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ОБЗОР
REVIEW

Intronic enhancers: regulatory roles in tissue differentiation and human diseases

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Abstract. *Relevance*. Intronic enhancers are cis-regulatory DNA elements located within introns of protein-coding or non-coding genes. Although introns were historically regarded mainly as non-coding interruptions removed during pre-mRNA splicing, contemporary functional genomics has shown that they are repositories of regulatory information. Intronic enhancers can control the expression of their host genes, neighboring genes, or even distant genes. Their activity is usually cell-type-specific and is associated with open chromatin, transcription-factor binding, enhancer-associated histone modifications such as H3K4me1 and H3K27ac, recruitment of coactivators, enhancer-promoter looping, and in many cases transcription of enhancer RNAs. *Results and discussion*. This article reviews the biological significance of intronic enhancers with particular attention to two areas: tissue differentiation and disease. During differentiation, intronic enhancers integrate lineage-determining transcription factors, developmental signals and determine tissue specificity. They contribute to hematopoietic, endothelial, muscle, adipocyte, neuronal, and immune-cell identity by controlling the timing, intensity, and specificity of gene expression. In disease, intronic enhancers are vulnerable sites for pathogenic single-nucleotide variants, insertions, deletions, copy-number changes, epigenetic disruption, and aberrant enhancer hijacking. Examples include GATA2 enhancer mutations in immunodeficiency and myeloid malignancy predisposition, FTO intronic variants affecting IRX3/IRX5 regulation in obesity, and oncogenic enhancer activation near TAL1 in T-cell acute lymphoblastic leukemia. *Conclusion.* Thus intronic enhancers should not be treated as secondary regulatory elements merely because they lie inside genes. Instead, they represent a major layer of genome regulation, connecting non-coding variation to developmental biology, complex traits, and disease mechanisms. Their study is increasingly important

for precision medicine, functional interpretation of genome-wide association studies, and future enhancer-targeted therapeutic strategies.

Keywords: intronic enhancers; cis-regulatory elements; tissue differentiation; chromatin; enhancer RNA; GATA2; FTO; TAL1; non-coding variants; disease genetics

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Introduction

The human genome contains approximately 20,000 protein-coding genes, yet protein-coding sequences occupy only 1,5% of total genomic DNA [1–3]. The larger biological question is not simply where genes are located, but how they are regulated in time and cellular microenvironment. A neuron, a hepatocyte, a myoblast, an endothelial cell, and a hematopoietic stem cell carry essentially the same genome, but they use different regulatory instructions. Enhancers are among the most important of these instructions. They are cis-regulatory elements that increase transcription of target genes independently of their orientation and often at considerable genomic distance from the promoters they regulate.

Importantly, the localization of enhancers within introns allows modulation of gene expression without altering the amino acid sequence of the genome. As a result, intronic enhancers are considered an important source of evolutionary variation in gene regulatory programs [4].

In addition to intronic enhancers, enhancers can be classified according to their genomic location into intergenic and promoter-associated enhancers. Unlike intronic enhancers, intergenic enhancers are located within non-coding regions between genes. Among intergenic enhancers, a subset known as distal enhancers can be distinguished. These regulatory elements are typically located at considerable distances from the promoters they regulate — up to 500–1000 kilobases in the human genome — whereas intronic enhancers are generally situated much closer to their target promoters, usually within 1–10 kilobases [5,6]. Promoter-associated enhancers are located in close proximity to the promoter of the gene whose transcription they enhance (Figure 1).

Intergenic distal enhancers are more frequently involved in the formation of complex regulatory networks, in which a single enhancer may simultaneously regulate the expression of multiple genes. In contrast, intronic enhancers generally exhibit a closer functional relationship with a specific gene or a group of closely related genes [6].

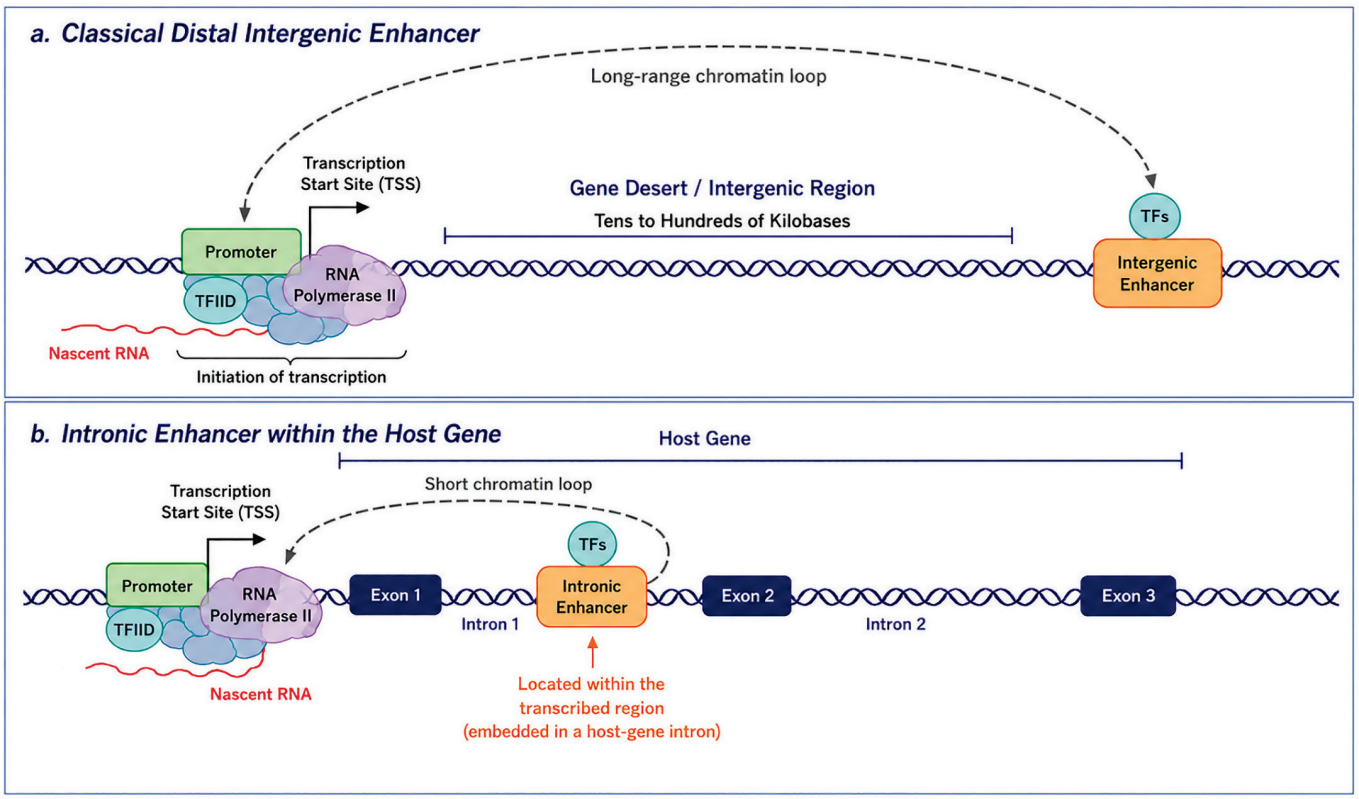

Figure 1. Distal intergenic and intronic enhancers. (*a*) Comperison of classical distal intergenic enchancer and entronic enhancer within the host gene. Classical intergenic enhancers are located in gene-poor genomic regions and regulate target promoters via long-range chromatin looping across large genomic distances. (*b*) Intronic enhancers are embedded within introns of protein-coding genes and operate within compact chromatin domains, forming short-range regulatory interactions with nearby promoters in the context of host gene transcription

Significantly, the functional differences associated with enhancer localization within the genome. Intronic enhancers have been shown to predominantly regulate the expression of tissue-specific genes involved in cellular differentiation and specialized biological functions, often referred to as luxury genes. In contrast, intergenic and promoter-associated enhancers are more commonly linked to genes responsible for cellular homeostasis and basic cellular functions, commonly known as housekeeping genes [6]. Notably, the proportion of intronic enhancers increases substantially from approximately 38–40% across the human genome as a whole to 63–74% in certain tissues characterized by complex cellular organization and a high degree of cellular differentiation, including blood, muscle, and nervous tissues. This observation was confirmed through bioinformatic analyses of publicly available genomic datasets from both humans (*Homo sapiens*) and rats (*Rattus norvegicus*) [5–9]. A more detailed comparison of intronic, intergenic and promoter-associated enhancers is presented in Table.

This comparison further demonstrates that enhancer function may depend on its genomic location and highlights the strong association between intronic enhancers and tissue-specific biological functions, particularly in tissues characterized by complex cellular differentiation.

Table

Comparison of intronic, intergenic, and distal enhancers

Enhancer category	Genomic location	Distance from promoter	Tissue specifi-city	Role in cell differen-tiation	Overall proportion in the human genome	Proportion in human neural tissue
Intronic	Within gene introns	From several hundred to tens of thousands of nucleotides	High	Often regulate tissue-specific genes	≈ 38–40%	≈ 63–74%
Intergenic	Between two genes in a non-coding region that is not intronic	From tens of kilobases to several megabases	Can be both high and low	More often involved in general processes (homeostasis maintenance)	≈ 50–58%	≈ 22–35%
Promoter-associated	Near promoters in exonic and intronic regions	Minimal — up to 1–2 kilobases	Usually low or moderate	Low	≈ 2–3%	-

More detailed analyses of embryonic and postnatal samples of blood, muscle, and nervous tissues revealed a shift in the proportion of predominant enhancer classes from intergenic enhancers during embryonic development to intronic enhancers in postnatal tissues. These findings suggest an important role for intronic enhancers in the establishment and maintenance of differentiated cellular identities [6].

Intronic enhancers should also be distinguished from intronic splicing enhancers. The latter are RNA sequence motifs that influence splice-site recognition after transcription. Intronic enhancers in the sense used in this article are DNA regulatory elements that influence transcription. The two categories can overlap because transcription, chromatin state, elongation, and splicing are coupled processes. Confusing those leads to a common but serious error: interpreting every intronic functional sequence as a splicing element when many intronic regions act at the chromatin and transcriptional level.

Intronic enhancers are biologically important for several reasons. First, their position within genes makes them efficient platforms for coordinating host-gene expression with broader regulatory networks. Second, because introns can be very large, they provide extensive sequence space in which lineage-specific transcription-factor binding sites can evolve. Third, intronic enhancers may be insulated within topologically associating domains, allowing them to contact specific promoters while avoiding inappropriate activation of unrelated genes. Fourth, they are frequent locations of disease-associated non-coding variants discovered by genome-wide association studies. A variant inside an intron may be mistakenly assumed to be harmless if analysis is restricted to protein sequence or canonical splice sites. In reality, such a variant can disrupt a transcription-factor motif, alter chromatin accessibility, change enhancer-promoter contact frequency, and modify disease risk.

Intronic enhancers are particularly important for the development and maintenance of the nervous system, especially the brain. A study published in 2014 demonstrated that disruption of enhancer activity in the genomes of embryonic mouse brain cells resulted in severe neurodevelopmental abnormalities and irreversible defects in brain formation that were incompatible with normal organismal development and survival [10]. Furthermore, accumulating evidence suggests that dysfunction of enhancers and other non-coding regulatory elements may contribute to the pathogenesis of various neuropsychiatric and neurodegenerative disorders [11–13].

Mechanisms of intronic enhancer function

It is known that introns occupy 24% of all DNA compared to 1.5% for exons [6]. Intronic enhancers are enhancers embedded within introns. The intron belongs structurally to a gene, but the enhancer within it may regulate the host gene, a neighboring gene, or a distant gene. A sequence may be "inside" one gene in genomic coordinates but functionally assigned to another gene through chromatin looping and three-dimensional genome organization.

This distinction has become central in modern genomics. Large-scale projects such as ENCODE, Roadmap Epigenomics, and FANTOM5 have demonstrated that active enhancers can be identified using combinations of chromatin accessibility, transcription-factor binding, histone marks, enhancer-associated transcription, and enhancer-promoter correlations. ENCODE classified candidate cis-regulatory elements using marks such as DNase hypersensitivity, H3K27ac, H3K4me3, and CTCF binding. FANTOM5 used cap analysis of gene expression to detect transcribed enhancers across a wide panel of human tissues and cell types. These resources have revealed that enhancers are not randomly distributed; many show strong tissue specificity, and substantial fractions occur within introns [14–16].

According to some researchers, enhancers represent the most abundant class of regulatory elements in the human genome, exceeding promoters, silencers, and insulators in number [17].

Importantly, intronic enhancers share many functional mechanisms with other classes of enhancers; however, their localization within introns confers several distinctive regulatory features.

Cells achieve differential gene expression through complex gene regulatory networks. In many cases, activation of a target gene requires the participation of specialized regulatory proteins known as transcription factors (TFs). These proteins recognize and bind specific DNA sequences within enhancer regions and recruit additional regulatory complexes involved in transcriptional activation [18].

The primary mechanism of intronic enhancer function is believed to be the enhancement of transcription through physical interactions with the promoter of a target gene. Experimental evidence indicates that enhancers can establish direct contacts with promoters even when located at considerable genomic distances from their target genes. These interactions are mediated by the formation of chromatin loops during transcriptional activation and were directly visualized using advanced microscopy techniques in 2022 [19].

The interaction between an enhancer and its target promoter is a highly complex process that remains incompletely understood despite extensive research conducted throughout the 2020s [20]. This process critically depends on the recruitment of transcription factors and numerous additional regulatory proteins. Many of these proteins are involved in altering chromatin conformation and include co-regulators, chromatin remodelers, and chromatin-modifying enzymes. In addition, RNA polymerase II (RNAPII) plays a central role in enhancer-mediated transcriptional activation. Conservative estimates suggest that enhancer function may involve interactions with up to 200 proteins [21]. Although not all of these proteins are likely to be indispensable, many of them cooperate to mediate a series of molecular interactions and biochemical processes that ultimately result in activation of the target promoter and increased transcriptional output.

The function of an enhancer is largely determined by its underlying nucleotide sequence, which typically contains dense clusters of transcription factor binding sites. The functional potential of an enhancer depends on several factors, including the types of transcription factors capable of binding to the enhancer sequence, their binding affinity, orientation, arrangement, number, and spacing of individual binding sites, as well as the surrounding DNA sequence context [5].

A single enhancer often contains multiple transcription factor binding sites. From an evolutionary perspective, the clustering of binding sites within the same regulatory element is advantageous because the cooperative binding of several transcription factors can substantially increase the transcriptional activity of a target gene. Furthermore, such an organization enables a single enhancer to function in different cell types by integrating distinct combinations of transcription factors. The availability of multiple transcription factor binding sites allows different cell types to utilize the same enhancer while regulating the timing, magnitude, and context of its activity according to their specific transcriptional programs. Importantly, a single enhancer may regulate multiple target promoters, while the promoter of a single gene can be controlled by several

enhancers acting simultaneously. This property of enhancers as cis-regulatory elements contributes to the precise and robust control of gene expression. In the case of intronic enhancers, such regulatory flexibility is thought to facilitate tissue-specific gene expression programs and cellular specialization. This phenomenon is particularly evident in blood, nervous, and muscle tissues, which are characterized by a high abundance of active intronic enhancers [6].

In addition to DNA and proteins, non-coding RNAs constitute another essential component of enhancer function. One example is enhancer RNA (eRNA), a class of non-coding transcripts produced from active enhancer regions. Researchers have reported that vertebrate cells contain tens of thousands of distinct eRNAs, with their number potentially exceeding that of matrix RNAs (mRNAs) [5]. The transcription of eRNAs often precedes promoter activation or occurs simultaneously with transcription of the target gene. eRNAs are generally short-lived molecules, and both their biogenesis and abundance are regulated by other classes of RNA [22]. Notably, a subset of polyadenylated eRNAs has been reported to interact with promoters located on different chromosomes and contribute to the regulation of target gene transcription [21]. Some researchers have proposed that eRNAs may serve as markers of enhancer activity. The prevailing view is that eRNAs contribute to maintaining an open chromatin conformation at active enhancers, thereby facilitating transcription. However, alternative hypotheses suggest that eRNAs may represent a by-product of enhancer activation rather than functional regulatory molecules [21]. Several studies have demonstrated that enhancers producing eRNAs tend to exhibit stronger regulatory activity than those that do not [23]. Furthermore, eRNAs have been shown to interact with key components of enhancer-mediated transcriptional regulation, including the mediator complex, transcriptional activators and co-activators, as well as proteins involved in epigenetic chromatin remodeling [21].

It is important to note that transcriptional activity is also influenced by the efficiency of pre-mRNA splicing. Splicing and transcription are functionally interconnected processes, and accumulating evidence suggests that splicing can enhance transcription through a positive feedback mechanism. In general, genes undergoing more efficient splicing tend to exhibit higher transcriptional activity. One proposed mechanism is that splicing factors associated with nascent RNA transcripts interact with RNA polymerase II (RNAPII), thereby promoting the formation and stabilization of the transcription initiation complex and enhancing transcriptional output.

Enhancers can be either inducible (active only in response to specific stimuli) or constitutive (active continuously). Constitutive enhancers most commonly promote the expression of so-called housekeeping genes, which are expressed in virtually all cell types regardless of their differentiation status [24]. Inducible enhancers are considerably more abundant in the human genome than constitutive ones [24]. The interaction of extracellular signaling molecules with specific cell-surface receptors initiates a variety of intracellular signaling cascades. The ultimate outcome of these pathways is the activation of transcription factors that bind to enhancer elements. In some cases, these signaling molecules are hormones, including steroid hormones. It is well established that nuclear hormone receptors, such as the progesterone receptor, androgen receptor, glucocorticoid receptor, and estrogen receptor, undergo conformational changes upon ligand binding and subsequently interact with specific hormone response elements located within enhancers [25]. However, their strong association with tissue-specific gene expression suggests that a substantial proportion of intronic enhancers are activated only in particular cellular contexts and at specific stages of organismal development. Such activation promotes the expression of luxury genes, thereby contributing significantly to cell differentiation and tissue-specific gene regulation.

Therefore, intronic enhancers regulate gene expression through interactions with transcription factors, the formation of physical contacts with promoters, and participation in maintaining an open chromatin state. Their activity may be associated with co-transcriptional splicing processes. Enhancer RNAs (eRNAs) also play an important role in transcriptional regulation. A substantial proportion of

intronic enhancers are activated only under specific conditions, such as hormonal stimulation. Collectively, these mechanisms ensure precise spatiotemporal regulation of gene expression, which is essential for cell differentiation and the establishment of tissue-specific functions.

The logic of intronic enhancer function is particularly visible during tissue differentiation. Differentiation requires a stable but flexible transition from one transcriptional state to another. A progenitor cell must silence some genes, activate others, and maintain a subset in a poised state. Enhancers mediate this by responding to lineage-determining transcription factors and extracellular signals. Intronic enhancers are prominent in this process because they often lie within genes that are themselves involved in development, signaling, chromatin control, or transcriptional regulation. For example, the GATA2 locus contains intronic enhancer elements required for hematopoietic regulation; the FTO locus contains intronic regulatory sequences that influence IRX3 and IRX5 during adipocyte biology; and muscle differentiation involves extensive enhancer activation by MyoD and related transcription factors [26].

The role of intronic enhancers in disease follows naturally from their developmental role. If an enhancer determines when and where a gene is expressed, then mutations in that enhancer can cause disease without altering protein-coding sequence. Disease mechanisms include loss of enhancer activity, gain of enhancer activity, creation of novel transcription-factor binding sites, disruption of chromatin loops, enhancer adoption by oncogenes, and epigenetic reprogramming. These mechanisms are particularly important in cancer, immunological disorders, developmental syndromes, metabolic and neurodegenerative diseases.

Intronic enhancers in tissue differentiation

General principles of enhancer-mediated differentiation

The proper functional activity of tissues is ensured by the stepwise differentiation of cells from less differentiated progenitor cells. It is evident that all cells contain an identical set of genetic material, whereas their specialization is achieved through epigenetic regulation of the genome. Intronic enhancers play a key role in the epigenetic regulation of cellular differentiation.

Enhancers exhibiting tissue-specific activity are highly enriched within non-coding intronic regions and regulate the expression of genes involved in tissue-specific functions, whereas housekeeping genes are more frequently controlled by intergenic enhancers shared across multiple tissues. Notably, during the transition from developmental to adult stages, the predominant class of active enhancers shifts from intergenic to intronic. The most highly differentiated tissues contain a greater proportion of intronic enhancers responsible for the establishment of tissue-specific characteristics and the activation of the corresponding luxury genes, whereas the lowest proportion of intronic enhancers is observed in embryonic stem cells. Researchers have concluded that the genomic location of active enhancers is a key determinant of tissue-specific gene expression control. This concept was demonstrated by the research group led by Beatrice Borsari through the analysis of genomic data from 70 human cell types generated within the Encyclopedia of DNA Elements (ENCODE) project using computational and bioinformatic approaches [6, 27]. It is also well established that epigenetic features, including enhancer activity, can change throughout an individual's lifetime. During development, embryos undergo extensive morphological and functional transformations. These changes determine cell fate and cellular identity through tightly regulated transcriptional programs, thereby generating the remarkable diversity of cell types characteristic of multicellular organisms [28]. Most genes associated with tissue-specific functions are actively transcribed in more than one tissue; however, they differ in their expression levels as well as their temporal and spatial expression patterns, suggesting that their regulatory mechanisms vary among tissues. Nevertheless, approximately 10–20% of all genes are ubiquitously expressed housekeeping genes that participate in the fundamental processes required for cellular maintenance and survival [29].

During differentiation, enhancers often are modified in different ways. A future enhancer may be in a closed or inactive state. It may then become primed, marked by factors such as H3K4me1 but

lacking strong H3K27ac. When differentiation cues activate lineage-determining transcription factors, the enhancer may gain chromatin accessibility, recruit p300/CBP coactivators, acquire H3K27ac, and contact a promoter through chromatin looping. This transition from inactive or primed enhancer to active enhancer is one of the molecular foundations of cell-fate commitment [30].

Intronic enhancers participate in this process in several ways. Some regulate the same gene in whose intron they reside. This arrangement may allow feedback or feed-forward regulation, especially when the host gene encodes a transcription factor or signaling protein. Other intronic enhancers bypass the host gene and regulate a different gene. This is common in loci where three-dimensional chromatin architecture brings an intronic element into contact with a distal promoter. Therefore, the physical position of an intronic enhancer does not automatically determine its target.

Tissue-specific intronic enhancers are often enriched for motifs recognized by lineage-determining transcription factors. In myogenesis, these include MyoD, MYF5, myogenin, MEF2, and related regulators. In hematopoiesis, GATA, RUNX, TAL1, LMO2, and ETS-family factors are important. In adipogenesis, C/EBP and PPAR-family factors play major roles [31]. In neuronal differentiation, proneural factors, bHLH proteins, and activity-dependent transcription factors contribute to enhancer selection. Intronic enhancers act as genomic landing platforms for these factors.

A useful way to understand intronic enhancers is to view them as regulatory "switchboards". A promoter may define where transcription begins, but enhancers determine whether transcription occurs strongly, weakly, transiently, or in a specific lineage. Intronic enhancers can also help fine-tune expression rather than simply turning genes on or off. This is critical in differentiation, where dosage matters. Too little expression of a developmental transcription factor may prevent lineage commitment; too much may produce aberrant proliferation or inappropriate differentiation.

Intronic enhancers and three-dimensional genome organization

Enhancer function cannot be fully understood from linear genome coordinates alone. Enhancers usually regulate genes through physical proximity created by chromatin folding [32]. The genome is organized into compartments, topologically associating domains, and smaller enhancer-promoter loops [33]. Intronic enhancers operate inside this architecture (Figure 2).

A major implication is that an intronic enhancer may regulate a gene located tens or hundreds of kilobases away. It may even skip the promoter of its host gene. This is not an exception but a basic property of enhancer biology. The target gene is determined by chromatin contacts, boundary elements, promoter compatibility, transcription-factor context, and cell type. Thus, assigning intronic enhancers to genes solely by nearest-gene annotation is often misleading.

This matters during differentiation because chromatin architecture itself changes. As cells commit to a lineage, some enhancer-promoter contacts are strengthened while others weaken. A progenitor cell may contain poised enhancer-promoter configurations that become active only after differentiation signals. In other cases, differentiation reorganizes the local chromatin environment, allowing intronic enhancers to contact promoters that were previously inaccessible.

Intronic enhancers may also contribute to regulatory insulation. If an enhancer lies inside a gene within a particular chromatin domain, it may act only on promoters inside that domain. Boundary proteins such as CTCF and cohesin help shape these domains. Disruption of boundaries can allow intronic enhancers to activate inappropriate genes, a mechanism that becomes especially important in disease [34].

Enhancer RNAs and intronic enhancer activity

Many active enhancers are transcribed into short non-coding RNAs called enhancer RNAs, or eRNAs [23]. These RNAs are often unstable, bidirectional, and non-polyadenylated, although exceptions exist. The presence of eRNA transcription

is frequently correlated with enhancer activity. In the context of intronic enhancers, eRNA biology is especially complex because enhancer transcription occurs within or near a host gene transcription unit.

There are at least three possible relationships between intronic enhancer transcription and host-gene transcription. First, the enhancer may produce its own eRNA independently of host-gene transcription. Second, the enhancer may influence transcription elongation through the host gene. Third, enhancer-associated transcription may interact with splicing, RNA polymerase II pausing, or local chromatin modifications.

The functional role of eRNAs remains debated, but several mechanisms have been proposed. eRNAs may stabilize enhancer-promoter loops, recruit coactivators, facilitate transcription-factor residence, modulate chromatin accessibility, or help release paused RNA polymerase II at target promoters [35, 36]. In differentiation, eRNA production can serve as a sensitive marker of enhancer activation, sometimes preceding measurable changes in mRNA abundance. This makes eRNA profiling useful for identifying lineage-specific enhancers.

Intronic eRNAs also create interpretive challenges. RNA-seq signals inside introns may be dismissed as unspliced pre-mRNA or transcriptional noise. However, some intronic transcription signals represent active enhancers. Distinguishing these requires integration of chromatin marks, strand specificity, and enhancer-associated histone modifications.

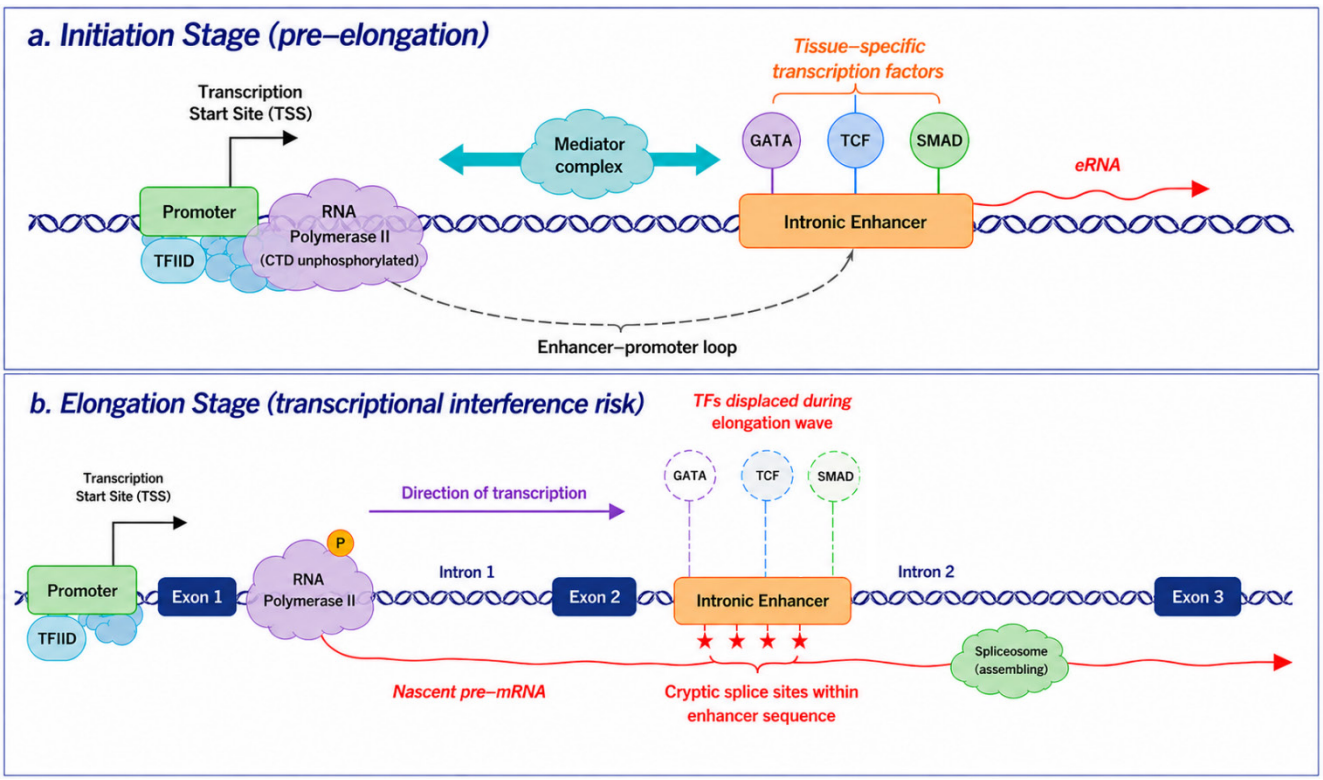

Figure 2. Transcription–splicing conflict at an intronic enhancer. (*a*) During the initiation stage, tissue-specific transcription factors bind the intronic enhancer, which communicates with the pre-initiation complex at the promoter via the Mediator complex. The enhancer transcribes a single eRNA, while splicing is inactive. (*b*) During elongation, phosphorylated RNA Polymerase II transcribes the gene, producing nascent pre-mRNA. The elongation wave displaces transcription factors from the enhancer. The spliceosome assembles on nascent RNA but must ignore cryptic splice sites within the enhancer sequence; SR proteins and hnRNPs mask these sites to prevent aberrant splicing

Hematopoietic differentiation and the GATA2 locus

One of the best-studied examples of intronic enhancer function in differentiation is the GATA2 locus. GATA2 encodes a transcription factor essential for hematopoietic stem and progenitor cells, vascular biology, and immune-cell development. Its expression must be precisely regulated: insufficient GATA2 impairs hematopoietic stem-cell function, while dysregulated expression can contribute to malignancy [37].

The GATA2 locus contains conserved intronic enhancer elements, including the well-known +9.5 or +9.8 kb enhancer region, depending on species and coordinate convention. This enhancer binds hematopoietic transcription factors and is necessary for proper GATA2 expression in specific developmental contexts. Experimental and clinical evidence shows that disruption of this enhancer can cause GATA2 haploinsufficiency [38]. Patients with GATA2 deficiency may develop immunodeficiency, monocytopenia, susceptibility to infections, lymphedema, myelodysplastic syndrome, or acute myeloid leukemia.

The importance of this example is broader than one gene. It demonstrates that an intronic enhancer can be clinically equivalent to a coding mutation. If an enhancer is required for expression of a dosage-sensitive transcription factor, then enhancer disruption can produce disease even when the coding sequence is intact. It also shows why non-coding regions must be included in genetic diagnosis when phenotype strongly suggests a regulatory defect.

During hematopoietic differentiation, GATA2 regulation is stage-specific. Hematopoietic stem cells and progenitors require GATA2, but differentiation toward mature lineages involves coordinated changes in GATA-factor expression. Intronic enhancers help implement this timing. They allow transcription-factor networks to maintain progenitor identity while preparing for lineage-specific transitions. In this sense, intronic enhancers do not merely activate genes; they help define developmental competence.

Muscle differentiation and myogenic enhancer networks

Skeletal muscle differentiation provides another clear model of enhancer-driven lineage commitment. Myogenesis is controlled by a hierarchy of transcription factors, including MyoD, MYF5, myogenin, and MEF2 [39]. These factors bind to enhancers and promoters to activate muscle-specific genes while repressing alternative lineage programs. Genome-wide studies have shown that myogenic differentiation involves widespread enhancer activation, including enhancers located in intronic regions.

MyoD is especially important because it can act as a pioneer-like factor in muscle gene regulation. It binds E-box motifs and recruits chromatin modifiers to establish active enhancer states. During the transition from myoblasts to myotubes, many enhancers gain H3K27ac and show increased accessibility. Some of these enhancers are located within introns of genes involved in muscle structure, metabolism, and differentiation.

Intronic muscle enhancers often contribute to fiber-type specificity and developmental timing. For example, enhancers within or near muscle genes can distinguish expression in slow, fast, or intermediate fibers. This is biologically important because skeletal muscle is not one uniform tissue. It contains fibers with different contractile properties, metabolic profiles, and responses to exercise or injury. Intronic enhancers help encode this diversity by responding to transcription-factor combinations and physiological cues.

Another important feature of muscle enhancer biology is regeneration. Adult skeletal muscle contains satellite cells that can activate myogenic programs after injury. Enhancers involved in embryonic or developmental myogenesis may be reused, modified, or supplemented by regeneration-specific enhancers [40]. Intronic enhancers therefore contribute not only to initial differentiation but also to tissue repair.

Adipocyte differentiation and the FTO/IRX regulatory landscape

The FTO locus is one of the most famous examples of non-coding variation associated with a complex trait. Variants within introns of FTO are strongly associated with body mass index and obesity risk. For years, the intuitive assumption was that these variants affected FTO itself. Functional studies later showed that the regulatory story is more complex: intronic sequences within FTO can form long-range contacts with IRX3 and IRX5, genes involved in adipocyte biology and energy balance [26, 41].

This example is important for differentiation because the disease-associated regulatory effects are linked to adipocyte precursor cells. The risk-associated enhancer state can influence the balance between energy-dissipating and energy-storing adipocyte programs. In simplified terms, non-coding variants in the FTO intronic region can alter enhancer activity and change expression of IRX3 and IRX5, thereby affecting adipocyte function [41].

The FTO case illustrates three general principles. First, an intronic enhancer does not necessarily regulate its host gene. Second, disease-associated variants can act during a specific developmental window, such as precursor-cell differentiation, rather than in mature tissue alone. Third, enhancer-mediated disease risk may involve quantitative shifts in cell-state programming rather than complete loss of gene function.

Adipogenesis depends on transcription factors such as PPARγ and C/EBPα, which establish and maintain adipocyte identity. Intronic enhancers in adipogenic genes contribute to this regulatory program by integrating hormonal, metabolic, and developmental signals. The result is a transcriptional network that determines whether precursor cells become mature adipocytes and what functional subtype they adopt.

Endothelial, neural and immune differentiation

Intronic enhancers also play important roles in endothelial, neural, and immune-cell differentiation. Endothelial cells require precise regulation of genes controlling vascular identity, angiogenesis, barrier function, and response to shear stress. Intronic enhancers within vascular regulatory genes can confer endothelial-specific expression by binding ETS-family transcription factors and other endothelial regulators [42].

In neural development, intronic enhancers contribute to the differentiation of neurons and glia. Neural genes are often large, with long introns that contain regulatory elements. These intronic enhancers may regulate temporal waves of neurogenesis, regional identity, synapse formation, and activity-dependent transcription. Because the nervous system requires exceptional cell-type diversity, it relies heavily on combinatorial enhancer logic. Intronic enhancers provide sequence space for this complexity.

In immune-cell differentiation, intronic enhancers are involved in lineage specification, activation, and memory formation. B cells, T cells, macrophages, dendritic cells, and innate lymphoid cells each use distinct enhancer landscapes. Activation of immune cells by fragments of bacterial cell wall or viruses can rapidly remodel enhancer states, creating *de novo* enhancers or activating latent enhancers [43–50]. Some of these elements reside in introns of cytokine genes, transcription factors, or signaling molecules. This allows immune cells to respond quickly to environmental stimuli while maintaining lineage identity.

Intronic enhancers as fine-tuners rather than simple switches

A simplistic model would describe enhancers as switches that turn genes on or off. This is sometimes useful, but it is incomplete. Many intronic enhancers act as fine-tuners. They regulate expression level, timing, cell-type specificity, responsiveness to signals, and robustness against transcriptional noise.

Fine-tuning is especially important in differentiation. A developmental gene may need to be expressed at low levels in progenitors, high levels during commitment, and reduced levels after maturation. A single promoter cannot easily encode all these states. Multiple enhancers, including intronic enhancers, can provide modular control. Some enhancers respond to

early signals, others to late differentiation factors, and others to tissue-specific physiological inputs [51].

This modularity also creates redundancy. Several enhancers may regulate the same gene, forming shadow enhancers or enhancer clusters. Redundancy can buffer development against mutations or environmental variation. However, it can also complicate functional interpretation: deleting one enhancer may have modest effects under laboratory conditions but strong effects under stress, during development, or in a specific tissue [45].

Intronic enhancers are therefore part of the regulatory grammar that allows multicellular organisms to generate stable but adaptable cell identities. Their location inside introns is not incidental; it reflects the dense regulatory use of gene as platforms for chromatin-based control.

The influence of intronic enhancers in disease

Non-coding variation and the disease problem

Most disease genetics initially focused on coding mutations because they are easier to interpret. A missense, nonsense, or frameshift mutation can be linked directly to protein structure. Intronic variants, by contrast, were often treated as variants of uncertain significance unless they affected canonical splice sites. This approach is no longer adequate. Many disease-associated variants identified by genome-wide association studies lie in non-coding regions, including introns. A substantial fraction of these variants likely influence gene regulation rather than protein sequence [52].

Intronic enhancer variants can cause disease through several mechanisms. A variant may disrupt a transcription-factor binding motif, reducing enhancer activity. It may create a new motif, increasing enhancer activity or changing the cell type in which the enhancer functions. It may alter chromatin accessibility, DNA methylation, nucleosome positioning, or histone modification. It may affect enhancer RNA transcription or enhancer-promoter looping. Structural variants may delete an enhancer, duplicate it, reposition it, or place it near an oncogene.

These mechanisms are difficult to interpret computationally because enhancer function is context-dependent. A variant may have no effect in one cell type but strong effects in another. A variant may affect a gene that is not the nearest gene [53]. A variant may act only during differentiation, inflammation, hypoxia, hormonal stimulation, or other conditions. Therefore, functional validation often requires disease-relevant cell types, developmental stages, and perturbation methods [54].

GATA2 intronic enhancer mutations and hematological disease

GATA2 enhancer disruption is one of the clearest examples of intronic enhancer disease. Germline mutations in the conserved intronic enhancer of GATA2 can lead to GATA2 haploinsufficiency [38, 55]. Clinically, this is associated with immunodeficiency, monocytopenia, dendritic-cell and natural-killer-cell defects, pulmonary alveolar proteinosis, lymphedema, myelodysplastic syndrome, and acute myeloid leukemia predisposition.

The mechanistic logic is direct. GATA2 is dosage-sensitive. If an intronic enhancer required for GATA2 expression in hematopoietic cells is disrupted, the coding sequence may remain normal but total functional expression is insufficient. This produces a phenotype similar to loss-of-function coding mutations. In diagnostic practice, this means that sequencing only exons may miss pathogenic regulatory variants [56].

The GATA2 example also reveals why enhancer disease can be pleiotropic. Because GATA2 acts in multiple developmental and immune contexts, enhancer disruption can affect several tissues and cell lineages. The phenotype may vary depending on the exact mutation, genetic background, environmental exposures, and stochastic effects in hematopoietic stem-cell populations.

From a broader perspective, GATA2 disease demonstrates that intronic enhancers can be essential developmental elements. They are not optional decorations of gene architecture. In some loci, they are required for life-long maintenance of stem-cell systems.

Intronic enhancers in cancer

Cancer is fundamentally a disease of dysregulated growth, survival, and cell identity. Enhancers are deeply involved in all three. Cancer cells can acquire new enhancer activity, amplify enhancer regions, hijack existing enhancers, or become dependent on super-enhancers that drive oncogene expression. Intronic enhancers contribute to this process in multiple cancers [57].

One prominent example is TAL1 activation in T-cell acute lymphoblastic leukemia. TAL1 is normally involved in hematopoiesis, but aberrant TAL1 expression in T cells contributes to leukemogenesis. Studies have shown that non-coding mutations can create or strengthen enhancer activity near TAL1, including enhancer mechanisms involving transcription-factor recruitment and monoallelic expression. Such mutations can generate oncogenic regulatory elements without changing the TAL1 protein sequence [58].

Cancer-associated enhancer activation may involve several molecular events. A small insertion or point mutation may create a binding motif for a transcription factor such as MYB or ETS-family proteins. A structural variant may bring an enhancer into contact with an oncogene. Epigenetic reprogramming may activate enhancers that are normally silent in the relevant tissue. Enhancer clusters or super-enhancers may drive very high expression of oncogenic transcription factors [59].

Intronic enhancers are also relevant to tumor suppressor genes. Loss or methylation of an intronic enhancer can reduce expression of a gene needed for differentiation, DNA repair, apoptosis, or immune recognition. In this case, the disease mechanism is not enhancer gain but enhancer loss. Because many tumor suppressors are dosage-sensitive, partial regulatory reduction may contribute to cancer risk or progression.

Another major issue is enhancer dependency. Cancer cells may depend on specific enhancer-driven transcriptional circuits. This creates therapeutic possibilities. Drugs targeting chromatin regulators such as BET proteins, CDK7, CDK9, or p300/CBP may preferentially affect enhancer-dependent oncogenic programs [60]. However, enhancer-targeted therapy remains difficult because enhancers are not proteins with simple active sites. The more realistic near-term approach is to target coactivators or transcriptional dependencies rather than individual DNA elements.

FTO intronic enhancer variants and metabolic disease

The FTO obesity locus is a classic case of how intronic regulatory variants can influence complex disease. Obesity-associated variants within FTO introns were initially interpreted as implicating FTO. Later functional work showed that these variants are part of a regulatory landscape affecting IRX3 and IRX5. These genes influence adipocyte differentiation and energy metabolism [26].

The disease mechanism is not a simple Mendelian loss of function. Instead, risk alleles modify enhancer activity in adipocyte precursor cells, shifting transcriptional programs related to thermogenesis, lipid storage, and adipocyte identity [61]. This is characteristic of many common disease variants: they produce modest but biologically meaningful changes in gene regulation, often in a specific cell type or developmental state.

The FTO example has several implications. First, intronic location does not identify the disease gene. The disease-relevant target may be distant. Second, enhancer variants can affect disease through developmental programming, not merely adult tissue function. Third, functional genomics can revise gene-trait assumptions produced by association studies. Without chromatin interaction data and enhancer assays, the regulatory connection to IRX3 and IRX5 would be difficult to infer.

This case also illustrates why intronic enhancers are important for metabolic medicine. Metabolic traits are often polygenic and regulated through tissue-specific networks in adipose tissue, liver, pancreas, muscle, and brain. Intronic enhancers are likely to explain many risk loci whose coding consequences are absent or weak [62].

Intronic enhancers in autoimmune and inflammatory disorders

Autoimmune and inflammatory diseases are strongly enriched for non-coding risk variants [63]. Many of these variants map to enhancers active in

immune cells. Because immune-cell activation involves rapid enhancer remodeling, intronic enhancer variants can alter immune responsiveness without causing obvious developmental defects [64].

For example, a variant in an intronic enhancer of an immune regulatory gene may increase transcription-factor binding after cytokine stimulation [65–69]. The result may be excessive inflammatory gene expression. Another variant may weaken enhancer activity and impair tolerance, pathogen response, or immune-cell differentiation. Because immune enhancers are highly cell-state-specific, a variant may act only in activated T cells, macrophages exposed to microbial products, or B cells undergoing differentiation.

Intronic enhancers also participate in the formation of immunological memory. After stimulation, some enhancers remain epigenetically primed, allowing faster response to future stimuli [70]. Variants that alter such enhancers may influence chronic inflammation, autoimmunity, or vaccine response. This area remains challenging because disease-relevant cell states are often transient and difficult to capture in patient samples.

Neurological and developmental disorders

The nervous system is particularly sensitive to regulatory variation. Neural genes are often large and contain long introns enriched for regulatory elements. Brain development requires precise temporal and spatial gene expression across many cell types. Consequently, intronic enhancers are plausible contributors to neurodevelopmental disorders, psychiatric disease, epilepsy, and neurodegeneration.

Enhancer disruption can affect neuronal proliferation, migration, axon guidance, synapse formation, neurotransmitter identity, and activity-dependent plasticity [71]. In developmental disorders, enhancer mutations may alter gene expression during a narrow embryonic window, leaving only indirect traces in adult tissue. This creates a major diagnostic challenge: the pathogenic effect may occur in a cell type that is unavailable for testing.

Structural variants are especially important in neurodevelopmental disease [72]. A deletion may remove an intronic enhancer; a duplication may increase enhancer dosage; an inversion may separate enhancer and promoter; a translocation may expose a gene to an inappropriate enhancer. These mechanisms can produce disease even when all coding exons are intact.

Because brain tissue is difficult to sample, induced pluripotent stem cells, organoids, and single-cell epigenomic methods are increasingly used to model regulatory disease. These approaches are imperfect, but they allow functional testing of intronic enhancer variants in more relevant developmental contexts than blood-derived DNA alone.

Copy-number variants, enhancer dosage, and structural rearrangements

Intronic enhancers are not affected only by single-nucleotide variants. Copy-number variants and structural rearrangements can have strong effects [73]. A deletion may remove an enhancer, reducing target-gene expression. A duplication may increase enhancer dosage or create ectopic contacts. An inversion may change regulatory topology. A translocation may place an enhancer near a new promoter.

Enhancer dosage is particularly important for genes that require precise expression levels [74]. Developmental transcription factors, signaling molecules, and chromatin regulators often fall into this category. Too little expression may cause haploinsufficiency; too much may cause overgrowth, cancer, or inappropriate lineage specification. Intronic enhancer CNVs can therefore produce both loss-of-function and gain-of-function regulatory phenotypes.

Structural variants can also disrupt topological domains. If a boundary is deleted, an intronic enhancer may escape its normal regulatory neighborhood and activate a gene in an adjacent domain. This mechanism is sometimes called enhancer adoption or enhancer hijacking. It is well established in developmental disorders and cancer [75].

Epigenetic dysregulation of intronic enhancers

Not all enhancer disease is caused by DNA sequence mutation. Enhancers can also be dysregulated epigenetically. DNA methylation,

histone modifications, chromatin accessibility, and nucleosome positioning can alter intronic enhancer activity. In cancer, enhancer landscapes are often globally reprogrammed [76]. In inflammatory disease, chronic stimulation can reshape enhancer states. In aging, enhancer activity may drift, contributing to altered tissue function.

Illustration of results of epigenetic changes and mutations in intron enhancers shown in figure 3.

Epigenetic enhancer dysregulation is difficult to classify because cause and consequence often overlap. A cancer cell may activate an intronic enhancer because of oncogenic transcription factors, but the enhancer may then help maintain the malignant state. Similarly, inflammation may activate enhancers that further promote inflammatory gene expression, creating a self-reinforcing loop.

Epigenetic reversibility makes these mechanisms therapeutically attractive [77]. In theory, enhancer activity can be modified without changing DNA sequence. In practice, current epigenetic drugs are broad and can affect many genes. More precise strategies, such as CRISPR-based epigenome editing, may eventually allow targeted repression or activation of disease-relevant intronic enhancers [78]. However, delivery, specificity, durability, and safety remain major barriers.

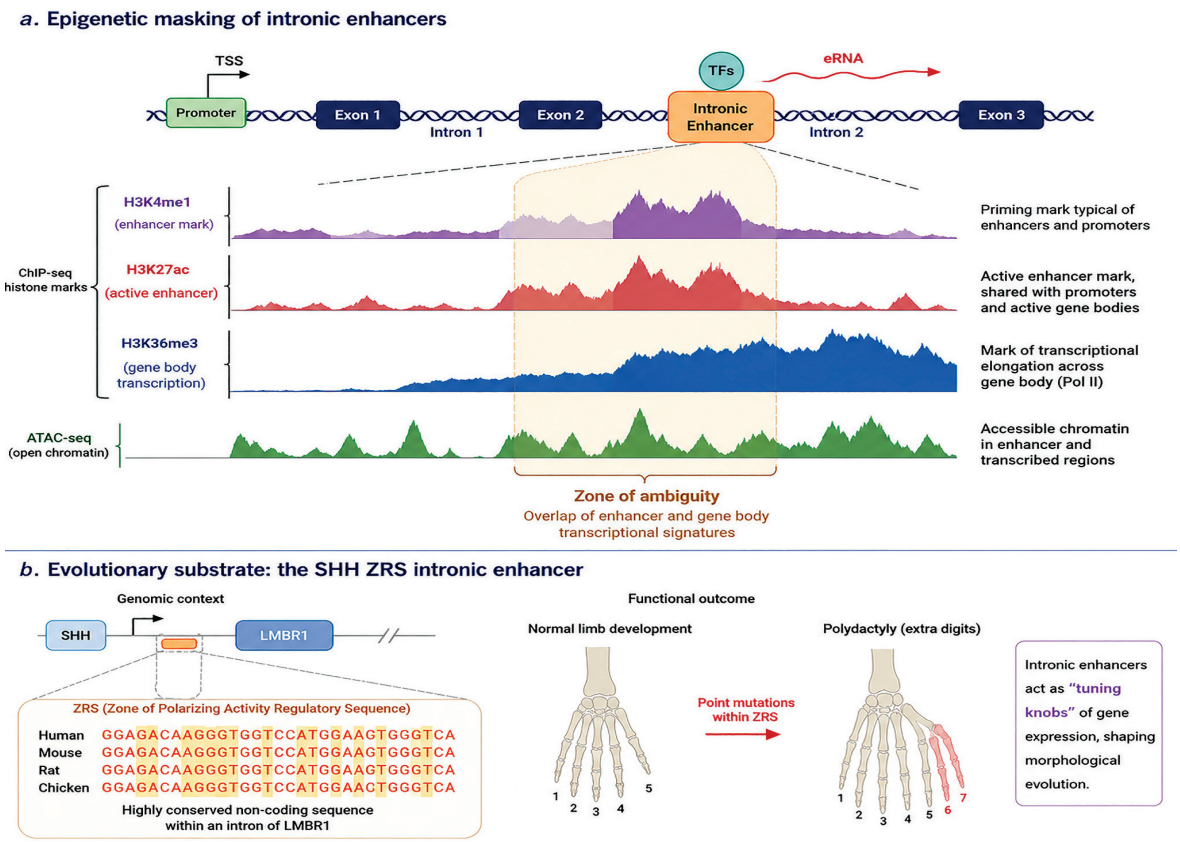

Figure 3. Epigenetic and evolutionary landscape of intronic enhancers. (*a*) Intronic enhancers show overlapping enhancer-associated and transcription-associated chromatin signatures, creating a zone of epigenetic ambiguity that complicates functional annotation. (*b*) The evolutionarily conserved SHH ZRS intronic enhancer illustrates how mutations in non-coding intronic regulatory elements can drive major morphological changes such as polydactyly, highlighting their role as key modulators of vertebrate evolution

Methods for studying intronic enhancers in disease

Interpreting intronic enhancer function requires multiple methods. No single assay is sufficient. Chromatin accessibility assays such as ATAC-seq and DNase-seq identify open regulatory regions [79]. ChIP-seq or CUT&Tag for H3K27ac, H3K4me1, p300, and transcription factors helps distinguish active or poised enhancers [80]. CAGE, GRO-seq, PRO-seq, and related methods detect enhancer-associated transcription. Hi-C, Capture-C, promoter capture Hi-C, and related methods identify physical enhancer-promoter contacts [81].

Functional validation is essential. Reporter assays can test whether a sequence has enhancer activity, but they remove the element from its native chromatin context. Massively parallel reporter assays allow high-throughput testing of many variants, but they also have context limitations. CRISPR deletion, CRISPR interference, CRISPR activation, base editing, and prime editing can test enhancer function at the endogenous locus [82]. These approaches are especially valuable for intronic enhancers because the native genomic position strongly influences target-gene selection.

Expression quantitative trait locus analysis can link genetic variants to gene expression, but cell-type specificity is a limitation. A variant may show no eQTL effect in bulk blood but strong effects in a rare immune subset or during differentiation. Single-cell multi-omics is beginning to address this by connecting genotype, chromatin accessibility, and gene expression in specific cell populations.

Disease interpretation increasingly requires an integrated framework: variant location, chromatin state, transcription-factor motifs, evolutionary conservation, enhancer-promoter contacts, gene expression, phenotype relevance, and experimental perturbation. Intronic enhancer variants should not be dismissed because they are non-coding. They should be prioritized when they overlap active enhancers in disease-relevant cells and connect to plausible target genes.

Databases are being created using systems biology approaches to systematize molecular genetic features in various diseases for accurate diagnostics and precision medicine [83–85].

Therapeutic implications

Intronic enhancers create both diagnostic and therapeutic opportunities. Diagnostically, they expand the search space for pathogenic variants. Whole-genome sequencing is superior to exome sequencing for detecting enhancer mutations, structural variants, and deep intronic regulatory changes [86]. However, interpretation remains the bottleneck. Many intronic variants are found; few can be confidently classified.

Therapeutically, several strategies are possible. One is indirect targeting of enhancer-dependent transcription through chromatin regulators. This is already being explored in cancer. Another is correction of causal variants through genome editing, although this remains technically and ethically complex. A third is epigenome editing, in which catalytically inactive Cas proteins are fused to repressors or activators to modify enhancer states without cutting DNA [87]. A fourth is oligonucleotide-based intervention when enhancer-associated transcription or splicing interactions are involved.

The most realistic near-term impact is improved diagnosis and patient stratification. For example, identifying a pathogenic GATA2 intronic enhancer mutation can change clinical surveillance, family testing, and transplant decisions [88]. In complex disease, enhancer variants may help define molecular subtypes or predict response to therapy. Over time, enhancer maps may become as clinically important as coding-gene panels are today.

Conclusion

Intronic enhancers are central components of the regulatory genome. Their location within introns once made them easy to overlook, but functional genomics has shown that introns contain dense regulatory information. Intronic enhancers can regulate host genes, neighboring genes, or distant genes through chromatin looping and three-dimensional genome organization. Their activity is highly dependent on cell type, developmental stage, chromatin state, and transcription-factor context.

During tissue differentiation, intronic enhancers help establish and stabilize cell identity. They integrate lineage-determining transcription factors, extracellular signals, enhancer-associated transcription, and chromatin remodeling. Examples from hematopoiesis, myogenesis, adipogenesis, endothelial biology, neural differentiation, and immune-cell activation show that intronic enhancers are not rare exceptions but a recurring regulatory strategy.

In disease, intronic enhancers provide a mechanistic explanation for many non-coding variants. They can be disrupted by point mutations, indels, copy-number changes, structural rearrangements, enhancer hijacking, and epigenetic reprogramming. GATA2 enhancer mutations demonstrate that intronic enhancer disruption can cause severe Mendelian disease. FTO intronic variants illustrate how enhancer variation can influence complex metabolic traits through distal gene regulation. TAL1 enhancer activation in leukemia shows how non-coding enhancer changes can drive oncogene expression.

The main conclusion is that intronic enhancers should be treated as functional genomic elements with direct biological and clinical relevance. Exome-centered thinking is insufficient for many diseases. Future research should combine whole-genome sequencing, single-cell epigenomics, chromatin interaction mapping, and endogenous enhancer perturbation. The long-term goal is not merely to annotate intronic enhancers but to understand their causal roles in development and disease. Once this is achieved, intronic enhancers may become important targets for precision diagnostics, risk prediction, and regulatory therapeutics.

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Интронные энхансеры: регуляторная роль в дифференцировке тканей и влияние на заболевания человека

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Аннотация. *Актуальность*. Интронные энхансеры — это цис-регуляторные элементы ДНК, локализованные внутри интронов генов, кодирующих белки, либо внутри интронов некодирующих генов. Хотя интроны исторически рассматривались в основном как не кодирующие последовательности, удаляемые во время сплайсинга пре-мРНК, современные данные функциональной геномики показали, что они являются регуляторами транскрипции. Интронные энхансеры могут контролировать экспрессию своих генов, соседних или даже дальних генов. Их активность обычно специфична для каждого типа клеток и ассоциирована с открытым хроматином, связыванием транскрипционных факторов, энхансер-ассоциированными метками гистона, такими как H3K4me1 и H3K27ac, рекрутированием коактиваторов, формированием петлей между энхансером и промотором, и во многих случаях транскрипцией энхансерной РНК (эРНК). *Результаты и обсуждение*. Эта статья рассматривает биологическую значимость интронных энхансеров, уделяя особое внимание двум областям: дифференциации тканей и заболеваниям. Во время дифференциации интронные энхансеры интегрируют факторы транскрипции, определяющие направление развития, регуляторные сигналы и формируют тканеспецифичность. Они способствуют формированию идентичности клеток гемопоэза, эндотелия, мышц, адипоцитов, нейронов и иммунной системы, контролируя время, интенсивность и специфику экспрессии генов. При заболеваниях в интронных энхансерах обнаруживаются одиночные нуклеотидные замены, вставки, делеции, изменения числа копий, эпигенетические нарушения и аномальный перехват энхансера. Примеры включают мутации энхансера GATA2 при иммунодефицитах и предрасположенности к миелоидным злокачественным опухолям, интронные варианты гена FTO, влияющие на регуляцию IRX3/IRX5 при ожирении, и онкогенный активатор энхансера возле TAL1 при остро-клиническом лимфобластном лейкозе Т-клеток. Выводы. Интронные энхансеры не следует рассматривать как вторичные регуляторные элементы лишь потому, что они располагаются внутри генов. Они скорее представляют собой важные элементы регуляции

генома, связывающие не кодирующую вариацию с развитием, сложными признаками и механизмами заболеваний. Их изучение становится все более важным для прецизионной медицины, функциональной интерпретации исследований ассоциаций генома на уровне всего генома (GWAS) и будущих стратегий терапии, нацеленных на энхансеры.

Ключевые слова: интронные энхансеры, цис-регуляторные элементы, дифференцировка тканей, хроматин, энхансерная РНК, GATA2, FTO, TAL1, некодирующие варианты, генетика заболеваний

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