Common SNP, flagged SNP (h)
• miRNA-IRES interaction (h)
• Sequence conservation (h)
• PubMed ID, Ref.
Gene record (e)
• Gene ID, symbol, synonym, note
• OMIM ID, phenotype, HGNC ID (h)
• GO process, function, component
• KEGG pathway, IRES ID
Transcript record
• Transcript ID, version, name (e)
• IRES ID &alignment result (e)
• NCBI locus, accession, version (v)
• Virus name, organism, type, group, shape (v)
• gene tag, gene function (v)
• IRES location, strand (v)
• Gene ID, symbol, CCDS ID (e)
• Protein ID, name, sequence
• circRNA ID, genomic position (e)
• Sequence, length; CDS region
• ORFs (circRNAs & lncRNAs) (e)
i. Coding potential score
ii. Sequence conservation

IRES Information

IRES ID	hsa_ires_00089.1	
Experimental Assay Information	Type	mRNA-derived IRES
	Organism	Homo sapiens (human)
	Host gene	FUBP1
	Host transcript	NM_003902.4
	Bicistronic backbone	mRFP and eGFP reporters
	Negative control	Empty vector
	Positive control	NA
	Second cistron expression	~3.33-fold (negative control)
	Analysis of RNA structure	NA
	Tested cell type	HEK 293T cells
	In vitro translation (dicistronic or monocistronic)	NA
	PMID	26816383
IRES Length	174	

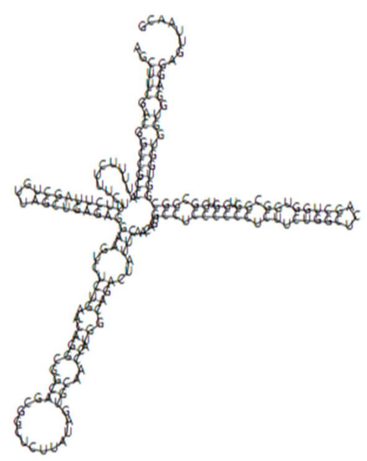
IRES sequence Download

```
  1  AGCTT CGACG GCCGC CATTT TCTTT CTTTC TTAGC
 36  TGTTA GCTGA GAGGA AGTCT CTGAA CAGGC GGCAG
 71  CGGCT CTTAT AGTGC AACCA TGGCA GACTA TTCAA
106  CAGTG CCTCC CCCCT CTTCT GGCTC AGCTG GTGGC
141  GGTGG TGGCG GCGGT GGTGG TGGAG GAGTT AACG
```

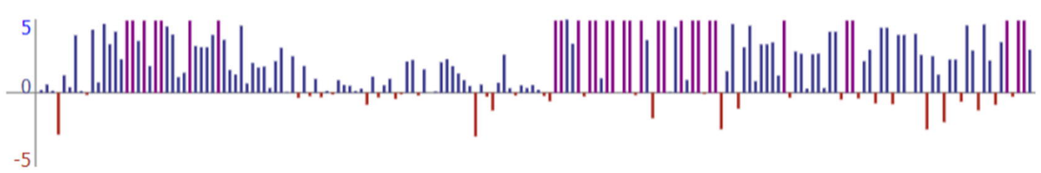
IRES secondary structure (RNAfold) Download

```
  1  ..((( (.((. ((((( (.... ..... ..((( (((((
 36  (...) ))))) )))(( (...( (((.. ((((. .(((.
 71  ..... ..... ..))) ..)). )).)) )).... )))..
106  ....( ((.(( ((((. ((.(( (((.. .)))) ).)).
141  )).)) .)).) ))))) )))).) ).))) ).... ....
```

Minimum free energy (MFE) : -62.20kg/mol



Sequence conservation (hg38 100way) Click here to view/hide detail information



Location		Position	Strand
	hg19	chr1:78,444,604-78,444,777	-
	hg38	chr1:77,978,920-77,979,093	-

N6-Methyladenosines	m6A_site_19129 m6A_site_19130
Host Gene	FUBP1

Host Transcript

Type	ID	Mapped region: Transcript	Mapped region: IRES	Sequence identity	Gap
mRNA	NM_001303433.1	113-286	1-174	100%	N
	NM_003902.4	**113-286**	**1-174**	**100%**	**N**
lncRNA	NR_130152.1	113-286	1-174	100%	N
circRNA	hsa_circ_0013024	1-174	1-174	100%	N
	hsa-FUBP1_000094	1-140	35-174	80.45%	N
	hsa-FUBP1_000091	1-140	35-174	80.45%	N

microRNA — miRNA-IRES interaction predicted by miRanda

microRNA	Total Score	Total Energy	Max Score	Max Energy
hsa-miR-197-3p	154.00	-28.06	154.00	-28.06
hsa-miR-622	151.00	-20.82	151.00	-20.82
hsa-miR-758-5p	160.00	-18.10	160.00	-18.10

Reference

PUBMED ID	Reference
26816383	Weingartengabbay S, Eliaskirma S, Nir R, et al. Comparative genetics. Systematic discovery of cap-independent translation sequences in human and viral genomes.[J]. Science, 2016, 351(6270):240-240.

IRES Information

IRES ID	vir_ires_00484.1	
Experimental Assay Information	Type	linear virus-derived IRES
	Organism	Plautia stali intestine virus (PSIV)
	Host gene	NA
	Host transcript	AB006531.1
	Bicistronic backbone	Renilla and Firefly luciferase reporters
	Negative control	Empty vector
	Positive control	NA
	Second cistron expression	>10-fold (negative control)
	Analysis of RNA structure	NA
	Tested cell type	Rosetta DE3 cells
	In vitro translation (dicistronic or monocistronic)	Rabbit reticulocyte lysate, Di, translatable
	PMID	25652826
IRES Length	191	

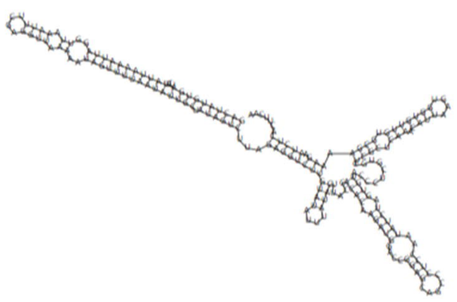
IRES sequence Download

```
  1  GACTA TGTGA TCTTA TTAAA ATTAG GTTAA ATTTC
 36  GAGGT TAAAA ATAGT TTTAA TATTG CTATA GTCTT
 71  AGAGG TCTTG TATAT TTATA CTTAC CACAC AAGAT
106  GGACC GGAGC AGCCC TCCAA TATCT AGTGT ACCCT
141  CGTGC TCGCT CAAAC ATTAA GTGGT GTTGT GCGAA
176  AAGAA TCTCA CTTCA A
```

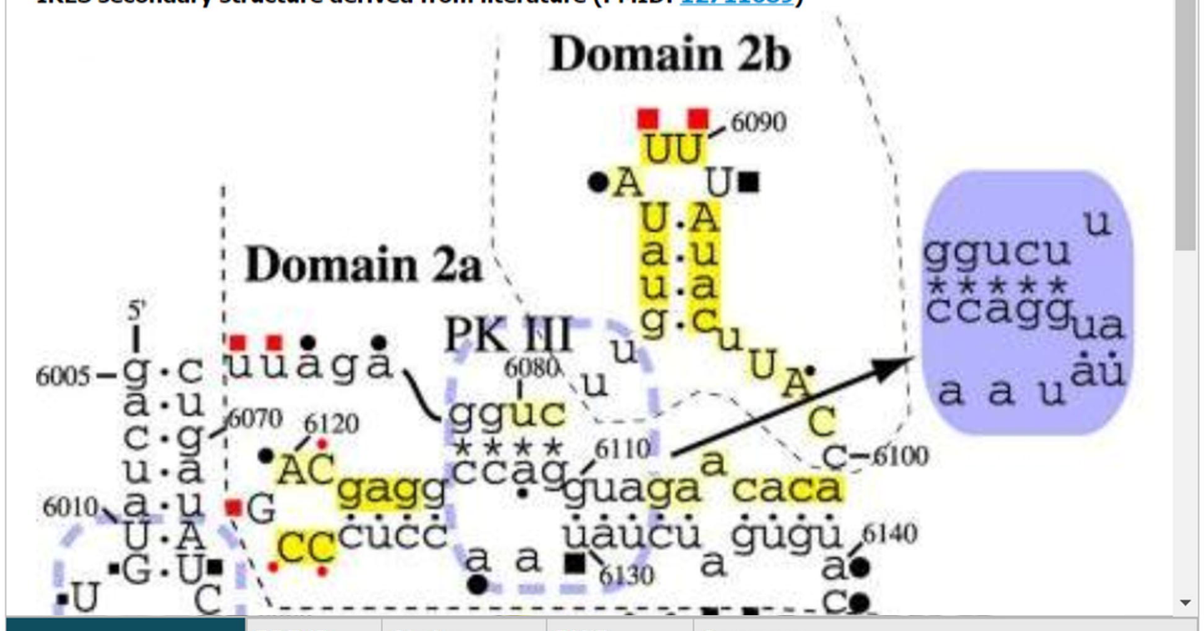
IRES secondary structure (RNAfold) Download

```
  1  ((((( ((((( ...(( ((((( ((((. .((.( (((..
 36  ..))) ).)). .)))) ))))) ))))) ).))) )))..
 71  .(((( ((((( (((.. ..))) ).... .(((( .((((
106  (.... ((((. ....) )))).. ))))) .)))) .....
141  ..... ((((. (((.( (((.. ..))) )))). )))).
176  )))).) )))). ..... .
```

Minimum free energy (MFE) : -40.80kg/mol



IRES secondary structure derived from literature (PMID: 12711689)



IRES 3D structure

PDB ID	Chains	PMID	Sequence
4XEJ	AIRE,BIRE	25652826	AAGCUGACUAUGUGAUCUUAUUAAAAUUAGGUUAAAUUUCGAGGUUAAAAAUAGUUUUAAUAUUGCUAUAGUCUUAGAGGUCUUGUAUAUUUAUACUUACCACACAAGAUGGACCGGAGCAGCCCUCCAAUAUCUAGUGUACCCUCGUGCUCGCUCAAACAUUAAGUGGUGUUGUGCGAAAAGAAUCUCACUUCAA
4V83	AV,CV	21245352	UCGCUCAAACAUUAAGUGGUGUUGUGCGACACUUA
2IL9	A,M	17124290	GCUGACUAUGUGAUCUUAUUAAAAUUAGGUUAAAUUUCGAGGUUAAAAAUAGUUUUAAUAUUGCUAUAGUCUUAGAGGUCUUGCGAAAGCUUACCACACAAGAUGGACCGGAGCGAAAGCUCCAAUAUCUAGUGUACCCUCG

Transcript Information

Transcript ID	Shape	CDS	IRES position	Strand
AB006531.1	linear	<6193..8628	6005..6195	+

Reference

PUBMED ID	Reference
25652826	Colussi T M, Costantino D A, Zhu J, et al. Initiation of translation in bacteria by a structured eukaryotic IRES RNA.[J]. Nature, 2015, 519(7541):110-3.

Gene Information

Gene ID	8880
Gene Symbol	FUBP1
Gene Synonym	FBP; FUBP; hDH V
Gene Note	far upstream element binding protein 1
HGNC	HGNC:4004
OMIM ID	603444
OMIM phenotype	NA
Biological process (Gene Ontology)	regulation of transcription, DNA-templated transcription from RNA polymerase II promoter positive regulation of gene expression
Molecular function (Gene Ontology)	single-stranded DNA binding transcription factor activity, sequence-specific DNA binding RNA binding protein binding
Cellular component (Gene Ontology)	nucleus
IRES ID	hsa_ires_00089.1

Transcript Information (NM_003902.4)

Transcript ID	NM_003902
Transcript name	Homo sapiens far upstream element binding protein 1 (FUBP1), transcript variant 2, mRNA.
Version	NM_003902.4
Length	2522
Gene symbol	FUBP1

IRES

ID	Mapped region		Sequence identity	Gap
	IRES	Transcript		
hsa_ires_00089.1	1-174	113-286	100%	N

CDS region	202..2136
Protein ID	NP_003893.2
Protein name	far upstream element-binding protein 1 isoform 2
CCDS ID	CCDS683.1

mRNA Sequence

```
  1 GTTCT TTCTC AGCCC TAACC CACAC CAGCG CGTTG CCTCG GAAAC ATCGC GAGAT TTTGT TCCTT
 66 CAGTC TCCGC CCCTT TACGG CACGA TGGTC GCGCA AGAAT GTAAT AGAGC TTCGA CGGCC GCCAT
131 TTTCT TTCTT TCTTA GCTGT TAGCT GAGAG GAAGT CTCTG AACAG GCGGC AGCGG CTCTT ATAGT
196 GCAAC CATGG CAGAC TATTC AACAG TGCCT CCCCC CTCTT CTGGC TCAGC TGGTG GCGGT GGTGG
261 CGGCG GTGGT GGTGG AGGAG TTAAC GACGC TTTCA AAGAT GCACT GCAGA GAGCC CGGCA GATTG
326 CAGCA AAAAT TGGAG GTGAT GCAGG GACAT CACTG AATTC AAATG ACTAT GGTTA TGGGG GACAA
391 AAAAG ACCTT TAGAA GATGG AGATC AACCA GATGC TAAGA AAGTT GCTCC TCAAA ATGAC TCTTT
456 TGGAA CACAG TTACC ACCGA TGCAT CAGCA GCAAA GCAGA TCTGT AATGA CAGAA GAATA CAAAG
521 TTCCA GATGG AATGG TTGGA TTCAT AATTG GCAGA GGAGG TGAAC AGATC TCACG CATAC AACAG
586 GAATC TGGAT GCAAA ATACA GATAG CTCCT GACAG TGGTG GCCTT CCAGA AAGGT CCTGT ATGTT
651 AACTG GAACA CCTGA ATCTG TCCAG TCAGC AAAAC GGTTA CTGGA CCAGA TTGTT GAAAA AGGAA
716 GACCA GCTCC TGGCT TCCAT CATGG CGATG GACCG GGAAA TGCAG TTCAA GAAAT CATGA TTCCA
```

Protein Sequence

```
  1 MADYS TVPPP SSGSA GGGGG GGGGG GVNDA FKDAL QRARQ IAAKI GGDAG TSLNS NDYGY GGQKR
 66 PLEDG DQPDA KKVAP QNDSF GTQLP PMHQQ QSRSV MTEEY KVPDG MVGFI IGRGG EQISR IQQES
131 GCKIQ IAPDS GGLPE RSCML TGTPE SVQSA KRLLD QIVEK GRPAP GFHHG DGPGN AVQEI MIPAS
196 KAGLV IGKGG ETIKQ LQERA GVKMV MIQDG PQNTG ADKPL RITGD PYKVQ QAKEM VLELI RDQGG
261 FREVR NEYGS RIGGN EGIDV PIPRF AVGIV IGRNG EMIKK IQNDA GVRIQ FKPDD GTTPE RIAQI
326 TGPPD RCQHA AEIIT DLLRS VQAGN PGGPG PGGRG RGRGQ GNWNM GPPGG LQEFN FIVPT GKTGL
391 IIGKG GETIK SISQQ SGARI ELQRN PPPNA DPNMK LFTIR GTPQQ IDYAR QLIEE KIGGP VNPLG
456 PPVPH GPHGV PGPHG PPGPP GPGTP MGPYN PAPYN PGPPG PAPHG PPAPY APQGW GNAYP HWQQQ
521 APPDP AKAGT DPNSA AWAAY YAHYY QQQAQ PPPAA PAGAP TTTQT NGQGD QQNPA PAGQV DYTKA
586 WEEYY KKMGQ AVPAP TGAPP GGQPD YSAAW AEYYR QQAAY YAQTS PQGMP QHPPA PQGQ
```

circRNA information

circBase ID	hsa_circ_0013024
Location (hg19)	chr1:78414839-78444777
Strand	-
Gene Symbol	FUBP1
Transcript ID	NM_003902

IRES

ID	Mapped region		Sequence identity	Gap
	IRES	Transcript		
hsa_ires_00089.1	1-174	1-174	100%	N

ORF region	90..1r+45
Protein length	657
Coding Probability	99.99%

CircRNA Sequence

```
  1 AGCTT CGACG GCCGC CATTT TCTTT CTTTC TTAGC TGTTA GCTGA GAGGA AGTCT CTGAA CAGGC
 66 GGCAG CGGCT CTTAT AGTGC AACCA TGGCA GACTA TTCAA CAGTG CCTCC CCCCT CTTCT GGCTC
131 AGCTG GTGGC GGTGG TGGCG GCGGT GGTGG TGGAG GAGTT AACGA CGCTT TCAAA GATGC ACTGC
```

Protein Sequence

```
  1 MADYS TVPPP SSGSA GGGGG GGGGG GVNDA FKDAL QRARQ IAAKI GGDAG TSLNS NDYGY GGQKR
 66 PLEDG DQPDA KKVAP QNDSF GTQLP PMHQQ QSRSV MTEEY KVPDG MVGFI IGRGG EQISR IQQES
131 GCKIQ IAPDS GGLPE RSCML TGTPE SVQSA KRLLD QIVEK GRPAP GFHHG DGPGN AVQEI MIPAS
196 KAGLV IGKGG ETIKQ LQERA GVKMV MIQDG PQNTG ADKPL RITGD PYKVQ QAKEM VLELI RDQGG
261 FREVR NEYGS RIGGN EGIDV PIPRF AVGIV IGRNG EMIKK IQNDA GVRIQ FKPDD GTTPE RIAQI
326 TGPPD RCQHA AEIIT DLLRS VQAGN PGGPG PGGRG RGRGQ GNWNM GPPGG LQEFN FIVPT GKTGL
391 IIGKG GETIK SISQQ SGARI ELQRN PPPNA DPNMK LFTIR GTPQQ IDYAR QLIEE KIGGP VNPLG
456 PPVPH GPHGV PGPHG PPGPP GPGTP MGPYN PAPYN PGPPG PAPHG PPAPY APQGW GNAYP HWQQQ
521 APPDP AKAGT DPNSA AWAAY YAHYY QQQAQ PPPAA PAGAP TTTQT NGQGD QQNPA PAGQV DYTKA
586 WEEYY KKMGQ AVPAP TGAPP GGQPD YSAAW AEYYR QQAAY YAQTS PQGMP QHPPA PQSFD GRHFL
651 SFLAV S*
```

lncRNA information (NR_130152.1)

Transcript ID	NR_130152
Transcript type	lncRNA
Transcript name	Homo sapiens far upstream element binding protein 1 (FUBP1), transcript variant 3, non-coding RNA.
Version	NR_130152.1
Transcript length	2376
Gene symbol	FUBP1
Gene ID	8880

IRES

ID	Mapped region		Sequence identity	Gap
	IRES	Transcript		
hsa_ires_00089.1	1-174	113-286	100%	N

ORF

ORF region	ORF length	Small Peptide Sequence	Conservation Score	Coding probability
299..361	63	MHCREPGRLQQKLEVMQGHH*	4.57	0.55%
407..499	93	MEINQMLRKLLLKMTLLEHSYHRCISSKDL*	4.18	1.27%
1199..1369	171	MLQKLLQTFFEVFRLVILVDLDLVVEEEVEVKATGTWDHLVDYRNLILLCQLGKLD*	5.10	11.47%

lncRNA Sequence

```
  1 GTTCT TTCTC AGCCC TAACC CACAC CAGCG CGTTG CCTCG GAAAC ATCGC GAGAT TTTGT TCCTT
 66 CAGTC TCCGC CCCTT TACGG CACGA TGGTC GCGCA AGAAT GTAAT AGAGC TTCGA CGGCC GCCAT
131 TTTCT TTCTT TCTTA GCTGT TAGCT GAGAG GAAGT CTCTG AACAG GCGGC AGCGG CTCTT ATAGT
196 GCAAC CATGG CAGAC TATTC AACAG TGCCT CCCCC CTCTT CTGGC TCAGC TGGTG GCGGT GGTGG
261 CGGCG GTGGT GGTGG AGGAG TTAAC GACGC TTTCA AAGAT GCACT GCAGA GAGCC CGGCA GATTG
```

BLAST Result

Posted date: Apr 28, 2019 9:27 AM	Database : All IRESbase
Molecule type : nucleic acid	Program : BLASTN 2.2.31+

Job title	IRES ID	Score	Expect	Identity	Gaps	Strand
query1	hsa_ires_00089.1	207 bits (112)	6e-056	120/123 (98%)	3/123 (2%)	Plus/Plus
query2	dme_ires_00003.1	248 bits (134)	4e-068	146/151 (97%)	4/151 (3%)	Plus/Plus
query3	-	-	-	-	-	-
query4	vir_ires_00410.1	158 bits (85)	4e-041	85/85 (100%)	0/85 (0%)	Plus/Plus
query5	vir_ires_00320.1	165 bits (89)	2e-043	89/89 (100%)	0/89 (0%)	Plus/Plus

Job title: query1

Length : 121

Descriptions

IRES ID	Score	E value	Identity	Gap	Strand
hsa_ires_00089.1	207 bits (112)	6e-056	120/123 (98%)	3/123 (2%)	Plus/Plus

Alignment

```
            Query  1    CGACGGCCGCCATTTTCTT--TTTCTTAGCTGTTAGCTGAGAGGAAGTCTCTGAACAGGC  58
                        ||||||||||||||||||  ||||||||||||||||||||||||||||||||||||||||
hsa_ires_00089.1  6    CGACGGCCGCCATTTTCTTTCTTTCTTAGCTGTTAGCTGAGAGGAAGTCTCTGAACAGGC  65

            Query  59   GGCAGCGGCTCTTATAGTGCAACCATGGCAGAGCTATTCAACAGTGCCTCCCCCCTCTTC  118
                        ||||||||||||||||||||||||||||||| |||||||||||||||||||||||||||||
hsa_ires_00089.1  66   GGCAGCGGCTCTTATAGTGCAACCATGGCAGA-CTATTCAACAGTGCCTCCCCCCTCTTC  124

            Query  119  TGG  121
                        |||
hsa_ires_00089.1  125  TGG  127
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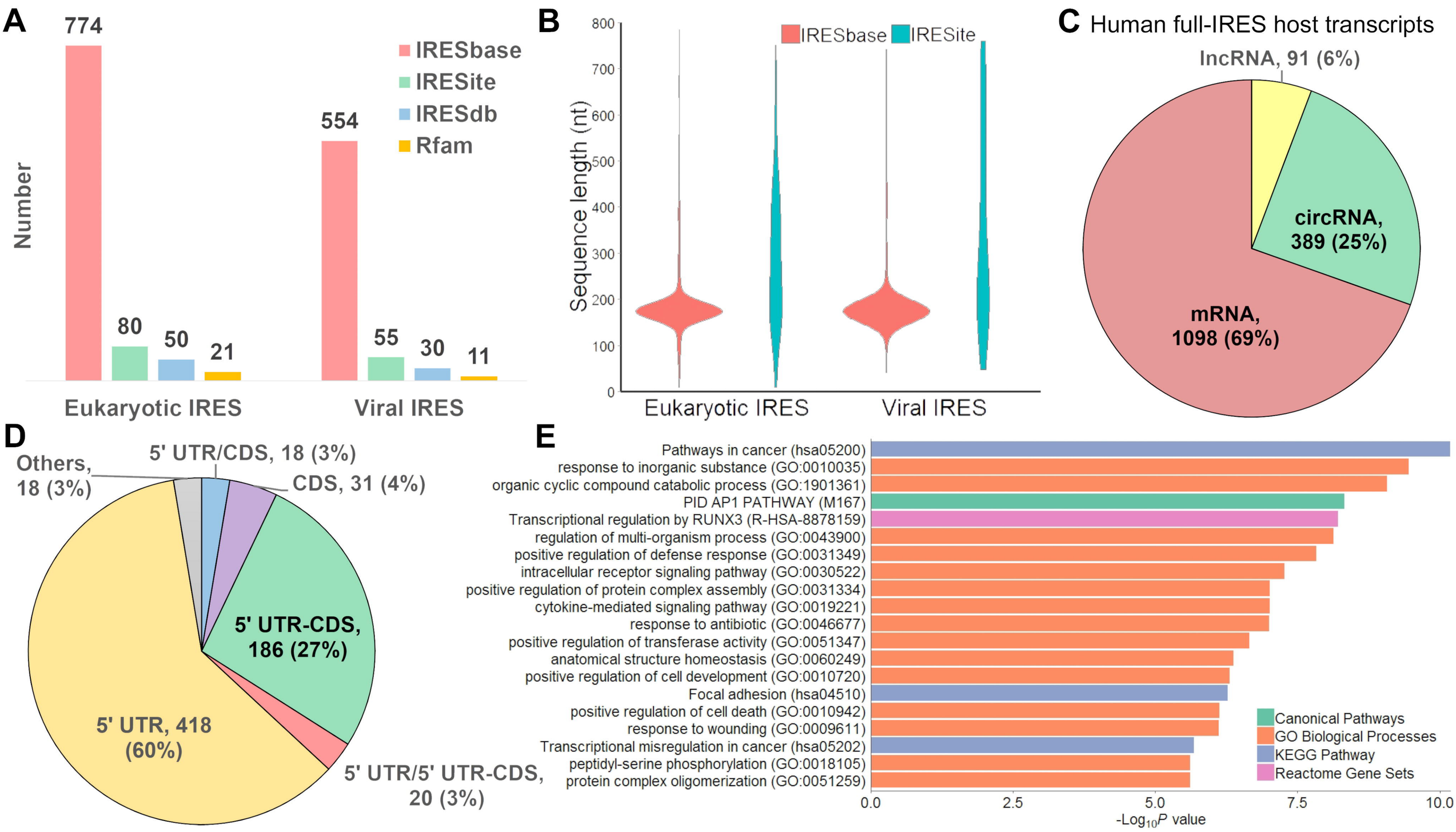
A
774
80
50
21
554
55
30
11
IRESbase
IRESite
IRESdb
Rfam
Number
Eukaryotic IRES
Viral IRES
B
IRESbase
IRESite
Sequence length (nt)
800
700
600
500
400
300
200
100
0
Eukaryotic IRES
Viral IRES
C Human full-IRES host transcripts
lncRNA, 91 (6%)
circRNA, 389 (25%)
mRNA, 1098 (69%)
D
Others, 18 (3%)
5' UTR/CDS, 18 (3%)
CDS, 31 (4%)
5' UTR-CDS, 186 (27%)
5' UTR, 418 (60%)
5' UTR/5' UTR-CDS, 20 (3%)
E
Pathways in cancer (hsa05200)
response to inorganic substance (GO:0010035)
organic cyclic compound catabolic process (GO:1901361)
PID AP1 PATHWAY (M167)
Transcriptional regulation by RUNX3 (R-HSA-8878159)
regulation of multi-organism process (GO:0043900)
positive regulation of defense response (GO:0031349)
intracellular receptor signaling pathway (GO:0030522)
positive regulation of protein complex assembly (GO:0031334)
cytokine-mediated signaling pathway (GO:0019221)
response to antibiotic (GO:0046677)
positive regulation of transferase activity (GO:0051347)
anatomical structure homeostasis (GO:0060249)
positive regulation of cell development (GO:0010720)
Focal adhesion (hsa04510)
positive regulation of cell death (GO:0010942)
response to wounding (GO:0009611)
Transcriptional misregulation in cancer (hsa05202)
peptidyl-serine phosphorylation (GO:0018105)
protein complex oligomerization (GO:0051259)
0.0
2.5
5.0
7.5
10.0
-Log10P value
Canonical Pathways
GO Biological Processes
KEGG Pathway
Reactome Gene Sets