# **SnapShot: The Splicing Regulatory Machinery**

Mathieu Gabut, Sidharth Chaudhry, and Benjamin J. Blencowe

Banting and Best Department of Medical Research, University of Toronto, Toronto, ON M5S 3E1, Canada

	Namo	Other Names	Protoin Domains	Rinding Sites	Target Conec/Mouse Phonetypes/Disease Associations	हे है.	d K	вş	υΣo	τΣ	≤ q b	an	<u>a</u> 5	의교	P P		8.5 10.5
				Diffully Sites		< 0:	II	ОШ	S B C			20	<u> </u>	S O F			
	SRp20	Sirsa, X10	RRIVI, RS	GCOCCOCOUC													
su	966	Sirs/	RRIVI, RS, C2HC ZIII		Iau, GIRH, 9Go		_	_									
otei	A5F/5F2	Sirsi	RRIVI, RS	RGAAGAAC	HipK3, Cardioniyopathy												
Å	SU35	Sirsz	RRIVI, RS		ACIE; -/- embryonic lethal, cond. KO delicient I-cell maturation, cardiomyopathy; LS											++	
ted	SRp30C	Sirsy	RRIVI, RS														
Sela	SRp38	Fusipit, INSS	RRIVI, RS	ACAAAGACAA	CREB, type if and type XI collagens												
4	SRp40	Sirso, HRS	RRIVI, RS	AGGAGAAGGGA													
d S	SRppp	Sirso	RRIVI, RS	GGCAGCACCUG													
an	SRP/5	Sirs4	RRIVI, RS	GAAGGA	FNT, ETA, CD45; overexpression enhances chordrogenic differentiation												
ц В	Traza	Iraza	RRIVI, RS	GAAARGARR													
	Ira2p	Strs IU	RRM, RS	(GAA)n	HIPK3, SMIN, Tau												
	SRM 160	Srrm I	RS, PWI	AUGAAGAGGA													
-	SWAP	Sirso	RO, SWAP		SWAR, OD45, rau; possible astrima susceptibility gene												
VP Proteins			RRM, RGG	UAGGGA/U	HIPK3, SMIN2, C-H-ras; meumatoid arthritis, systemic lupus erythematosus			-									
	hanne A2/B1	Hnmpazbi, Hnmpaz	RRIVI, RGG		4. TR, HIV Tat, INBKAP; medinatoid antihitis, systemic tupus erythematosus		_										
		Hnmpc, Hnmpc1/c2			p-amyloid receptor; -/- embryonic lethal E6.5; systemic scierosis, psonatic artimus												
		Hripi Dhrevit Lleves a	RRM, RGG, GT	GGGA, G-rich	PLP, C-SRU, BCI-X												
		Romxn, Hnrnpg	RRM, RGG, SRGT	AAGU	SMN2, a-tropomyosin; -/- Impaired spermatogenesis												
L R		Hnrpni	RRM, RGG, GTR, GT	GGGA, G-rich	PLP, HIV tat, BCI-X; possible implication in MD		_										
2		Dtho1 Horoi			PRTP, a SPC, Fea, aTNT, CCPR, NMDA, CLPC, heRNR A1												
					TIFTD, C-Sho, Fas, CTNT, CORF, NWDA, CEDU, TITRINF AT		_					_					
-	TPTB	Plbp2, brP1B	RRIVI					_		┼┼┼		+				++	
	FoxT	A2001			NMHO-B, CGRP, F17; possible autism association, sporadic epilepsy					+		_				++	
	FUX2	Rumpal Brunola		(U)GCAUG													
	Cugpp			U/G-rich	CTNT, insulin Receptor; overexpression MD symptoms; MD, DD and BD												
	Cugpp2	Brunold		U/G-rich	Mtmr1 aTaTi / poppetal lathelity existing disorder CELEA cardiamyopathy					+						++	
		Brunoi4		U/G-rich	Mitmin, chin; -/- neonatal lethality, selzure disorder. CELFA cardiomyopathy					+++		_				++	
	Nova 1	Liavi4			CluBer2, CARAet, / postatel lethelity by mater payrap death; POMA syndrome, PE												
S	Nova-1	Neveo	KH	VCAV	Clynuz, GADAa, -/- positiatal remainly by motor neuron death, POMA syndrome						NI						
Other Facto	TIA 1	mTia1		YCAY	ANVESTI For CORD FOFED TIAD II A VECT / contraction lathelity												
			RRIVI	U-rich	TIA1_CODD TIAD: (												
	Maria	Mari Mari			TAT, CGRP, TIAR; -/- early empryonic retriainty												
				rgcu(u/g)r	CD11, insulin receptor, Cich1, mints; -/- mice develop MD-like disease; MD												
	Ougling	Churdso, I-STAR			MAC DLP. ( ambrance label also ONC/DNC duranteliantics to successful 007												
	Quaking			ACUAAY[JUAAY	MAG, PLP; -/- embryonic lethal, qkv UNS/PNS dysmyelination, tremors; ataxia, SCZ												
	P3F	Sipq															
	OPF45	RDITIT/	RRIVI, G patch		SXI, ras; overexpression mutilorug-resistance phenotypes												
		RUM4a, Lark		0/U-rich	MAP I, α-troportiyosifi, Tau												
	ST3D1	SAP155, SF3D155	KKIM, HEAI	ND A (Luish	Bcl-x; +/- skeletal transformations concomitant with ectopic Hox expression												
	Sam68	Knarbs1	КН	A/U-rich	BCI-x; -/- Increased osteoblast differentiation, reduced adipocyte differentiation												

Expression in mouse

Low

High

## SnapShot: The Splicing Regulatory Machinery



## Mathieu Gabut, Sidharth Chaudhry, and Benjamin J. Blencowe

Banting and Best Department of Medical Research, University of Toronto, Toronto, ON M5S 3E1, Canada

Alternative splicing is the process by which pairs of splice sites are differentially selected to generate multiple mRNA variants from a single precursor (pre-) mRNA. It represents a frequent mechanism underlying the expansion of the proteome and regulation of gene expression in higher eukaryotes and is known to play numerous critical roles in both normal and disease processes. Among the different types of alternative splicing are variable inclusion of exons, selection of alternative 5' and 3' splice sites, inclusion of mutually exclusive exons, and retention of introns.

Many alternative splicing events are regulated in a cell/tissue type-, development stage-, and/or growth condition-specific manner, and emerging evidence indicates that many such events are coordinated by the action of individual or combinations of *trans*-acting regulatory proteins that bind to specific sites within pre-mRNA. These binding sites, referred to as enhancers or silencers, are generally located proximal to splice sites within intron and exon sequences. Binding of splicing factors to these sites serves to promote or repress the formation of the spliceosome, the large (~60S) RNA-protein machinery that catalyzes intron removal.

This SnapShot provides a quick guide to the growing list of mammalian protein factors known to regulate alternative splicing. Information provided for each factor includes the following: common name (1st column), Mouse Genome Informatics (MGI) symbol and/or other common names (2nd column), key domains (3rd column), reported RNA binding sites (4th column), and examples of alternatively spliced target transcripts, associated phenotypes, and diseases (5th column). In addition, heat maps generated using published microarray data (see below) are provided to show the mRNA expression profiles for each factor across diverse mouse tissues.

In addition to the factors shown, other proteins, including constitutive components of the spliceosome, and in a few cases small RNAs, have also been reported to regulate alternative splicing. Among the proteins not listed in the table are members of the SR family (SRp46, SRp54), SR-related proteins (SRrp35, SRrp86, RNPS1), hnRNP family (hnRNP M), CELF family (CELF3, CELF5, CELF6), and other factors (Raver1, SIm-1, SKIP, Slu7, TDP43, YB-1). Specific kinases (e.g., SRPK1, SRPK2, Clk/Sty, DNA Topoisomerase I, Akt, PKC), phosphatases (e.g., PP1, PP2A, PP2C<sub>7</sub>), and methylases can also control alternative splicing by modulating the posttranslational modification status of splicing factors, which can affect their ability to promote or repress spliceosome formation. Given the complexity and extent of regulated splicing decisions in metazoan organisms (it is estimated that more than two-thirds of human multiexon genes undergo alternative splicing) as well as the large number of RNA-binding domain proteins and other protential *trans*-acting factors that currently lack assigned functions, we anticipate the list of important splicing regulators to greatly expand in the next several years. **Abbreviations** 

Protein domains: C2HC Znf, CCHC zinc finger domain; C3H1 Znf, CCCH zinc finger domain; G Patch, glycine-rich nucleic binding domain; HEAT, HEAT repeats; GY, glycineand tyrosine-rich domain; GYR, glycine-, tyrosine-, and arginine-rich domain; KH, RNA-binding domain; PWI, PWI nucleic acid-binding domain; RGG, RGG box: arginineglycine-glycine repeats; RRM, RNA recognition motif; RS, arginine-serine repeats-containing domain; SWAP, RNA-binding domain derived from the *Drosophila* Suppressorof-White-APricot splicing regulator; SRGY, motif enriched in serine, arginine, glycine, and tyrosine.

Binding sites: [...], spacer sequence of 1 to 20 nucleotides; n, motif repetitions; ND, not determined; R, purine; Y, pyrimidine.

Mouse phenotypes and disease associations: -/-, homozygous knockout; -/+, heterozygous knockout; CNS, central nervous system; Cond. KO, conditional knockout; BD, Becker muscular dystrophy; DD, Duchenne muscular dystrophy; LS, Leigh's syndrome; MD, Myotonic dystrophy; PE, Paraneoplastic Encephalomyelitis; PNS, peripheral nervous system, POMA, Paraneoplastic Opsoclonus-Myoclonus Ataxia; RA, retinoic acid; SCZ, Schizophrenia.

Mouse tissues: Amy, amygdala; Čeb, cerebellum; Hip, hippocampus; Hyp, hypothalamus; OB, olfactory bulb; SC, spinal cord; BM, bone marrow; Bo, bone; Ht, heart; SM, skeletal muscle; Epd, epidermis; Kd, kidney; Liv, liver; Lu, lung; Pan, pancreas; Pla, placenta; Pro, prostate; Sto, stomach; Spl, spleen; Thy, thymus; Thd, thyroid; Te, testis; Ut, uterus; Ov, ovary; E3.5, embryo day 3.5; E6.5, embryo day 6.5; E8.5, embryo day 8.5; E10.5, embryo day 10.5.

### **Data Analysis**

The mouse mRNA expression profiles were generated using the TreeView v1.60 program and microarray data from the study of Su et al. (2002). The color scale indicates signal intensity over the mean intensity value for the 28 tissues shown. The mean-subtracted intensity values range from -606.9 to +7680.7.

### REFERENCES

Blencowe, B.J. (2006). Alternative splicing: New insights from global analyses. Cell 126, 37-47.

Bourgeois, C.F., Lejeune, F., and Stévenin, J. (2004). Broad specificity of SR (serine/arginine) proteins in the regulation of alternative splicing of pre-messenger RNA. Prog. Nucleic Acid Res. Mol. Biol. 78, 37–88.

Graveley, B.R. (2000). Sorting out the complexity of SR protein functions. RNA 6, 1197-1211.

Krecic, A.M., and Swanson, M.S. (1999). hnRNP complexes: Composition, structure, and function. Curr. Opin. Cell Biol. 11, 363–371.

Li, Q., Lee, J.A., and Black, D.L. (2007). Neuronal regulation of alternative pre-mRNA splicing. Nat. Rev. Neurosci. 8, 819–831.

Lin, S., and Fu, X.D. (2007). SR proteins and related factors in alternative splicing. In Alternative Splicing in the Postgenomic Era, B.J. Blencowe and B.R. Graveley, eds. (Georgetown, TX: Landes Biosciences), pp. 108–123.

Matlin, A.J., Clark, F., and Smith, C.W. (2005). Understanding alternative splicing: Towards a cellular code. Nat. Rev. Mol. Cell Biol. 6, 386–398.

Martinez-Contreras, R., Cloutier, P., Shkreta, L., Fisette, J.F., Revil, T., and Chabot, B. (2007). hnRNP proteins and splicing control. In Alternative Splicing in the Postgenomic Era, B.J. Blencowe and B.R. Graveley, eds. (Georgetown, TX: Landes Biosciences), pp. 124–148.

Möröy, T., and Heyd, F. (2007). The impact of alternative splicing in vivo: Mouse models show the way. RNA 13, 1155–1171.

Musunuru, K. (2003). Cell-specific RNA-binding proteins in human disease. Trends Cardiovasc. Med. 13, 188–195.

Pascual, M., Vicente, M., Monferrer, L., and Artero, R. (2006). The Muscleblind family of proteins: An emerging class of regulators of developmentally programmed alternative splicing. Differentiation 74, 65–80.

Park, J.W., Parisky, K., Celotto, A.M., Reenan, R.A., and Graveley, B.R. (2004). Identification of alternative splicing regulators by RNA interference in *Drosophila*. Proc. Natl. Acad. Sci. USA *101*, 15974–15979.

Ranum, L.P.W., and Cooper, T.A. (2006). RNA-mediated neuromuscular disorders. Annu. Rev. Neurosci. 29, 259–277.

Singh, R., and Valcárcel, J. (2005). Building specificity with nonspecific RNA-binding proteins. Nat. Struct. Mol. Biol. 12, 645–653.

Su, A.I., Cooke, M.P., Ching, K.A., Hakak, Y., Walker, J.R., Wiltshire, T., Orth, A.P., Vega, R.G., Sapinoso, L.M., Moqrich, A., et al. (2002). Proc. Natl. Acad. Sci. USA 99, 4465–4470.

Ule, J., and Darnell, R.B. (2006). RNA binding proteins and the regulation of neuronal synaptic plasticity. Curr. Opin. Neurobiol. 16, 102–110.