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Spliceosomopathies: Diseases and mechanisms

Casey Griffin, **Jean-Pierre Saint-Jeannet**

Department of Molecular Pathobiology, New York University College of Dentistry, New York, New York

Abstract

The spliceosome is a complex of RNA and proteins that function together to identify intron-exon junctions in precursor messenger-RNAs, splice out the introns, and join the flanking exons. Mutations in any one of the genes encoding the proteins that make up the spliceosome may result in diseases known as spliceosomopathies. While the spliceosome is active in all cell types, with the majority of the proteins presumably expressed ubiquitously, spliceosomopathies tend to be tissue-specific as a result of germ line or somatic mutations, with phenotypes affecting primarily the retina in retinitis pigmentosa, hematopoietic lineages in myelodysplastic syndromes, or the craniofacial skeleton in mandibulofacial dysostosis. Here we describe the major spliceosomopathies, review the proposed mechanisms underlying retinitis pigmentosa and myelodysplastic syndromes, and discuss how this knowledge may inform our understanding of craniofacial spliceosomopathies.

Keywords

mandibulofacial dysostosis; myelodysplastic syndromes; retinitis pigmentosa; spliceosome

1 | INTRODUCTION

The spliceosome is an RNA and protein complex responsible for recognizing noncoding introns in precursor messenger-RNA (pre-mRNA) and promoting accurate splicing at the 5′- and 3′-splice-sites. The core of the major spliceosome is composed of five small nuclear RNAs (snRNAs) known as U1, U2, U4, U5, and U6, each of which is associated with a large number of small nuclear ribonucleoproteins (snRNPs), as well as other non-snRNP proteins. Each subunit of the major spliceosome contains an snRNA, seven core spliceosomal proteins (Sm proteins), and a variable number of subunit-specific proteins.[1] A second spliceosome, known as the minor spliceosome, coexists in most metazoans. Its activity is dependent on the presence of the U12 snRNA rather than the U2 subunit, allowing for the recognition of a different set of rare introns.[2] This review focuses on the major spliceosome.

Correspondence: Jean-Pierre Saint-Jeannet, Department of Molecular Pathobiology, New York University College of Dentistry, 345 East 24th Street, New York, NY 10010. jsj4@nyu.edu.

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During the process of pre-mRNA splicing, the U1 complex recognizes the 5′ intronic splice site, while the U2 complex recognizes the 3′ intronic splice site. The U4/U6. U5 tri-snRNP is then recruited to the intron, where complex rearrangement accompanies catalytic activation. The intron is then cut at both splice sites, while the flanking exons are joined.[1] Substantial remodeling is required throughout the splicing process, as no preformed active sites exist in any of the snRNPs. At each one of these steps, different sets of snRNPs are recruited, and the combination of RNA, snRNA, snRNP, and non-snRNP protein interactions allows for splicing to occur at the proper location.

Mutations in genes encoding components of the spliceosome have been shown to cause diseases in humans, referred to as spliceosomopathies. Although the spliceosome is required in all cell and tissue types to properly process pre-mRNA, spliceosomopathies are typically cell- or tissue-specific, resulting in restricted defects often affecting only one cell type or lineage and its derivatives. Interestingly, ribosomopathies which represent a group of diseases arising from defects in ribosome biogenesis, another global process occurring in all cells, can also result in tissue-specific defects.[3] Here we describe the major diseases associated with mutations in proteins of the spliceosome, review the current understanding of the mechanisms underlying two of these conditions, retinitis pigmentosa and myelodysplastic syndromes (MDS), and discuss how this information and our understanding of ribosomopathies may direct further studies to dissect the etiology of spliceosomopathies affecting the craniofacial complex.

2 | SPLICEOSOMOPATHIES

Spliceosomopathies include conditions affecting tissues as diverse as the retina, hematopoietic lineage, craniofacial skeleton, spinal cord, and limbs. In most cases, a single tissue or cell type is preferentially affected in these pathologies (Figure 1).

2.1 | Retinitis pigmentosa

Retinitis pigmentosa (RP) is a genetic disorder characterized by gradual deterioration of the photoreceptors within the retina, ultimately resulting in blindness. RP as a whole encompasses multiple diseases and therefore is considered to be a complex and genetically heterogeneous disease. Mutations can be autosomal dominant or recessive, X-linked, or digenic, and RP can be nonsyndromic or syndromic.[4] RP occurs in about 1:3000 to 1:7000 people worldwide.[5] There is no cure for RP, only mitigation of the symptoms. Current treatments range from optical aids to cataract surgery and retinal prosthetics depending on the stage of degeneration and severity of the symptoms.

Mutations in more than 50 genes have been linked to RP, among which several encode splicing factors.[6] They include mutations in pre-mRNA processing factors (PRPFs) and SNRNP200,[7] which are ubiquitously expressed members of the spliceosome[8] (Figure 1; Table 1). PRPFs are part of the U4/U6.U5 tri-snRNP, which makes up the precatalytic complex and part of the catalytic complex (Figure 2).[1] Although the tri-snRNP is assembled and functions in all cell types, the pathology of RP is restricted to the retina (see subsequent section on Mechanisms Underlying Spliceosomopathies). RP-associated spliceosomopathies are almost exclusively due to heterozygous mutations specific to members of the tri-snRNPs

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associated with U4/U6 complex (Figure 2; Table 1) that disrupt splicing decisions and proper processing of pre-mRNAs.

2.2 | Myelodysplastic syndromes

MDS constitute a set of disorders characterized by defective hematopoiesis, resulting in deficiencies in one or more hematopoietic lineages (Figure 1; Table 1).[30,31] There are approximately 55 000 MDS patients in the United States, with incidence increasing substantially over the age of 70 years.[30] MDS often manifests as bone marrow failure, resulting in transfusion-dependent anemia, increased risk of hemorrhage, infections, and potential progression to acute myeloid leukemia (AML).[32] Treatment for MDS falls into two categories: supportive care to correct symptoms such as anemia, increased infection, and low hematocrit, and curative treatments including stem cell therapy or chemotherapy to eliminate cancerous cells and improve bone marrow function.[30]

Over half of all patients affected by MDS, MDS-related AML, and blood cancers have mutations in splicing factor genes including SF3B1, SRSF2, U2AF1, and ZRSR2 (Figure 1).[9] These mutations converge to disrupt pre-mRNA splicing and increase DNA damage resulting in hematopoietic lineage dysfunction.[33] Proteins mutated in MDS-related spliceosomopathies are primarily associated with U2 complex (Figure 2; Table 1).

2.3 | Craniofacial disorders

In most craniofacial spliceosomopathies, the skeletal elements affected are primarily derived from the neural crest, an embryonic cell population that makes major contributions to the orofacial complex (Figure 1; Table 1).[34] These disorders have very restricted pathologies, specifically characterized by mandibular deformations accompanied by other face and/or limb defects. Although these conditions are relatively rare, they all fall under the umbrella of facial dysostoses, which represent one-third of all live births with congenital anomalies.[35] Depending on the severity, the management of facial dysostoses typically starts at birth and may extent throughout adolescence with multiple reconstructive surgeries.[35] Mutations in *PUF60* are found in Verheij syndrome, a condition characterized by coloboma, ventricular septal defects, digit and hip abnormalities, developmental delay, and facial dysmorphisms.[12,13] *EFTUD2* mutations occur in mandibulofacial dysostosis, Guion-Almeida type (MFDGA), which presents microcephaly, developmental delay, and craniofacial malformations.[14] *SF3B4* mutations are associated with Nager syndrome (NS), in which patients exhibit midface retrusion, micrognathia, absent thumbs, and radial hypoplasia.[15–17] *SNRPB* mutations in cerebro-costo-mandibular syndrome are characterized by rib defects, intellectual disability, cleft palate, glossoptosis, and microretrognathia.[18] Mutations in the related factor *SNRPA* also cause craniofacial defects, intellectual disability, as well as short stature and hand anomalies.[19] *EIF4A3* mutations are associated with acrofacial dysostosis Richieri-Costa-Pereira syndrome, in which patients present Robin sequence (micrognathia, glossoptosis and cleft palate), laryngeal abnormalities, clubfeet, and midline cleft mandible.[20] *TXNL4A* mutations in Burn-McKeown syndrome are associated with choanal atresia, sensorineural deafness, cardiac defects, and craniofacial dysmorphism.[21] *RBM8A* haploinsufficiency has been linked to a condition known as thrombocytopenia-absent radius syndrome which presents skeletal anomalies, craniofacial

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defects, and microcephaly.[22,23] *HNRNPR* mutations are associated with Au-Kline syndrome, Bain type mental retardation, and early infantile epileptic encephalopathy-54, which are characterized by intellectual disability, seizures, and abnormalities of the skeleton and face.[24] Finally, *RBM10* mutations have been linked to TARP syndrome, a rare condition that causes Talipes equinovarus (clubfoot), Atrial septal defect, Robin sequence and Persistence left superior vena cava.[25] Unlike RP and MDS, the proteins mutated in craniofacial spliceosomopathies are distributed across all complexes spliceosome (Figure 2; Table 1).

2.4 | Other spliceosomopathies

Spinal muscular atrophy (SMA) is an autosomal recessive disorder, characterized by progressive loss of spinal cord motor neurons. SMA has been linked to mutations in survivor of motor neuron 1 (*SMN1*) gene, a factor involved in the assembly of snRNPs.[26]

Amyotrophic lateral sclerosis (ALS) is a progressive adult onset disorder also characterized by progressive loss of spinal cord motor neurons (Figure 1). A subset of ALS patients have mutations in TAR DNA-binding protein (*TARDBP*) or fused in sarcoma (*FUS*), two genes encoding proteins responsible for spliceosome maintenance.[26,34] Genodermatosis poikiloderma with neutropenia, Clericuzio-type, is characterized by an inflammatory rash accompanied by sinopulmonary infections and bronchiectasis.[27] These patients have mutations in *USB1*, a gene that encodes a protein responsible for U6 snRNA processing.[28] In some rare cases, spliceosomopathies can display a broad array of clinical manifestations. For example, mutations in *CWC27*, encoding spliceosome-associated cyclophilin, lead to a spectrum of conditions including retinal degeneration, short stature, craniofacial abnormalities, brachydactyly, and neurological defects.*29*

3 | MECHANISMS UNDERLYING SPLICEOSOMOPATHIES

While it is known that mutations in splicing factors can lead to spliceosome dysfunction, resulting in mis-splicing of pre-mRNA, the exact mechanism by which these mutations cause tissue- or cell type-specific pathologies remains largely unknown. As the spliceosome is comprised of five snRNAs and over 100 associated proteins in five distinct complexes (Figure 2; Table 1), proposed underlying mechanisms/etiology of spliceosomopathies have been driven by the idea that mutations in splicing factors disrupt protein-protein or protein-RNA interactions within the complex creating aberrant transcripts that are uniquely required for one cell type or another.

In the context of human disease, mutations in splicing factors are usually heterozygous mutations. Therefore, with some wild-type protein remaining, the spliceosome as a whole is expected to be at least partially functional in patients. Because of the presence of some wild-type protein, not all pre-mRNAs within the cell are expected to be mis-spliced, rather one would predict a shift in the ratio of normal vs mis-spliced mRNAs.

3.1 | Retinitis pigmentosa

To understand how mutations affect pre-mRNA processing, the formation, composition, and stability of the spliceosome have been investigated in the context of RP. Mutations

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in PRPF proteins—most commonly PRPF3, PRPF4, PRPF8, and PRPF31—have been found to disrupt the overall kinetics and composition of the spliceosome.[8] Specifically, there is a reduction in snRNA levels, affecting the relative composition of the tri-snRNPs, accompanied by delayed and less efficient tri-snRNPs and spliceosome assembly, resulting in reduced rate of pre-mRNA splicing.

Disrupted interactions within the spliceosome as a result of PRPF-mediated RP have been studied in a number of organisms. In yeast and zebrafish, introduction of RP-associated PRPF mutations resulted in disruption of protein-protein or protein-RNA interactions that are necessary for proper tri-snRNP assembly[36,37] leading to compromised splicing function.

SNRNP200 encodes a protein that is involved in unwinding of the U4/U6 snRNAs during spliceosome assembly and disassembly.[7] Unwinding is required both for formation of the catalytic form of the spliceosome as well as disassembly of the complex after splicing.[38] Mutations in the proteins involved in this process may disrupt spliceosome activity at both of these steps, compromising the overall splicing activity of the complex.

The retina-specific effects of RP spliceosomopathies have been attributed mostly to the sensitivity of the retina to spliceosomal defects. The retina is both a region of high metabolic rate[37] and high pre-mRNA splicing activity as the retina expresses higher levels of sn-RNAs compared to other human tissues.[8] For this reason, the threshold for sensitivity to mutations specifically in the tri-snRNP may be much lower in the retina than in other tissues, leading to tissue-specific defects. Consistent with this view, RP patients have splicing defects in other tissues; however, these defects did not result in any notable pathology outside the retina.[8] However, tissue sensitivity cannot be the only explanation for RP tissue-specificity, since several spliceosome do not exhibit retinopathies.

3.2 | Myelodysplastic syndromes

Unlike RP and craniofacial spliceosomopathies, MDS are usually due to somatic mutations within hematopoietic cells in the bone marrow, which accounts for the tissue specificity of the spliceosome dysfunction. Familial MDS do exist, due to heritable germ line mutations, but the majority of these cases have been linked to mutations in GATA2, a transcription factor essential for the development of the hematopoietic lineage.[39] Despite differences in how the mutations occur in patients, the underlying mechanism of the mutations in MDS can still inform the mechanism of splicing factor mutations in other diseases.

The activity of several splicing factor proteins has been examined in the context of MDS, such as serine/ arginine-rich splicing factor 2 (SRSF2), a protein involved in recognizing and binding to the exonic splicing enhancer (ESE) sequences[11] (Table 1). The ESE sequences within the exon recruit proteins to establish and stabilize an exon definition complex during spliceosome assembly, identifying the region surrounding the splice site.[1] SRSF2 mutations disrupt the ESE sequence-specific functions, leading to ESE sequence skipping, and resulting in abnormal splicing.[40] Furthermore, these mutations have been reported to change the conformation of the RNA binding motifs of SRSF2 protein, thereby preventing interaction with its natural targets.[40] SRSF2, along with its role in the spliceosome, has been found to associate with the P300/CBP complex near immune checkpoint genes.[41] In this

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role, SRSF2 is able to alter the H3K27Ac level thereby influencing the epigenetic landscape and the transcription of target genes.

MDS can progress to leukemia and blood cancers, and some splicing factor mutations can promote malignancy. For example, mutations in U2 snRNA auxiliary factor 1 (U2AF1) cause aberrant splicing, which can result in the production of different isoforms of the target proteins. One such target is IRAK4 for which the alternative splice variant IRAK4-L potentiates MAPK and NF-κB signaling, both of which increase fitness of malignant progenitor cells.[10,33] However, work in mouse models of the disease indicates that full-fledged MDS and MDS-leukemia do not occur simply as a result of U2AF1 mutations but require a second MDS-related mutation, such as mutations in *RUNX1* gene.[31] Therefore, in some contexts, splicing factor mutations act as facilitators of the disease, rather than being the actual drivers of the phenotype.

SF3B1 is the most frequently mutated gene in MDS, particularly in patients with refractory anemia with ring sideroblasts. Mutations in SF3B1 affect its binding affinity for other components of the spliceosome,[42] preventing its proper arrangement during splice site recognition and rearrangement during catalytic activation, resulting in the production of aberrant transcripts. The ultimate outcome is a specific decrease in hematopoietic progenitors and mature blood cell formation[43] due to the large number of hematopoietic lineage-specific genes that are directly targeted by SF3B1.[42]

An important step in understanding the mechanisms underlying these conditions is to identify which factors normally interact with the splicing proteins and how these interactions are disrupted in the mutated proteins. For example, mutations in SF3B1 associated with MDS cause a decrease in the overall affinity for one of its binding partners, SUGP1, thus compromising spliceosome function.[42] Defining the specificity of these interactions is also important for understanding the pathways that are affected in the disease state. In MDS, the splicing of key regulators of hematopoiesis is disrupted, affecting processes such as iron transport,[44] regulation of granulopoiesis,[45] and hematopoietic stem cell maintenance.[46] SF3B1 mutant cell lines were found to have differential expression of genes involved in iron homeostasis and MDS pathogenesis, as well as mitochondrial metabolism and RNA splicing.[47] On the other hand, aberrant splicing of certain kinases in MDS results in hyperactivation of NF-κB signaling pathway, disrupting normal physiological processes in the cells and promoting malignant precursors.[10]

An underlying theme in MDS-related spliceosomopathies is the resulting genomic instability. Mutations in SRSF2 and U2AF1 have been found to activate the DNA damage response pathway.[33,47,48] In addition, disruption of the spliceosome structure has been shown to decrease RNA Polymerase II transcription speed, which in turn induces R-loop formation.[48,49] DNA damage combined with transcriptional stress activates the ATR-Chk1 pathway, compromising cell cycle progression and resulting in cell death. As a consequence, these patients exhibit a loss of hematopoietic progenitor populations.

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3.3 | Craniofacial disorders

With regard to craniofacial spliceosomopathies, the literature remains largely descriptive in nature. Clinical phenotypes have been attributed to specific mutations, but the pathways from mutation to clinical readout are unknown. While the pathology of craniofacial disorders, retina degeneration, and blood cancers are quite different, the etiology underlying these conditions may have some commonality, and the underlying mechanisms in each one of these conditions may therefore inform the others. For example, as has been the case in MDS, to better understand the mechanisms underlying craniofacial spliceosomopathies, it is necessary to identify and characterize the normal targets of these splicing factors, as well as the mis-spliced genes.

Although spliceosomopathies involve mutations in splicing factors, it is also important to consider that the splicing activity of these proteins might not be at the crux of the disease pathology but may depend on unrelated functions. Many splicing factors have been proposed to have non-canonical roles that could contribute to specific disease phenotypes. For example, SF3B4 is part of the U2 complex in the spliceosome (Figure 2; Table 1) but also functions as a cofactor for p180 in the rough endoplasmic reticulum to facilitate translation of secretory proteins.[50] SF3B4 also has a potential role in BMP signaling, since the protein was found to bind to BMPR-1A in a yeast two-hybrid screen,[51] and to interfere with BMP signaling in mammalian cells in culture[52]; however, this connection to BMP signaling could not be confirmed in *Xenopus* laevis.[53]

There is an interesting parallel that can be drawn between spliceosomopathies and ribosomopathies. Ribosomopathies encompass a group of diseases due to mutations in ribosomal proteins or ribosome biogenesis factors.[54] Like the spliceosome, ribosomes are an essential component of the cell machinery, ubiquitously required in all cell types, and yet ribosomopathies also frequently present tissue-specific disorders[3] as seen in Treacher Collins syndrome (TCS)[55] and Diamond-Blackfan anemia,[56] both characterized by mandibulofacial dysostosis (MFD).[35] It has been proposed that different ribosome biogenesis requirements across tissues during development could lead to the tissue specificity of ribosomopathies or that expression levels of certain components of the ribosome differ across cell types.[57] The tissue specificity of spliceosomopathies may have a similar origin with developmental processes regulating the differential distribution of various spliceosome components. Most craniofacial structures affected in MFD are derived from neural crest cells, which have a high metabolic rate and high demand in splicing activity, and this could also account for their susceptibility to defects in both ribosomopathies and spliceosomopathies.

Both ribosomopathies and spliceosomopathies have been connected to DNA damage/repair mechanisms. The nucleolar protein Treacle, which is mutated in TCS, has been found to interact with the MRNM complex that is critical in DNA damage response/repair to limit oxidative stress-induced cell death, and in mouse models of TCS, this repair process is perturbed.[58] In MDS, SF3B1 has been found to form a complex with BRCA1 and BCLAF1 at sites of DNA damage and to regulate pre-mRNA splicing of genes involved in DNA damage signaling and repair.[47] Impaired DNA damage response often lead to apoptosis, underlying the MDS-associated pathology. Interestingly, animal models of both

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the ribosomopathy TCS[59,60] and the spliceosomopathy NS[53] indicate that loss of neural and neural crest progenitors occurs through mechanisms that involve apoptosis[53,59,60] and decreased proliferation,[59] pointing to a common root cause for these craniofacial pathologies.

3.4 | Perspectives

Much remains to be learned on the mechanisms underlying spliceosomopathies. While the spliceosome is part of the general cell machinery, it is likely that associated proteins and/or interacting partners and/or target mRNAs could be differentially expressed and may explain the tissue-specific pathologies associated with these conditions. The mere observation that spliceosomopathies can affect tissues as diverse as the retina, bone marrow, and neural crest clearly indicates that all components of the spliceosome are not equal. Therefore, studies aimed at characterizing these specific interactions will be critical to gain novel insights into these pathologies, while keeping in mind that some of these splicing proteins may also carry non-canonical functions in addition to their pre-mRNA processing activity.

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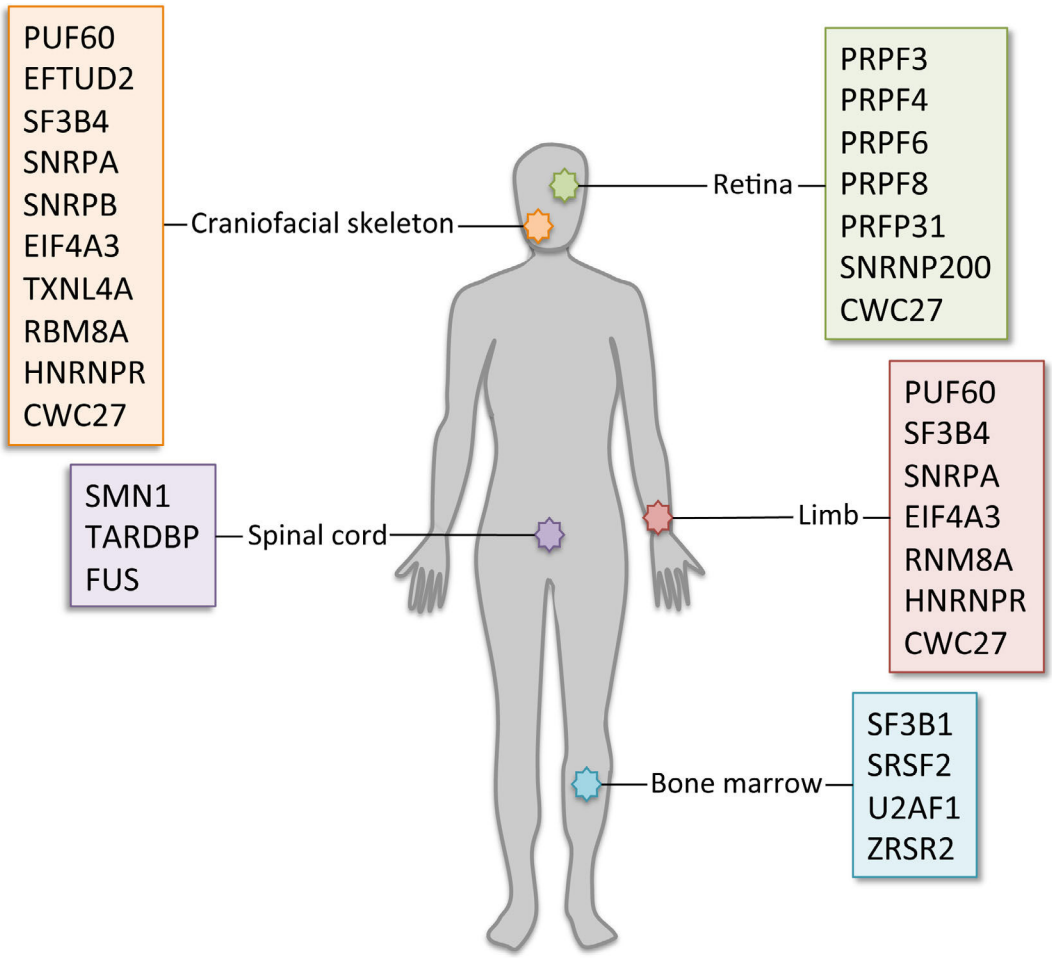

FIGURE 1.

Spliceosomopathies are largely tissue-specific. The tissues affected by these pathologies and their association with mutations in genes encoding components of the spliceosome are indicated

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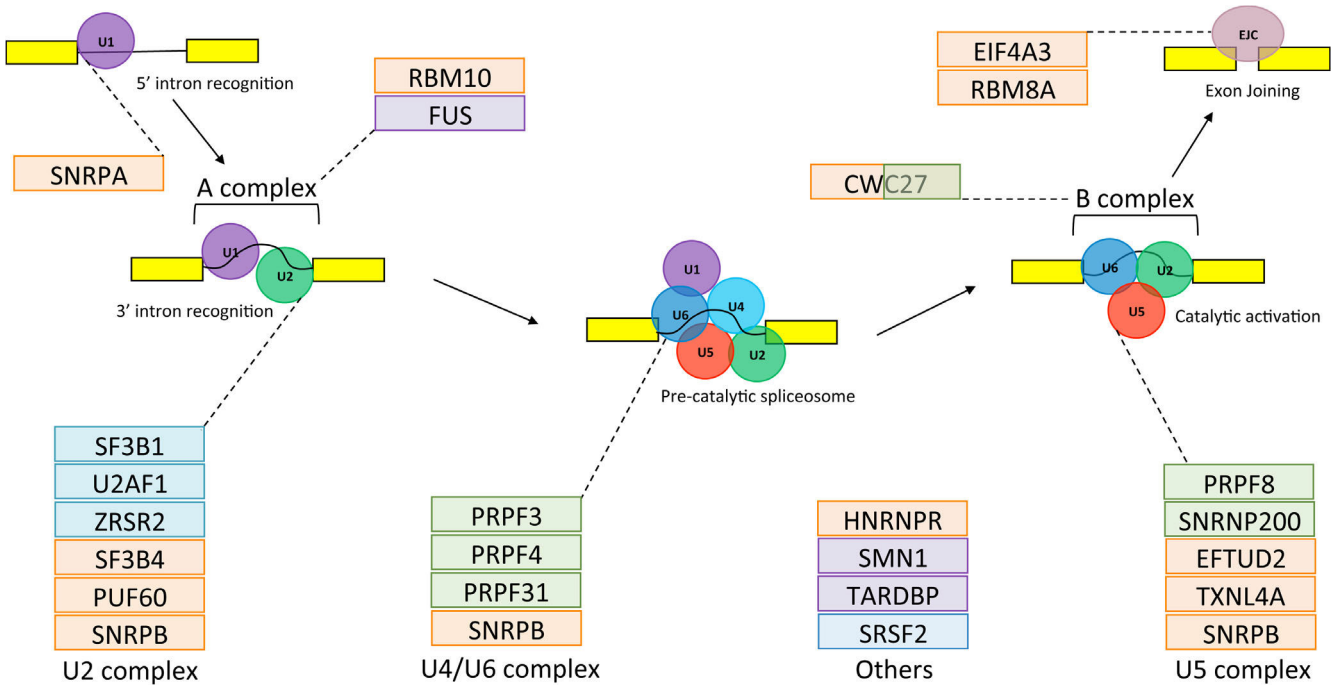

FIGURE 2.

Schematic representation of the major steps of precursor messenger-RNA splicing and the involvement of the proteins that have been linked to spliceosomopathies. Proteins are grouped based on their activity and association with a specific complex of the spliceosome. The link to a specific disease is color-coded based on Figure 1. Proteins mutated in retinitis pigmentosa (green) are primarily associated with U4/U6 complex. Proteins mutated in myelodysplastic syndromes (blue) are primarily associated with U2 complex. Proteins mutated in craniofacial spliceosomopathies (orange) are distributed across all complexes. Exons are represented as yellow boxes. EJC, exon-junction complex

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TABLE 1

List of mutated proteins in various diseases, and their association with the spliceosomal machinery

Diseases	Phenotype MIM number	Mutated proteins	Spliceosomal complexes	References
Retinitis pigmentosa	268000	PRPF3	U4/U6 complex	1,6,8
		PRPF4	U4/U6 complex	1,6,8
		PRPF31	U4/U6 complex	1,6,8
		PRPF8	U5 complex	1,6,8
		SNRNP200	U4/U6 complex	1,7
Myelodysplastic syndromes	614286	SF3B1	U2 complex	1,9
		U2AF1	U2 complex	1,10
		ZRSR2	U2 complex	1,9
		SRSF2	Exonic splicing enhancer	1,11
Verheij syndrome	615583	PUF60	U2 complex	1,12,13
Mandibulofacial dysostosis, Guion-Almeida type	610536	EFTUD2	U5 complex	1,14
Nager syndrome	154400	SF3B4	U2 complex	1,15–17
Cerebro-costo-mandibular syndrome	117650	SNRPB	All U complexes	1,18
—	*182285	SNRPA	U1 complex	1,19
Acrofacial dysostosis Richieri-Costa-Pereira syndrome	268 305	EIF4A3	Exon junction complex	1,20
Burn-McKeown syndrome	608572	TXNL4A	U5 complex	1,21
Thrombocytopenia-absent radius syndrome	274000	RBM8A	Exon junction complex	1,22,23
Au-Kline syndrome	616580	HNRNPR	Other	1,24
Bain type mental retardation	300986	HNRNPR	Other	1,24
Early infantile epileptic encephalopathy-54	617391	HNRNPR	Other	1,24
TARP syndrome	311900	RBM10	A complex	1,25
Spinal muscular atrophy	253300	SMN1	Other	1,26
Amyotrophic lateral sclerosis	105400	TARDBP	Other	1,26
		FUS	A complex	1,14,26
Genodermatosis poikiloderma with neutropenia, Clericuzio-type	604173	USB1	U6 associated	1,27,28
CWC27 spectrum disorders	250410	CWC27	B complex	1,29

Notes: “Other” is used when a protein is not associated with one of the major complexes.

*indicates gene/locus MIM number, when the disease name is not available.