

Intron Retention: Organisation, Genome and Biological Roles and Associated Diseases

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ABSTRACT

Alternative splicing expands transcript and protein diversity by generating multiple isoforms from individual genes. Intron retention (IR), a major form of alternative splicing, occurs when intronic sequences remain in mature RNA transcripts and is now recognized as a regulated mechanism of post-transcriptional gene control. IR can influence mRNA stability, localization, translation, and degradation, leading to transcript clearance through nonsense-mediated decay, nuclear retention, or production of alternative protein isoforms. Its regulation involves splice-site features, cis-regulatory elements, chromatin state, DNA methylation, transcriptional kinetics, and splicing factors. IR displays cell- and tissue-specific patterns and contributes to development and cellular responses to stresses such as hypoxia, heat, and infection. Aberrant IR is associated with cancer, neurodegeneration, aging, and immune dysfunction and may contribute to altered protein function and the generation of immunogenic peptides. Advances in RNA sequencing, long-read technologies, and computational tools have facilitated genome-wide detection and functional analysis of IR. This review summarizes current knowledge of the mechanisms, regulation, detection, function and biological significance of IR, with emphasis on its roles in normal cellular processes, stress adaptation, and disease.

ARTICLE DETAILS

Published On:
07 October 2026

Available on:
<https://ijmscrs.com>

INTRODUCTION

Numerous research investigations have demonstrated the enormous regulatory complexity of RNAs. Alternative splicing (AS) is a method that allows the human genome to diversify transcription output (Carrion et al., 2023). Remarkably, transcripts from over 90% of human genes pass through AS, which alternately connects and skips coding and non-coding sections to guarantee the production of appropriate protein isoforms in the appropriate cellular settings. The mature, polyadenylated mRNA transcript retains one or more introns in certain illnesses, a phenomenon known as intron retention (IR). Mammalian biologists have recently shown a great deal of interest in this genetic pathway. Once dismissed as "splicing noise," IR is now acknowledged as a dynamic, evolutionarily conserved process of post-transcriptional gene regulation (Hua and Xing 2025). IR selectively preserves intronic sequences, albeit at seemingly random locations, in contrast to canonical splicing, which eliminates all introns from pre-mRNAs (Golicz et al., 2021). IR affects mRNA stability, localisation, and translational

potential, according (Biayna and Dumbovic 2025). The long-held notion that IR is merely "transcriptional noise" has been questioned by research data accessible today because of the enormous number of IRTs. IR is now acknowledged as a regulated process that has several effects on gene expression. Retained introns can produce new protein isoforms that aid in expanding proteome and transcriptome profiles, promote nuclear retention, or induce nonsense-mediated decay (Wong et al., 2016; Jacob et al., 2017). Splice site strength, splicing regulatory elements, chromatin structure, methylation patterns, RNA polymerase II elongation rates, and the presence of co-transcriptional splicing factors are some of the mechanisms that are engaged in IR-mediated control (Ge and Porse 2014; Wei et al. 2018). IR has a significant impact on tissue-specific and cell-type-specific gene expression patterns, according to several studies (Zhu et al., 2025). Additionally, it acts as a molecular switch in response to physiological and environmental stresses such infection, heat shock, and hypoxia (Vu et al., 2022). A number of human disorders are increasingly linked to dysregulated IR (Li et al.,

2021). The question of why certain introns are preserved while others are still unanswered questions. Additionally, the relationships between spliceosome subunits and transcripts are yet unknown and the patterns of cis- and trans-acting components are still being investigated. Therefore, it is still necessary to gather crucial evidence to define IR patterns and processes. This field of genomics is at a turning point due to the abundance of genome sequences and bioinformatics tools now available. In this case, staying up to date with knowledge and technological advancements is essential to prioritise research objectives, creates novel detection techniques which opens up therapeutic possibilities for illnesses.

Intrinsic and extrinsic features of IR

RNA splicing, a crucial post-transcriptional process in the majority of eukaryotic cells, combines protein-coding exons to create a mature, translatable mRNA transcript by removing non-coding introns from precursor messenger RNA (pre-mRNA). Proteome integrity and appropriate gene expression depend on this mechanism (Rogalska et al., 2023). The spliceosome, a dynamic ribonucleoprotein (RNP) complex consisting of several related proteins and small nuclear RNAs (snRNAs), aids in splicing. This molecular machine identifies conserved splice sites at the 5' and 3' ends of introns as well as a branch point sequence. It then carries out two sequential reactions: (1) cleaves at the 5' splice site and forms a lariat structure at the branch point, and (2) cleaves at the 3' splice site and ligates nearby exons to form a continuous coding sequence (Wahl et al., 2009). Alternative splicing (AS) promotes diversity by enabling pre-mRNA to be spliced in various ways, whereas canonical splicing typically leads to whole intron deletion. With this technique, a single gene can produce many mRNA isoforms. IR is a distinct and well-known mechanism among the many types of AS (Monteuuis et al., 2019).

Splice sites, sequences, binding proteins

Cis-elements, trans-factors, and epigenetic markers are all part of the multifactorial mechanism that controls IR. Retained introns can be removed during splicing because they are usually shorter, GC-rich, and surrounded by weak splice sites (Golicz et al., 2021). Numerous studies on global gene regulation have examined the characterisation of certain sequence features that are associated with a higher chance of an intron being retained (Braunschweig et al., 2014). Higher relative frequencies of IR are caused by a decrease in splice site strength (Monteuuis et al., 2019). Weak splice sites in protists, fungi, and plants have also been connected to IR. Weak 5' and 3' splice sites, which obstruct appropriate intron excision, are closely linked to IR. Spermatogenesis and the immune response, for instance, often have suboptimal splice site sequences that reduce splicing efficiency (Naro et al., 2019). The presence of intragenic and promoter-associated motifs, which modify IR dynamics in a context-dependent manner, is another crucial sequence-dependent regulation to take into account (Ullah et al., 2023). Certain introns may be retained in part due to GC repeating throughout the intronic

sequence. Sznajder et al. (2018) discovered that very stable RNA secondary structures (hairpins and G-quadruplexes) are formed as a result of GC microsatellite expansion in human tissues and peripheral blood cells. Additionally, a positional bias in the positioning of GC repeats within introns around splice sites (between 0.07-0.8 kb) was found by the study. In a different study, Veloso et al. (2014) discovered an inverse relationship between RNA Pol II elongation and a rise in GC content in human cells. Through binding sites and splicing regulatory elements, transcription factors (TFs) are potential splicing enhancers with sequence patterns that aid in the regulation of IR. Ahrazem et al. (2016) came to the conclusion that IR is a crucial type of AS using RNA-seq datasets from the stages of saffron stigma development. IR was more common in developmental stages and tissues without crocetin accumulation in the saffron CsCCD2 gene, which correlated with particular cis-regulatory promoter motifs that respond to circadian, light, and temperature cues. In plants and vertebrates, retained introns are often shorter than non-retained introns (Schmitz et al., 2017). For instance, the mean size of retained introns in rice is approximately 183 bp, which is much smaller than the mean size of introns (470 bp) (Zhang et al., 2010). Furthermore, motifs for the binding of splicing factors that would otherwise cause the intron to be spliced may be less likely to be present in a short intron. Additionally, longer introns are more likely to have one or more alternative splice sites, which can lead to incomplete splicing or retention and prevent them from being identified or regarded as (fully) retained introns. Other distinctive structural characteristics include different RNA binding proteins, as hnRNPLL, PTBP1, and ASF/SF2, which bind unique SREs, altering IR patterns in a cell-specific way and promoting splicing processes.

The most prominent IR is seen in the SFPQ transcript, where the SFPQ protein binds to the retained intron, is absent from motor neuron nuclei in both mouse models and human sporadic ALS, and has a reduced nuclear presence in valosin-containing protein mutant cells (Luisier et al., 2018). Additional elements in the complex regulation of IR include polypyrimidine tract-binding protein (PTBP1), which, depending on the cell environment, leads to different outcomes for intron-retaining transcripts, including nuclear sequestration, destruction, or translation. By preventing these mRNAs from being exported to the cytoplasm, PTBP1 triggers nuclear degradation through the nuclear RNA surveillance mechanism (Yap et al., 2025).

Insights from genome studies

Researchers link intact introns to the enrichment of serine-arginine (SR) protein binding sites using ENCODE (Encyclopedia of DNA Elements, ENCODE Project Consortium, 2012). An enrichment of IR transcripts in SR protein-depleted HEPG2 cells was found in a database of SR protein knockdown experiments in HepG2 cells to examine the impact on IR (Wang et al., 2011). It is anticipated that intron-bound SR proteins will lower IR by encouraging

splicing (Moon et al., 2017). Certain introns can be retained by RNA-binding proteins such as hnRNPLL. Introns surrounding the exons bound in hnRNPLL may be retained when hnRNPLL binds to certain PTRPC gene exons that produce the CD45 mRNA transcript (Cho et al, 2014).

Some of the differences in IR frequencies between plants and vertebrates may be explained by the presence of transposable elements within retained introns. In the plant species *Gossypium raimondii*, where IR accounts for 40% of all AS events, transposable elements are present in 43% of retained introns. Nevertheless, just 2.9% of all introns have them. A crucial and fascinating characteristic of conserved introns was also revealed by an analysis of IR events and their conservation in a number of vertebrate taxa (Moon et al., 2017). According to research, the untranslated regions (UTR) of intron-retaining genes contain more microRNA (miRNA) binding sites. This is further supported by the longer UTR sequences found in human, mouse, dog, chicken, and zebrafish (Farberov et al., 2023). These results imply that miRNA-induced translational repression and IR-mediated decay may be complementary mechanisms for post-transcriptional gene expression regulation (Iwakawa and Tomari, 2015; Kilchert et al., 2015). The concept of IR has been reinforced and its management clarified by growing knowledge of the conservation of IR features across species and cancer malignancies (Dvinge and Bradley 2015). The extensive Cancer Genome Atlas (TCGA) (Weinstein et al., 2013) makes it simpler to assess IR features by providing genomic data and significant genomic alterations from 33 different types of malignancies. According to the study's findings, the significantly changed form of AS was IR, suggesting that the quantity of IR transcripts in cancer cells may significantly contribute to transcriptome diversity. Except for breast cancer, nearly all malignancies exhibited a considerable increase in IR levels when compared to normal controls (Huang et al., 2023). In order to get insight into the conservation of IR properties, Braunschweig et al. (2014) investigated online databases in seven similar tissues from eleven vertebrate species. Functional conservation has been demonstrated in certain tissues (such as the brain and cerebellum) when compared to other tissues, despite the evolutionary divergence of IR patterns in the analysed vertebrate tissues (Schmitz et al., 2017). Weaker splice sites, a higher GC content, shorter intronic lengths, and a continuing tendency for preserved introns are characteristics of tissue-specific IR. This in-depth evolutionary analysis of IR indicated that intron retaining genes are transcriptionally co-regulated by bidirectional promoters, and retained introns have a higher density of miRNA binding sites.

Epigenetic factors

CpG dinucleotide density is frequently higher in IR, retained introns than in non-retained introns (Wong et al., 2017). A recent investigation into the function of DNA methylation changes in IR control was prompted by this observation. The

findings point to decreased DNA methylation in introns and around splice junctions in a range of normal and malignant cells, such as fibroblasts, blood, neurons, embryos, and colon. While methylation attracts MeCP2, which improves the binding of splicing factors like Tra2b and lowers IR, intronic region hypomethylation is linked to increased IR (Wong et al., 2017). Reduction of the histone methyltransferase SDG725 in rice influences IR in a position-specific way, connecting splicing control to chromatin methylation (Mukherjee et al., 2019). Chromatin state models reduce DNA-only models in predicting IR events, and chromatin structure is a key regulator of IR (Daoud et al., 2015). IR is strongly associated with certain chromatin characteristics, such as extended H3K4me3 histone marks and DNase I hypersensitive sites, especially in short initial introns (Dey and Mattick 2021). A functional connection between IR, long non-coding RNAs, and higher-order chromatin architecture may be suggested by these markers, which may also show clustered nucleosomes (Petrova et al., 2022). IR has been associated with post-translational lysine 36 modifications in histone 3, particularly H3K36me3, in both humans and plants (Guo, 2014). In human kidney tumours, the deletion of the SETD2 gene, which codes for the H3K36me3 methylase, markedly increased IR, indicating the importance of post-translational functions (Simon et al., 2014).

Cellular roles of IR

Although IR has been thoroughly studied in plants, fungi, and viruses, its significance in mammalian physiology has only been acknowledged in the past 20 years. In fact, one study found that IR occurs in a cell type-dependent manner and that transcripts from about three-quarters of human genes have at least one retained intron. Additionally, it was shown that IR was often trying to reduce the quantity of transcripts when and where they were unnecessary (Monteuuis et al., 2019). The regulatory relevance of non-coding regions of mRNA in connection to transcripts that code for proteins has long been studied. Mattick proposed in 1994 that RNAs derived from introns might have developed functional roles in the cell. Since then, a growing body of research indicates that introns and other non-coding regions—which make up over 90% of pre-mRNA—perform autonomous catalytic and regulatory functions (Mockenhaupt and Makeyev 2015). For instance, stable RNA fragments that stay in nuclear and cytoplasmic compartments can be produced via intronic sequences. Stable intronic sequence RNAs, or sisRNAs, were found in *Xenopus* oocytes a little over ten years ago and were identified as coming from excised intronic sections. These were shown to be abundant in the nucleus and surprisingly stable (up to 48 hours) (Gardner et al., 2012). Therefore, the idea that non-coding sections of mRNA, like as introns, have comparatively limited regulatory actions connected to their associated proteins is quickly being contested, highlighting the necessity of exploring their full potential. Changes in IR of particular groups of functionally relevant transcripts are now linked to numerous critical processes, such as cell cycle

progression and differentiation, apoptosis, and stress responses (Dominguez et al., 2016; Wong et al., 2013; Ni et al., 2016).

The transcript may have multiple outcomes if an intronic sequence is retained within mRNA; these outcomes are partly determined by the transcript's location within the cell. In order to prevent translation, IRTs are often erased or degraded, making them almost undetectable using standard experimental techniques (Gudipati et al., 2012). These, however, have distinct roles and characteristics and can either localise in the nucleus (nIRTs) or be steadily expressed in the cytoplasm (cIRTs). IRT stability varies greatly requiring different times to reach their target, according to fate mapping testing (Naro et al., 2017). Additionally, transcripts with intact introns seem to be less stable, suggesting a connection between degradation and IR in regulating gene expression (Dominguez et al., 2016). Interestingly, a number of research results suggest a closer connection between IRTs and their function in the regulation of transcriptional and co-transcriptional splicing (Pek et al. 2015). It has been demonstrated that IRTs operate as nuclear-detained "poised" transcripts that undergo post-transcriptional splicing in reaction to a particular stimulus (Boutz et al., 2015; Mauger et al., 2016).

Nuclear detention of incompletely spliced transcripts appears to be a post-transcriptional mechanism for limiting the production of mRNAs with translation potential in the cytoplasm, as transcripts with a high number of retained introns tend to be primarily localised in the nucleus. The nuclearly pooled Cdc-like Kinases 1 and 4 (Clk1/4) IRT is one such example. Stress-specific splicing enables its export and translation, which in turn permits the phosphorylation of the Serine/Arginine-rich (SR) family of splicing factors (Ninomiya et al., 2011). SR factors can be transported into the nucleus and aid in spliceosome assembly following phosphorylation. Nevertheless, this paradigm depends on the context and transcript and is not applicable in all circumstances. IRTs can simply downregulate the expression of the homologous canonically spliced transcript, as mentioned. The exosome machinery may facilitate IRT breakdown in the nucleus (Humphrey et al., 2020). The typical production of particular haematological components such neutrophils, eosinophils, and basophils is one example (Wong, 2013). Khaladkar et al. (2013) discovered that some intronic sequences are permanently localised in the cytoplasm of neurons, despite the fact that the majority of cIRTs are quickly destroyed and should not be identifiable by RNA sequencing. In mouse cortical neurons experiencing synaptic stimulation, cIRTs have been demonstrated to coordinate the regulation of gene expression programs in a spatiotemporal manner (Mauger et al., 2016). The NMD quality control system's capacity to break down faulty RNA species may be compromised or even overloaded by widespread cIRTs, which could result in the buildup of "faulty" transcripts (Nguyen et al., 2014).

Under stress or certain stimuli, IRTs targeted by NMD may momentarily avoid degradation, possibly gaining translational capacity in a context-dependent way. For instance, following neuronal activity, an IRT of the Arc gene, which has two introns in its 3' UTR, localises to dendrites. The IRT is translated after stimulation prior to NMD (Farris et al., 2014).

By affecting exon inclusion, IR has also been demonstrated to have a role in the control of protein variety in neurons. For instance, cIRTs in combination with proposed cytoplasmic splicing, enhance the variety of BKCa splice variants in hippocampal neurons by directing the stress axis-regulated exon (STREX) to a subset of calcium-activated big potassium channel (BKCa) mRNAs (Bell et al., 2010).

In other situations, RBP nucleocytoplasmic localisation is influenced by the availability of RNA targets (Burke et al., 2022). RBP localisation will therefore be influenced by transcription, RNA stability, RNA export, and compartment-specific RNA decay. RBPs may be sequestered from the nucleus by cIRTs, or they may function as a "poised" reserve of extra-nuclear RBPs in case they are needed to react to a particular stress. IRTs may also control noncoding RNAs present in introns (Ziff et al., 2021). It has been demonstrated that IRTs interact with both canonical and non-canonical miRNA processing pathways. Additionally, they may contain miRNA response elements and compete with miRNA targets to reroute miRNA binding (Melamed et al., 2013).

Short nucleolar RNAs (snoRNAs) may also decrease as a result of IR (Rambaldelli et al., 2026). ID elements found in introns include the Short Interspersed Nuclear Element (SINE) retrotransposons, which have been shown to be a mechanism for dendritic localisation (Buckley et al., 2011). Variations in the assembly and/or disassembly of RNPs into "granules" or biocondensates are among the many stress-reduction strategies used by eukaryotic cells. Prion-like polymerisation of RNPs (or their constituents) most likely closely regulates these activities (Riback et al., 2017). One likely explanation is that IRTs combine with biocondensates to form complexes that make them comparatively stable in the cytoplasm or nucleus. Granules may serve more structural functions as molecular "plasters" following organelle damage, according to a significant recent study. According to research data, intronic sequences show a high affinity for stress granules, a type of biocondensate (Martin et al., 2016). Neeves et al., 2025 report splicing factor proline- and glutamine-rich (SFPQ) and an alternative cytoplasm-predominant isoform with context-specific translation potential both exhibits significantly increased phase separation when exposed to an intronic sequence derived from an annotated SFPQ intron 9 retention sequence.

IR Functions

Recent research has demonstrated the physiological significance of IR in several animals and show that it is involved in numerous biological processes (Wong & Schmitz, 2022). By affecting mRNA stability, localisation,

degradation, translation, and protein synthesis, IR is a significant type of AS that controls post-transcriptional gene expression (Ge & Porse, 2014; Wong et al., 2016). Premature termination codons (PTCs) introduced by retained introns can cause nonsense-mediated mRNA decay (NMD), which regulates the quantity of transcripts and proteins (Lewis et al. 2003). Additionally, intron retention helps regulate cell-type-specific and developmental processes. For instance, AS-NMD controls splicing-factor expression during neural differentiation, whereas IR in *Drosophila* P-element transposase generates diverse protein activity in somatic and germ cells (Adams et al., 1997; Boutz et al., 2007). Thus, auto-regulation and cross-regulation of RNA-binding proteins are made possible by AS-NMD processes in transcripts encoding splicing regulators, which preserve robust and well-coordinated post-transcriptional regulatory networks (Garcia-Moreno and Romao, 2020; Jangi and Sharp, 2014). Therefore, by regulating the quantity of important regulatory proteins, IR might indirectly affect the expression of many downstream genes. According to IR research, they also control the location and accessibility of mRNA for translation. Because intron-retaining transcripts are kept in the nucleus, they cannot be translated right away, enabling the regulation of gene expression in accordance with cellular needs (Wong et al., 2016). IR is a potentially reversible regulatory process since retained introns can occasionally be eliminated, offering a mechanism for quick changes in transcript availability.

IR is especially prevalent in plants, fungi, and other organisms and helps control gene expression throughout development and environmental reactions (Pleiss et al., 2007; Syed et al., 2012). This has been demonstrated by a number of genetic investigations. IR in almost 4,700 genes changed when the rice H3K36-specific methyltransferase gene *SDG725* was knocked out. IR increased near the 5' region and decreased toward the 3' region of gene bodies. These alterations are linked to positional shifts in H3K36me2 and H3K36me3, indicating that IR in rice is position-specifically regulated (Wei et al., 2018). By controlling mRNA accumulation and stability, IR helps regulate gene expression in the fungus *Cryptococcus neoformans*. Intron-dependent effects are partially mediated by nuclear factors like Pab2p and Xrn2p (Goebels., et.al, 2013). Research on quiescent muscle stem cells reveals extensive IR reductions during activation, indicating a function in preserving quiescence and priming transcripts for quick regeneration (Yue et al., 2020). Additionally, IR is linked to the nuclear retention of partially spliced transcripts, which may restrict their translation and export. Furthermore, faulty splicing is linked to transposon silencing and genome defence through the activation of the Spliceosome-Coupled and Nuclear RNAi (SCANR) SCANR-mediated RNAi pathway by stalled spliceosomes (Dumesic et al., 2013). IR may limit transcripts immediate expression while facilitating quick transcript maturation and translation upon activation by keeping them in a poised state

(Yue et al., 2020; Wong et al., 2016). One illustration is the dynamic post-transcriptional regulation mechanism mediated by IR during the differentiation and activation of monocytes into macrophages (Wong et al., 2020). IR of genes such as *ID2*, *IRF7*, *TYMP*, *LAT*, and *ENG* in monocytes prevents early protein synthesis while keeping transcripts ready for later macrophage differentiation. On the other hand, inefficient splicing reduces the expression of *SNRPA1*, *HNRNPH1*, and *THOC6* genes, controlling splicing-factor homeostasis (Wong et al., 2020). According to Wong et al. (2020), IR functions as a molecular switch that suppresses unwanted gene expression, keeps transcripts in a poised position, controls RNA-processing networks, and permits quick innate immune responses. Additionally, IR has a dynamic post-transcriptional system that controls cell fate, development, and differentiation. While IR and NMD work together to regulate genes involved in cell differentiation during granulopoiesis, the elimination of retained introns during neural maturation permits the expression of genes necessary for neuronal development (Boutz et al., 2007; Wong et al., 2016). Additionally, IR plays a developmental role as a developmental switch that controls IR and removal to fine-tune transcript stability, protein synthesis, and cell destiny (Wong et al., 2016; Wong & Schmitz, 2022). As a result, IR aids in regulating inflammation, immunological activation, antiviral defences and infection-induced reactions. According to Deveson et al. (2017), IR controls temperature-dependent sex-specific development sex determination. Lark/RBM4-mediated IR affects host survival and controls gastrointestinal reactions to infection in *Drosophila* (Bou Sleiman et al., 2020). According to Ni et al. (2016), IR mediates the stage-specific gene expression of T immune-cell development. IR regulates gene expression, transcript stability, and antiviral activity as a post-transcriptional regulator of immune responses. According to Li et al. (2021), type I interferon signalling is restricted by LUC7L2-mediated IR of *MITA/STING* genes, which gives innate immunity negative feedback. BUD13, on the other hand, encourages appropriate *Ir7* splicing, whereas its absence raises IR and impairs antiviral defence (Frankiw et al., 2019). Additionally, IR supports transcript variety, stress adaptability, and cardiac gene control. Functional isoforms that are co-expressed with intron-less transcripts in a chamber-specific and stress-responsive manner are produced by IR of the *ANKRD1* gene in cardiomyocytes. These isoforms are translated and rise in diastolic heart failure, indicating that IR plays a role in the self-regulation of cardiac stress responses and isoform diversification (Torrado et al., 2009). Similar to this, AS of *Hltf* gene results in a shortened isoform by partial IR, which connects IR with the control of cardiac transcriptional networks. However, NMD in the heart may also affect the shortened transcript (Wang et al., 2013). During development and cardiac stress, IR offers an extra layer of post-transcriptional regulation that can control the expression of cardiac genes and produce functionally distinct isoforms

(Hunt et al., 2026). Splicing alterations brought on by stress can quickly alter transcript populations, enabling cells to regulate gene expression in response to external stimuli (Pleiss et al., 2007). While aberrant IR brought on by mutations or flaws in splicing control might interfere with gene expression, as in cancer, regulated IR serves physiological purposes (Jung et al., 2015).

Diseases associated with IR

A growing number of human diseases, including cancer, neurodegeneration, aging-related disorders, and hereditary disorders, are linked to aberrant IR. Around 27,049 IR-associated variations (IRAVs) have been found by extensive transcriptome analysis, including over 3,000 potential disease-associated variants connected to autosomal recessive illnesses and cancer drivers (Shiraishi et al., 2022). IR plays a part in disease progression, tumour growth, and immunogenicity. While variations among molecular subtypes point to a connection between IR, tumour phenotype, and disease progression, breast cancer has a unique IR profile with less IR events than nearby normal tissue (Shah et al., 2022). Loss of the *SMARCA4* gene causes extensive IR and produces retained-intron-derived peptides that activate T cells, suggesting roles in tumour immunogenicity in small cell carcinoma of the ovary, hypercalcemic type (SCCOHT) (Raupach et al., 2025). Through telomere maintenance and genomic stability, a functional 5'-UTR IR event in the *STN1* gene controls translation and affects tumour proliferation in lung adenocarcinoma (Huang et al. 2023). By inhibiting the IR of the *MCM7* gene, dysregulation of the splicing factor WBP11 accelerates the growth of ovarian cancer (OC). WBP11 overexpression increases *MCM7* expression and promotes the growth of cancer cells via decreasing the retention of intron 4 of *MCM7*. On the other hand, studies show that WBP11 silencing slows tumour growth, lowers *MCM7* expression, and restores IR (Wei et al., 2024). In addition to non-canonical peptides presented by MHC-I that excite tumor-specific T cells, PRMT5–E2F1-mediated IR can produce ds RNA that triggers innate immune responses. Studies have shown that IR may provide antigens and facilitate treatment. Research on colorectal cancer suggests that IR-derived peptides are identified by patient T lymphocytes and encourage the destruction of tumour cells (Blaszczak et al., 2026). High IR-derived neoantigen (IR-neoAg) load was linked to improved overall survival in pancreatic ductal adenocarcinoma (PDAC), according to Dong et al. (2022). Tumours with high IR-neoAg and HLA-I expression also displayed characteristics of tumours responsive to immune-checkpoint blockade and increased CD8⁺ T-cell infiltration. Several studies have implicated aging as connected with increasing IR which can lead to cellular senescence and age-related dysfunction. IR in genes related to transcription, metabolism, and stress responses is encouraged by an age-dependent decrease in splicing-factor activity. It is shown that IR accumulates in several tissues, especially the liver, in pre-symptomatic *Klotho* animals.

Retained transcripts were concentrated in genes linked to splicing and liver metabolism. The Japanese herbal remedy Juzentaihoto (JTT) partially restores the IR retention, which is linked to starvation-like metabolic stress, together with the recovery of hepatic metabolic gene expression (Katsube et al., 2022). Additionally, it has been shown that aberrant IR results in an extended 5' UTR with additional uORFs and complex secondary structures, which reduces translation of the downstream coding sequence and contributes to disease-associated protein deficiency, a characteristic of several aging-related diseases (Shang et al., 2021).

IR builds up in the ageing mouse and *Drosophila* brains. Also it is further changed in the cerebellum and frontal cortex of AD patients. These alterations include genes that control protein homeostasis and mRNA processing, indicating that abnormal IR may play a role in the shift from healthy ageing to AD pathogenesis (Adusumalli et al., 2021). While *MAPT* gene intron 11 retention results in the shortened Tau11i isoform, which has changed aggregation and microtubule-binding characteristics, IR in the *DDIT4L* gene produces a toxic isoform (DIR) that encourages amyloid- β aggregation and synaptic dysfunction. In ageing and AD models, IR of the *Slc16a3* (*MCT4*) gene has also been found in astrocytes and endothelial cells, especially in inflammatory settings, indicating altered lactate metabolism. Furthermore, sex-dependent IR patterns have been seen in AD brains, especially in genes related to Tau-related pathways and ubiquitin signalling (Adusumalli et al., 2021). IR of stress-responsive genes such *Nr1h2* and *Slc16a3* (*MCT4*) happens before to neurodegenerative alterations in ageing animals, indicating that IR could be an early indicator of ageing and age-related brain dysfunction (Adusumalli et al., 2019; Adusumalli et al., 2021). Congenital and cardiac disorders are linked to IR. By interfering with the translation of *SCN5A* mRNA and generating a shortened Nav1.5 protein, IR can result in hereditary cardiac arrhythmia. 79 bp of intron 14 is retained when the *SCN5A* splice variant c.2262+3A>T activates a cryptic splice donor site. This results in a shortened Nav1.5 protein linked to early-onset persistent ventricular tachycardia and introduces an early stop codon [p. (R818*)]. The findings show that hereditary arrhythmia and cardiac electrophysiological dysfunction can be directly caused by disease-associated IR (Yin et al., 2021). Allgrove (Triple-A) syndrome, a rare autosomal-recessive condition marked by adrenal insufficiency, achalasia, and alacrima, is caused by IR abnormalities. Exon 14 skipping and partial retention of intron 14 are caused by a splice-site mutation (c.1331+1G>A) in the *AAAS* gene, which results in frameshifted transcripts and impairs the function of the ALADIN protein (Kallabi et al., 2016). A splice-site variation in the *WT1* gene (c.1437A>G) causes retention of intron 9 in 46, XX DSD, resulting in an aberrant shortened +KTS isoform and upsetting the usual +KTS/–KTS isoform balance. Despite having a 46, XX karyotype, this mutation can cause testicular or ovotesticular development by

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impairing WT1-dependent regulation of genes involved in gonadal development (Sirokha et al., 2021). As a result, 46, XY people may experience female or ambiguous genitalia and gonadal dysgenesis. Denys-Drash syndrome, which is linked to renal illness and gonadal dysgenesis, is caused by mutations in the *WT1* gene. This illustrates how aberrant intron-dependent splicing can interfere with sex determination and gonadal development (Barbosa et al., 2021; Hammes et al., 2001). Chronic kidney disease and renal fibrosis are caused by aberrant *ENG* gene splicing. The anti-fibrotic short-*ENG* isoform is expressed at lower levels in fibrotic kidneys, although total *ENG* expression is elevated. Antisense oligonucleotides targeting *ENG* splicing is shown to increase the protective isoform and reduced TGF- β -induced pro-fibrotic responses, highlighting IR modulation as a potential therapeutic strategy for renal fibrosis (Gerrits et al., 2024).

DISCUSSION

In recent years, a picture showing a high frequency of AS in the human transcriptome has surfaced (Jiang and Chen 2021). At least half of all human genes appear to undergo alternative splicing, although the actual number is probably higher due to the difficulty in identifying splicing variants of genes with low expression. The biological significance of AS is established for several models. One well-known example of how AS acts as a genetic trigger is the determination of sex in *Drosophila*. Another well-known example is the gene *slo*, which is linked to a calcium-activated potassium channel (Contreras et al., 2013). Although these examples are extremely significant due to their biological significance, they are isolated instances that reflect the particular interests of different laboratories. Because of the breakthrough in genomics and bioinformatics, the cDNA databases are still growing at an exponential rate. This has enabled the detection of splicing variants using an integrated method, in conjunction with the availability of the human genome sequence (Li et al., 2016; Nurk et al., 2022). Additional research is required to completely comprehend the significance of IR in defining RBP function and RBP localisation, as the role of IR in regulating gene expression is becoming increasingly recognised (Mehta et al., 2022). As interest in this kind of AS increases, it is critical to identify optimal practices for future study. RNA sequencing research requires consideration of read depth, library preparation, strandedness, analytical tools, and techniques. For instance, IR will be underestimated by reduced sequencing depth, such as deep sequencing. The methods have high error rates and can identify shorter transcripts. High phase separation propensity should be used in conjunction with heating and shearing techniques to ensure efficient isolation (Vendruscolo and Fuxreiter, 2023). Making sure that reads spanning intron-exon junctions are identified is essential to lessen the chance of incorrectly identifying intron-derived non-coding RNA as intron-retaining transcripts (IRTs).

Understanding antisense transcripts and overlapping genes requires strand-specific sequencing in order to preserve transcript orientation information.

In addition to these technological challenges, there are additional conceptual barriers to overcome in order to guarantee detection accuracy. Beyond cis-features and RBPs, more comprehensive identification of IR regulators is required, taking into account the effects of transcriptional rate, epigenetics, and epitranscriptomics. To fully explore the diversity of IRTs, effective ways to stop their deterioration are required. These days, small drugs (such SMG1 nonsense-mediated mRNA decay associated PI3K related kinase (SMG1) inhibitors) (Cook et al., 2024) or genetic methods (like Up-frameshift 1 (UPF1) knockdown) (Fang et al., 2022) can suppress cytoplasmic RNA degradation pathways like NMD. However, there is still much to learn about the nuclear RNA degradation mechanism in many cellular and environmental contexts. Future research will need to include findings and leads from other disciplines. For example, studies on IR in cancer have demonstrated that IRTs have a range of impacts, such as oncoprotein synthesis, tumour suppressor gene suppression, and neoantigen formation (Manoharan et al., 2026). Because neoantigens are predicted from patient tumour samples, neoantigen cancer vaccines are extremely customised. Cancer vaccines work to activate the adaptive immune system to target tumours and increase antitumor immunity by immunising patients against their neoantigens (Bobisse et al., 2016). These discoveries have shed important light on the biology of IR. The roles of intron retention in physiology and disease are becoming increasingly clear. Further research is necessary to address the many unresolved questions regarding the relationship between intron retention and disease pathogenesis. In disease, is aberrant IR harmful, compensatory, or both? Could this alteration be based on the illness's stage? Is it adequate to treat an aberrant condition by focusing on one or a limited number of events?

IRTs may also be helpful as biomarkers. Sensitivity is one of the advantages, as IR changes often take place before usual differential gene expression changes under cellular stress, making it an ideal biomarker for early detection. IRs can be effectively identified from easily obtained tissues and liquid biopsies using standard RNA sequencing (RNA-seq) processes. Moreover, IRs are dynamic readouts that monitor changes in cellular homeostasis and pharmacodynamic reactions to therapies in real time. For a variety of disorders, targeting subsets of functional coherent IRTs appears to be a manageable therapeutic strategy (Naro et al., 2024). RNA treatments will be advanced in the future by the convergence of several cell and molecular biology approaches.

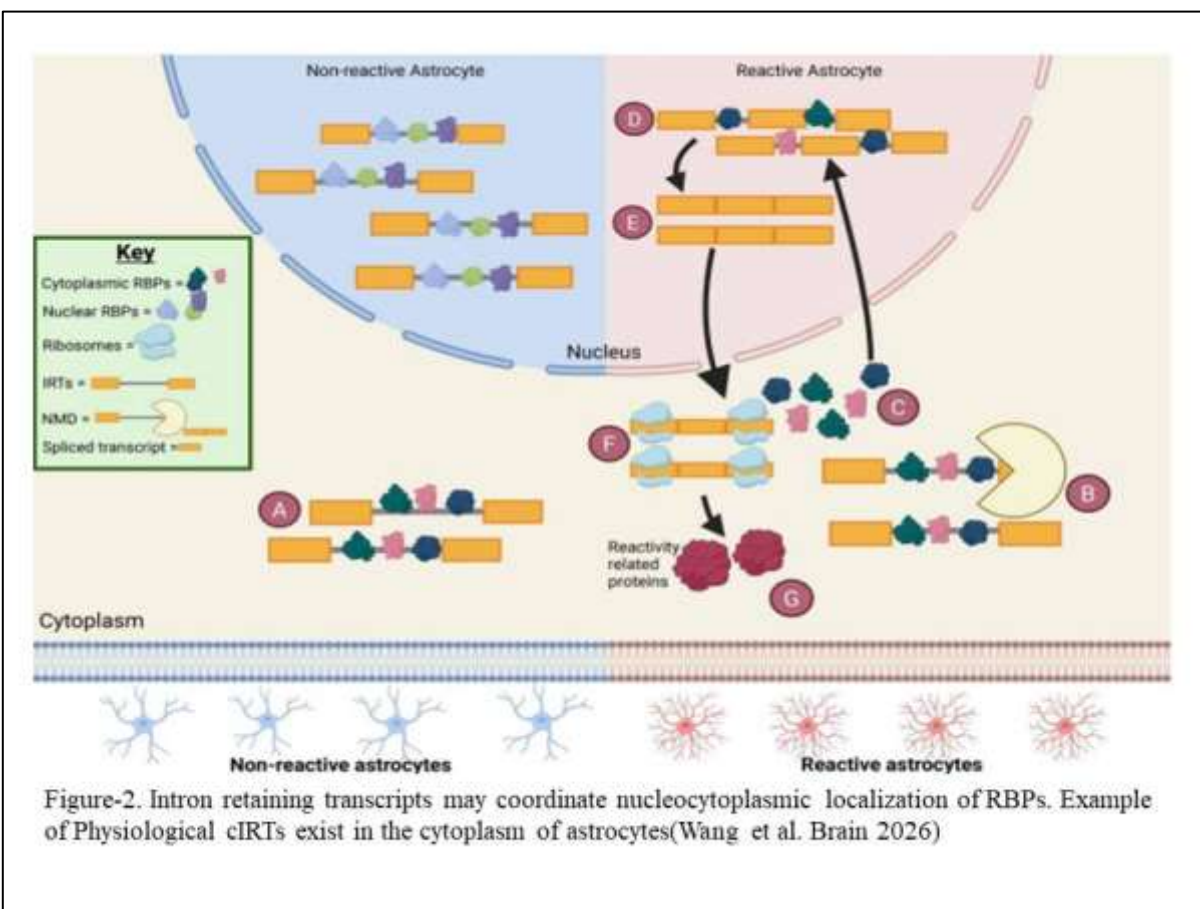
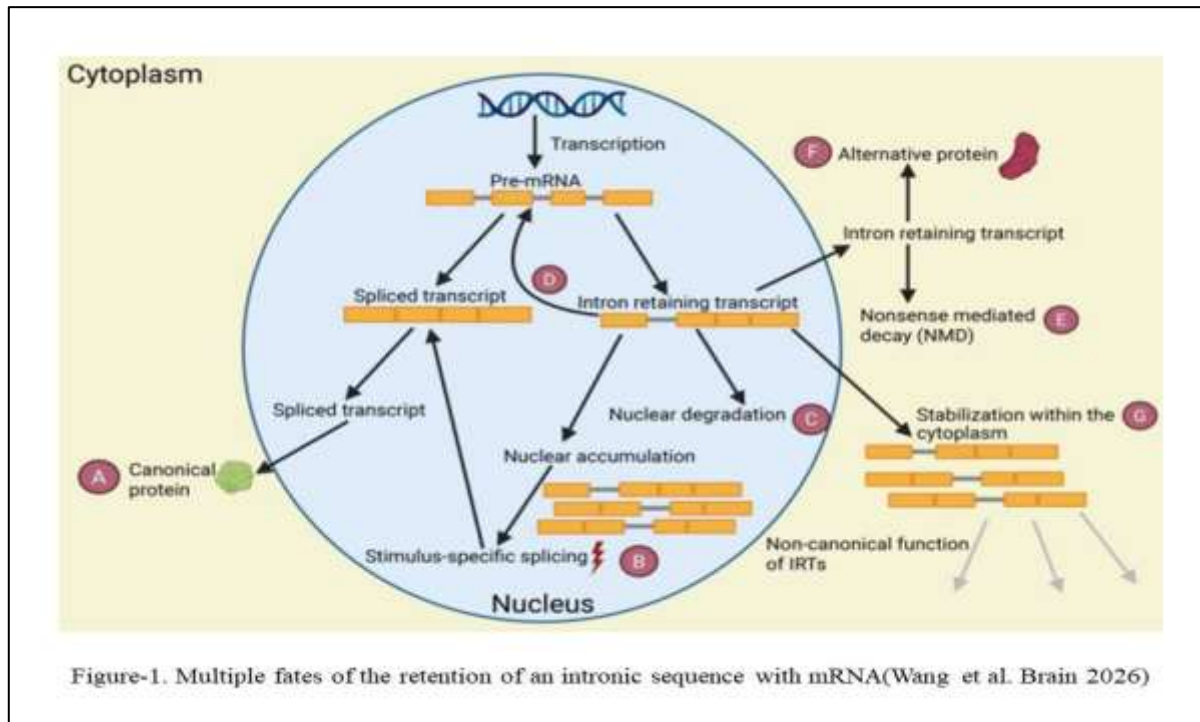
ACKNOWLEDGEMENT

The VC, Principal of Nrupathunga University,

Dr.KiranKumar H B, resource person

Dedicated to Sripada Vallabha Guru and Guru Parampara

Figures:



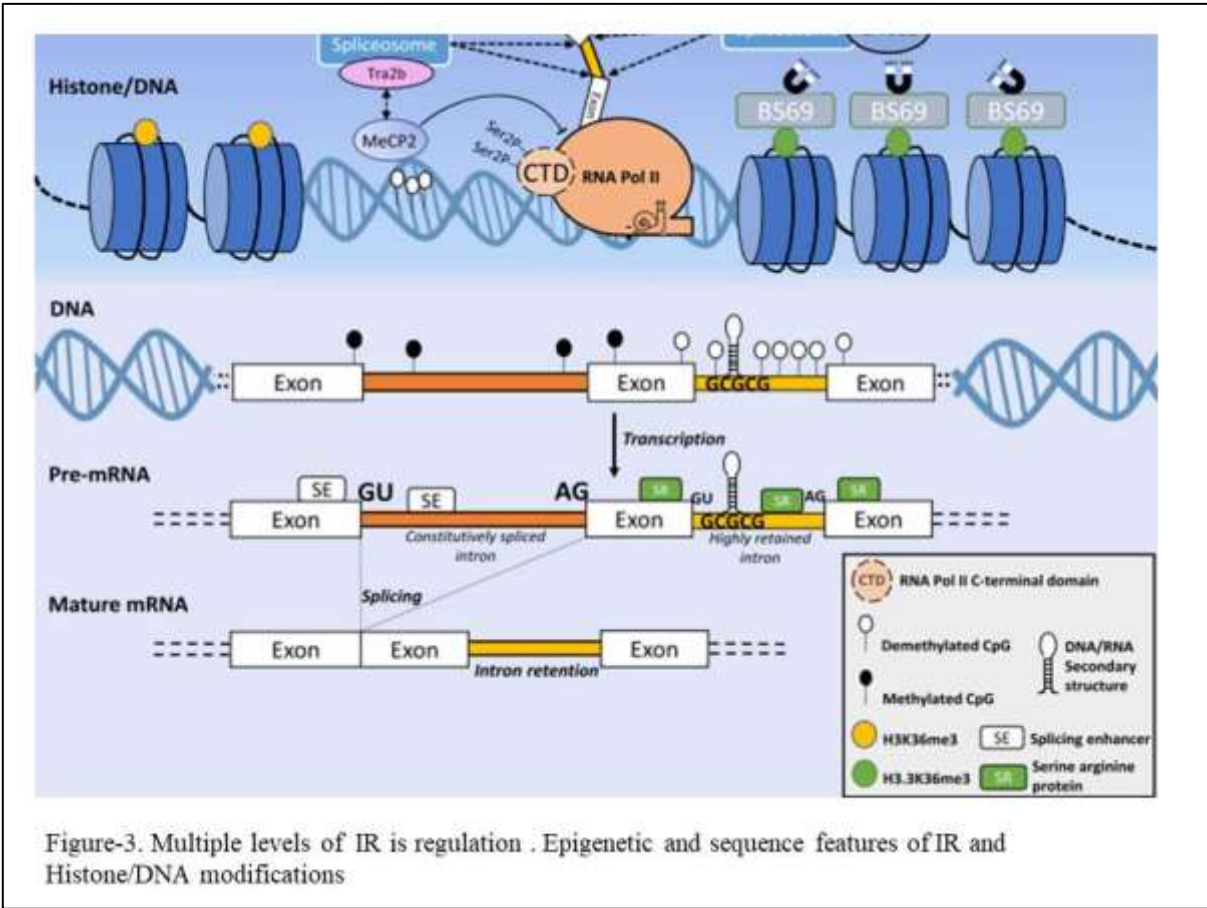


Table-1: Few computational tools for IR detection

Tool/Approach	Highlights	Reference
IRFinder/IRFinder-S	Benchmark and integrated differential IR analysis IRFinder-S adds CNN filtering, long-read support,	Porrás-Tobías et al., genes 2025
iREAD	Uses entropy scoring across independent introns to detect flat read distributions; avoids exon overlap	
KMA	Involves transcript quantification; suitable for differential analysis with minimal artifacts	
IntERESt	Supports non-annotated introns; integrates statistical tests for intra- and inter- sample comparisons	
IRAVNet	Identifies IR-causing variants directly from transcriptomic data; assesses the connection between genomic variant status and the number of splicing changes	
SpliceAI/SpliceAI-10k	Deep learning model for splicing prediction; identifies partial IR and spliceogenic variants with high sensitivity	

Table-2: Detection methods

Method	Description	Reference
RNA sequencing	Specific sequential and structural characteristics associated with retained introns and their host genes	Monteuuis et al., 2019
RNA Capture sequencing (CaptureSeq)	Detection of known IR events	
RNA-based in situ hybridization techniques (RNA ISH or smFISH)	Subcellular location	

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PacBio Single-Molecule, Real-Time (SMRT) Sequencing or Oxford Nanopore sequencing,	Genomic context and the impact of DNA mutations,	
Methylated DNA immunoprecipitation sequencing (MeDIP) whole genome bisulphite sequencing (WGBS)	Epigenetic regulators of IR. Methylation status of cytosines at single base resolution	
Nucleosome Occupancy and Methylome sequencing (NOME-Seq)	Determine the footprint of nucleosome positioning.	
Chromatin immunoprecipitation sequencing (ChIPseq)	Elucidate the impact of histone modifications on IR.	
3C, 4C, 5C-seq	Chromatin 3D configuration and chromatin interactions	
RNA immunoprecipitation (low throughput) or variants of RNA cross-linking immunoprecipitation sequencing (highthroughput), such as HITS-CLIP, PAR-CLIP	Footprinting of RBP binding	

Table-2: List of few Human disorders caused due to intron retention

Disease	Gene/IR feature	Functional consequence	Reference
Aging	<i>MCT4 / Slc16a3</i> <i>YRA1 & UBC5</i> Increased IR in genes	Impaired metabolic homeostasis; functional marker for anti-aging therapies	Porras-Tobias et al., genes 2025
Hepatocellular Carcinoma	<i>KLF4</i> IR generates a non-coding isoform (KLF-003) that is downregulated	Epigenetic silencing of IR transcript via CpG methylation; loss may contribute to recurrence	
Multiple Myeloma	RNA splicing machinery; immune checkpoint pathway genes Elevated IR events → generation of IR-neoantigens	High IR-neoAg load correlates with poor survival, immune suppression via co-inhibitory molecules, reduced MHC-II, and immune escape	
46,XX DSD	<i>WT1</i> IR in WT1 alters isoform ratio → sex development disruption	Mechanism affecting human sexual differentiation	
Renal Fibrosis	<i>ENG</i> ASO-induced IR in ENG shifts isoform balance to anti-fibrotic variant	Demonstrates therapeutic modulation of IR to treat fibrosis via isoform control	
Allgrove Syndrome	AAAS Partial retention of 99 bp of intron 14 plus exon 14 skipping	Frameshift mutations causing PTCs, likely resulting in non-functional protein and disease phenotype	

Hypoplastic Amelogenesis Imperfecta	<i>ENAM</i> (enamelin) Retention of intron 1 and normally skipped exon 2 → elongated 5' UTR	Complex 5' UTR secondary structure attenuates translation → reduced enamel → defective enamel	
ALS	<i>SFPQ</i> Premature and increased IR during motor neuron differentiation	Reduced nuclear SFPQ protein; disrupted RNA metabolism; ALS pathogenesis marker	
SMA	<i>SMN2</i> Intron 7 retention in SMN2 transcripts	Longer 3' UTR → translational repression of SMN protein	

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