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Conserved functions of RNA-binding proteins in muscle

Elena Nikonova[a,1], Shao-Yen Kao[a,1], Keshika Ravichandran[a], Anja Wittner[a], Maria L. Spletter[a,b,*]

[a] Biomedical Center, Department of Physiological Chemistry, Ludwig-Maximilians-University München, Großhaderner Str. 9, 82152, Martinsried-Planegg, Germany
[b] Center for Integrated Protein Science Munich (CIPSM) at the Department of Chemistry, Ludwig-Maximilians-Universität München, Munich, Germany

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ABSTRACT

Animals require different types of muscle for survival, for example for circulation, motility, reproduction and digestion. Much emphasis in the muscle field has been placed on understanding how transcriptional regulation generates diverse types of muscle during development. Recent work indicates that alternative splicing and RNA regulation are as critical to muscle development, and altered function of RNA-binding proteins causes muscle disease. Although hundreds of genes predicted to bind RNA are expressed in muscles, many fewer have been functionally characterized. We present a cross-species view summarizing what is known about RNA-binding protein function in muscle, from worms and flies to zebrafish, mice and humans. In particular, we focus on alternative splicing regulated by the CELF, MBNL and RBFOX families of proteins. We discuss the systemic nature of diseases associated with loss of RNA-binding proteins in muscle, focusing on mis-regulation of CELF and MBNL in myotonic dystrophy. These examples illustrate the conservation of RNA-binding protein function and the marked utility of genetic model systems in understanding mechanisms of RNA regulation.

1. Introduction

Across the animal kingdom, muscles are necessary for essential processes from feeding and digestion to motility, reproduction, circulation and respiration. Comparing vulval versus body muscle in *C. elegans*, flight versus leg muscle in *D. melanogaster* or heart versus skeletal muscle in vertebrates suggests that morphological and structural differences support functional diversity. Muscles have evolved many specialized morphologies, extracellular attachments, cytoskeletal architectures and contractile properties for different functions (Schnorrer and Dickson, 2004). One of the major challenges in the muscle field is deciphering how this vast array of functional specialization arises developmentally through transcriptional and post-transcriptional regulation of gene expression. Here we review what is known about the contribution of RNA-binding proteins and post-transcriptional regulation to myogenesis.

1.1. Muscle structure is evolutionarily conserved

Muscles are formed from repetitive arrays of the same basic, structural unit: the sarcomere. Sarcomeres are the motors that drive muscle contraction and thus movement. They are cytoskeletal elements consisting of interleaved thin filaments (Actin and actin binding proteins) and thick filaments (Myosin and myosin binding proteins) organized in a series of parallel arrays extending from one end of the muscle cell to the other (Lemke and Schnorrer, 2017). Actin filaments are anchored in the Z-discs, while myosin filaments are anchored in the M-lines (Squire et al., 2017), leading to a "ribbed" appearance in striated muscle. A third filament system, consisting of the Titin connecting filaments, provides stability, contributes to stiffness and may help regulate overall sarcomere length (Tskhovrebova and Trinick, 2017). In addition, there are many sarcomere associated regulatory and structural proteins, for example the Troponin complex regulating actomyosin contractility (Lin et al., 2017) or α-Actinin ensuring stability of the Z-disc (Sanger et al., 2017). Detailed reviews of muscle structure are available for further reference (*i.e.* (Gautel and Djinović-Carugo, 2016; Lemke and Schnorrer, 2017; Lin et al., 2017; Sanger et al., 2017). These associated proteins are essential for structural integrity of the sarcomere and influence contractile ability through the accessibility of myosin-binding sites on actin, the affinity of myosin for actin and the generation of tension.

Abbreviations: RNA, ribonucleic acid; mRNA, messenger RNA; PEVK, proline, glutamic acid, valine, lysine rich domain; RBPs, RNA binding proteins; UTR, untranslated region; UAS, upstream activating sequence; AS, alternative splicing; IFM, indirect flight muscle; DM, myotonic dystrophy; SMA, spinal muscular atrophy; ALS, amyotrophic lateral sclerosis; CELF, CUGBP, ELAV-like family; MBNL, muscleblind; RBFOX, RNA-binding FOX; FOX, Forkhead box; NMD, nonsense-mediated decay; RRM, RNA recognition motif; dsRBD, double-stranded RNA binding domain; KH, K-Homology (domain); Pum, Pumilio; GAPDH, Glyceraldehyde 3-phosphate dehydrogenase; RIC, RNA interactome capture; GO, gene ontology; GLAD, gene list annotation for Drosophila; RNAi, RNA interference; IR, interfering RNA; Zn-finger, zinc-finger; LASR, large assembly of splicing regulators

* Corresponding author at: Biomedical Center, Department of Physiological Chemistry, Ludwig-Maximilians-University München, Großhaderner Str. 9, 82152, Martinsried-Planegg, Germany.
E-mail address: maria.spletter@bmc.med.lmu.de (M.L. Spletter).
[1] These authors contributed equally.

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Basic sarcomere structure and components, as well as their mechanisms of development, are evolutionarily conserved (Buckingham, 2017; Fukushige et al., 2006; Schnorrer and Dickson, 2004; Spletter and Schnorrer, 2014). Cnidarians, in particular free-swimming medusa such as *Aglantha digitale*, have a striated, circular muscle in the medusa bell containing 30–50 sarcomeres (Singla, 1978). These sarcomeres consist of ordered arrays of Actin thin filaments and Myosin II thick filaments separated by Z-discs and M-lines (Leclère and Röttinger, 2016). Cephalopod mollusks contain striated body muscle with Z-disc delimited sarcomeres built of conserved Actin, Myosin heavy chain and Tropomyosin proteins (Nödl et al., 2015), although their contraction control kinetics are likely different than vertebrates (Zullo et al., 2017). Tunicates such as *Ciona intestinalis* and *Diplosoma macdonaldi* have body and heart muscle with highly organized Z-discs and M-lines built of Actin, Myosin, Troponin and other conserved structural proteins (Cavey, 1983; Cavey and Cloney, 1976; Miyakawa and Konishi, 1984; Ohtsuka and Okamura, 2007) that share many developmental characteristics with vertebrate muscles (Buckingham, 2017; Diogo et al., 2015; Kaplan et al., 2015). *C. elegans* contain striated body wall muscle with clearly defined Z-discs and M-lines and built of highly conserved structural proteins including Actin, Myosin, Paramyosin, Troponin, Tropomyosin, α-actinin, etc. (Gieseler et al., 2017; Krause and Liu, 2012). *Drosophila* muscles also show conservation of structure and protein composition, with the flight muscle even displaying a 3.2 μm sarcomere length as compared to the 3.0–3.4 μm length observed in relaxed human skeletal muscle (Lemke and Schnorrer, 2017). Adult muscles in the fly also reflect the functional specialization observed in vertebrates, with distinct muscle morphologies, cytoskeletal structures and connectivity to allow for flight, locomotion, mating and feeding (Schnorrer and Dickson, 2004). These examples illustrate that striated muscles in animal models, even primitive organisms, share the same basic structure observed in humans.

Although all muscles share the same basic sarcomere structure, different muscle types display different contractile properties. These differences can be achieved by muscle-type specific protein or protein isoform expression (Narici et al., 2016). For example, heart muscle is stiffer than skeletal muscle. This high passive tension is essential to proper function, as the Frank-Starling mechanism describes how the stretching induced when the ventricles fill with blood increases cardiomyocyte contractility (Shiels and White, 2008). This stiffness in the heart is provided by alternatively-spliced isoforms of Titin with short PEVK domains, while skeletal muscle with a lower passive tension generates Titin isoforms with long PEVK domains (Gautel and Goulding, 1996; Guo et al., 2010; Li et al., 2013; Linke et al., 2002, 1999). A similar situation is observed in *Drosophila* flight muscle, which requires a high passive stiffness for stretch-activation (Peckham et al., 1990). Alternatively spliced short-PEVK containing Titin (Projectin) isoforms are found in flight muscle, while isoforms with long PEVK regions are found in more pliable body muscles (Moore et al., 1999). These examples suggest that muscles can "tune" their contractile properties and cytoskeletal architectures through muscle-type specific transcription or alternative splicing programs. Mechanisms of muscle-type specific transcription have been discussed elsewhere (de Joussineau et al., 2012; Dong et al., 2017; Estrella and Naya, 2014; Imbriano and Molinari, 2018; Spletter and Schnorrer, 2014), so below we focus on the role of alternative splicing and more broadly RNA-binding proteins in muscle.

1.2. Expression of RNA-binding proteins in muscle

RNA is regulated at each step of its life within the cell. mRNAs are transcribed, spliced, edited, capped, poly-adenylated, exported from the nucleus, trafficked and translated (Bock et al., 2015). RNA stability and quality are controlled through nonsense mediated decay (NMD) and targeted degradation (Nasif et al., 2018). All of these processes are controlled by RNA-binding proteins (RBPs). Multiple protein domains have been biochemically shown to bind RNA, for example the canonical RNA-recognition motif (RRM), double-stranded RNA-binding domain (dsRBD), K-homology domain (KH), DEAD/DEAH box, Zn-fingers (CCCH-type, RanBP2-type, etc.) and the Pumilio (Pum) domain (Font and Mackay, 2010; Glisovic et al., 2008; Nakka et al., 2018). The recent RNA interactome capture approach, where mass-spectrometry is used to identify proteins cross-linked to oligo-dT isolated mRNAs, has also identified many new RBPs with no previous link to RNA regulation, notably intermediary metabolic and mitochondrial enzymes (Hentze et al., 2018; Liao et al., 2016). These proteins likely have important regulatory functions in muscle, as for example aldolase A and GAPDH were previously identified to bind the 3′-UTR region of myosin heavy chain (Kiri and Goldspink, 2002). In general, a wide variety of proteins can be identified that bind RNA or "moonlight" as RBPs under specific conditions.

Estimates of the total number of RBPs in a given genome are challenging to obtain and can be quite variable (Gerstberger et al., 2014). The RNA-binding gene ontology category in AmiGO identifies 1649, 1020, 865, 579 and 552 RPBs in the genomes of human, mouse, zebrafish, fruit fly and the nematode *C. elegans*, respectively (Fig. 1A) (Ashburner et al., 2000; The Gene Ontology Consortium, 2017). RNA interactome capture (RIC) identified 1393, 1914, 227, 777 and 594 RBPs in the same organisms (Hentze et al., 2018). However, as nearly 50% of the RIC RBPs were novel binders, the number of RBPs may be significantly higher. For example, in *Drosophila* of the 579 RBPs in AmiGO, the 577 RBPs in GLAD (Gene List Annotation for Drosophila) (Hu et al., 2015) and the 777 RBPs identified from RIC in embryos, only 188 RBPs overlap in all three datasets and 517 overlap in at least two datasets (Fig. 1B). If all these proteins do in fact bind RNA, the fly genome may encode 1229 RBPs, which constitutes 11% of all coding genes! These numbers indicate that somewhere between 3–10% of a given genome likely encodes RBPs.

Using published mRNA-Seq datasets from muscle (see Methods), we estimated how many of the above RBPs are expressed in muscle tissue. 66% of AmiGO RBPs are expressed in muscle in mouse, 80% in *Drosophila* and 65% in *C. elegans* (Fig. 1C). If we take all possible RBPs predicted in *Drosophila*, 84% (1038 genes) are expressed in muscle (Fig. 1B). These numbers may be higher, as existing mRNA-Seq datasets do not account for all muscle-type specific and temporal expression. It is clear, however, that hundreds of RBPs are expressed in muscle. Using data from a genome-wide RNAi screen (Schnorrer et al., 2010), nearly 40% of AmiGO RBPs have a phenotype in *Drosophila* muscle. We manually curated RBPs with a published function in muscle from the mouse, zebrafish, fruit fly, and *C. elegans* literature (Table 1). Strikingly, only a small proportion (2–4%) of muscle-expressed RBPs have been studied (Fig. 1C). Given the large number of RBPs expressed and with potential phenotypes in muscle, this clearly illustrates a need for further studies examining the function of RBPs in myogenesis.

Our curated list of RBPs contains 51 genes from mouse, 15 from zebrafish, 28 from *Drosophila* and 17 RBPs from *C. elegans* (Table 1). Most major classes of RBPs are represented, such as DEAD/DEAH-box helicases, KH domain proteins, dsRBD proteins, RNA-binding Zn-fingers and many RRM domain proteins. We noted homology/orthology relationships between species, and in many cases found a function for the same protein across species. For example, Quaking, which is also known for functions in neuronal (Shu et al., 2017) and macrophage (de Bruin et al., 2016) development, functions in muscle development in all model species we curated, controlling splicing and translation during mouse myoblast differentiation (Fagg et al., 2017; Hall et al., 2013), myofibril assembly in zebrafish (Bonnet et al., 2017), myotube migration and attachment and tendon development in *Drosophila* (Baehrecke, 1997; Nabel-Rosen et al., 2002; Zaffran et al., 1997) and muscle-specific *unc-60* splicing in *C. elegans* (Ohno et al., 2012). We will discuss several additional examples below, including functions of CELF, MBNL and FOX family RBPs. We also note that after accounting for sequence conservation, our list includes 82 distinct RBPs, which falls far short of attributing a function to the several hundred (or perhaps thousand) RBPs expressed in muscle.

1.3. RNA-binding protein function in muscle

As RNA is regulated at many steps of its life cycle in the cell, it perhaps is not surprising that muscle RBPs we found in the literature have diverse functions such as alternative splicing, mRNA editing, mRNA decapping, nuclear export, cytoplasmic trafficking and localization, P-granule formation and translational regulation (Table 1). This indicates the general importance of RNA regulation to muscle development and function, and moreover suggests many of these functions may be evolutionarily conserved. It also suggests that there is no single phenotype that may be expected when screening to identify novel RBPs that regulate myogenesis.

To support this interpretation, we performed UAS-RNAi knockdown of different types of RBPs in *Drosophila* muscle. Here we present five examples (Rm62, Sf3b2, Sf3a2, noi and Sbr), all of which displayed lethal or flightless phenotypes in a muscle-specific genome-wide RNAi screen (Schnorrer et al., 2010), to illustrate different myofibrillar phenotypes. We confirmed that all five genes result in lethality or flightlessness when knocked-down in all muscles using *Mef2*-Gal4 or specifically in flight muscle using *Act88F*-Gal4 (Fig. 2A). Rm62 is a DEAD-box

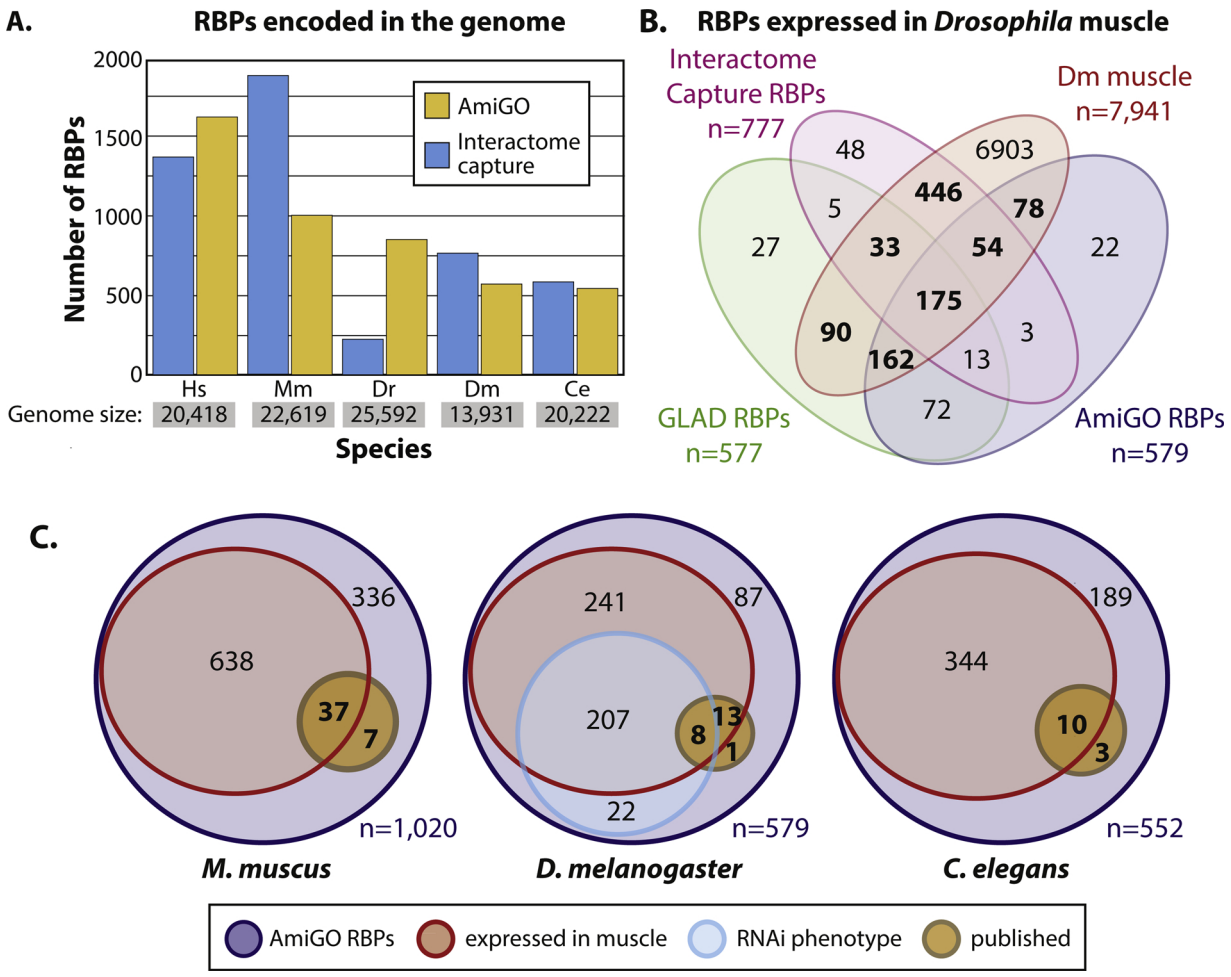


Fig. 1. Numbers of expressed RBPs with a function in muscle.
A. Numbers of RBPs encoded in the genome of *Homo sapiens* (human, Hs), *Mus musculus* (mouse, Mm), *Danio rerio* (zebrafish, Dr), *Drosophila melanogaster* (fruit fly, Dm) and *Caenorhabditis elegans* (nematode, Ce) as predicted by RNA-binding gene ontology terms in AmiGO (Ashburner et al., 2000; The Gene Ontology Consortium, 2017) (orange) or from RNA interactome capture (Hentze et al., 2018) (blue). Genome sizes from Ensembl. **B.** Venn diagram of the overlap of Dm RBP predictions from GLAD (Hu et al., 2015) (green, n = 577), RNA interaction capture (magenta, n = 777) and AmiGO (blue, n = 579) with RBPs expressed in mRNA-seq data from Dm muscle (red, n = 7941) (Spletter et al., 2018, 2015). Bold highlights the 1038 putative RBPs expressed in muscle. **C.** Circle diagrams of the number of published RBPs compared to total RBPs expressed in muscle in mouse, *Drosophila* and *C. elegans*.

helicase previously shown to control a wide variety of alternative splicing events in *Drosophila* S2 cells (Brooks et al., 2011) and promote persistent larval muscle survival in pupae (Kuleesha et al., 2016). Another DEAD-box helicase Smg-2, an essential component of the nonsense mediated decay (NMD) pathway, has been shown to mediate CUG- and CAG-repeat toxicity in muscle in *C. elegans* (Garcia et al., 2014). Loss of the zebrafish DEAD-box helicase Ddx39ab results in cardiac and skeletal muscle dystrophy and mis-splicing (Linlin Zhang et al., 2018), while loss of the Ddx27 helicase affects rRNA maturation resulting in translation defects in myogenesis (Bennett et al., 2018). We find that loss of Rm62 in flight muscle results in too thick myofibrils that split (Fig. 2C), indicating Rm62 influences myofibril formation and stability.

Sf3b2 (*Splicing factor 3b, subunit 2*), *Sf3a2* (*Splicing factor 3a, subunit 2*) and *noi* (*noisette*) encode components of the U2 snRNP, which is essential for spliceosomal assembly and U2-dependent alternative splicing (Will and Lührmann, 2011). *Drosophila* Hoip (Hoi Polloi) as well as its zebrafish homologue Snu13b, conserved components of the U4/5/6 snRNP complex, have previously been reported to control myotube extension, sarcomere protein expression and skeletal muscle myogenesis (Johnson et al., 2013). We observe that knockdown of *Sf3b2* results in strong actin inclusions at Z-discs (so called Zebra bodies) and long filamentous actin extensions (Fig. 2D). Knockdown of *Sf3a2* results in complete loss of muscle fibers with severely disrupted myofibrillar structure including splitting, too short sarcomeres, fraying and Zebra bodies (Fig. 2E). Too short sarcomeres can reflect mis-regulation of myosin activity and hypercontraction (Nongthomba et al., 2003). Knockdown of *noi* results in myofibrillar fraying, breaking and Zebra bodies (Fig. 2F). Due to the nature of RNAi knockdown experiments these are likely hypermorphic phenotypes, as one would predict that a complete loss of splicing would result in muscle loss as observed for Sb3a2, but they illustrate variability in observed morphological defects.

Last we examined Sbr (Small bristles), homolog of human TAP/NXF-1, a nuclear export factor reported to be responsible for developmental export of all mRNAs (Wilkie et al., 2001). Another *Drosophila* nuclear transport factor 2-like family protein Rin (Rasputin) is associated with the formation of hypoxic stress granules in larval muscle (van der Laan et al., 2012), while in *C. elegans* the Nup62 homolog Npp-4, a structural component of the nuclear pore, modulates CUG toxicity in muscle (Garcia et al., 2014). Myofibrils of *sbr* knockdown animals are too thick, display periodic zebra bodies, break and are wavy. This may indicate a defect in export of specific mRNAs involved in myofibrillogenesis, but this remains to be determined in future studies.

Taken together, these data show that different RBPs and indeed different components of the same RBP complex can cause distinct myofibrillar phenotypes. This suggests there is no “general” RNA regulation or splicing morphological phenotype. These examples also illustrate how genes of the same functional type, in particular direct homologs, have functions in muscle across species.

1.4. Functional conservation of RBPs across species

RBPs can display high levels of sequence conservation between species, particularly in their functional RNA-binding domains, indicating they may be

Table 1
RBPs with published phenotypes in muscle.

	Domain(s)	Model organism				Associated Human disease	Comments	References
		Mm	Dr	Dm	Ce			
Helicases	RNA helicase				smg-2		{Upf1}; RNA interference, nuclear mRNA surveillance	(Garcia et al., 2014)
	DEAD-box			Rm62			{Ddx5}; regulates AS	(Kuleesha et al., 2016)
	DEAD-box		ddx27				Regulates rRNA maturation and mRNA translation	(Bennett et al., 2018)
	DEAD/ DEAH-box		ddx39ab				mutations cause cardiac and trunk muscle dystrophy	(Zhang et al., 2018)
	DEAD/ DEAH-box			Gem3			{Ddx30}; SMN complex, snRNP assembly	(Cauchi et al., 2008)
Tudor	Tudor	Smn1	smn1	Smn	smn-1	Werdnig-Hoffmann disease, SMA	SMN complex, snRNP assembly	Mm: (Cifuentes-Diaz et al., 2001; Shafey et al., 2005) Dr: (Laird et al., 2016) Dm: (Chan, 2003; Rajendra et al., 2007) Ce: (Schultz et al., 2017)
Gemin	Gemin2			Gem2		SMA	SMN complex, snRNP assembly	(Borg and Cauchi, 2013; Borg et al., 2015)
WD40	WD40 repeat			rig		Muscular atrophy	{Gemin5}; SMN complex, snRNP assembly	(Borg and Cauchi, 2013; Borg et al., 2015)
	WD40 repeat	Plrg1	plrg1				Cell division and spliceosome C complex	(Kleinridders et al., 2009)
	WD40 repeat				smu-1		{Smu1}; Splicesomal factor	(Spike et al., 2001)
	WD40, ZF (C2H2)	Zfp106				ALS	interacts with TDP-43 and FUS	(Anderson et al., 2016)
KH	KH	Fmr1		Fmr1		Fragile X syndrome, intellectual disability, premature ovarian failure, autism	interacts with Fxr1, regulates mRNA trafficking	Mm: (Fujita et al., 2017) Dm: (Novak et al., 2015; van der Laan et al., 2012)
	KH, RGG box	Fxr1	fxr1			Fragile X syndrome, FSHD	interacts with Fmr1, regulates mRNA translation	Mm: (Chu et al., 2018; Dubé et al., 2000; Mientjes et al., 2004) Dr: (Engels et al., 2004; Van't Padje et al., 2009)
	KH	Igf2bp2				diabetes, cancer	Regulates mRNA translation	(Boudoukha et al., 2010; Li et al., 2012; Zhou et al., 2016)
	KH	Khsrp					Regulates transcription, AS and mRNA localization	(Amirouche et al., 2014; Cammas et al., 2014)
	KH	Pcbp1					C-rich single-stranded nucleic acid binding	(Espinoza-Lewis et al., 2017)
	KH	Pcbp2				cancer	C-rich single-stranded nucleic acid binding	(Yunjiao Zhang et al., 2015)
	KH	Qk	qkia	how	asd-2	Schizophrenia, ganglioglioma, cancer	Regulates mRNA stability, AS, mRNA export and translation	Mm: (Guo et al., 2014) Dr: (Bonnet et al., 2017; Lobbardi et al., 2011) Dm: (Baehrecke, 1997; Nir et al., 2012; Zaffran et al., 1997) Ce: (Ohno et al., 2012)
PH	PH-like DCP1			DCP1			mRNA decapping	(van der Laan et al., 2012)
	PH		exosc9			ALS, myositis	exosome, AU-rich element binding, RNA processing	(Burns et al., 2018)
dsRBD	dsRBD	Adar				Aicardo-Goutieres syndrome, dyschromatosis	A-to-I editing activity	(Meltzer et al., 2010; Tan et al., 2017)
	dsRBD	Adarb1		Adar			A-to-I editing activity	Mm: (Tan et al., 2017) Dm: (Keegan et al., 2005)
	dsRBD, Staufen	Stau1					mRNA localization	(Crawford Parks et al., 2017; Ravel-Chapuis et al., 2016; Yamaguchi et al., 2008)
RRM	RRM	Celf1		bru1	etr-1	DM	CELF family, regulates AS, mRNA stability, translation; [CUGBP1]	Mm: (Gu et al., 2017; Orengo et al., 2008) Dm: (Oas et al., 2014; Spletter et al., 2015) Ce: (Milne and Hodgkin, 1999)
	RRM	Celf2		bru3		DM	CELF family, regulates AS, mRNA stability, translation	Mm: (Lu et al., 1999; Wang et al., 2015) Dm: (Picchio et al., 2018)
	RRM	Elavl1				cancer	RBP in AREs; [HuR]	(Figueroa et al., 2003; Phillips et al., 2018; van der Giessen et al., 2003)
	RRM, ZF (RanBP2)	Ewsr1				Ewing sarcoma, myoepithelioma	Muscular atrophy phenotype	(Park et al., 2015; Tanaka et al., 2015)
	RRM	Fus				ALS, essential tremor, dementia, cancer, connective tissue disease, aphasia, Pick's disease, progressive supranuclear palsy	hnRNP complex, FET family	(Wächter et al., 2015)
	RRM			Hrb98DE		ALS	{Hnrnpa2b1/Hnrnpa1}; controls hnRNA stability and splicing	(Kim et al., 2013; Li et al., 2016)
	RRM	Hnrnpd				ALS, chromosome 4q21 deletion syndrome, brachyolmia-amelogenesis imperfecta syndrome	hnRNP subfamily	(Chenette et al., 2016; Panda et al., 2014)
	RRM		Hnrpdl			chromosome 4q21 deletion syndrome, mixed connective tissue disease	{Hnrnpd paralog}	(Vieira et al., 2014)
	RRM, ZF (C2H2)	Matr3				ALS, myopathy	mRNA stability	(Banerjee et al., 2017)
	RRM	Pabpn1		Pabp2		OPMD, myopathy of extraocular muscle, ptosis, ophthalmoplegia	mRNA binding, poly(A) binding	Mm: (Apponi et al., 2013; Davies et al., 2005; Phillips et al., 2018) Dm: (Chartier et al., 2006, 2015)
		Ptbp1				multiple sclerosis	[hnRNPI]	(Lin and Tarn, 2011; Llorian et al., 2016)

(*continued on next page*)

Table 1 (*continued*)

	Domain(s)	Model organism				Associated Human disease	Comments	References
		Mm	Dr	Dm	Ce			
	RRM, HnRNP- L/PTB							
	RRM	Rbfox1	rbfox1	Rbfox1	fox-1	Spinocerebellar ataxia, autistic disorder	FOX family, cardiac hypertrophy and heart failure; [A2BP1]	Mm: (Nakahata and Kawamoto, 2005; Sellier et al., 2018) Dr:(Gallagher et al., 2011; Jin et al., 2003) Dm: (Schnorrer et al., 2010) Ce: (Kuroyanagi et al., 2007, 2006)
	RRM	Rbfox2	rbfox2				Fox family, AS; [RBM9]	Mm: (Nakahata and Kawamoto, 2005; Nutter et al., 2016) Dr: (Gallagher et al., 2011)
	RRM, ZF (CCHC)	Rbm4					Regulates AS and mRNA translation	(Lin and Tarn, 2011, 2009)
	RRM, ZF (C2H2)	Rbm20				DCM	Regulates AS, single RRM domain	(Beraldi et al., 2014; Chen et al., 2018)
	RRM	Rbm24	rbm24a				Hypertrophic and DCM in mouse, regulates AS	Mm: (Miyamoto et al., 2009; van den Hoogenhof et al., 2018) Dr: (Poon et al., 2012)
	RRM	Rbm38					mRNA stability	(Miyamoto et al., 2009)
	RRM	Rbpms					Transcriptional coactivator; [Hermes]	(Gerber et al., 2002, 1999)
	RRM		sfpq				binds RNA and DNA, spliceosome formation; [PSF]	(Lowery et al., 2007)
	RRM, SR	Srsf1				cancer	DCM in mouse, regulates AS	(Xie et al., 2017)
	RRM, SR	Srsf2				Myelodysplastic syndrome, cancer	DCM in mouse	(Klein et al., 2016)
	RRM, SR	Srsf10				alexithymia	deletion causes heart defects in mouse; [SRp38]	(Feng et al., 2009; Wei et al., 2015)
	RRM			Syp			{SYNCRIP}; mRNA binding, major hnRNP protein	(Halstead et al., 2014; McDermott et al., 2014)
	RRM	Tardbp		TBPH		ALS, FTD, dementia, aphasia, Pick's disease, progressive supranuclear palsy	{TDP-43}; regulates AS, mRNA stability, localization, and translation	Mm: (Stallings et al., 2013; Wächter et al., 2015) Dm: (Songqing Li et al., 2016; Llamusi et al., 2012)
	RRM	Tra2b					Interacts with SAFB/SAFB1; regulates AS	(Zheng et al., 2015)
	RRM				asd-1		FOX family, regulates AS	(Garcia et al., 2014; Kuroyanagi et al., 2006)
	RRM				cfim-2		{CFIm}	(Garcia et al., 2014)
	RRM				grid-1		{SPEN}, RNA-binding	(Garcia et al., 2014)
	RRM				R06C1.4		Predicted to bind RNA, regulate AS	(Garcia et al., 2014)
	RRM				mec-8		Binds mRNA	(Lundquist and Herman, 1994)
	RRM			sm			{Hnrnpl}; mRNA binding and processing	(Draper et al., 2009)
	RRM				sup-12		Interacts with asd-1, muscle-specific RNA binding protein	(Anyanful et al., 2004; Kuroyanagi et al., 2007)
ZF	ZF (TFIIB)	Brf1				Goldenhar syndrome	TF2B family, subunit of RNA PolIII complex	(Gan et al., 2017)
	ZF (CCCH)	Mbnl1		mbl	mbl-1	DM	dsRNA binding, binds CUG repeats	Mm: (Lee et al., 2007; Sellier et al., 2018) Dm: (Artero et al., 1998; Cerro-Herreros et al., 2016) Ce: (Garcia et al., 2014; Wang et al., 2008a)
	ZF (CCCH)	Mbnl2	mbnl2			DM	dsRNA binding, binds CUG repeats, [MBLL39 or MBLL]	Mm: (Hao et al., 2008; Thomas et al., 2017) Dr: (Machuca-Tzili et al., 2011; Todd et al., 2014)
	ZF (CCCH)	Mbnl3				DM, cancer	Regulates AS, [MBLX39, MBXL]	(Lee et al., 2010a, 2010b; Thomas et al., 2017)
	ZF (CXXC), oxygenase			Tet		Coronary artery disease	hydroxylates 5MeC in RNA	(Delatte et al., 2016; F. Wang et al., 2018)
	ZF (CCCH)	Zfp36					AU-rich element binding, regulates mRNA stability and translation [TTP]	(Hausburg et al., 2015)
	ZF (CCCH)	Zfp36l1					Tis11 gene family	(Bye-A-Jee et al., 2018)
	ZF (CCCH)	Zfp36l2					Tis11 gene family	(Bye-A-Jee et al., 2018)
	ZF (CCCH), NYN	Zc3h12a					Endoribonuclease, involved in mRNA decay	(Min Li et al., 2018a, 2018b)
Other domains	no known domain			Arc1			ARC family; intercellular RNA transfer at NMJ	(Ashley et al., 2018)
	TCP-like helical			bsf		Leigh disease	{Lrpprc}; localized to sarcomeric bands, misregulated in DM1 model	(Llamusi et al., 2012)
	DnaJ			mrj		Myopathy, pathological gambling	{DNAJB6}	(Songqing Li et al., 2016)
	RNB				disl-2		Binds polyuridylated 3' ends and mediates degradation	(Garcia et al., 2014)
	FRG1	Frg1		FRG1		FSHD, suppurative lymphadenitis	Actin-crosslinking, RNA binding	Mm: (Pistoni et al., 2013; Sun et al., 2011) Dm: (Jones et al., 2016)
	SPRY, SAP, P-loop	Hnrnpu				Cancer, microcephaly	Deletion causes DCM in mouse, regulates AS	(Ye et al., 2015)
	La-type HTH, SUZ-C	Larp6	larp6				RNA and DNA binding, mRNA stability; [Achn]	Mm & Dr: (Wang et al., 2009)
	bHLH DNA-binding	Myf5				Myopathy, rhabdomyosarcoma	Translational repression	(Panda et al., 2016)
	P-loop				nol-9		{NOL9}	(Garcia et al., 2014)
	Nucleoporin FG repeat region				npp-4		{Nup62}; structural constituent of nuclear pore	(Garcia et al., 2014)

(*continued on next page*)

Table 1 (*continued*)

Domain(s)	Model organism				Associated Human disease	Comments	References
	Mm	Dr	Dm	Ce			
Winged helix DNA-binding	Pa2g4					Post-transcriptional repression	(Figeac et al., 2014)
TCP-like helical	Ptcd1					RNA metabolism and stability	(Perks et al., 2018)
TCP-like helical	Ptcd2					mRNA nuclear export	(Xu et al., 2008)
Pumilio repeat	Pum2		pum	puf-8		mRNA 3'-UTR binding	Mm: (Marrero et al., 2011) Dm: (Chartier et al., 2015) Ce: (D'Amico et al., 2019)
NTF2, RRM			rin			{G3BP1}; NTF2-like family	(van der Laan et al., 2012)
SAM	Samd4		smg			Post-transcriptional regulator	Mm: (Chen et al., 2014) Dm: (Chartier et al., 2015; de Haro et al., 2013) Dr & Dm: (Johnson et al., 2013)
RP L7Ae/ Gadd45		snu13b	hoip			{SNU13}; U4/5/6 snRNP	
TAP-C			sbr		Noonan syndrome	{Nxf1}; NTF2-like family; mRNA nuclear export	(Korey et al., 2001)
Total RBPs:	**51**	**15**	**28**	**17**			

RBPs with published muscle phenotypes from *Mus musculus* (mouse, Mm), *Danio rerio* (zebrafish, Dr), *Drosophila melanogaster* (fruit fly, Dm) and *Caenorhabditis elegans* (Ce). RNA-binding domains as listed. Associated human diseases are from the DISEASES database (https://diseases.jensenlab.org/). Likely orthologs are in the same row (only orthologs with a published function in muscle are listed). One exception is Celf1, as Dm Bru1, Dm Bru 2 and Ce Etr-1 are closely related to both MmCelf1 and MmCelf2 (see Fig. 3A). Proteins with multiple domains are listed with the domain group appearing first in the table. {Human homologs} and [alternative names] are listed under Comments.

Abbreviations— RP: ribosomal protein, dsRNA: double stranded RNA, rRNA: ribosomal RNA, snRNP: small nuclear ribonucleoproteins, NMJ: neuromuscular junction, 5MeC: 5-methylcytosine, RRM: RNA recognition motif, TCP: tetratricopeptide, KH: K-homology, ZF: zinc-finger, dsRBD: double stranded RNA binding domain, SAM: sterile alpha motif, AREs: AU-rich elements, hnRNP: heterogeneous ribonucleoprotein particle, hnRNA: heterogenous nuclear RNA, FSHD: Facioscapulohumeral muscular dystrophy, LGMD: Limb-Girdle Muscular Dystrophy, DM: myotonic dystrophy, SMA: spinal muscular atrophy, ALS: amyotrophic lateral sclerosis, OPMP: oculopharyngeal muscular dystrophy, HLHS: hypoplastic left heart syndrome, DCM: dilated cardiomyopathy, FTD: fronto-temporal dementia.

conserved not only on the level of sequence, but also functionally (Fig. 3A-C). To a first approximation, this is supported by conservation of tissue-specific expression as observed for Rbm24 in myoblasts from frog, mouse and chicken (Grifone et al., 2014) or heart and skeletal muscle tissue-specific expression patterns in chicken, cow, mouse, rat and rhesus macaque (Merkin et al., 2012). Sequence analysis indicating evolutionary conservation of targets and RBP recognition sites also supports functional conservation. For example, Rbfox recognition elements in selected exons are conserved from sea squirt to humans (Venables et al., 2012) and MBNL, PTB, RBFOX, STAR and TIA recognition elements neighboring conserved exons can be found from chicken to primates (Merkin et al., 2012).

More convincing are biochemical, transfection or genetic experiments indicating conserved function. For example, *Drosophila* Bru1 is able to correctly splice a rat α–*actinin* reporter in monkey kidney epithelial CV-1 cells (Suzuki et al., 2002). *Drosophila* Mbl sequesters with human CUG-repeats in human COSM6 cells, the same as human MBNL (Vicente et al., 2007). Moreover, MBNL homologs from human, *Ciona*, *Drosophila*, *C. elegans* and *Trichoplax* are all able to mediate alternative splicing of reporter mini-genes for human *TNNT2* exon 5, mouse *Nfix* exon 8, human *MBNL1* exon 5, human *ATP2 A1* exon 22, mouse *Vldlr* exon 16 and human *INSR* exon 11 when transfected into human HeLa cells (Oddo et al., 2016). When transfected into MNBL knock-out cells, these proteins all rescue endogenous splice events, from 91 exons in the *Trichoplax* rescue to 194 exons with the human rescue (Oddo et al., 2016). SMN orthologues from zebrafish and *C. elegans* display binding selectivity to poly(G) homopolymers *in vitro*, like the human protein, and allowed identification of a conserved RNA-binding element of SMN in exon 2a (Bertrandy et al., 1999).

Human RBPs are also often functional in model organisms. Human SMN-1 is able to rescue defects when injected into ubiquitous *smn1* knockdown zebrafish (Laird et al., 2016). Human FXR1P is able to rescue phenotypes in *Fxr1* knockdown mouse C2C12 cells (Davidovic et al., 2013) and both human TDP-43 and FUS are functional when transfected into differentiated mouse embryonic stem cells (Wächter et al., 2015). Human TDP-43 and disease variants are sufficient to induce ALS models in zebrafish (Lissouba et al., 2018). Human hnRNPA1 and hnRNPA2 localize appropriately to nuclei in transgenic *Drosophila* and mutant, disease-associated versions lead to flight muscle degeneration and cytoplasmic inclusion pathology (Kim et al., 2013). Expression of human NHP2 L1 in muscle founder cells of *Drosophila* embryos mutant for its homolog Hoip significantly restored myotube elongation and Mhc expression, although not as effectively as Hoip itself (Johnson et al., 2013). UAS-mediated expression of human MBNL1 is able to rescue lethality associated with loss of endogenous Mbl (Monferrer and Artero, 2006) and overexpression of human MBNL1 in $(iCUG)_{480}$ expanded repeat bearing flies is able to suppress both associated eye and somatic muscle phenotypes, while overexpression of human CELF1 aggravates eye and muscle phenotypes (de Haro et al., 2006).

The above examples suggest that beyond conservation in sarcomere structure and cytoskeletal protein expression, muscle displays functional conservation of regulatory proteins such as RBPs. RBP-associated domains including the Tudor domain, RNA-binding zinc fingers, RRM and KH domains are demonstrably functionally conserved across multiple species. It is certainly the case that RBPs are not universally conserved and have indeed evolved distinct targets in different species, but we believe the above examples illustrate that conservation of target recognition and mechanisms do generally exist, but will need to be verified on a case-by-case basis.

1.5. Muscle-type specific alternative splicing

One important function of RBPs is the regulation of alternative splicing. Genome-wide mRNA-Seq datasets suggest that more than 90% of genes are alternatively spliced in humans and nearly 70% of these alternative splice (AS) events are tissue-specific (Merkin et al., 2012; Pan et al., 2008; Wang et al., 2008a, 2008b). AS is also prevalent in model organisms, with estimates of 40–60% of genes alternatively spliced in mouse (Lambert et al., 2015; Mouse Genome Sequencing Consortium et al., 2002), ~50% in zebrafish (Lambert et al., 2015), 31–60% in *D. melanogaster* (Brown, 2014; Daines et al., 2011; Graveley et al., 2011; Stolc et al., 2004) and ~25% in *C. elegans* (Ramani et al., 2011). Muscle in particular displays high levels of AS (Castle et al., 2008; Pan et al., 2008; Wang et al., 2008a, 2008b), as observed in human, mouse and chicken (Tapial et al., 2017). Moreover, different muscle types show dramatically different patterns of splice-isoform expression. This is exemplified by the distinct patterns of AS in

Drosophila fibrillar flight muscle and tubular leg or jump muscle (Schönbauer et al., 2011; Spletter et al., 2015) or by different patterns of AS in mouse heart and skeletal muscle (Guo et al., 2012; Li et al., 2013; Söllner et al., 2017).

Alternative splicing in muscle controls fiber-type specific and temporal expression profiles of myofibrillar proteins, allowing for differential contractile properties of individual muscle-fiber types (Andreadis et al., 1987; Schiaffino and Reggiani, 1996). One of the first such examples is the alternative splicing of rat fast troponin-T (Tnnt3) giving rise to 64 isoforms (Breitbart et al., 1985). Cardiac troponin T exon 5 is included in embryonic heart muscle but is skipped in the adult heart, promoting a change in myofibrillar sensitivity to calcium that determines the contractile properties of maturing heart muscle (Godt et al., 1993; McAuliffe et al., 1990). Misregulation of cardiac troponin-T (TNNT2) splicing in zebrafish has been shown to lead to misregulation of other thin-filament proteins including Tpma and Tnni3, leading to severe sarcomere defects and heart failure (Sehnert et al., 2002). *Drosophila* Troponin-T (*upheld, up*) also displays distinct isoform expression in flight and body muscle (Benoist et al., 1998), and incorrect splicing in flight muscle causes sarcomere defects and flightlessness (Fyrberg et al., 1990; Nongthomba et al., 2007). These examples illustrate the cross-species importance of proper muscle-type specific splicing of Troponin-T.

A second example of alternative splicing affecting myofibrillar properties is the regulation of Myosin Heavy Chain (MHC). Vertebrate genomes encode multiple MHC genes expressed in muscle-fiber type specific patterns (Bloemberg and Quadrilatero, 2012). Beyond transcription, alternative splicing generates over 30 distinct transcripts from the 8 MHC loci in mouse (Dennehey et al., 2006). MYH6 is associated with congenital heart defects (CHD) in humans and different functional variants differentially inhibit or enhance myofibril formation (Granados-Riveron et al., 2010). Loss of smooth muscle myosin exon 5B results in an isoform switch that decreases maximum force generation and shortening velocity during contraction (Babu et al., 2001). The most systematic studies of myosin isoform function have been performed in *Drosophila*, which has a single MHC gene with distinct isoform expression in flight, leg, jump and larval body wall muscles (Bernstein et al., 1986; Falkenthal et al., 1987). Flies provide a useful model to examine tissue-specific MHC mutants and evaluate morphology and biophysical properties after rescue with different MHC isoforms or chimeras (Swank et al., 2000). For example, while embryonic MHC versions support myofibril assembly in flight muscle lacking endogenous MHC, flies are flightless and myofibrils progressively deteriorate (Wells et al., 1996), possibly because variations in MHC exon 7 between embryonic and flight muscle myosin impact ATPase activity and affect myofibril structural stability (Miller et al., 2005). The slow myosin hinge region encoded by MHC exon 15b is stiffer than the fast hinge region encoded by MHC exon 15a, and swapping exon 15a and 15b impairs flight ability, increases sarcomere length and disrupts sarcomere structure (Suggs et al., 2007). Differences in force generation, ATPase activity and rate-limiting cross-bridge steps between embryonic and flight muscle MHC isoforms can be attributed to the relay (exon 9) and converter (exon 11) domains, which also differentially impact myofibril ultrastructure (Kronert et al., 2012; Yang et al., 2010, 2008). These studies illustrate that from flies to mammals, different MHC isoforms confer distinct biophysical properties on the sarcomere and differentially affect myofibril development.

Beyond Troponin-T and MHC, muscle-type specific AS and isoform function has been demonstrated in multiple sarcomere genes. Tropomyosin I (Tm1/*lev-11*) has been demonstrated to have isoform-specific expression and function in *Drosophila* (Basi et al., 1984) and *C. elegans* (Barnes et al., 2018; Kagawa et al., 1995). Titin, Tropomyosin 1 (TPM1) and Myosin alkali light chain (MLC) have all been demonstrated to have isoform-specific expression and possibly function in vertebrates (Venables et al., 2011; Weeland et al., 2015; Yin et al., 2015). In

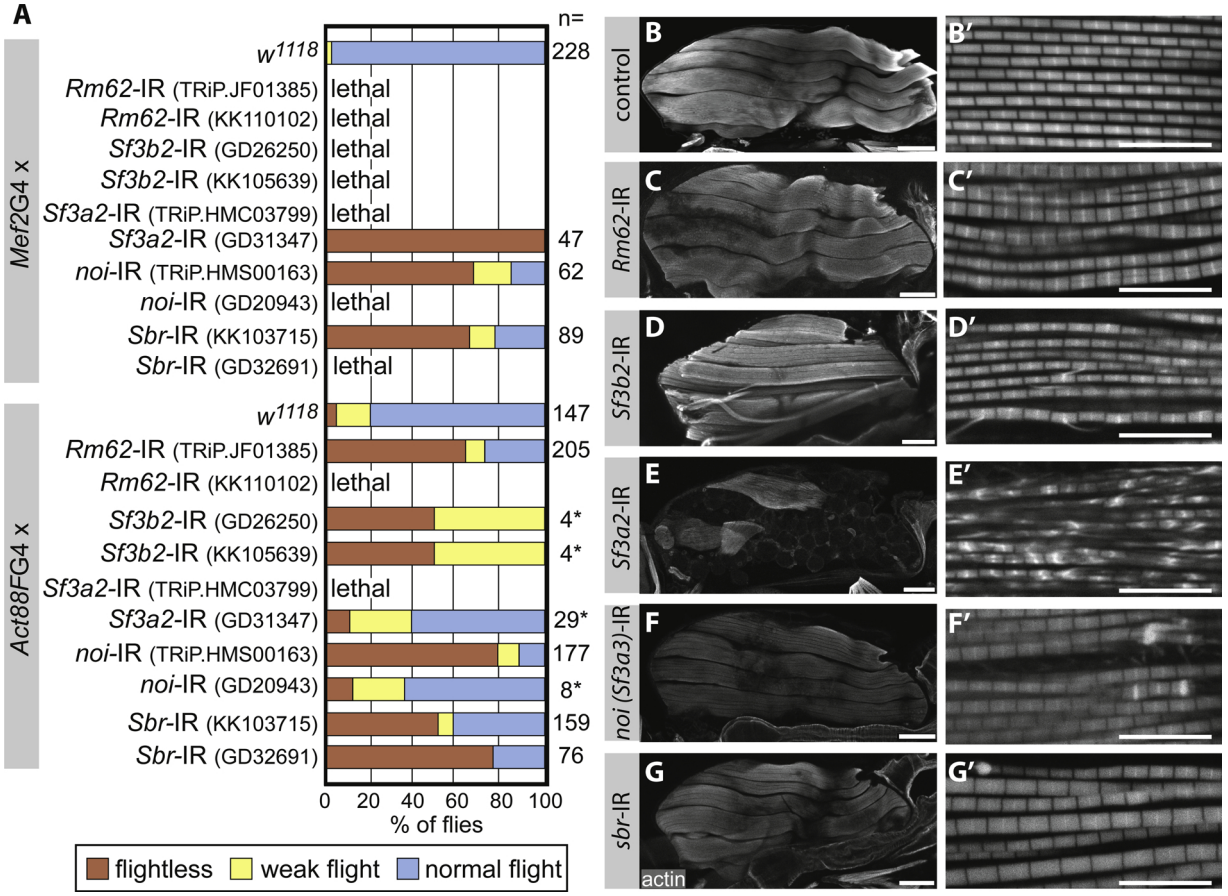


Fig. 2. Diverse RBP morphological phenotypes in muscle.

A. Flight test results for UAS-RNAi lines as labeled when driven in all muscles with *Mef2*-Gal4 or specifically in flight muscles from about 20 h after puparium formation (APF) with *Act88F*-Gal4. Number of flies tested as labeled. * denotes high rates of pupal lethality. **B–G.** Flight muscle fiber (B–G) and myofibril (B'-G') phenotypes in 90 h APF in *Mef2*-Gal4 crossed to control w^{1118} (B) and driving *Rm62-IR* (TRiP.JF01385) (C), *Act88F*-Gal4 driving *Sf3b2-IR* (GD26250) (D), and *Mef2*-Gal4 driving *Sf3a2-IR* (TRiP.HMC03799) (E), *noi(Sf3a3)-IR* (TRiP.HMS00163) (F) and *sbr-IR* (GD32691) (G). Phalloidin stained actin in greyscale. Scale bars in B–G = 100 μM; B'-G' = 10 μM.

fact, mRNA-Seq data from *Drosophila* flight, leg and jump muscle suggests the majority of sarcomeric genes are alternatively spliced between muscle-types (Spletter et al., 2015), suggesting there is a wide genetic space available through AS to fine-tune sarcomere function. Disruption of the flight-muscle specific splicing program in CELF1 homolog *bru1* mutant flies leads to defects in sarcomere growth and myosin function (Oas et al., 2014; Spletter et al., 2015). Such tissue-level splicing regulators are also found in vertebrates, where mutations in *Rbm20* lead to dilated cardiomyopathy by disrupting conserved heart-specific splicing patterns of more than 30 genes in humans and rats (Guo et al., 2012; Rexiati et al., 2018). In addition to components of the myofibril, myogenic transcription factors and metabolic enzymes as well as RBPs themselves are also regulated by AS in muscle (Ladd et al., 2001; Sebastian et al., 2013). The above discussion highlights the diversity of RBP targets, and suggest that AS may be a general, conserved principle used to fine-tune muscle-type specific development and function.

In addition to muscle-type specific splicing, developmental shifts in splicing have been characterized in muscle. In C2C12 mouse myoblast cells, at least 95 strong differentiation-linked splice events were confirmed and shown to increase exon inclusion or skipping in proteins enriched for cytoskeletal, actin binding, integrin signaling and cell junction gene ontology terms (Bland et al., 2010). Human muscle also displays developmental-associated shifts between the muscle precursor cell and fetal AS patterns. Important structural and regulatory proteins, such as *tropopmyosin1* (*TPM1)* exon 6, *muscleblind1* (*MBNL1)* exon 7 and *integrin subunit α7* (*ITGA7)* exon 25, which undergoes a striking 70% shift in prenatal inclusion, show developmental splicing transitions and are mis-spliced in congenital myotonic dystrophy type 1 (Thomas et al., 2017). During heart development in mouse three distinct temporal splicing patterns in 63 distinct AS events are observed affecting mostly exon inclusion in intact reading frames, increasing the functional diversity of proteins involved in cardiomyocyte remodeling, cytoskeletal rearrangement, nucleic acid binding and signaling (Kalsotra et al., 2008). More than 40% of examined events are conserved in birds in the alternatively spliced region, direction of AS and timing of transition (Kalsotra and Cooper, 2011). Mouse gastrocnemius muscle undergoes a large shift in AS during the 2 weeks after birth as it transitions from fetal to adult AS patterns, with 50% of tested events conserved between mouse and human. These shifts in AS were demonstrated to change contractile properties and calcium handling dynamics, and gain of CELF1 (normally downregulated) or loss of MBNL1 (normally translocated to nucleus) caused reversion of AS events to the fetal pattern (Brinegar et al., 2017). These examples suggest shifts in patterns of AS during muscle differentiation and normal skeletal muscle maturation are general mechanisms to fine-tune functional properties.

1.6. Regulation by CELF, MBNL and FOX family RBPs

Among the most heavily studied RBPs in the literature are members of the CELF (CUG-BP and ETR-3 like) (Goo and Cooper, 2009; Ladd et al., 2001), Muscleblind-like (MBNL) (Pascual et al., 2006) and FOX (Kuroyanagi, 2009) families. These RBPs are frequently referenced for controlling muscle-specific splice events, for their cross-regulatory interactions and for their roles in muscle diseases. We examine them in more detail below.

1.6.1. Functions of Rbfox family members

The highly conserved RNA-binding fox (Rbfox) proteins (Fig. 3B) contain a single RRM that recognizes intronic (U)GCAUG motifs (Auweter et al., 2006; Jin et al., 2003; Kuroyanagi, 2009; Lambert et al., 2014), but can recognize other motifs in the context of the large assembly of splicing regulators (LASR) complex consisting of hnRNP M, hnRNPH, hnRNPC, Matrin3, NF110/NFAR-2 and DDX5 in mouse and HEK293 T cells (Damianov et al., 2016). Rbfox proteins typically promote exon skipping (repress exon expression) when they target an upstream intronic flanking sequence and enhance exon inclusion when they bind in downstream intronic flanking sequences (Jin et al., 2003; Tang et al., 2009). Rbfox is also found as cytosolic regulator that binds the 3′-UTR (Lee et al., 2016) to regulate mRNA stability (Kim et al., 2014). The cytosolic isoform of Rbfox is observed from *Drosophila* (Carreira-Rosario et al., 2016) to mouse (Weyn-Vanhentenryck et al., 2014), suggesting its multifunctional conservation.

Rbfox is characterized to play an important role in muscle development. Rbfox1 and Rbfox2 are expressed in heart and skeletal muscle in mouse (Jin et al., 2003; Kalsotra et al., 2008), zebrafish (Frese et al., 2015) and *C. elegans* (Kuroyanagi et al., 2007). Rbfox recognition elements are abundant in muscle-specific alternatively spliced exons (Bland et al., 2010; Das et al., 2007; Wang et al., 2008a, 2008b) and in a human embryonic muscle cell line form a co-regulatory splicing network with MBNL1 (Klinck et al., 2014). Knockdown of Rbfox1 and Rbfox2 in C2C12 mouse myoblasts impairs myoblast fusion during differentiation and changes AS of Mef2D and ROCK2 (Runfola et al., 2015; Singh et al., 2014). *Rbfox1* mutant mice show muscle weakness, defective calcium handling, irregular sarcomere structure and loss of skeletal muscle fibers accompanied by mis-splicing of cytoskeletal, calcium signaling and skeletal muscle development genes (Pedrotti et al., 2015). Further, Rbfox1 protein levels are decreased in failing heart, regulate global cardiac mRNA splicing and knock down of both Rbfox1 and Rbfox 2 result in pressure overload in mouse heart (Gao et al., 2016; Wei et al., 2015). Loss of Rbfox family members Fox-1 and Asd-1 cause aberrant splicing in the body wall muscles of *C. elegans* (Kuroyanagi et al., 2006) and together with Sup-12 regulate AS of *egl-15* exon 4 and 5 (Kuroyanagi et al., 2007). Knockdown of the Rbfox homolog A2BP1 in *Drosophila* in muscle is lethal (Schnorrer et al., 2010) or results in flightlessness (Fig. 3D). Myofibrils in a flight-muscle specific A2BP1 knockdown show severe fraying and too short sarcomeres (Fig. 3H), likely a sign of hypercontraction (Nongthomba et al., 2003). Sarcomeric components including *wupA* (troponin I) and *Mhc* (myosin heavy chain) are aberrantly spliced in *Rbfox*-IR IFM (Fig. 3I-K). These examples illustrate that Rbfox is involved in muscle development across the animal kingdom.

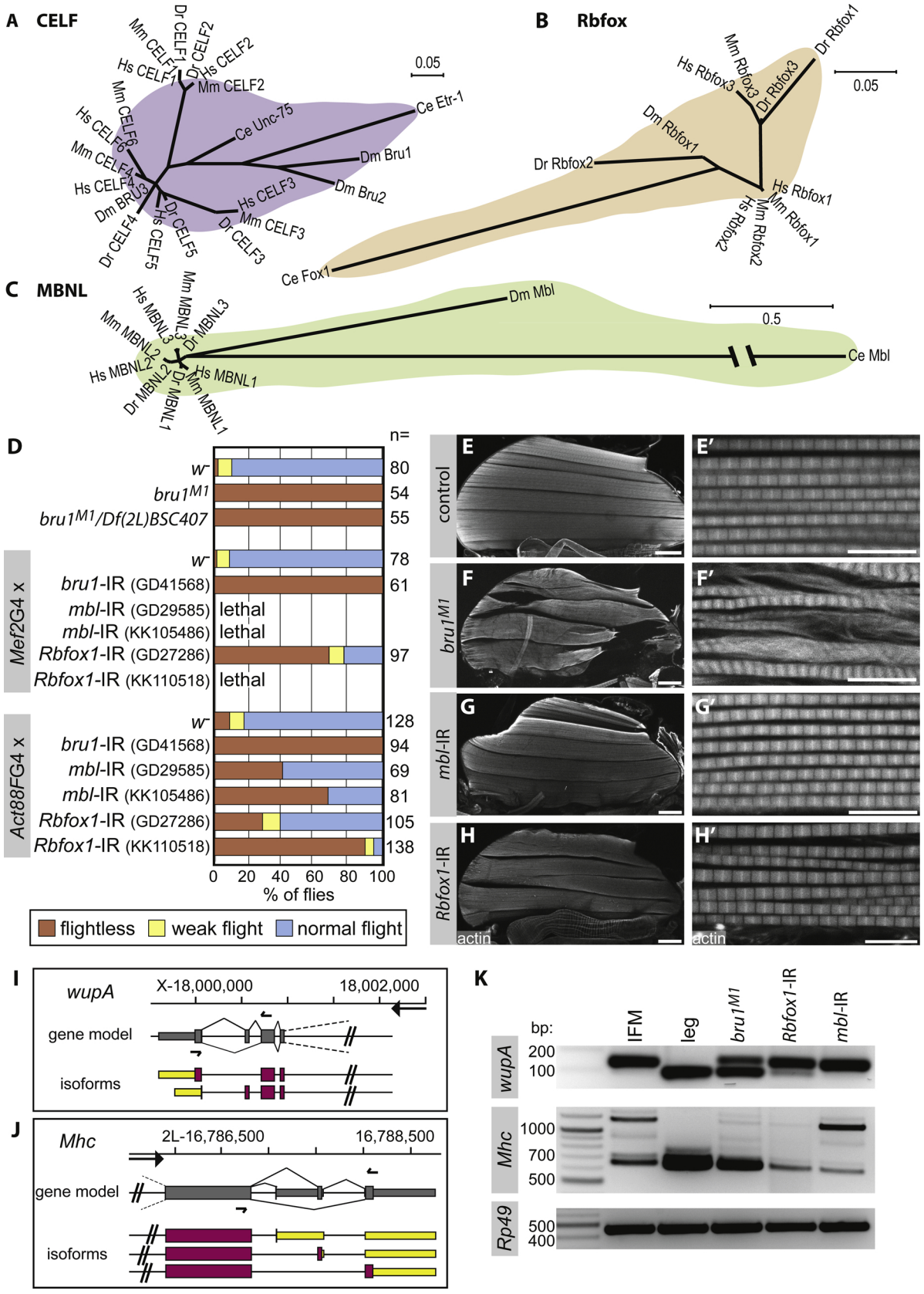
Rbfox proteins are also implicated in several human diseases. Rbfox1 and Rbfox2 are implicated in heart disease and congenital heart defects (Homsy et al., 2015; Lale et al., 2011), and decreased expression of Rbfox1 in mouse heart results in pressure overload and the same aberrant splicing events observed in heart samples from dilated cardiomyopathy (DCM) human patients (Gao et al., 2016). In a mouse model of facioscapulohumeral muscular dystrophy (FSHD) that overexpresses FRG1, Rbfox expression is decreased and Rbfox-dependent alternative splice events are misregulated (Pistoni et al., 2013). Beyond the musculature, Rbfox1 dysregulation causes epilepsy in human patients (Bhalla et al., 2004; Lal et al., 2013) and is associated with autism spectrum disorders (Bill et al., 2013; Martin et al., 2007). It also regulates *ataxin2*, the gene affected in spinocerebellar ataxia type 2 patients (Gehman et al., 2011; Shibata et al., 2000). These likely represent conserved functions, as knockdown of Rbfox2 in mouse causes cerebellar defects, abnormal Purkinje cell function, ataxia and mis-splicing (Gehman et al., 2012; Kim et al., 2011). Rbfox1l and Rbfox2 are similarly expressed in the cerebellum and Purkinje cells in zebrafish brain (Ma et al., 2019). However, as a muscle-specific Rbfox isoform is unable to promote neuronal-specific splicing, tissue-specific functions may be mediated by tissue-specific isoform expression (Nakahata and Kawamoto, 2005). These disease associations suggest that the Rbfox family plays a key role in the regulation of AS and cell function in both muscle and neurons.

1.6.2. Functions of CELF family members

CUG-BP and ETR-3 like factors (CELF) are a highly conserved protein family (Fig. 3A) with a characteristic 3 RRM domain structure where RRM2 and RRM3 are separated by a 160–230 residue “divergent domain” important for target binding specificity and regulation of alternative splicing (Han, 2005; Ladd et al., 2001; Mori et al., 2007; Singh, 2004). RRM crystal structures imply that RRM1 and RRM2 bind mRNA in a similar fashion distinct from that of the RRM3 (Sugnet et al., 2006; Tazi et al., 2009). Indeed, RRM1 and RRM2 alone are able to bind and activate alternative splicing despite RRM3 having the highest sequence conservation (Good, 2000; Singh, 2004), suggesting that different RRMs may have distinct substrate specificity. CELF1 and CELF2 were identified as proteins that bind to CUG repeats and UG-repeat elements typically located within introns adjacent to the regulated exon (Blech-Hermoni et al., 2016; Lu et al., 1999; Timchenko et al., 1996), but a recent study using CLIP tags on embryonic chicken hearts suggests that CELF proteins can also regulate splicing via exonic binding sites (Blech-Hermoni et al., 2016). In general, CUG repeats located within the first 250 bp of the downstream intron are associated with exon inclusion, while those located in the last 250 bp are associated with exon exclusion (Ule et al., 2006; Wang et al., 2006). In addition to demonstrated roles in alternative splicing (Blech-Hermoni et al., 2016), CELF1 has been show to regulate polyadenylation status, transcript stability (Lee et al., 2010a, 2010b; Masuda, 2012; Zhang et al., 2008a, 2008b) and translation of target transcripts in the cytoplasm (Dasgupta and Ladd, 2011; Louis et al., 2013; Timchenko et al., 2001).

CELF family proteins have important roles in muscle development. Muscle expression is observed for CELF1 and CELF2 proteins in mouse and rat (Blech-

Hermoni et al., 2013; Good, 2000; Ladd et al., 2001, 2004), Bru-1 (Oas et al., 2014; Spletter et al., 2015) and Bru-3 (Picchio et al., 2018) in *Drosophila* and Etr-1 in *C. elegans* (Milne and Hodgkin, 1999). CELF protein levels are elevated in heart and skeletal muscle during neonatal stages and decrease throughout development via a protein kinase C-dependent pathway (Dasgupta and Ladd, 2011; Kuyumcu-Martinez et al., 2007; Roberts et al., 1997). The decline in



(caption on next page)

Fig. 3. Functional conservation of CELF, Rbfox and MBNL family proteins.
A-C. Dendrogram drawn to scale showing sequence conservation of RRM3 from CELF family proteins (A), RRM1 from Rbfox family proteins (B) and the zinc fingers from MBNL family proteins (C) from *Homo sapiens* (human, Hs), *Mus musculus* (mouse, Mm), *Danio rerio* (zebrafish, Dr), *Drosophila melanogaster* (fruit fly, Dm) and *Caenorhabditis elegans* (Ce). **D.** Flight test results performed as in Fig. 2 for Dm homologs of the CELF, Rbfox and MBNL families. $bru1^{M1}$ is a CRISPR-mediated deletion allele and *Df(2 L)BSC407* is a characterized deficiency covering *bru1*. **E-H**. Myofiber (E–H) and myofibril (E'-H') phenotypes in 1 d adults for *Mef2*-Gal4 crossed to control w^{1118} (E), $bru1^{M1}$ homozygous mutants (F), *Mef2*-Gal4 driving *mbl-IR* (KK105486) (G) and *Mef2*-Gal4 driving *Rbfox1-IR* (GD27286) (H). Phalloidin stained actin in greyscale. Scale bars in E–H = 100 μM; E'-H' = 10 μM. **I–J.** Gene models of AS events in *wupA* (*wings up A*, DmTnI) (I) and *Mhc* (*myosin heavy chain)* (J). Coding exons in magenta, UTR regions in yellow. Black arrowhead denotes direction of transcription. Small arrows mark positions of RT-PCR primers. **K.** RT-PCR results for selected events in *wupA, Mhc* and *Rp49* as a control. Note muscle-type specific splice events in flight muscle (IFM) and leg that are misregulated in IFM from both $bru1^{M1}$ and *Rbfox1-IR*, but not *mbl-IR*.

CELF1 expression after birth is thought to drive fetal-to-adult transitions in AS (Kalsotra et al., 2008; Ladd et al., 2005a), and upregulation of CELF1 in postnatal tissues recapitulates fetal splicing patterns that are also observed in myotonic dystrophy (DM) patients and mouse models (Ladd et al., 2001; Philips et al., 1998; Wang et al., 2007).

MHC-ΔCELF mice, where a dominant-negative CELF1 is targeted to the nucleus in muscle tissue (Charlet-B et al., 2002a), have severe cardiomyopathy leading to premature lethality, variable fiber size in skeletal muscle, altered AS and display an increase in the slow-fiber type (Berger et al., 2011; Ladd et al., 2005b; Wang et al., 2015). At least 45 AS events, many of which are also observed in C2C12 cells and correlate with normal development shifts in AS in genes related to chromatin organization, cytoskeleton functions and cell-cell contact, are directly regulated by CELF in neonatal mouse heart (Dujardin et al., 2010; Giudice et al., 2016; Wang et al., 2015). Similar AS events including troponin T (cTNT) exon 5, human insulin receptor IR1, human muscle-specific chloride channel CIC-2 intron 2, rat NMDA receptor exons 5 and 11 and rat alpha-actinin are regulated by CELF1 in human and chicken heart (Charlet-B et al., 2002a; 2002b; Ladd et al., 2001; Philips et al., 1998; Savkur et al., 2001; Suzuki et al., 2002; Zhang et al., 2002). As the heart and skeletal muscles develop, they undergo structural reorganization, accumulation of contractile proteins and changes in Ca^{2+} sensitivity (Siedner et al., 2003), suggesting shifts in AS events regulated by CELF are necessary for proper function.

CELF1 homologs in model organisms also regulate muscle development. In *C. elegans* knockdown of Etr-1 results in developmental arrest at the 2-fold embryonic stage with a prominent muscle detachment defect (Milne and Hodgkin, 1999). Overexpression of *Drosophila* Bru-3 in muscle causes defects in larval motility and myofibril structure by potentially regulating both release of sarcomeric protein mRNAs from P-granules and co-translational mRNA decay (Picchio et al., 2018). Loss of Bru-1, the second CELF1 homolog in *Drosophila*, in indirect flight muscle (IFM) results in defects in sarcomere growth, hollow myofibrils and hypercontraction (Oas et al., 2014; Spletter et al., 2015) (Fig. 3D, F). Bru-1 regulates hundreds of IFM-specific AS events (Spletter et al., 2015), for example in cytoskeletal genes, including *wupA* and *Mhc* (Fig. 3I, J, K). This suggests that CELF homologs have conserved functions in muscle development across evolution.

1.6.3. Functions of MBNL family members

The highly conserved MBNL family encodes RNA-binding zinc-finger proteins of type CCCH (Fig. 3C). Vertebrate genomes encode three MBNL homologs while *Drosophila* and *C. elegans* have a single, albeit less sequence conserved, family member (Oddo et al., 2016; Pascual et al., 2006). MBNL proteins bind in a sequence specific manner (Worthington et al., 1996), with both human and *Drosophila* MBNL preferring (C/U)GC(C/U) containing RNA motifs (Goers et al., 2008; Ho et al., 2004), although binding to suboptimal sites including GCUU and UGCU has been observed (Lambert et al., 2014; Wang et al., 2012). Across species, intronic motifs downstream of the target exon are associated with MBNL-dependent exon inclusion, while motifs in upstream introns or the target exon itself are associated with exon exclusion (Du et al., 2010; Goers et al., 2010; Oddo et al., 2016). MBNL is also involved in the regulation of gene expression (Du et al., 2010; Osborne et al., 2009), mRNA stability (Masuda et al., 2012), mRNA localization (Adereth et al., 2005; Wang et al., 2012) and microRNA processing (Rau et al., 2011).

MBNL family proteins play essential roles in the development of muscle. MBNL1 and MBNL2 are expressed in skeletal muscle and heart in vertebrates (Fardaei et al., 2002; Kanadia et al., 2003b; Miller et al., 2000; Pascual et al., 2006; Squillace et al., 2002) and in differentiated mouse C2C12 cells (Miller et al., 2000), while MBNL3 is expressed in muscle satellite cells (Poulos et al., 2013) and C2C12 myoblasts (Squillace et al., 2002). Consistent with this expression pattern, MBNL1 promotes while MBNL3 inhibits muscle differentiation (Adereth et al., 2005; Miller et al., 2000; Squillace et al., 2002). MBNL mutant mice develop myotonia and cataracts and display aberrant AS of transcripts such as Clcn1, cTNT and Tnnt3 (Kanadia et al., 2003a). These phenotypes are similar to symptoms observed in myotonic dystrophy (DM) patients, and about 80% of AS events changed in DM mouse models expressing expanded CUG repeats (discussed below) are also observed in MBNL1 mutant mice (Du et al., 2010). *Mbnl1, Mbnl2* double mutant mice display spontaneous arrhythmias and conduction defects as well as disrupted myofibrillar arrangement (Choi et al., 2017), and *Mbnl1* mutant mice display loss of developmentally regulated AS changes in heart, with a reversion to embryonic splicing patterns (Kalsotra et al., 2008). Morpholino knock-down of MBNL2 in zebrafish results in abnormal somite shape, Z-band disruption, reduction of fast and slow fibers and aberrant AS of cTNT and clc1 in heart with a shift to early developmental isoforms (Machuca-Tzili et al., 2011), indicating that MBNL, like CELF1, also regulates developmental shifts in AS in vertebrate muscle.

Invertebrates display a similar requirement for MBNL in muscle development. *Drosophila* and *C. elegans* express Mbl in muscle throughout larval and adult stages (Monferrer and Artero, 2006; Wang et al., 2008a, 2008b) and Mbl regulates splicing of sarcomere components including Troponin T (Vicente-Crespo et al., 2008). *Drosophila* Mbl is expressed during myoblast differentiation, similar to mammalian MBNL1 (Pascual et al., 2006). RNAi mediated knockdown of *Mbl* in *C. elegans* results in severe defects in motility and disruption of myofiber structure (Wang et al., 2008a). Mbl mutant flies are lethal at the first instar larvae stage and show paralysis due to hypercontracted muscles and Z-disc disruption (Artero et al., 1998; Ludatscher et al., 1978). RNAi knockdown of Mbl in all muscle is lethal (Schnorrer et al., 2010), but flight-muscle specific (IFM) knockdown is flightless (Fig. 3D). Similar to mutant larval muscle, IFM sarcomeres appear short and likely hypercontracted (Nongthomba et al., 2003) in *mbl*-IR (Fig. 3G). These data show a conserved function for MBNL in muscle development.

Beyond muscle, MBNL family members play important roles in nervous system development. MBNL is expressed in neurons in mouse (Kanadia et al., 2003b), zebrafish (Machuca-Tzili et al., 2011), *Drosophila* (Prokopenko et al., 2000) and *C. elegans* (Spilker et al., 2012). In mouse, the differential localization of alternative mRNA isoforms to neurites versus the soma is dependent upon MBNL binding (Taliaferro et al., 2016). Morpholinos targeting *mbnl2* in zebrafish result in loss of normal midbrain morphology and enlargement of the hindbrain ventricles as well as splicing defects, which can be rescued by injection of human *MBNL2* (Machuca-Tzili et al., 2011). In *C. elegans*, Mbl mutants exhibit loss of distal synapses of the DA9 motor neuron (Spilker et al., 2012). In *Drosophila*, Mbl is required during development of the embryonic peripheral nervous system and is essential for final steps of neuron differentiation and morphogenesis (Kania et al., 1995; Prokopenko et al., 2000) as well as differentiation of photoreceptor cells (Begemann et al., 1997). These data demonstrate that MBNL family members play important roles in developmental regulation of RNA in multiple tissues across animal evolution.

1.6.4. CELF – MBNL – FOX cross-regulatory interactions

As Rbfox, CELF and MBNL proteins all regulate AS during muscle development, multiple studies have begun characterizing the intersections in their regulatory networks. Analysis of mRNA-seq datasets indicates an often evolutionarily conserved preferential enrichment of binding motifs around groups of exons, for example MBNL and RBFOX motifs (Merkin et al., 2012). In mouse heart, developmentally included exons are highly enriched in downstream intronic FOX and CELF binding motifs, while skipped exons are enriched in

upstream intronic MBNL motifs (Bland et al., 2010; Kalsotra et al., 2008), suggestive of antagonistic regulation. CELF1 promotes whereas MBNL1 inhibits inclusion of cTNT exon 5 in chicken and mouse heart, while CELF1 promotes skipping whereas MBNL1 promotes inclusion of human insulin receptor exon 11 (Charlet-B et al., 2002b; Ladd et al., 2001; Philips et al., 1998; Savkur et al., 2001). Other examples include antagonistic regulation of MBNL2 exon 8 and Actn4 exon 5 (Kalsotra et al., 2008). Such antagonism is also observed in skeletal muscle, where 65% of exons responsive to CELF1 and MBNL1 are regulated antagonistically and moreover, those exons affected by CELF1 or CELF2 induction are often responsive to MBNL1 depletion and tend to additionally be developmentally regulated (Wang et al., 2015). This antagonism is thought to be functional and not direct competition, as *cis*-regulatory elements for MBNL1 and CELF1 are distinct and minigenes with mutated MBNL1 motifs are still sensitive to CELF1, and *vice versa* (Ho et al., 2004). In addition to antagonism of AS, the extent of CELF1 and MBNL co-binding to mRNA 3′UTRs in mouse heart correlates to the degree of transcript repression (CELF1 enriched) or stabilization (MBNL1 enriched) (Wang et al., 2015).

A similar antagonistic relationship between CELF2 and Rbfox has been characterized in mouse heart and skeletal muscle. Significant overlap is observed between AS events co-regulated by CELF2 and RBFOX2 as compared to other UG-rich RBPs such as HNRNPU and RBM24 (Gazzara et al., 2017). Overexpression of CELF1/2 or depletion of Rbfox2 causes splice events to change in the same direction, suggestion one factor promotes and the other inhibits distinct events. 85% of AS events that exhibit antagonistic CELF and RBFOX regulation also change during heart development, myogenesis and/or in hearts from diabetic patients (Gazzara et al., 2017). This form of antagonism with upstream CELF and downstream Rbfox binding is also observed in chicken cardiomyocytes, *Drosophila* IFM (Bru1/A2BP1) and in *C. elegans* (Unc-75/Fox-1) (Gazzara et al., 2017). Taken together, these data suggest that antagonistic cross-regulatory interactions between the CELF, FOX and MBNL networks define the activity of these RBP families.

1.7. RBP associated muscle disease

Current estimates suggest that 15–60% of human disease mutations arise from *cis* splicing mutations (Wang and Cooper, 2007). Certain muscle diseases fall into this category, such as *cis* mutations that disrupt the splicing of dystrophin complex members and cause Duchennes and Becker muscular dystrophy (Pagliarini et al., 2017) or a c.-32-13T > G variant that weakens the splice acceptor of *alpha-glucosidase* (*GAA*) exon 2 resulting in Pompe disease (van der Wal et al., 2017). These types of genetic lesions are potentially amenable to antisense oligonucleotide therapies, and following the success of SPINRAZA™ (Nusinersen) for modifying SMN2 splicing to improve function in spinal muscular atrophy (Gidaro and Servais, 2018; Zanetta et al., 2014), many such drugs will likely be developed in the coming years (Li et al., 2018a, 2018b). However, many muscle diseases arise from mutation or sequestration of the RBPs themselves rather than lesions affecting a single splice event.

Lesions in RBPs or sequestration of an RBP resulting in loss of normal function result in phenotypically complex disorders that molecularly can be traced to pleiotropisms in RBP function. For example, mouse models have shown the pleiotropic effects of mutations leading to myotonic dystrophy (DM) in alternative splicing, transcription, translation, intracellular RNA localization, polyadenylation, miRNA metabolism and phosphorylation of disease intermediates (Braz et al., 2018). RNA regulation beyond AS plays important roles in muscle, for example higher levels of utrophin expression in slow muscle are controlled by increased mRNA stability in slow muscle through 3′-UTR binding (Gramolini et al., 2001). Moreover, RBP lesions typically have a multi-faceted impact affecting multiple tissues, as well as the complete life history of muscle – development, growth, regeneration and ageing (André et al., 2018). There is the additional challenge when analyzing vertebrate mRNA-Seq data of determining which splicing patterns are clearly associated with the disease, and which are associated with the dedifferentiation necessary for muscle regeneration (Orengo et al., 2011). Although multiple examples demonstrating the complex molecular pathology of RBP disease exist, including for example dilated cardiomyopathy (DCM) resulting from mutation of Rbm20 (McNally and Mestroni, 2017; Rexiati et al., 2018) or oculopharyngeal muscular dystrophy (OPMD) resulting from expansion of a GCN repeat found in PABPN1 (Luigetti et al., 2015; Raz and Raz, 2014), below we discuss myotonic dystrophy (DM) as an example of pleiotropic function and systemic nature in RBP disease.

1.7.1. Disease mechanisms underlying myotonic dystrophy

Myotonic dystrophy (DM) is a microsatellite expansion disorder affecting 1 in 8000 people worldwide (Faustino and Cooper, 2003; Wheeler, 2008). DM can be divided into two types based on the affected muscle fiber: type 1 (DM1, OMIM #160900) results from a CTG repeat expansion in the *DMPK* gene and affects the distal musculature while type 2 (DM2, OMIM #602668) results from a CCTG repeat expansion in the *CNBP* gene and affects mainly the proximal musculature (Liquori et al., 2003; Mahadevan et al., 1992). DM1 is characterized by myotonia, progressive muscle weakness and wasting in distal muscles, but often affects multiple tissues additionally causing cardiac dysfunction, insulin resistance, excessive sleepiness, intellectual disability and cognitive deficits (André et al., 2018; Emery, 2002; Mahadevan et al., 1992; Tawil, 2008; Wheeler, 2008). DM2 is phenotypically milder and typically diagnosed in adult patients, affecting the proximal muscles and resulting in a milder myotonia than DM1 (Meola and Cardani, 2015a). Repeat copy number is a major determinant of DM disease severity, with expansions that range from 75-11,000 repeats in human patients (Meola and Cardani, 2015b). Across metazoans, MBNL paralogues are able to bind $(CUG)_{480}$-expanded repeats and co-localize in nuclear foci (Oddo et al., 2016), thus effectively promoting sequestration of MBNL and driving *trans* effects resulting in disruption of the processing of many RNAs (Rohilla and Gagnon, 2017).

Genomic integration and expression of $(CUG)_x$ repeats has allowed the development of DM animal models. $(CUG)_{960}$ repeats in *Drosophila* result in severe muscle disruption and nuclear RNA foci (Picchio et al., 2013). $(CUG)_{125\text{-}213}$ repeats in *C. elegans* result in embryonic lethality, uncoordinated muscle function and abnormal muscle morphology (Chen et al., 2007). $(CUG)_{960}$ repeats in mice result in muscle wasting accompanied by central nuclear localization, reduced fiber cross-sectional area, nuclear RNA foci and increased CELF1 expression (Morriss et al., 2018). Direct injection of $(CUG)_{91}$ repeats in zebrafish results in lethality associated with abnormal development of both forebrain and muscle (Todd et al., 2014). In all models, MBNL1 strongly binds to the repeat expansions and is sequestered to nuclear foci, decreasing nucleoplasmic levels of the active protein and leading to aberrant splicing in adult tissues (Fardaei et al., 2002; Mankodi et al., 2003; Miller et al., 2000; Ranum and Cooper, 2006). In addition hnRNP F, hnRNP H, DDX5, DDX6, DDX17 and Staufen have all been shown to anomalously localize with DM RNA foci (Bondy-Chorney et al., 2016; Pettersson et al., 2015). Loss of RBP function is in turn exacerbated by concomitant up regulation of CELF1 through PKC phosphorylation-mediated protein stabilization (Kuyumcu-Martinez et al., 2007; Mahadevan et al., 2006; Nezu et al., 2007; Orengo et al., 2008). All together this results in a general imbalance in cellular proteostasis and changes to alternative splicing, alternative polyadenylation and nucleocytoplasmic transport (André et al., 2018).

Given that CELF1/2 proteins are normally downregulated more than 10-fold and MBNL1 is upregulated nearly 4-fold during heart and skeletal muscle development (Kalsotra et al., 2008; Ladd et al., 2005a), the upregulation of CELF1 and downregulation of MBNL observed in DM leads to a reversion to embryonic splicing patterns and mis-splicing. Decreased insulin sensitivity in DM is associated with expression of the embryonic isoform of Insulin receptor (IR1) (Savkur et al., 2001, 2004). Cardiac troponin T (cTNT, TNNT2) and fast skeletal muscle troponin T (TNNT3) shift to their embryonic splicing patterns (Philips et al., 1998). In addition to AS, MBNL-regulated polyadenylation status of for example *Pdlim5* and *Dnajb6* are disrupted in DM, resulting in activation of polyadenylation sites normally expressed during embryogenesis (Batra et al., 2014). Mis-splicing of Myotubularin related 1 (MTRM1) results in abnormal isoforms at the expense of muscle isoforms (Buj-Bello et al., 2002), while DM1 myotonia symptoms in part arise from loss of chloride channel (CLCN1) activity due to inclusion of premature stop codons (Charlet-B et al., 2002a; Mankodi et al., 2002). Ryanodine receptor (RyR1), sarcoplasmic/endoplasmic reticulum Ca^{2+} ATPase (SERCA) (Kimura et al., 2005), alpha-actinin (Suzuki et al., 2002), Myh14 (Rinaldi et al., 2012) and Tau (Dhaenens et al., 2011) transcripts are also mis-spliced in DM skeletal muscle. Abnormal splicing of ZASP/LDB3 (Z-band alternatively spliced protein/ LIM domain-binding protein 3) cytoskeletal protein is observed in DM patients, and mis-splicing of *Drosophila* homolog Zasp52 in MBNL deficient flies leads to sarcomeric Z-disc disruption (Machuca-Tzili et al., 2006). Z-disc disruption is also observed in heart and skeletal muscles of zebrafish MBNL mutants (Klinkerfuss, 1967; Ludatscher et al., 1978) and in Mbl RNAi in *C. elegans* (Wang et al., 2008a, 2008b). These studies illustrate the pleiotropic effects on cellular differentiation, RNA processing, cation homeostasis, cytoskeletal architecture and muscle contractility

observed in DM and the conservation of $(CUG)_n$ toxicity mechanisms.

DM phenotypes are well characterized in muscle, but DM also leads to cardiac, endocrine and central nervous system defects (André et al., 2018). DM can result in sleep abnormalities, anxiety, apathy and memory deficits (Charizanis et al., 2012; Matynia et al., 2010; Suenaga et al., 2012) and mouse models display impairment of NMDAR-mediated responses and pattern-induced long-term potentiation (Vuong et al., 2016). This suggests an important function for MBNL in neurons. MBNL knockout mice show transcript expression changes in heart and muscle as well as brain (Wang et al., 2012). MBNL binding sites are found enriched around developmentally regulated exons in neurons (Weyn-Vanhentenryck et al., 2018), and MBNL binds directly to these sites (Wang et al., 2012) to regulate neuronal specific alternative splicing of for example *NF1* exon 23a (Fleming et al., 2012). The hundreds of exons mis-spliced in MBNL2 mutant mouse brain overlap significantly with genes mis-spliced in DM, leading to expression of fetal isoforms of Kcnma1, Cacna1d and Grin1 (Vuong et al., 2016). MBNL sites are enriched in differential alternative exons and MBNL shows strong binding to 3′-UTR regions in neurons, resulting in MBNL-dependent subcellular localization of mRNA transcripts, for example to the neurites (Taliaferro et al., 2016; Wang et al., 2012). MBNL2 has also been shown to directly bind $(CUG)_n$ repeat expansions in the brain in DM mice, resulting in downstream RNA processing defects such as dysregulation of Camk2d and Grin splicing and fetal tau isoform expression. Similar patterns of dysregulation and MBNL2 binding in both intronic and 3′ UTR regions are also found in DM1 and DM2 patient samples (Goodwin et al., 2015). Thus, the changes to AS and RNA regulation observed in DM also likely underlie cognitive deficits in human patients and brain defects observed in animal models, and illustrate the neuromuscular or systemic nature of DM.

1.7.2. Systemic nature of neuromuscular disease

It is also interesting to note the growing appreciation for the systemic nature of neuromuscular disorders in the literature. Spinal muscular atrophy (SMA), characterized by selective degeneration of α-motor neurons in the anterior horn of the spinal cord causing myotonia and muscle atrophy (Pagliarini et al., 2017), is caused by loss of function lesions in *SMN1*. SMN1 has basic housekeeping function in the assembly of snRNPs (Lanfranco et al., 2017) resulting in dysregulation of both gene expression and splicing (Bäumer et al., 2009; Zhang et al., 2008a, 2008b, 2013) and high rates of intron retention (Jangi et al., 2017) in SMA. While classically considered a neuronal disease (Gavrilina et al., 2008), more recent studies suggest depletion of SMN1 function is deleterious in muscle and bone and negatively impacts endocrine, lymphatic and reproductive function (Nash et al., 2016). Knockdown of SMN protein in C2C12 mouse myoblasts results in defects in myoblast fusion and malformed myotubes (Shafey et al., 2005), and deletion of SMN exon 7 specifically in mouse skeletal muscle leads to necrosis and dystrophic phenotypes, resulting in muscle paralysis and death (Cifuentes-Diaz et al., 2001). SMN1 in *Drosophila* also appears to have muscle-specific functions, resulting in abnormal thin filament structures and loss of flight-muscle specific Act88 F expression (Rajendra et al., 2007). This suggests that perhaps defects on the muscle side also contribute to SMA pathogenesis.

Another example of an RBP-related systemic disease is amyotrophic lateral sclerosis (ALS). ALS is characterized by progressive muscular atrophy and motor neuron loss (Tortarolo et al., 2017). ALS-associated genes include multiple RBPs such as TAR DNA-binding protein 43 (TDP-43), fused in sarcoma (FUS) (Kwiatkowski et al., 2009), C9orf72 (DeJesus-Hernandez et al., 2011; Renton et al., 2011), matrin 3, hnRNP A1, hnRNP A2B1 and TIA1 (Johnson et al., 2014). These RBPs are often found in pathological inclusions and thought to contribute to ALS (Purice and Taylor, 2018). Interestingly, several of these RBPs have also been characterized to have function specifically in muscle (Table 1). Recent interpretations have started to consider that muscle may indeed have a cell-autonomous ALS phenotype, as beyond the classical denervation atrophy, ALS muscle has been described to have distinct myopathic features (Iwasaki et al., 1991), inflammation (Al-Sarraj et al., 2014) and hallmarks of apoptosis (Tews et al., 1997). A phenotypic pattern of combined features of ALS and myopathy is observed with ALS-causing genes such as CHCHD10, VCP, hnRNPA1 and hnRNPA2B1 (Ajroud-Driss et al., 2015; Bannwarth et al., 2014; Johnson et al., 2010; Kim et al., 2013; Palmio et al., 2016; Watts et al., 2004). MATR3 specifically is linked to myopathy via its interaction with Lamin A (LMNA) and TDP-43 (Depreux et al., 2015) and regulates muscle-specific polyadenylation, intron retention and paraspeckle function through an interaction with PABPN1 (Banerjee et al., 2017). Patients with a p.S85C mutation in MATR3 can show muscle pathology without observable neuronal affects (Müller et al., 2014), although this may be a slow progressive form of ALS with neuronal defects appearing later (Eisen and Kuwabara, 2012). By contrast, patients with a p.F115C mutation in MATR3 have ALS and dementia symptoms (Johnson et al., 2014). TDP-43 inclusion pathology, most often co-localized with p62, is found specifically in muscle in a subset of human ALS patients (Cykowski et al., 2018). In the mouse mSOD1 ALS model, muscle autonomous phenotypes such as muscle-specific SOD1 aggregates (Atkin et al., 2005), dysregulated calcium homeostasis (Chin et al., 2014), mitochondrial dysfunction, endoplasmic reticulum stress response and heat shock protein expression (Bhattacharya et al., 2014; Chen et al., 2015) are observed. Strikingly, mice expressing mutant hSOD1 only in muscle develop muscle weakness, motor deficits, NMJ abnormalities, myopathy and motor neuron axonopathy and degeneration (Wong and Martin, 2010), suggesting muscle disease or injury can trigger MN degeneration. This illustrates that muscle likely plays an active role in ALS pathology and moreover illustrates the multi-tissue, systemic nature of RBP-associated disease.

1.8. Future prospects

The field of alternative splicing and post-transcriptional regulation is diverse and challenging, yet offers many opportunities. We are still in the process of defining what it means to be an RNA-binding protein and identifying a complete inventory of RBPs. Interactome capture approaches have expanded our concept of what proteins can bind RNA, but there will likely be marked differences in the RNA interactome between tissues and across development. The majority of RBPs await verification and in-depth biological analysis of their physiological function. There are certainly connections between RNA regulation and metabolism, chromatin state and mitochondrial status waiting to be explored.

Another open field is RBP regulation and mechanisms of target recognition. Many RBPs are themselves heavily alternatively spliced, potentially affecting functional specificity and target recognition. Few post-translational modifications of RBPs have been characterized, but phosphorylation, ubiquitination, methylation and other modifications likely modulate RBP activity, localization and target specificity. For example, phosphorylation of *Drosophila* How enhances AS activity (Nir et al., 2012) and phosphorylation of SRSF1 controls its subcellular localization and mRNA processing function (Aubol et al., 2018). Intracellular assemblies of RBPs, such as the LASR complex, can promote changes in target specificity, but few such RBP complexes have been described. It is likely that different RBP assemblies with defined functions exist in a temporal and spatial specific manner.

Finally, the role of RBPs in disease and development will certainly expand in the coming years. RBPs are causal for muscle diseases such as myotonic dystrophy or dilated cardiomyopathy, and are disease modifiers in cancer or muscular dystrophy. There are more disease-related RBPs awaiting discovery, and novel pathological mechanisms await characterization. The full utility of RBPs and their targets for novel therapies is just beginning to be explored. We have just scratched the surface of the proverbial RBP iceberg, and supported by technological developments stand poised to discover how broadly RBPs impact muscle development and disease.

2. Methods

2.1. Fly strains

Fly stocks were maintained using standard culture conditions. $bru1^{M1}$ is a deletion allele with breakpoints CCAGTCTCGAAGCTT to CCGCGGAACGAG AGA generated using CRISPR and inserting a selectable cassette by homologous recombination (Zhang et al., 2014). RNAi was performed in all muscle using *Mef2*-GAL4 (maintained at 27 °C) and specifically in flight muscle after 24 h APF (after puparium formation) using *Act88F*-GAL4 (maintained at 25 °C). *Mef*2-GAL4 x w^{1118} or *Act88F*-GAL4 x w^{1118} served as control. *bru1* RNAi was performed with previously characterized GD41568 (referred to as *bru1*-IR) (Spletter et al., 2015) from VDRC (http://stockcenter.vdrc.at) (Dietzl et al., 2007). Stocks obtained from Bloomington include the deficiency Df(2 L)BSC407 covering *bru1* and TRiP hairpins *Rm62*-IR (JF01385), *Sf3b2 (CG3605)*-IR (HMS00056), *Sf3a2 (CG10754)*-IR (HMC03799), *noi (Sf3a3)*-IR (HMS00163). Stocks obtained from the VDRC include hairpins *mbl*-IR (GD29585 and

KK105486), *Rbfox1 (A2BP1)*-IR (GD27286 and KK110518), *Rm62*-IR (GD46908 and KK110102), *Sf3b2 (CG3605)*-IR (GD26250, GD26252 and KK105639), *Sf3a2 (CG10754)*-IR (GD31346 and GD31347), *noi (Sf3a3)*-IR (GD20943, GD20945 and KK105354) and *Sbr*-IR (GD32691 and KK103715).

2.2. Flight tests

Flight tests were performed by introducing flies into the top of a 1 m long cylinder as previously described (Schnorrer et al., 2010). Flies that land near the top are "normal fliers", in the middle are "weak fliers" and that fell to the bottom are "flightless." Adult males were anesthetized during collection and recovered at least 1 day at 25 °C before testing.

2.3. Immuno-staining

Flight muscles were dissected and stained as described (Weitkunat and Schnorrer, 2014). Thoraxes were fixed for 20 min. in 4% PFA in 0.5% PBS-Triton-X100 (PBS-T) and washed in PBS-T. Thoraxes were cut sagittally with a microtome blade. Samples were stained at least 3 h at RT with rhodamine phalloidin (Molecular Probes, 1:500) in PBS-T. Samples were washed three times in 0.5% PBS-T and mounted in Vectashield containing DAPI. Samples were imaged on a Leica SP8X WLL upright confocal with a HC PL APO 63x/1.4 OIL CS2 objective in the Core Facility Bioimaging at the Biomedical Center of the Ludwig-Maximilians-Universität München.

2.4. RT-PCR

Indirect flight muscles (IFM) or whole legs were dissected in PBS. PBS was removed and RNA was isolated using Trizol following the manufacturer's protocol. Reverse transcription and first strand synthesis was performed with the SuperScript™ III First-Strand Synthesis System (Invitrogen) following the manufacturer's protcol. PCR was performed with previously reported splice-sensitive primers against *Mhc* or control *Rp49* (Orfanos and Sparrow, 2013) or in *wupA* (forward-CGCTGAGTTCAACTTCCGCAACC, reverse-ATTGTTTAGGGCGG GAGTCACGG). PCR products were examined by electrophoresis on a standard 2% agarose gel next to a 100 bp ladder (NEB).

2.5. Calculation of evolutionary distance

Sequences were curated from NCBI (https://www.ncbi.nlm.nih.gov/) for MBNL and from UniProt (https://www.uniprot.org/) for CELF and Rbfox family homologs in *Homo sapiens* (human, Hs), *Mus musculus* (mouse, Mm), *Danio rerio* (zebrafish, Dr), *Drosophila melanogaster* (fruit fly, Dm) and *Caenorhabditis elegans* (nematode, Ce) and are provided in Supplemental Materials. Alignments were performed using the "Align by Muscle" option with a neighbor joining clustering method in MEGA6 (Tamura et al., 2013) after removing gaps and missing data. The analysis of the third RRM from CELF proteins involved 21 amino acid sequences for a total of 59 positions. The analysis of the RRM from Rbfox involved 11 amino acid sequences for a total of 77 positions. The analysis of the zinc fingers from MBNL involved 11 amino acid sequences for a total of 54 positions. For Rbfox, the evolutionary tree was inferred using a neighbor joining method with distances computed using the p-distance method with a final branch length = 0.41736348. For CELF and MBNL, evolutionary trees were inferred using a maximum likelihood method based on a JTT matrix-based model and the tree constructed by applying neighbor-join and BioNJ algorithms. The tree with the highest log likelihood (for MBNL = -477.2156 and CELF = -553.0751) is shown in Fig. 3.

2.6. Bioinformatics

RBPs published to have a function in muscle in mouse, zebrafish, fly or *C. elegans* were curated by hand. We required biochemical function or genetic phenotype either *in vivo* in muscle or from a muscle-derived cell line (mostly C2C12). Additional information on each gene was obtained from MouseMine (http://www.mousemine.org/), ZebrafishMine (http://www.zebrafishmine.org/), Flybase (http://flybase.org/) or Wormbase (https://www.wormbase.org/). Protein domains are from SMART (Letunic and Bork, 2018) and PFAM (https://pfam.xfam.org/). Genome sizes were obtained from Ensembl (https://www.ensembl.org/) for human (GRCh38.p12), mouse (GRCm38.6), zebrafish (GRCz11), fruitfly (BDGP6) and *C. elegans* (WBcel235). We utilized the following published datasets: AmiGO2 gene ontology database (Munoz-Torres and Carbon, 2017), compiled lists of RNA interactome capture identified RBPs (Hentze et al., 2018), Gene List Annotation for *Drosophila* (GLAD) (Hu et al., 2015), genome-wide muscle RNAi phenotypes in *Drosophila* (Schnorrer et al., 2010), and mRNA-Seq data specifically from muscle in mouse (Pedrotti et al., 2015; Söllner et al., 2017), *Drosophila* (Spletter et al., 2015, 2018) and *C. elegans* (Blazie et al., 2015; Meissner et al., 2009). Data was analysed and plotted in R version 3.4.3 using the following packages: plyr (Software, 2011, n.d.), reshape2 (Software, 2007, n.d.), VennDiagram (Chen and Boutros, 2011) and ggplot2 (Wickham, 2011).

Author contributions

EN performed Bru-1, Mbl and A2BP1 experiments. SYK and AW screened and tested RBPs presented in Fig. 2. KR performed the conservation analysis. EN, SYK, KR and MLS wrote the manuscript. MLS conceived and supervised the study.

Conflict of interest

The authors declare that they have no conflict of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.biocel.2019.02.008.

References

Adereth, Y., Dammai, V., Kose, N., Li, R., Hsu, T., 2005. RNA-dependent integrin alpha3 protein localization regulated by the muscleblind-like protein MLP1. Nat. Cell Biol. 7, 1240–1247. https://doi.org/10.1038/ncb1335.

Ajroud-Driss, S., Fecto, F., Ajroud, K., Lalani, I., Calvo, S.E., Mootha, V.K., Deng, H.-X., Siddique, N., Tahmoush, A.J., Heiman-Patterson, T.D., Siddique, T., 2015. Mutation in the novel nuclear-encoded mitochondrial protein CHCHD10 in a family with autosomal dominant mitochondrial myopathy. Neurogenetics 16, 1–9. https://doi.org/10.1007/s10048-014-0421-1.

Al-Sarraj, S., King, A., Cleveland, M., Pradat, P.-F., Corse, A., Rothstein, J.D., Leigh, P.N., Abila, B., Bates, S., Wurthner, J., Meininger, V., 2014. Mitochondrial abnormalities and low grade inflammation are present in the skeletal muscle of a minority of patients with amyotrophic lateral sclerosis; an observational myopathology study. Acta Neuropathol. Commun. 2, 165. https://doi.org/10.1186/s40478-014-0165-z.

Amirouche, A., Tadesse, H., Miura, P., Bélanger, G., Lunde, J.A., Côté, J., Jasmin, B.J., 2014. Converging pathways involving microRNA-206 and the RNA-binding protein KSRP control post-transcriptionally utrophin A expression in skeletal muscle. Nucleic Acids Res. 42, 3982–3997. https://doi.org/10.1093/nar/gkt1350.

Anderson, D.M., Cannavino, J., Li, H., Anderson, K.M., Nelson, B.R., McAnally, J., Bezprozvannaya, S., Liu, Y., Lin, W., Liu, N., Bassel-Duby, R., Olson, E.N., 2016. Severe muscle wasting and denervation in mice lacking the RNA-binding protein ZFP106. Proc. Natl. Acad. Sci. U. S. A. 113, E4494–503. https://doi.org/10.1073/pnas.1608423113.

André, L.M., Ausems, C.R.M., Wansink, D.G., Wieringa, B., 2018. Abnormalities in skeletal muscle myogenesis, growth, and regeneration in myotonic dystrophy. Front. Neurol. 9, 368. https://doi.org/10.3389/fneur.2018.00368.

Andreadis, A., Gallego, M.E., Nadal-Ginard, B., 1987. Generation of protein isoform diversity by alternative splicing: mechanistic and biological implications. Annu. Rev. Cell Biol. 3, 207–242. https://doi.org/10.1146/annurev.cb.03.110187.001231.

Anyanful, A., Ono, K., Johnsen, R.C., Ly, H., Jensen, V., Baillie, D.L., Ono, S., 2004. The RNA-binding protein SUP-12 controls muscle-specific splicing of the ADF/cofilin pre-mRNA in C. Elegans. J. Cell Biol. 167, 639–647. https://doi.org/10.1083/jcb.200407085.

Apponi, L.H., Corbett, A.H., Pavlath, G.K., 2013. Control of mRNA stability contributes to low levels of nuclear poly(A) binding protein 1 (PABPN1) in skeletal muscle. Skelet. Muscle 3, 23. https://doi.org/10.1186/2044-5040-3-23.

Artero, R., Prokop, A., Paricio, N., Begemann, G., Pueyo, I., Mlodzik, M., Perez-Alonso, M., Baylies, M.K., 1998. The muscleblind gene participates in the organization of Z-bands and epidermal attachments of Drosophila muscles and is regulated by Dmef2. Dev. Biol. 195, 131–143. https://doi.org/10.1006/dbio.1997.8833.

Ashburner, M., Ball, C.A., Blake, J.A., Botstein, D., Butler, H., Cherry, J.M., Davis, A.P., Dolinski, K., Dwight, S.S., Eppig, J.T., Harris, M.A., Hill, D.P., Issel-Tarver, L., Kasarskis, A., Lewis, S., Matese, J.C., Richardson, J.E., Ringwald, M., Rubin, G.M., Sherlock, G., 2000. Gene ontology: tool for the unification of biology. Gene Ontol. Consortium. Nat. Genet. 25, 25–29. https://doi.org/10.1038/75556.

Ashley, J., Cordy, B., Lucia, D., Fradkin, L.G., Budnik, V., Thomson, T., 2018. Retrovirus-like gag protein Arc1 binds RNA and traffics across synaptic boutons. Cell 172, 262–274. https://doi.org/10.1016/j.cell.2017.12.022. e11.

Atkin, J.D., Scott, R.L., West, J.M., Lopes, E., Quah, A.K.J., Cheema, S.S., 2005. Properties of slow- and fast-twitch muscle fibres in a mouse model of amyotrophic lateral sclerosis. Neuromuscul. Disord. 15, 377–388. https://doi.org/10.1016/j.nmd.2005.02.005.

Aubol, B.E., Serrano, P., Fattet, L., Wuthrich, K., Adams, J.A., 2018. Molecular interactions connecting the function of the serine-arginine-rich protein SRSF1 to protein phosphatase 1. J. Biol. Chem. jbc. RA118 004587. https://doi.org/10.1074/jbc.RA118.004587.

Auweter, S.D., Fasan, R., Reymond, L., Underwood, J.G., Black, D.L., Pitsch, S., Allain, F.H.T., 2006. Molecular basis of RNA recognition by the human alternative splicing factor Fox-1. EMBO J. 25, 163–173. https://doi.org/10.1038/sj.emboj.7600918.

Babu, G.J., Loukianov, E., Loukianova, T., Pyne, G.J., Huke, S., Osol, G., Low, R.B., Paul, R.J., Periasamy, M., 2001. Loss of SM-B myosin affects muscle shortening velocity and maximal force development. Nat. Cell Biol. 3, 1025–1029. https://doi.org/10.1038/ncb1101-1025.

Baehrecke, E.H., 1997. Who encodes a KH RNA binding protein that functions in muscle development. Development 124, 1323–1332.

Banerjee, A., Vest, K.E., Pavlath, G.K., Corbett, A.H., 2017. Nuclear poly(A) binding protein 1 (PABPN1) and Matrin3 interact in muscle cells and regulate RNA processing. Nucleic Acids Res. 45, 10706–10725. https://doi.org/10.1093/nar/gkx786.

Bannwarth, S., Ait-El-Mkadem, S., Chaussenot, A., Genin, E.C., Lacas-Gervais, S., Fragaki, K., Berg-Alonso, L., Kageyama, Y., Serre, V., Moore, D.G., Verschueren, A., Rouzier, C., Le Ber, I., Augé, G., Cochaud, C., Lespinasse, F., N'Guyen, K., de Septenville, A., Brice, A., Yu-Wai-Man, P., Sesaki, H., Pouget, J., Paquis-Flucklinger, V., 2014. A mitochondrial origin for frontotemporal dementia and amyotrophic lateral sclerosis through CHCHD10 involvement. Brain 137, 2329–2345. https://doi.org/10.1093/brain/awu138.

Barnes, D.E., Watabe, E., Ono, K., Kwak, E., Kuroyanagi, H., Ono, S., 2018. Tropomyosin isoforms differentially affect muscle contractility in the head and body regions of the nematode Caenorhabditis elegans. Mol. Biol. Cell 29, 1075–1088. https://doi.org/10.1091/mbc.E17-03-0152.

Basi, G.S., Boardman, M., Storti, R.V., 1984. Alternative splicing of a Drosophila tropomyosin gene generates muscle tropomyosin isoforms with different carboxy-terminal ends. Mol. Cell. Biol. 4, 2828–2836.

Batra, R., Charizanis, K., Manchanda, M., Mohan, A., Li, M., Finn, D.J., Goodwin, M., Zhang, C., Sobczak, K., Thornton, C.A., Swanson, M.S., 2014. Loss of MBNL leads to disruption of developmentally regulated alternative polyadenylation in RNA-mediated disease. Mol. Cell 56, 311–322. https://doi.org/10.1016/j.molcel.2014.08.027.

Bäumer, D., Lee, S., Nicholson, G., Davies, J.L., Parkinson, N.J., Murray, L.M., Gillingwater, T.H., Ansorge, O., Davies, K.E., Talbot, K., 2009. Alternative splicing events are a late feature of pathology in a mouse model of spinal muscular atrophy. PLoS Genet. 5, e1000773. https://doi.org/10.1371/journal.pgen.1000773.

Begemann, G., Paricio, N., Artero, R., Kiss, I., Perez-Alonso, M., Mlodzik, M., 1997. Muscleblind, a gene required for photoreceptor differentiation in Drosophila, encodes novel nuclear Cys3His-type zinc-finger-containing proteins. Development 124, 4321–4331.

Bennett, A.H., O'Donohue, M.-F., Gundry, S.R., Chan, A.T., Widrick, J., Draper, I., Chakraborty, A., Zhou, Y., Zon, L.I., Gleizes, P.-E., Beggs, A.H., Gupta, V.A., 2018. RNA helicase, DDX27 regulates skeletal muscle growth and regeneration by modulation of translational processes. PLoS Genet. 14, e1007226. https://doi.org/10.1371/journal.pgen.1007226.

Benoist, P., Mas, J.A., Marco, R., Cervera, M., 1998. Differential muscle-type expression of the Drosophila troponin T gene. A 3-base pair microexon is involved in visceral and adult hypodermic muscle specification. J. Biol. Chem. 273, 7538–7546.

Beraldi, R., Li, X., Martinez Fernandez, A., Reyes, S., Secreto, F., Terzic, A., Olson, T.M., Nelson, T.J., 2014. Rbm20-deficient cardiogenesis reveals early disruption of RNA processing and sarcomere remodeling establishing a developmental etiology for dilated cardiomyopathy. Hum. Mol. Genet. 23, 3779–3791. https://doi.org/10.1093/hmg/ddu091.

Berger, D.S., Moyer, M., Kliment, G.M., van Lunteren, E., Ladd, A.N., 2011. Expression of a dominant negative CELF protein in vivo leads to altered muscle organization, Fiber size, and subtype. PLoS One 6, e19274–11. https://doi.org/10.1371/journal.pone.0019274.

Bernstein, S.I., Hansen, C.J., Becker, K.D., Wassenberg, D.R., Roche, E.S., Donady, J.J., Emerson, C.P., 1986. Alternative RNA splicing generates transcripts encoding a thorax-specific isoform of Drosophila melanogaster myosin heavy chain. Mol. Cell. Biol. 6, 2511–2519.

Bertrandy, S., Burlet, P., Clermont, O., Huber, C., Fondrat, C., Thierry-Mieg, D., Munnich, A., Lefebvre, S., 1999. The RNA-binding properties of SMN: deletion analysis of the zebrafish orthologue defines domains conserved in evolution. Hum. Mol. Genet. 8, 775–782.

Bhalla, K., Phillips, H.A., Crawford, J., McKenzie, O.L.D., Mulley, J.C., Eyre, H., Gardner, A.E., Kremmidiotis, G., Callen, D.F., 2004. The de novo chromosome 16 translocations of two patients with abnormal phenotypes (mental retardation and epilepsy) disrupt the A2BP1 gene. J. Hum. Genet. 49, 308–311. https://doi.org/10.1007/s10038-004-0145-4.

Bhattacharya, A., Wei, R., Hamilton, R.T., Chaudhuri, A.R., 2014. Neuronal cells but not muscle cells are resistant to oxidative stress mediated protein misfolding and cell death: role of molecular chaperones. Biochem. Biophys. Res. Commun. 446, 1250–1254. https://doi.org/10.1016/j.bbrc.2014.03.097.

Bill, B.R., Lowe, J.K., Dybuncio, C.T., Fogel, B.L., 2013. Orchestration of neurodevelopmental programs by RBFOX1: implications for autism spectrum disorder. Int. Rev. Neurobiol. 113, 251–267. https://doi.org/10.1016/B978-0-12-418700-9.00008-3.

Bland, C.S., Wang, E.T., Vu, A., David, M.P., Castle, J.C., Johnson, J.M., Burge, C.B., Cooper, T.A., 2010. Global regulation of alternative splicing during myogenic differentiation. Nucleic Acids Res. 38, 7651–7664. https://doi.org/10.1093/nar/gkq614.

Blazie, S.M., Babb, C., Wilky, H., Rawls, A., Park, J.G., Mangone, M., 2015. Comparative RNA-Seq analysis reveals pervasive tissue-specific alternative polyadenylation in Caenorhabditis elegans intestine and muscles. BMC Biol. 13https://doi.org/10.1186/s12915-015-0116-6. 1775–21.

Blech-Hermoni, Y., Stillwagon, S.J., Ladd, A.N., 2013. Diversity and conservation of CELF1 and CELF2 RNA and protein expression patterns during embryonic development. Dev. Dyn. 242, 767–777. https://doi.org/10.1002/dvdy.23959.

Blech-Hermoni, Y., Dasgupta, T., Coram, R.J., Ladd, A.N., 2016. Identification of targets of CUG-BP, elav-like family member 1 (CELF1) regulation in embryonic heart muscle. PLoS One 11, e0149061. https://doi.org/10.1371/journal.pone.0149061.

Bloemberg, D., Quadrilatero, J., 2012. Rapid determination of myosin heavy chain expression in rat, mouse, and human skeletal muscle using multicolor immunofluorescence analysis. PLoS One 7, e35273. https://doi.org/10.1371/journal.pone.0035273.

Bock, F.J., Todorova, T.T., Chang, P., 2015. RNA regulation by poly(ADP-Ribose) polymerases. Mol. Cell 58, 959–969. https://doi.org/10.1016/j.molcel.2015.01.037.

Bondy-Chorney, E., Crawford Parks, T.E., Ravel-Chapuis, A., Klinck, R., Rocheleau, L., Pelchat, M., Chabot, B., Jasmin, B.J., Côté, J., 2016. Staufen1 regulates multiple alternative splicing events either positively or negatively in DM1 indicating its role as a disease modifier. PLoS Genet. 12, e1005827. https://doi.org/10.1371/journal.pgen.1005827.

Bonnet, A., Lambert, G., Ernest, S., Dutrieux, F.X., Coulpier, F., Lemoine, S., Lobbardi, R., Rosa, F.M., 2017. Quaking RNA-Binding proteins control early myofibril formation by modulating tropomyosin. Dev. Cell 42, 527–541. https://doi.org/10.1016/j.devcel.2017.08.004. e4.

Borg, R., Cauchi, R.J., 2013. The Gemin associates of survival motor neuron are required for motor function in Drosophila. PLoS One 8, e83878. https://doi.org/10.1371/journal.pone.0083878.

Borg, R.M., Bordonne, R., Vassallo, N., Cauchi, R.J., 2015. Genetic interactions between the members of the SMN-Gemins complex in Drosophila. PLoS One 10, e0130974. https://doi.org/10.1371/journal.pone.0130974.

Boudoukha, S., Cuvellier, S., Polesskaya, A., 2010. Role of the RNA-binding protein IMP-2 in muscle cell motility. Mol. Cell. Biol. 30, 5710–5725. https://doi.org/10.1128/MCB.00665-10.

Braz, S.O., Acquaire, J., Gourdon, G., Gomes-Pereira, M., 2018. Of mice and men: advances in the understanding of neuromuscular aspects of myotonic dystrophy. Front. Neurol. 9, 519. https://doi.org/10.3389/fneur.2018.00519.

Breitbart, R.E., Nguyen, H.T., Medford, R.M., Destree, A.T., Mahdavi, V., Nadal-Ginard, B., 1985. Intricate combinatorial patterns of exon splicing generate multiple regulated troponin T isoforms from a single gene. Cell 41, 67–82.

Brinegar, A.E., Xia, Z., Loehr, J.A., Li, W., Rodney, G.G., Cooper, T.A., 2017. Extensive alternative splicing transitions during postnatal skeletal muscle development are required for calcium handling functions. Elife 6, 399. https://doi.org/10.7554/eLife.27192.

Brooks, A.N., Yang, L., Duff, M.O., Hansen, K.D., Park, J.W., Dudoit, S., Brenner, S.E., Graveley, B.R., 2011. Conservation of an RNA regulatory map between Drosophila and mammals. Genome Res. 21, 193–202. https://doi.org/10.1101/gr.108662.110.

Brown, S., 2014. Animal models: mouse already being charted gene by gene. Nature 508https://doi.org/10.1038/508319d. 319–319.

Buckingham, M., 2017. Gene regulatory networks and cell lineages that underlie the formation of skeletal muscle. Proc. Natl. Acad. Sci. U. S. A. 114, 5830–5837. https://doi.org/10.1073/pnas.1610605114.

Buj-Bello, A., Furling, D., Tronchère, H., Laporte, J., Lerouge, T., Butler-Browne, G.S., Mandel, J.-L., 2002. Muscle-specific alternative splicing of myotubularin-related 1 gene is impaired in DM1 muscle cells. Hum. Mol. Genet. 11, 2297–2307.

Burns, D.T., Donkervoort, S., Müller, J.S., Knierim, E., Bharucha-Goebel, D., Faqeih, E.A., Bell, S.K., AlFaifi, A.Y., Monies, D., Millan, F., Retterer, K., Dyack, S., MacKay, S., Morales-Gonzalez, S., Giunta, M., Munro, B., Hudson, G., Scavina, M., Baker, L., Massini, T.C., Lek, M., Hu, Y., Ezzo, D., AlKuraya, F.S., Kang, P.B., Griffin, H., Foley, A.R., Schuelke, M., Horvath, R., Bönnemann, C.G., 2018. Variants in EXOSC9 disrupt the RNA exosome and result in cerebellar atrophy with spinal motor neuronopathy. Am. J. Hum. Genet. 102, 858–873. https://doi.org/10.1016/j.ajhg.2018.03.011.

Bye-A-Jee, H., Pugazhendhi, D., Woodhouse, S., Brien, P., Watson, R., Turner, M., Pell, J., 2018. The RNA-binding proteins Zfp36l1 and Zfp36l2 act redundantly in myogenesis. Skelet. Muscle 8, 37. https://doi.org/10.1186/s13395-018-0183-9.

Cammas, A., Sanchez, B.J., Lian, X.J., Dormoy-Raclet, V., van der Giessen, K., López de Silanes, I., Ma, J., Wilusz, C., Richardson, J., Gorospe, M., Millevoi, S., Giovarelli, M., Gherzi, R., Di Marco, S., Gallouzi, I.-E., 2014. Destabilization of nucleophosmin mRNA by the HuR/KSRP complex is required for muscle fibre formation. Nat. Commun. 5, 4190. https://doi.org/10.1038/ncomms5190.

Carreira-Rosario, A., Bhargava, V., Hillebrand, J., Kollipara, R.K., Ramaswami, M., Buszczak, M., 2016. Repression of pumilio protein expression by Rbfox1 promotes germ cell differentiation. Dev. Cell 36, 562–571. https://doi.org/10.1016/j.devcel.2016.02.010.

Castle, J.C., Zhang, C., Shah, J.K., Kulkarni, A.V., Kalsotra, A., Cooper, T.A., Johnson, J.M., 2008. Expression of 24,426 human alternative splicing events and predicted cis regulation in 48 tissues and cell lines. Nat. Genet. 40, 1416–1425. https://doi.org/10.1038/ng.264.

Cauchi, R.J., Davies, K.E., Liu, J.-L., 2008. A motor function for the DEAD-box RNA helicase, Gemin3, in Drosophila. PLoS Genet. 4, e1000265 doi:10.1371/journal.pgen.1000265.

Cavey, M.J., 1983. Ultrastructure and differentiation of ascidian muscle. II. Differentiation of the caudal muscle cells in the larva of Diplosoma macdonaldi. Cell Tissue Res. 230, 77–94.

Cavey, M.J., Cloney, R.A., 1976. Ultrastructure and differentiation of ascidian muscle. I. Caudal musculature of the larva of Diplosoma macdonaldi. Cell Tissue Res. 174, 289–313.

Cerro-Herreros, E., Fernandez-Costa, J.M., Sabater-Arcis, M., Llamusi, B., Artero, R., 2016. Derepressing muscleblind expression by miRNA sponges ameliorates myotonic dystrophy-like phenotypes in Drosophila. Sci. Rep. 6, 36230. https://doi.org/10.1038/srep36230.

Chan, Y.B., 2003. Neuromuscular defects in a Drosophila survival motor neuron gene mutant. Hum. Mol. Genet. 12, 1367–1376. https://doi.org/10.1093/hmg/ddg157.

Charizanis, K., Lee, K.-Y., Batra, R., Goodwin, M., Zhang, C., Yuan, Y., Shiue, L., Cline, M., Scotti, M.M., Xia, G., Kumar, A., Ashizawa, T., Clark, H.B., Kimura, T., Takahashi, M.P., Fujimura, H., Jinnai, K., Yoshikawa, H., Gomes-Pereira, M., Gourdon, G., Sakai, N., Nishino, S., Foster, T.C., Ares, M., Darnell, R.B., Swanson, M.S., 2012. Muscleblind-like 2-mediated alternative splicing in the developing brain and dysregulation in myotonic dystrophy. Neuron 75, 437–450. https://doi.org/10.1016/j.neuron.2012.05.029.

Charlet-B, N., Logan, P., Singh, G., Cooper, T.A., 2002a. Dynamic antagonism between ETR-3 and PTB regulates cell type-specific alternative splicing. Mol. Cell 9, 649–658.

Charlet-B, N., Savkur, R.S., Singh, G., Philips, A.V., Grice, E.A., Cooper, T.A., 2002b. Loss of the muscle-specific chloride channel in type 1 myotonic dystrophy due to misregulated alternative splicing. Mol. Cell 10, 45–53.
Chartier, A., Benoit, B., Simonelig, M., 2006. A Drosophila model of oculopharyngeal muscular dystrophy reveals intrinsic toxicity of PABPN1. EMBO J. 25, 2253–2262. https://doi.org/10.1038/sj.emboj.7601117.
Chartier, A., Klein, P., Pierson, S., Barbezier, N., Gidaro, T., Casas, F., Carberry, S., Dowling, P., Maynadier, L., Bellec, M., Oloko, M., Jardel, C., Moritz, B., Dickson, G., Mouly, V., Ohlendieck, K., Butler-Browne, G., Trollet, C., Simonelig, M., 2015. Mitochondrial dysfunction reveals the role of mRNA poly(A) tail regulation in oculopharyngeal muscular dystrophy pathogenesis. PLoS Genet. 11https://doi.org/10.1371/journal.pgen.1005092. e1005092–27.
Chen, H., Boutros, P.C., 2011. VennDiagram: a package for the generation of highly-customizable Venn and Euler diagrams in R. BMC Bioinformatics 12 (35). https://doi.org/10.1186/1471-2105-12-35.
Chen, K.-Y., Pan, H., Lin, M.-J., Li, Y.-Y., Wang, L.-C., Wu, Y.-C., Hsiao, K.-M., 2007. Length-dependent toxicity of untranslated CUG repeats on Caenorhabditis elegans. Biochem. Biophys. Res. Commun. 352, 774–779. https://doi.org/10.1016/j.bbrc.2006.11.102.
Chen, Z., Holland, W., Shelton, J.M., Ali, A., Zhan, X., Won, S., Tomisato, W., Liu, C., Li, X., Moresco, E.M.Y., Beutler, B., 2014. Mutation of mouse Samd4 causes leanness, myopathy, uncoupled mitochondrial respiration, and dysregulated mTORC1 signaling. Proc. Natl. Acad. Sci. U. S. A. 111, 7367–7372. https://doi.org/10.1073/pnas.1406511111.
Chen, D., Wang, Y., Chin, E.R., 2015. Activation of the endoplasmic reticulum stress response in skeletal muscle of G93A*SOD1 amyotrophic lateral sclerosis mice. Front. Cell. Neurosci. 9, 170. https://doi.org/10.3389/fncel.2015.00170.
Chen, Z., Maimaiti, R., Zhu, C., Cai, H., Stern, A., Mozdziak, P., Ge, Y., Ford, S.P., Nathanielsz, P.W., Guo, W., 2018. Z-band and M-band titin splicing and regulation by RNA binding motif 20 in striated muscles. J. Cell. Biochem. 119, 9986–9996. https://doi.org/10.1002/jcb.27328.
Chenette, D.M., Cadwallader, A.B., Antwine, T.L., Larkin, L.C., Wang, J., Olwin, B.B., Schneider, R.J., 2016. Targeted mRNA decay by RNA binding protein AUF1 regulates adult muscle stem cell fate, promoting skeletal muscle integrity. Cell Rep. 16, 1379–1390. https://doi.org/10.1016/j.celrep.2016.06.095.
Chin, E.R., Chen, D., Bobyk, K.D., Mázala, D.A.G., 2014. Perturbations in intracellular Ca2+ handling in skeletal muscle in the G93A*SOD1 mouse model of amyotrophic lateral sclerosis. Am. J. Physiol. Cell Physiol. 307https://doi.org/10.1152/ajpcell.00237.2013. C1031–8.
Choi, S.Y., Choi, B.G., Rha, S.-W., Baek, M.J., Ryu, Y.G., Park, Y., Byun, J.K., Shim, M., Li, H., Mashaly, A., Jang, W.Y., Kim, W., Choi, J.Y., Park, E.J., Na, J.O., Choi, C.U., Lim, H.E., Kim, E.J., Park, C.G., Seo, H.S., Oh, D.J., 2017. Percutaneous coronary intervention versus optimal medical therapy for chronic total coronary occlusion with well-developed collaterals. J. Am. Heart Assoc. 6. https://doi.org/10.1161/JAHA.117.006357.
Chu, M., Novak, S.M., Cover, C., Wang, A.A., Chinyere, I.R., Juneman, E.B., Zarnescu, D.C., Wong, P.K., Gregorio, C.C., 2018. Increased Cardiac Arrhythmogenesis Associated with gap junction remodeling with upregulation of RNA-binding protein FXR1. Circulation 137, 605–618 doi:10.1161/CIRCULATIONAHA.117.028976.
Cifuentes-Diaz, C., Frugier, T., Tiziano, F.D., Lacène, E., Roblot, N., Joshi, V., Moreau, M.H., Melki, J., 2001. Deletion of murine SMN exon 7 directed to skeletal muscle leads to severe muscular dystrophy. J. Cell Biol. 152, 1107–1114.
Crawford Parks, T.E., Ravel-Chapuis, A., Bondy-Chorney, E., Renaud, J.-M., Côté, J., Jasmin, B.J., 2017. Muscle-specific expression of the RNA-binding protein Staufen1 induces progressive skeletal muscle atrophy via regulation of phosphatase tensin homolog. Hum. Mol. Genet. 26, 1821–1838. https://doi.org/10.1093/hmg/ddx085.
Cykowski, M.D., Powell, S.Z., Appel, J.W., Arumanayagam, A.S., Rivera, A.L., Appel, S.H., 2018. Phosphorylated TDP-43 (pTDP-43) aggregates in the axial skeletal muscle of patients with sporadic and familial amyotrophic lateral sclerosis. Acta Neuropathol. Commun. 6, 28 doi:10.1186/s40478-018-0528-y.
D'Amico, D., Mottis, A., Potenza, F., Sorrentino, V., Li, H., Romani, M., Lemos, V., Schoonjans, K., Zamboni, N., Knott, G., Schneider, B.L., Auwerx, J., 2019. The RNA-Binding protein PUM2 impairs mitochondrial dynamics and mitophagy during aging. Mol. Cell. https://doi.org/10.1016/j.molcel.2018.11.034.
Daines, B., Wang, H., Wang, L., Li, Y., Han, Y., Emmert, D., Gelbart, W., Wang, X., Li, W., Gibbs, R., Chen, R., 2011. The Drosophila melanogaster transcriptome by paired-end RNA sequencing. Genome Res. 21, 315–324 doi:10.1101/gr.107854.110.
Damianov, A., Ying, Y., Lin, C.-H., Lee, J.-A., Tran, D., Vashisht, A.A., Bahrami-Samani, E., Xing, Y., Martin, K.C., Wohlschlegel, J.A., Black, D.L., 2016. Rbfox proteins regulate splicing as part of a large multiprotein complex LASR. Cell 165, 606–619. https://doi.org/10.1016/j.cell.2016.03.040.
Das, D., Clark, T.A., Schweitzer, A., Yamamoto, M., Marr, H., Arribere, J., Minovitsky, S., Poliakov, A., Dubchak, I., Blume, J.E., Conboy, J.G., 2007. A correlation with exon expression approach to identify cis-regulatory elements for tissue-specific alternative splicing. Nucleic Acids Res. 35, 4845–4857. https://doi.org/10.1093/nar/gkm485.
Dasgupta, T., Ladd, A.N., 2011. The importance of CELF control: molecular and biological roles of the CUG-BP, Elav-like family of RNA-binding proteins. WIREs RNA 3 104–121. https://doi.org/10.1002/wrna.107.
Davidovic, L., Durand, N., Khalfallah, O., Tabet, R., Barbry, P., Mari, B., Sacconi, S., Moine, H., Bardoni, B., 2013. A novel role for the RNA-binding protein FXR1P in myoblasts cell-cycle progression by modulating p21/Cdkn1a/Cip1/Waf1 mRNA stability. PLoS Genet. 9, e1003367 doi:10.1371/journal.pgen.1003367.
Davies, J.E., Wang, L., Garcia-Oroz, L., Cook, L.J., Vacher, C., O'Donovan, D.G., Rubinsztein, D.C., 2005. Doxycycline attenuates and delays toxicity of the oculopharyngeal muscular dystrophy mutation in transgenic mice. Nat. Med. 11, 672–677. https://doi.org/10.1038/nm1242.
de Bruin, R.G., Shiue, L., Prins, J., de Boer, H.C., Singh, A., Fagg, W.S., van Gils, J.M., Duijs, J.M.G.J., Katzman, S., Kraaijeveld, A.O., Böhringer, S., Leung, W.Y., Kielbasa, S.M., Donahue, J.P., van der Zande, P.H.J., Sijbom, R., van Alem, C.M.A., Bot, I., van Kooten, C., Jukema, J.W., Van Esch, H., Rabelink, T.J., Kazan, H., Biessen, E.A.L., Ares, M., van Zonneveld, A.J., van der Veer, E.P., 2016. Quaking promotes monocyte differentiation into pro-atherogenic macrophages by controlling pre-mRNA splicing and gene expression. Nat. Commun. 7, 10846. https://doi.org/10.1038/ncomms10846.
de Haro, M., Al-Ramahi, I., De Gouyon, B., Ukani, L., Rosa, A., Faustino, N.A., Ashizawa, T., Cooper, T.A., Botas, J., 2006. MBNL1 and CUGBP1 modify expanded CUG-induced toxicity in a Drosophila model of myotonic dystrophy type 1. Hum. Mol. Genet. 15, 2138–2145. https://doi.org/10.1093/hmg/ddl137.
de Haro, M., Al-Ramahi, I., Jones, K.R., Holth, J.K., Timchenko, L.T., Botas, J., 2013. Smaug/SAMD4A restores translational activity of CUGBP1 and suppresses CUG-induced myopathy. PLoS Genet. 9, e1003445 doi:10.1371/journal.pgen.1003445.
de Joussineau, C., Bataillé, L., Jagla, T., Jagla, K., 2012. Diversification of muscle types in Drosophila: upstream and downstream of identity genes. Curr. Top. Dev. Biol. 98, 277–301. https://doi.org/10.1016/B978-0-12-386499-4.00011-2.
DeJesus-Hernandez, M., Mackenzie, I.R., Boeve, B.F., Boxer, A.L., Baker, M., Rutherford, N.J., Nicholson, A.M., Finch, N.A., Flynn, H., Adamson, J., Kouri, N., Wojtas, A., Sengdy, P., Hsiung, G.-Y.R., Karydas, A., Seeley, W.W., Josephs, K.A., Coppola, G., Geschwind, D.H., Wszolek, Z.K., Feldman, H., Knopman, D.S., Petersen, R.C., Miller, B.L., Dickson, D.W., Boylan, K.B., Graff-Radford, N.R., Rademakers, R., 2011. Expanded GGGGCC hexanucleotide repeat in noncoding region of C9ORF72 causes chromosome 9p-linked FTD and ALS. Neuron 72, 245–256. https://doi.org/10.1016/j.neuron.2011.09.011.
Delatte, B., Wang, F., Ngoc, L.V., Collignon, E., Bonvin, E., Deplus, R., Calonne, E., Hassabi, B., Putmans, P., Awe, S., Wetzel, C., Kreher, J., Soin, R., Creppe, C., Limbach, P.A., Gueydan, C., Kruys, V., Brehm, A., Minakhina, S., Defrance, M., Steward, R., Fuks, F., 2016. RNA biochemistry. Transcriptome-wide distribution and function of RNA hydroxymethylcytosine. Science 351, 282–285 doi:10.1126/science.aac5253.
Dennehey, B.K., Leinwand, L.A., Krauter, K.S., 2006. Diversity in transcriptional start site selection and alternative splicing affects the 5'-UTR of mouse striated muscle myosin transcripts. J. Muscle Res. Cell. Motil. 27, 559–575. https://doi.org/10.1007/s10974-006-9071-8.
Depreux, F.F., Puckelwartz, M.J., Augustynowicz, A., Wolfgeher, D., Labno, C.M., Pierre-Louis, D., Cicka, D., Kron, S.J., Holaska, J., McNally, E.M., 2015. Disruption of the lamin A and matrin-3 interaction by myopathic LMNA mutations. Hum. Mol. Genet. 24, 4284–4295. https://doi.org/10.1093/hmg/ddv160.
Dhaenens, C.M., Tran, H., Frandemiche, M.L., Carpentier, C., Schraen-Maschke, S., Sistiaga, A., Goicoechea, M., Eddarkaoui, S., Van Brussels, E., Obriot, H., Labudeck, A., Gevaert, M.H., Fernandez-Gomez, F., Charlet-Berguerand, N., Deramecourt, V., Maurage, C.A., Buée, L., de Munain, A.L., Sablonnière, B., Caillet-Boudin, M.L., Sergeant, N., 2011. Mis-splicing of Tau exon 10 in myotonic dystrophy type 1 is reproduced by overexpression of CELF2 but not by MBNL1 silencing. BBA Mol. Basis Dis. 1812, 732–742. https://doi.org/10.1016/j.bbadis.2011.03.010.
Dietzl, G., Chen, D., Schnorrer, F., Su, K.-C., Barinova, Y., Fellner, M., Gasser, B., Kinsey, K., Oppel, S., Scheiblauer, S., Couto, A., Marra, V., Keleman, K., Dickson, B.J., 2007. A genome-wide transgenic RNAi library for conditional gene inactivation in Drosophila. Nature 448, 151–156. https://doi.org/10.1038/nature05954.
Diogo, R., Kelly, R.G., Christiaen, L., Levine, M., Ziermann, J.M., Molnar, J.L., Noden, D.M., Tzahor, E., 2015. A new heart for a new head in vertebrate cardiopharyngeal evolution. Nature 520, 466–473. https://doi.org/10.1038/nature14435.
Dong, C., Yang, X.-Z., Zhang, C.-Y., Liu, Y.-Y., Zhou, R.-B., Cheng, Q.-D., Yan, E.-K., Yin, D.-C., 2017. Myocyte enhancer factor 2C and its directly-interacting proteins: a review. Prog. Biophys. Mol. Biol. 126, 22–30. https://doi.org/10.1016/j.pbiomolbio.2017.02.002.
Draper, I., Tabaka, M.E., Jackson, F.R., Salomon, R.N., Kopin, A.S., 2009. The evolutionarily conserved RNA binding protein SMOOTH is essential for maintaining normal muscle function. Fly (Austin) 3, 235–246.
Du, H., Cline, M.S., Osborne, R.J., Tuttle, D.L., Clark, T.A., Donohue, J.P., Hall, M.P., Shiue, L., Swanson, M.S., Thornton, C.A., Ares, M., 2010. Aberrant alternative splicing and extracellular matrix gene expression in mouse models of myotonic dystrophy. Nat. Struct. Mol. Biol. 17, 187–193. https://doi.org/10.1038/nsmb.1720.
Dubé, M., Huot, M.E., Khandjian, E.W., 2000. Muscle specific fragile X related protein 1 isoforms are sequestered in the nucleus of undifferentiated myoblast. BMC Genet. 1, 4 doi:10.1186/1471-2156-1-4.
Dujardin, G., Buratti, E., Charlet-Berguerand, N., Martins de Araujo, M., Mbopda, A., Le Jossic-Corcos, C., Pagani, F., Ferec, C., Corcos, L., 2010. CELF proteins regulate CFTR pre-mRNA splicing: essential role of the divergent domain of ETR-3. Nucleic Acids Res. 38, 7273–7285. https://doi.org/10.1093/nar/gkq573.
Eisen, A., Kuwabara, S., 2012. The split hand syndrome in amyotrophic lateral sclerosis. J. Neurol. Neurosurg. Psychiatry 83, 399–403 doi:10.1136/jnnp-2011-301456.
Emery, A.E.H., 2002. The muscular dystrophies. Lancet 359, 687–695. https://doi.org/10.1016/S0140-6736(02)07815-7.
Engels, B., van' t Padje, S., Blonden, L., Severijnen, L.-A., Oostra, B.A., Willemsen, R., 2004. Characterization of Fxr1 in Danio rerio; a simple vertebrate model to study costamere development. J. Exp. Biol. 207, 3329–3338 doi:10.1242/jeb.01146.
Espinoza-Lewis, R.A., Yang, Q., Liu, J., Huang, Z.-P., Hu, X., Chen, D., Wang, D.-Z., 2017. Poly (C)-binding protein 1 (Pcbp1) regulates skeletal muscle differentiation by modulating microRNA processing in myoblasts. J. Biol. Chem. 292, 9540–9550. https://doi.org/10.1074/jbc.M116.773671.
Estrella, N.L., Naya, F.J., 2014. Transcriptional networks regulating the costamere, sarcomere, and other cytoskeletal structures in striated muscle. Cell. Mol. Life Sci. 71, 1641–1656. https://doi.org/10.1007/s00018-013-1512-0.
Fagg, W.S., Liu, N., Fair, J.H., Shiue, L., Katzman, S., Donohue, J.P., Ares, M., 2017. Autogenous cross-regulation of quaking mRNA processing and translation balances quaking functions in splicing and translation. Genes Dev. 31, 1894–1909 doi:10.1101/gad.302059.117.
Falkenthal, S., Graham, M., Wilkinson, J., 1987. The indirect flight muscle of Drosophila accumulates a unique myosin alkali light chain isoform. Dev. Biol. 121, 263–272.
Fardaei, M., Rogers, M.T., Thorpe, H.M., Larkin, K., Hamshere, M.G., Harper, P.S., Brook, J.D., 2002. Three proteins, MBNL, MBLL and MBXL, co-localize in vivo with nuclear foci of expanded-repeat transcripts in DM1 and DM2 cells. Hum. Mol. Genet. 11, 805–814.
Faustino, N.A., Cooper, T.A., 2003. Pre-mRNA splicing and human disease. Genes Dev. 17, 419–437 doi:10.1101/gad.1048803.
Feng, Y., Valley, M.T., Lazar, J., Yang, A.L., Bronson, R.T., Firestein, S., Coetzee, W.A., Manley, J.L., 2009. SRp38 regulates alternative splicing and is required for Ca(2+) handling in the embryonic heart. Dev. Cell 16, 528–538. https://doi.org/10.1016/j.devcel.2009.02.009.
Figeac, N., Serralbo, O., Marcelle, C., Zammit, P.S., 2014. ErbB3 binding protein-1 (Ebp1) controls proliferation and myogenic differentiation of muscle stem cells. Dev Biol 386, 135–151. https://doi.org/10.1016/j.ydbio.2013.11.017.
Figueroa, A., Cuadrado, A., Fan, J., Atasoy, U., Muscat, G.E., Muñoz-Canoves, P., Gorospe, M., Muñoz, A., 2003. Role of HuR in skeletal myogenesis through coordinate regulation of muscle differentiation genes. Mol. Cell. Biol. 23, 4991–5004 doi:10.1128/MCB.23.14.4991-5004.2003.
Fleming, V.A., Geng, C., Ladd, A.N., Lou, H., 2012. Alternative splicing of the

neurofibromatosis type 1 pre-mRNA is regulated by the muscleblind-like proteins and the CUG-BP and ELAV-like factors. BMC Mol. Biol. 13, 35 doi:10.1186/1471-2199-13-35.
Font, J., Mackay, J.P., 2010. Beyond DNA: zinc finger domains as RNA-binding modules. Methods Mol. Biol. 649, 479–491. https://doi.org/10.1007/978-1-60761-753-2_29.
Frese, K.S., Meder, B., Keller, A., Just, S., Haas, J., Vogel, B., Fischer, S., Backes, C., Matzas, M., Köhler, D., Benes, V., Katus, H.A., Rottbauer, W., 2015. RNA splicing regulated by RBFOX1 is essential for cardiac function in zebrafish. J. Cell. Sci. 128, 3030–3040 doi:10.1242/jcs.166850.
Fujita, R., Zismanov, V., Jacob, J.-M., Jamet, S., Asiev, K., Crist, C., 2017. Fragile X mental retardation protein regulates skeletal muscle stem cell activity by regulating the stability of Myf5 mRNA. Skelet. Muscle 7, 18 doi:10.1186/s13395-017-0136-8.
Fukushige, T., Brodigan, T.M., Schriefer, L.A., Waterston, R.H., Krause, M., 2006. Defining the transcriptional redundancy of early bodywall muscle development in C. elegans: evidence for a unified theory of animal muscle development. Genes Dev. 20, 3395–3406 doi:10.1101/gad.1481706.
Fyrberg, E., Fyrberg, C.C., Beall, C., Saville, D.L., 1990. Drosophila melanogaster troponin-T mutations engender three distinct syndromes of myofibrillar abnormalities. J. Mol. Biol. 216, 657–675. https://doi.org/10.1016/0022-2836(90)90390-8.
Gallagher, T.L., Arribere, J.A., Geurts, P.A., Exner, C.R.T., McDonald, K.L., Dill, K.K., Marr, H.L., Adkar, S.S., Garnett, A.T., Amacher, S.L., Conboy, J.G., 2011. Rbfox-regulated alternative splicing is critical for zebrafish cardiac and skeletal muscle functions. Dev. Biol. 359, 251–261. https://doi.org/10.1016/j.ydbio.2011.08.025.
Gan, Z., Powell, F.L., Zambon, A.C., Buchholz, K.S., Fu, Z., Ocorr, K., Bodmer, R., Moya, E.A., Stowe, J.C., Haddad, G.G., McCulloch, A.D., 2017. Transcriptomic analysis identifies a role of PI3K-Akt signalling in the responses of skeletal muscle to acute hypoxia in vivo. J. Physiol. 595, 5797–5813 doi:10.1113/JP274556.
Gao, C., Ren, S., Lee, J.-H., Qiu, J., Chapski, D.J., Rau, C.D., Zhou, Y., Abdellatif, M., Nakano, A., Vondriska, T.M., Xiao, X., Fu, X.-D., Chen, J.-N., Wang, Y., 2016. RBFox1-mediated RNA splicing regulates cardiac hypertrophy and heart failure. J. Clin. Invest. 126, 195–206 doi:10.1172/JCI84015.
Garcia, S.M.D.A., Tabach, Y., Lourenço, G.F., Armakola, M., Ruvkun, G., 2014. Identification of genes in toxicity pathways of trinucleotide-repeat RNA in C. elegans. Nat. Struct. Mol. Biol. 21, 712–720. https://doi.org/10.1038/nsmb.2858.
Gautel, M., Djinović-Carugo, K., 2016. The sarcomeric cytoskeleton: from molecules to motion. J. Exp. Biol. 219, 135–145 doi:10.1242/jeb.124941.
Gautel, M., Goulding, D., 1996. A molecular map of titin/connectin elasticity reveals two different mechanisms acting in series. FEBS Lett. 385, 11–14.
Gavrilina, T.O., McGovern, V.L., Workman, E., Crawford, T.O., Gogliotti, R.G., DiDonato, C.J., Monani, U.R., Morris, G.E., Burghes, A.H.M., 2008. Neuronal SMN expression corrects spinal muscular atrophy in severe SMA mice while muscle-specific SMN expression has no phenotypic effect. Hum. Mol. Genet. 17, 1063–1075. https://doi.org/10.1093/hmg/ddm379.
Gazzara, M.R., Mallory, M.J., Roytenberg, R., Lindberg, J.P., Jha, A., Lynch, K.W., Barash, Y., 2017. Ancient antagonism between CELF and RBFOX families tunes mRNA splicing outcomes. Genome Res. 27, 1360–1370 doi:10.1101/gr.220517.117.
Gehman, L.T., Stoilov, P., Maguire, J., Damianov, A., Lin, C.-H., Shiue, L., Ares, M., Mody, I., Black, D.L., 2011. The splicing regulator Rbfox1 (A2BP1) controls neuronal excitation in the mammalian brain. Nat. Genet. 43, 706–711. https://doi.org/10.1038/ng.841.
Gehman, L.T., Meera, P., Stoilov, P., Shiue, L., O'Brien, J.E., Meisler, M.H., Ares, M., Otis, T.S., Black, D.L., 2012. The splicing regulator Rbfox2 is required for both cerebellar development and mature motor function. Genes Dev. 26, 445–460 doi:10.1101/gad.182477.111.
Gerber, W.V., Yatskievych, T.A., Antin, P.B., Correia, K.M., Conlon, R.A., Krieg, P.A., 1999. The RNA-binding protein gene, hermes, is expressed at high levels in the developing heart. Mech. Dev. 80, 77–86.
Gerber, W.V., Vokes, S.A., Zearfoss, N.R., Krieg, P.A., 2002. A role for the RNA-binding protein, hermes, in the regulation of heart development. Dev. Biol. 247, 116–126. https://doi.org/10.1006/dbio.2002.0678.
Gerstberger, S., Hafner, M., Ascano, M., Tuschl, T., 2014. Evolutionary conservation and expression of human RNA-binding proteins and their role in human genetic disease. Adv. Exp. Med. Biol. 825, 1–55. https://doi.org/10.1007/978-1-4939-1221-6_1.
Gidaro, T., Servais, L., 2018. Nusinersen treatment of spinal muscular atrophy: current knowledge and existing gaps. Dev. Med. Child Neurol. 33, 831 doi:10.1111/dmcn.14027.
Gieseler, K., Qadota, H., Benian, G.M., 2017. Development, structure, and maintenance of C. Elegans body wall muscle. WormBook 2017, 1–59 doi:10.1895/wormbook.1.81.2.
Giudice, J., Xia, Z., Li, W., Cooper, T.A., 2016. Neonatal Cardiac Dysfunction And Transcriptome Changes Caused By The Absence of Celf1, vol. 6. Nature Publishing Group, pp. 35550. https://doi.org/10.1038/srep35550.
Glisovic, T., Bachorik, J.L., Yong, J., Dreyfuss, G., 2008. RNA-binding proteins and post-transcriptional gene regulation. FEBS Lett. 582, 1977–1986. https://doi.org/10.1016/j.febslet.2008.03.004.
Godt, R.E., Fogaça, R.T., Silva, I.K., Nosek, T.M., 1993. Contraction of developing avian heart muscle. Comp. Biochem. Physiol. Comp. Physiol. 105, 213–218.
Goers, E.S., Voelker, R.B., Gates, D.P., Berglund, J.A., 2008. RNA Binding Specificity of DrosophilaMuscleblind †. Biochemistry 47, 7284–7294. https://doi.org/10.1021/bi702252d.
Goers, E.S., Purcell, J., Voelker, R.B., Gates, D.P., Berglund, J.A., 2010. MBNL1 binds GC motifs embedded in pyrimidines to regulate alternative splicing. Nucleic Acids Res. 38, 2467–2484. https://doi.org/10.1093/nar/gkp1209.
Goo, Y.-H., Cooper, T.A., 2009. CUGBP2 directly interacts with U2 17S snRNP components and promotes U2 snRNA binding to cardiac troponin T pre-mRNA. Nucleic Acids Res. 37, 4275–4286. https://doi.org/10.1093/nar/gkp346.
Good, P.J., 2000. A family of human RNA-binding proteins related to the Drosophila bruno translational regulator. J. Biol. Chem. 275, 28583–28592. https://doi.org/10.1074/jbc.M003083200.
Goodwin, M., Mohan, A., Batra, R., Lee, K.-Y., Charizanis, K., Fernández Gómez, F.J., Eddarkaoui, S., Sergeant, N., Buée, L., Kimura, T., Clark, H.B., Dalton, J., Takamura, K., Weyn-Vanhentenryck, S.M., Zhang, C., Reid, T., Ranum, L.P.W., Day, J.W., Swanson, M.S., 2015. MBNL sequestration by toxic RNAs and RNA misprocessing in the myotonic dystrophy brain. Cell Rep. 12, 1159–1168. https://doi.org/10.1016/j.celrep.2015.07.029.
Gramolini, A.O., Bélanger, G., Thompson, J.M., Chakkalakal, J.V., Jasmin, B.J., 2001. Increased expression of utrophin in a slow vs. A fast muscle involves posttranscriptional events. Am. J. Physiol. Cell Physiol. 281 C1300–9. doi:10.1152/ajpcell.2001.281.4.C1300.
Granados-Riveron, J.T., Ghosh, T.K., Pope, M., Bu'Lock, F., Thornborough, C., Eason, J., Kirk, E.P., Fatkin, D., Feneley, M.P., Harvey, R.P., Armour, J.A.L., David Brook, J., 2010. Alpha-cardiac myosin heavy chain (MYH6) mutations affecting myofibril formation are associated with congenital heart defects. Hum. Mol. Genet. 19, 4007–4016. https://doi.org/10.1093/hmg/ddq315.
Graveley, B.R., Brooks, A.N., Carlson, J.W., Duff, M.O., Landolin, J.M., Yang, L., Artieri, C.G., van Baren, M.J., Boley, N., Booth, B.W., Brown, J.B., Cherbas, L., Davis, C.A., Dobin, A., Li, R., Lin, W., Malone, J.H., Mattiuzzo, N.R., Miller, D., Sturgill, D., Tuch, B.B., Zaleski, C., Zhang, D., Blanchette, M., Dudoit, S., Eads, B., Green, R.E., Hammonds, A., Jiang, L., Kapranov, P., Langton, L., Perrimon, N., Sandler, J.E., Wan, K.H., Willingham, A., Zhang, Y., Zou, Y., Andrews, J., Bickel, P.J., Brenner, S.E., Brent, M.R., Cherbas, P., Gingeras, T.R., Hoskins, R.A., Kaufman, T.C., Oliver, B., Celniker, S.E., 2011. The developmental transcriptome of Drosophila melanogaster. Nature 471, 473–479. https://doi.org/10.1038/nature09715.
Grifone, R., Xie, X., Bourgeois, A., Saquet, A., Duprez, D., Shi, D.-L., 2014. The RNA-binding protein Rbm24 is transiently expressed in myoblasts and is required for myogenic differentiation during vertebrate development. Mech. Dev. 134, 1–15. https://doi.org/10.1016/j.mod.2014.08.003.
Gu, L., Wang, H., Wang, J., Guo, Y., Tang, Y., Mao, Y., Chen, L., Lou, H., Ji, G., 2017. Reconstitution of HuR-Inhibited CUGBP1 expression protects cardiomyocytes from acute myocardial infarction-induced injury. Antioxid. Redox Signal. 27, 1013–1026. https://doi.org/10.1089/ars.2016.6880.
Guo, Wei, Bharmal, S.J., Esbona, K., Greaser, M.L., 2010. Titin diversity–alternative splicing gone wild. J. Biomed. Biotechnol. 2010, 753675–753678 doi:10.1155/2010/753675.
Guo, Wei, Schafer, S., Greaser, M.L., Radke, M.H., Liss, M., Govindarajan, T., Maatz, H., Schulz, H., Li, S., Parrish, A.M., Dauksaite, V., Vakeel, P., Klaassen, S., Gerull, B., Thierfelder, L., Regitz-Zagrosek, V., Hacker, T.A., Saupe, K.W., Dec, G.W., Ellinor, P.T., MacRae, C.A., Spallek, B., Fischer, R., Perrot, A., Özcelik, C., Saar, K., Hubner, N., Gotthardt, M., 2012. RBM20, a gene for hereditary cardiomyopathy, regulates titin splicing. Nat. Med. 18, 766–773. https://doi.org/10.1038/nm.2693.
Guo, Wangang, Jiang, T., Lian, C., Wang, H., Zheng, Q., Ma, H., 2014. QKI deficiency promotes FoxO1 mediated nitrosative stress and endoplasmic reticulum stress contributing to increased vulnerability to ischemic injury in diabetic heart. J. Mol. Cell. Cardiol. 75, 131–140. https://doi.org/10.1016/j.yjmcc.2014.07.010.
Hall, M.P., Nagel, R.J., Fagg, W.S., Shiue, L., Cline, M.S., Perriman, R.J., Donohue, J.P., Ares, M., 2013. Quaking and PTB control overlapping splicing regulatory networks during muscle cell differentiation. RNA 19, 627–638 doi:10.1261/rna.038422.113.
Halstead, J.M., Lin, Y.Q., Durraine, L., Hamilton, R.S., Ball, G., Neely, G.G., Bellen, H.J., Davis, I., 2014. Syncrip/hnRNP Q influences synaptic transmission and regulates BMP signaling at the Drosophila neuromuscular synapse. Biol. Open 3, 839–849 doi:10.1242/bio.20149027.
Han, J., 2005. Identification of CELF splicing activation and repression domains in vivo. Nucleic Acids Res. 33, 2769–2780. https://doi.org/10.1093/nar/gki561.
Hao, M., Akrami, K., Wei, K., De Diego, C., Che, N., Ku, J.-H., Tidball, J., Graves, M.C., Shieh, P.B., Chen, F., 2008. Muscleblind-like 2 (Mbnl2) -deficient mice as a model for myotonic dystrophy. Dev. Dyn. 237, 403–410. https://doi.org/10.1002/dvdy.21428.
Hausburg, M.A., Doles, J.D., Clement, S.L., Cadwallader, A.B., Hall, M.N., Blackshear, P.J., Lykke-Andersen, J., Olwin, B.B., 2015. Post-transcriptional regulation of satellite cell quiescence by TTP-mediated mRNA decay. Elife 4, e03390 doi:10.7554/eLife.03390.
Hentze, M.W., Castello, A., Schwarzl, T., Preiss, T., 2018. A Brave New World of RNA-Binding Proteins, vol. 19. Nature Publishing Group, pp. 327–341. https://doi.org/10.1038/nrm.2017.130.
Ho, T.H., Charlet-B, N., Poulos, M.G., Singh, G., Swanson, M.S., Cooper, T.A., 2004. Muscleblind proteins regulate alternative splicing. EMBO J 23 3103–3112. https://doi.org/10.1038/sj.emboj.7600300.
Homsy, J., Zaidi, S., Shen, Y., Ware, J.S., Samocha, K.E., Karczewski, K.J., DePalma, S.R., McKean, D., Wakimoto, H., Gorham, J., Jin, S.C., Deanfield, J., Giardini, A., Porter, G.A., Kim, R., Bilguvar, K., López-Giráldez, F., Tikhonova, I., Mane, S., Romano-Adesman, A., Qi, H., Vardarajan, B., Ma, L., Daly, M., Roberts, A.E., Russell, M.W., Mital, S., Newburger, J.W., Gaynor, J.W., Breitbart, R.E., Iossifov, I., Ronemus, M., Sanders, S.J., Kaltman, J.R., Seidman, J.G., Brueckner, M., Gelb, B.D., Goldmuntz, E., Lifton, R.P., Seidman, C.E., Chung, W.K., 2015. De novo mutations in congenital heart disease with neurodevelopmental and other congenital anomalies. Science 350, 1262–1266 doi:10.1126/science.aac9396.
Hu, Y., Comjean, A., Perkins, L.A., Perrimon, N., Mohr, S.E., 2015. GLAD: an online database of gene list annotation for Drosophila. J. Genomics 3, 75–81 doi:10.7150/jgen.12863.
Imbriano, C., Molinari, S., 2018. Alternative splicing of transcription factors genes in muscle physiology and pathology. Genes 9, 107 doi:10.3390/genes9020107.
Iwasaki, Y., Sugimoto, H., Ikeda, K., Takamiya, K., Shiojima, T., Kinoshita, M., 1991. Muscle morphometry in amyotrophic lateral sclerosis. Int. J. Neurosci. 58, 165–170.
Jangi, M., Fleet, C., Cullen, P., Gupta, S.V., Mekhoubad, S., Chiao, E., Allaire, N., Bennett, C.F., Rigo, F., Krainer, A.R., Hurt, J.A., Carulli, J.P., Staropoli, J.F., 2017. SMN deficiency in severe models of spinal muscular atrophy causes widespread intron retention and DNA damage. Proc. Natl. Acad. Sci. U.S.A. 114, E2347–E2356. https://doi.org/10.1073/pnas.1613181114.
Jin, Y., Suzuki, H., Maegawa, S., Endo, H., Sugano, S., Hashimoto, K., Yasuda, K., Inoue, K., 2003. A vertebrate RNA-binding protein Fox-1 regulates tissue-specific splicing via the pentanucleotide GCAUG. EMBO J. 22, 905–912. https://doi.org/10.1093/emboj/cdg089.
Johnson, J.O., Mandrioli, J., Benatar, M., Abramzon, Y., Van Deerlin, V.M., Trojanowski, J.Q., Gibbs, J.R., Brunetti, M., Gronka, S., Wuu, J., Ding, J., McCluskey, L., Martinez-Lage, M., Falcone, D., Hernandez, D.G., Arepalli, S., Chong, S., Schymick, J.C., Rothstein, J., Landi, F., Wang, Y.-D., Calvo, A., Mora, G., Sabatelli, M., Monsurrò, M.R., Battistini, S., Salvi, F., Spataro, R., Sola, P., Borghero, G., ITALSGEN Consortium, Galassi, G., Scholz, S.W., Taylor, J.P., Restagno, G., Chiò, A., Traynor, B.J., 2010. Exome sequencing reveals VCP mutations as a cause of familial ALS. Neuron 68, 857–864. https://doi.org/10.1016/j.neuron.2010.11.036.
Johnson, A.N., Mokalled, M.H., Valera, J.M., Poss, K.D., Olson, E.N., 2013. Post-transcriptional regulation of myotube elongation and myogenesis by Hoi Polloi. Development 140, 3645–3656 doi:10.1242/dev.095596.
Johnson, J.O., Pioro, E.P., Boehringer, A., Chia, R., Feit, H., Renton, A.E., Pliner, H.A., Abramzon, Y., Marangi, G., Winborn, B.J., Gibbs, J.R., Nalls, M.A., Morgan, S., Shoai, M., Hardy, J., Pittman, A., Orrell, R.W., Malaspina, A., Sidle, K.C., Fratta, P., Harms, M.B., Baloh, R.H., Pestronk, A., Weihl, C.C., Rogaeva, E., Zinman, L., Drory, V.E., Borghero, G.,

Mora, G., Calvo, A., Rothstein, J.D., ITALSGEN, Drepper C., Sendtner, M., Singleton, A.B., Taylor, J.P., Cookson, M.R., Restagno, G., Sabatelli, M., Bowser, R., Chiò, A., Traynor, B.J., 2014. Mutations in the Matrin 3 gene cause familial amyotrophic lateral sclerosis. Nat. Neurosci. 17, 664–666. https://doi.org/10.1038/nn.3688.

Jones, T.I., Parilla, M., Jones, P.L., 2016. Transgenic Drosophila for Investigating DUX4 and FRG1, Two Genes Associated with Facioscapulohumeral Muscular Dystrophy (FSHD). PLoS One 11, e0150938 doi:10.1371/journal.pone.0150938.

Kagawa, H., Sugimoto, K., Matsumoto, H., Inoue, T., Imadzu, H., Takuwa, K., Sakube, Y., 1995. Genome structure, mapping and expression of the tropomyosin gene tmy-1 of Caenorhabditis elegans. J. Mol. Biol. 251, 603–613. https://doi.org/10.1006/jmbi.1995.0459.

Kalsotra, A., Cooper, T.A., 2011. Functional consequences of developmentally regulated alternative splicing. Nat. Rev. Genet. 12, 715–729. https://doi.org/10.1038/nrg3052.

Kalsotra, A., Xiao, X., Ward, A.J., Castle, J.C., Johnson, J.M., Burge, C.B., Cooper, T.A., 2008. A postnatal switch of CELF and MBNL proteins reprograms alternative splicing in the developing heart. Proc. Natl. Acad. Sci. U. S. A. 105, 20333–20338. https://doi.org/10.1073/pnas.0809045105.

Kanadia, R.N., Johnstone, K.A., Mankodi, A., Lungu, C., Thornton, C.A., Esson, D., Timmers, A.M., Hauswirth, W.W., Swanson, M.S., 2003a. A muscleblind knockout model for myotonic dystrophy. Science 302, 1978–1980. https://doi.org/10.1126/science.1088583.

Kanadia, R.N., Urbinati, C.R., Crusselle, V.J., Luo, D., Lee, Y.-J., Harrison, J.K., Oh, S.P., Swanson, M.S., 2003b. Developmental expression of mouse muscleblind genes Mbnl1, Mbnl2 and Mbnl3. Gene Expr. Patterns 3, 459–462. https://doi.org/10.1016/S1567-133X(03)00064-4.

Kania, A., Salzberg, A., Bhat, M., D'Evelyn, D., He, Y., Kiss, I., Bellen, H.J., 1995. P-element mutations affecting embryonic peripheral nervous system development in Drosophila melanogaster. Genetics 139, 1663–1678.

Kaplan, N., Razy-Krajka, F., Christiaen, L., 2015. Regulation and evolution of cardiopharyngeal cell identity and behavior: insights from simple chordates. Curr. Opin. Genet. Dev. 32, 119–128. https://doi.org/10.1016/j.gde.2015.02.008.

Keegan, L.P., Brindle, J., Gallo, A., Leroy, A., Reenan, R.A., O'Connell, M.A., 2005. Tuning of RNA editing by ADAR is required in Drosophila. EMBO J. 24, 2183–2193. https://doi.org/10.1038/sj.emboj.7600691.

Kim, K.K., Kim, Y.C., Adelstein, R.S., Kawamoto, S., 2011. Fox-3 and PSF interact to activate neural cell-specific alternative splicing. Nucleic Acids Res. 39, 3064–3078. https://doi.org/10.1093/nar/gkq1221.

Kim, H.J., Kim, N.C., Wang, Y.-D., Scarborough, E.A., Moore, J., Diaz, Z., MacLea, K.S., Freibaum, B., Li, S., Molliex, A., Kanagaraj, A.P., Carter, R., Boylan, K.B., Wojtas, A.M., Rademakers, R., Pinkus, J.L., Greenberg, S.A., Trojanowski, J.Q., Traynor, B.J., Smith, B.N., Topp, S., Gkazi, A.-S., Miller, J., Shaw, C.E., Kottlors, M., Kirschner, J., Pestronk, A., Li, Y.R., Ford, A.F., Gitler, A.D., Benatar, M., King, O.D., Kimonis, V.E., Ross, E.D., Weihl, C.C., Shorter, J., Taylor, J.P., 2013. Mutations in prion-like domains in hnRNPA2B1 and hnRNPA1 cause multisystem proteinopathy and ALS. Nature 495, 467–473. https://doi.org/10.1038/nature11922.

Kim, K.K., Yang, Y., Zhu, J., Adelstein, R.S., Kawamoto, S., 2014. Rbfox3 controls the biogenesis of a subset of microRNAs. Nat. Struct. Mol. Biol. 21, 901–910. https://doi.org/10.1038/nsmb.2892.

Kimura, R., Nishioka, T., Soemantri, A., Ishida, T., 2005. Allele-specific transcript quantification detects haplotypic variation in the levels of the SDF-1 transcripts. Hum. Mol. Genet. 14, 1579–1585. https://doi.org/10.1093/hmg/ddi166.

Kiri, A., Goldspink, G., 2002. RNA-protein interactions of the 3' untranslated regions of myosin heavy chain transcripts. J. Muscle Res. Cell. Motil. 23, 119–129.

Klein, P., Oloko, M., Roth, F., Montel, V., Malerba, A., Jarmin, S., Gidaro, T., Popplewell, L., Perie, S., Lacau St Guily, J., la Grange, de, P., Antoniou, M.N., Dickson, G., Butler-Browne, G., Bastide, B., Mouly, V., Trollet, C., 2016. Nuclear poly(A)-binding protein aggregates misplace a pre-mRNA outside of SC35 speckle causing its abnormal splicing. Nucleic Acids Res. 44, 10929–10945. https://doi.org/10.1093/nar/gkw703.

Kleinridders, A., Pogoda, H.-M., Irlenbusch, S., Smyth, N., Koncz, C., Hammerschmidt, M., Brüning, J.C., 2009. PLRG1 is an essential regulator of cell proliferation and apoptosis during vertebrate development and tissue homeostasis. Mol. Cell. Biol. 29, 3173–3185. https://doi.org/10.1128/MCB.01807-08.

Klinck, R., Fourrier, A., Thibault, P., Toutant, J., Durand, M., Lapointe, E., Caillet-Boudin, M.-L., Sergeant, N., Gourdon, G., Meola, G., Furling, D., Puymirat, J., Chabot, B., 2014. RBFOX1 cooperates with MBNL1 to control splicing in muscle, including events altered in myotonic dystrophy type 1. PLoS One 9, e107324 10.1371/journal.pone.0107324.

Klinkerfuss, G.H., 1967. An electron microscopic study of myotonic dystrophy. Arch. Neurol. 16, 181–193.

Korey, C.A., Wilkie, G., Davis, I., Van Vactor, D., 2001. Small bristles is required for the morphogenesis of multiple tissues during Drosophila development. Genetics 159, 1659–1670.

Krause, M., Liu, J., 2012. Somatic muscle specification during embryonic and post-embryonic development in the nematode C. elegans. Wiley Interdiscip. Rev. Dev. Biol. 1, 203–214. https://doi.org/10.1002/wdev.15.

Kronert, W.A., Melkani, G.C., Melkani, A., Bernstein, S.I., 2012. Alternative relay and converter domains tune native muscle myosin isoform function in Drosophila. J. Mol. Biol. 416, 543–557. https://doi.org/10.1016/j.jmb.2011.12.044.

Kuleesha, Y., Puah, W.C., Wasser, M., 2016. Live imaging of muscle histolysis in Drosophila metamorphosis. BMC Dev. Biol. 16, 12 doi:10.1186/s12861-016-0113-1.

Kuroyanagi, H., 2009. Fox-1 family of RNA-binding proteins. Cell. Mol. Life Sci. 66, 3895–3907. https://doi.org/10.1007/s00018-009-0120-5.

Kuroyanagi, H., Kobayashi, T., Mitani, S., Hagiwara, M., 2006. Transgenic alternative-splicing reporters reveal tissue-specific expression profiles and regulation mechanisms in vivo. Nat Meth 3, 909–915. https://doi.org/10.1038/nmeth944.

Kuroyanagi, H., Ohno, G., Mitani, S., Hagiwara, M., 2007. The Fox-1 family and SUP-12 coordinately regulate tissue-specific alternative splicing in vivo. Mol. Cell. Biol. 27, 8612–8621 doi:10.1128/MCB.01508-07.

Kuyumcu-Martinez, N.M., Wang, G.-S., Cooper, T.A., 2007. Increased steady-state levels of CUGBP1 in myotonic dystrophy 1 are due to PKC-mediated hyperphosphorylation. Mol. Cell 28, 68–78. https://doi.org/10.1016/j.molcel.2007.07.027.

Kwiatkowski, T.J., Bosco, D.A., Leclerc, A.L., Tamrazian, E., Vanderburg, C.R., Russ, C., Davis, A., Gilchrist, J., Kasarskis, E.J., Munsat, T., Valdmanis, P., Rouleau, G.A., Hosler, B.A., Cortelli, P., de Jong, P.J., Yoshinaga, Y., Haines, J.L., Pericak-Vance, M.A., Yan, J., Ticozzi, N., Siddique, T., McKenna-Yasek, D., Sapp, P.C., Horvitz, H.R., Landers, J.E., Brown, R.H., 2009. Mutations in the FUS/TLS gene on chromosome 16 cause familial amyotrophic lateral sclerosis. Science 323, 1205–1208 doi:10.1126/science.1166066.

Ladd, A.N., Charlet, N., Cooper, T.A., 2001. The CELF family of RNA binding proteins is implicated in cell-specific and developmentally regulated alternative splicing. Mol. Cell. Biol. 21, 1285–1296 doi:10.1128/MCB.21.4.1285-1296.2001.

Ladd, A.N., Nguyen, N.H., Malhotra, K., Cooper, T.A., 2004. CELF6, a Member of the CELF Family of RNA-binding proteins, regulates muscle-specific splicing enhancer-dependent alternative splicing. J. Biol. Chem. 279, 17756–17764. https://doi.org/10.1074/jbc.M310687200.

Ladd, A.N., Stenberg, M.G., Swanson, M.S., Cooper, T.A., 2005a. Dynamic balance between activation and repression regulates pre-mRNA alternative splicing during heart development. Dev. Dyn. 233, 783–793. https://doi.org/10.1002/dvdy.20382.

Ladd, A.N., Taffet, G., Hartley, C., Kearney, D.L., Cooper, T.A., 2005b. Cardiac tissue-specific repression of CELF activity disrupts alternative splicing and causes cardiomyopathy. Mol. Cell. Biol. 25, 6267–6278 doi:10.1128/MCB.25.14.6267-6278.2005.

Laird, A.S., Mackovski, N., Rinkwitz, S., Becker, T.S., Giacomotto, J., 2016. Tissue-specific models of spinal muscular atrophy confirm a critical role of SMN in motor neurons from embryonic to adult stages. Hum. Mol. Genet. 25, 1728–1738. https://doi.org/10.1093/hmg/ddw044.

Lal, D., Reinthaler, E.M., Altmüller, J., Toliat, M.R., Thiele, H., Nürnberg, P., Lerche, H., Hahn, A., Møller, R.S., Muhle, H., Sander, T., Zimprich, F., Neubauer, B.A., 2013. RBFOX1 and RBFOX3 mutations in rolandic epilepsy. PLoS One 8, e73323 10.1371/journal.-pone.0073323.

Lale, S., Yu, S., Ahmed, A., 2011. Complex congenital heart defects in association with maternal diabetes and partial deletion of the A2BP1 gene. Fetal Pediatr. Pathol. 30, 161–166 doi:10.3109/15513815.2010.547555.

Lambert, N., Robertson, A., Jangi, M., McGeary, S., Sharp, P.A., Burge, C.B., 2014. RNA Bind-n-Seq: quantitative assessment of the sequence and structural binding specificity of RNA binding proteins. Mol. Cell 54, 887–900. https://doi.org/10.1016/j.molcel.2014.04.016.

Lambert, M.J., Cochran, W.O., Wilde, B.M., Olsen, K.G., Cooper, C.D., 2015. Evidence for widespread subfunctionalization of splice forms in vertebrate genomes. Genome Res. 25, 624–632 doi:10.1101/gr.184473.114.

Lanfranco, M., Vassallo, N., Cauchi, R.J., 2017. Spinal muscular atrophy: from defective chaperoning of snRNP assembly to neuromuscular dysfunction. Front. Mol. Biosci. 4, 41 doi:10.3389/fmolb.2017.00041.

Leclère, L., Röttinger, E., 2016. Diversity of Cnidarian Muscles: Function, Anatomy, Development and Regeneration. Front. Cell Dev. Biol. 4, 157 doi:10.3389/fcell.2016.00157.

Lee, K.-S., Squillace, R.M., Wang, E.H., 2007. Expression pattern of muscleblind-like proteins differs in differentiating myoblasts. Biochem. Biophys. Res. Commun. 361, 151–155. https://doi.org/10.1016/j.bbrc.2007.06.165.

Lee, J.E., Lee, J.Y., Wilusz, J., Tian, B., Wilusz, C.J., 2010a. Systematic analysis of cis-elements in unstable mRNAs demonstrates that CUGBP1 is a key regulator of mRNA decay in muscle cells. PLoS One 5, e11201 doi:10.1371/journal.pone.0011201.

Lee, K.-S., Cao, Y., Witwicka, H.E., Tom, S., Tapscott, S.J., Wang, E.H., 2010b. RNA-binding protein Muscleblind-like 3 (MBNL3) disrupts myocyte enhancer factor 2 (Mef2) {beta}-exon splicing. J. Biol. Chem. 285, 33779–33787. https://doi.org/10.1074/jbc.M110.124255.

Lee, S., Shang, Y., Redmond, S.A., Urisman, A., Tang, A.A., Li, K.H., Burlingame, A.L., Pak, R.A., Jovičić, A., Gitler, A.D., Wang, J., Gray, N.S., Seeley, W.W., Siddique, T., Bigio, E.H., Lee, V.M.-Y., Trojanowski, J.Q., Chan, J.R., Huang, E.J., 2016. Activation of HIPK2 promotes ER stress-mediated neurodegeneration in amyotrophic lateral sclerosis. Neuron 91, 41–55. https://doi.org/10.1016/j.neuron.2016.05.021.

Lemke, S.B., Schnorrer, F., 2017. Mechanical forces during muscle development. Mech. Dev. 144, 92–101. https://doi.org/10.1016/j.mod.2016.11.003.

Letunic, I., Bork, P., 2018. 20 years of the SMART protein domain annotation resource. Nucleic Acids Res. 46, D493–D496. https://doi.org/10.1093/nar/gkx922.

Li, Zhizhong, Gilbert, J.A., Zhang, Y., Zhang, M., Qiu, Q., Ramanujan, K., Shavlakadze, T., Eash, J.K., Scaramozza, A., Goddeeris, M.M., Kirsch, D.G., Campbell, K.P., Brack, A.S., Glass, D.J., 2012. An HMGA2-IGF2BP2 axis regulates myoblast proliferation and myogenesis. Dev. Cell 23, 1176–1188. https://doi.org/10.1016/j.devcel.2012.10.019.

Li, Shijun, Guo, W., Dewey, C.N., Greaser, M.L., 2013. Rbm20 regulates titin alternative splicing as a splicing repressor. Nucleic Acids Res. 41, 2659–2672. https://doi.org/10.1093/nar/gks1362.

Li, Songqing, Zhang, P., Freibaum, B.D., Kim, N.C., Kolaitis, R.-M., Molliex, A., Kanagaraj, A.P., Yabe, I., Tanino, M., Tanaka, S., Sasaki, H., Ross, E.D., Taylor, J.P., Kim, H.J., 2016. Genetic interaction of hnRNPA2B1 and DNAJB6 in a Drosophila model of multisystem proteinopathy. Hum. Mol. Genet. 25, 936–950. https://doi.org/10.1093/hmg/ddv627.

Li, Dunhui, Mastaglia, F.L., Fletcher, S., Wilton, S.D., 2018a. Precision medicine through antisense oligonucleotide-mediated exon skipping. Trends Pharmacol. Sci. https://doi.org/10.1016/j.tips.2018.09.001.

Li, Min, Yan, K., Wei, L., Yang, Y., Qian, Q., Xu, W., 2018b. MCPIP1 inhibits coxsackievirus B3 replication by targeting viral RNA and negatively regulates virus-induced inflammation. Med. Microbiol. Immunol. 207, 27–38. https://doi.org/10.1007/s00430-017-0523-0.

Liao, Y., Castello, A., Fischer, B., Leicht, S., Föehr, S., Frese, C.K., Ragan, C., Kurscheid, S., Pagler, E., Yang, H., Krijgsveld, J., Hentze, M.W., Preiss, T., 2016. The cardiomyocyte RNA-Binding proteome: links to intermediary metabolism and heart disease. Cell Rep. 16, 1456–1469. https://doi.org/10.1016/j.celrep.2016.06.084.

Lin, J.-C., Tarn, W.-Y., 2009. RNA-binding motif protein 4 translocates to cytoplasmic granules and suppresses translation via argonaute2 during muscle cell differentiation. J. Biol. Chem. 284, 34658–34665. https://doi.org/10.1074/jbc.M109.032946.

Lin, J.-C., Tarn, W.-Y., 2011. RBM4 down-regulates PTB and antagonizes its activity in muscle cell-specific alternative splicing. J. Cell Biol. 193, 509–520. https://doi.org/10.1083/jcb.201007131.

Lin, B.L., Song, T., Sadayappan, S., 2017. Myofilaments: movers and rulers of the sarcomere. Compr. Physiol. 7, 675–692. https://doi.org/10.1002/cphy.c160026.

Linke, W.A., Rudy, D.E., Centner, T., Gautel, M., Witt, C., Labeit, S., Gregorio, C.C., 1999. I-band titin in cardiac muscle is a three-element molecular spring and is critical for maintaining thin filament structure. J. Cell Biol. 146, 631–644.

Linke, W.A., Kulke, M., Li, H., Fujita-Becker, S., Neagoe, C., Manstein, D.J., Gautel, M., Fernandez, J.M., 2002. PEVK domain of titin: an entropic spring with actin-binding properties. J. Struct. Biol. 137, 194–205. https://doi.org/10.1006/jsbi.2002.4468.

Liquori, C.L., Ikeda, Y., Weatherspoon, M., Ricker, K., Schoser, B.G.H., Dalton, J.C., Day, J.W., Ranum, L.P.W., 2003. Myotonic dystrophy type 2: human founder haplotype and

evolutionary conservation of the repeat tract. Am. J. Hum. Genet. 73, 849–862. https://doi.org/10.1086/378720.
Lissouba, A., Liao, M., Kabashi, E., Drapeau, P., 2018. Transcriptomic analysis of zebrafish TDP-43 transgenic lines. Front. Mol. Neurosci. 11, 463 doi:10.3389/fnmol.2018.00463.
Llamusi, B., Bargiela, A., Fernandez-Costa, J.M., Garcia-Lopez, A., Klima, R., Feiguin, F., Artero, R., 2012. Muscleblind, BSF and TBPH are mislocalized in the muscle sarcomere of a Drosophila myotonic dystrophy model. Dis. Model. Mech. 6, 184–196 doi:10.1242/dmm.009563.
Llorian, M., Gooding, C., Bellora, N., Hallegger, M., Buckroyd, A., Wang, X., Rajgor, D., Kayikci, M., Feltham, J., Ule, J., Eyras, E., Smith, C.W.J., 2016. The alternative splicing program of differentiated smooth muscle cells involves concerted non-productive splicing of post-transcriptional regulators. Nucleic Acids Res. 44, 8933–8950. https://doi.org/10.1093/nar/gkw560.
Lobbardi, R., Lambert, G., Zhao, J., Geisler, R., Kim, H.R., Rosa, F.M., 2011. Fine-tuning of Hh signaling by the RNA-binding protein quaking to control muscle development. Development 138, 1783–1794 doi:10.1242/dev.059121.
Louis, I.V.-S., Dickson, A.M., Bohjanen, P.R., Wilusz, C.J., 2013. CELFish ways to modulate mRNA decay. BBA Gene Regul. Mech. 1829, 695–707. https://doi.org/10.1016/j.bbagrm.2013.01.001.
Lowery, L.A., Rubin, J., Sive, H., 2007. Whitesnake/sfpq is required for cell survival and neuronal development in the zebrafish. Dev. Dyn. 236, 1347–1357. https://doi.org/10.1002/dvdy.21132.
Lu, X., Timchenko, N.A., Timchenko, L.T., 1999. Cardiac elav-type RNA-binding protein (ETR-3) binds to RNA CUG repeats expanded in myotonic dystrophy. Hum. Mol. Genet. 8, 53–60.
Ludatscher, R.M., Kerner, H., Amikam, S., Gellei, B., 1978. Myotonia dystrophica with heart involvement: an electron microscopic study of skeletal, cardiac, and smooth muscle. J. Clin. Pathol. 31, 1057–1064.
Luigetti, M., Monaco, Lo M., Mirabella, M., Primiano, G., Lucchini, M., Monforte, M., Servidei, S., 2015. Oculopharyngeal muscular dystrophy: clinical and neurophysiological features. Clin. Neurophysiol. 126, 2406–2408. https://doi.org/10.1016/j.clinph.2015.03.005.
Lundquist, E.A., Herman, R.K., 1994. The mec-8 gene of Caenorhabditis elegans affects muscle and sensory neuron function and interacts with three other genes: unc-52, smu-1 and smu-2. Genetics 138, 83–101.
Ma, F., Dong, Z., Berberoglu, M.A., 2019. Expression of RNA-binding protein Rbfox1l demarcates a restricted population of dorsal telencephalic neurons within the adult zebrafish brain. Gene Expr. Patterns 31, 32–41. https://doi.org/10.1016/j.gep.2019.01.001.
Machuca-Tzili, L., Thorpe, H., Robinson, T.E., Sewry, C., Brook, J.D., 2006. Flies deficient in Muscleblind protein model features of myotonic dystrophy with altered splice forms of Z-band associated transcripts. Hum. Genet. 120, 487–499. https://doi.org/10.1007/s00439-006-0228-8.
Machuca-Tzili, L.E., Buxton, S., Thorpe, A., Timson, C.M., Wigmore, P., Luther, P.K., Brook, J.D., 2011. Zebrafish deficient for Muscleblind-like 2 exhibit features of myotonic dystrophy. Dis. Model. Mech. 4, 381–392 doi:10.1242/dmm.004150.
Mahadevan, M., Tsilfidis, C., Sabourin, L., Shutler, G., Amemiya, C., Jansen, G., Neville, C., Narang, M., Barceló, J., O'Hoy, K., 1992. Myotonic dystrophy mutation: an unstable CTG repeat in the 3' untranslated region of the gene. Science 255, 1253–1255.
Mahadevan, M.S., Yadava, R.S., Yu, Q., Balijepalli, S., Frenzel-McCardell, C.D., Bourne, T.D., Phillips, L.H., 2006. Reversible model of RNA toxicity and cardiac conduction defects in myotonic dystrophy. Nat. Genet. 38, 1066–1070. https://doi.org/10.1038/ng1857.
Mankodi, A., Takahashi, M.P., Jiang, H., Beck, C.L., Bowers, W.J., Moxley, R.T., Cannon, S.C., Thornton, C.A., 2002. Expanded CUG repeats trigger aberrant splicing of ClC-1 chloride channel pre-mRNA and hyperexcitability of skeletal muscle in myotonic dystrophy. Mol. Cell 10, 35–44.
Mankodi, A., Teng-Umnuay, P., Krym, M., Henderson, D., Swanson, M., Thornton, C.A., 2003. Ribonuclear inclusions in skeletal muscle in myotonic dystrophy types 1 and 2. Ann. Neurol. 54, 760–768. https://doi.org/10.1002/ana.10763.
Marrero, E., Rossi, S.G., Darr, A., Tsoulfas, P., Rotundo, R.L., 2011. Translational regulation of acetylcholinesterase by the RNA-binding protein Pumilio-2 at the neuromuscular synapse. J. Biol. Chem. 286, 36492–36499. https://doi.org/10.1074/jbc.M111.285510.
Martin, C.L., Duvall, J.A., Ilkin, Y., Simon, J.S., Arreaza, M.G., Wilkes, K., Alvarez-Retuerto, A., Whichello, A., Powell, C.M., Rao, K., Cook, E., Geschwind, D.H., 2007. Cytogenetic and molecular characterization of A2BP1/FOX1 as a candidate gene for autism. Am. J. Med. Genet. B Neuropsychiatr. Genet. 144B, 869–876. https://doi.org/10.1002/ajmg.b.30530.
Masuda, N., 2012. Evolution of cooperation driven by zealots. Sci. Rep. 2, 646. https://doi.org/10.1038/srep00646.
Masuda, A., Andersen, H.S., Doktor, T.K., Okamoto, T., Ito, M., Andresen, B.S., Ohno, K., 2012. CUGBP1 and MBNL1 preferentially bind to 3' UTRs and facilitate mRNA decay. Sci. Rep. 2, 209. https://doi.org/10.1038/srep00209.
Matynia, A., Ng, C.H., Dansithong, W., Chiang, A., Silva, A.J., Reddy, S., 2010. Muscleblind1, but not Dmpk or Six5, contributes to a complex phenotype of muscular and motivational deficits in mouse models of myotonic dystrophy. PLoS One 5, e9857. https://doi.org/10.1371/journal.pone.0009857.
McAuliffe, J.J., Gao, L.Z., Solaro, R.J., 1990. Changes in myofibrillar activation and troponin C Ca2 + binding associated with troponin T isoform switching in developing rabbit heart. Circ. Res. 66, 1204–1216.
McDermott, S.M., Yang, L., Halstead, J.M., Hamilton, R.S., Meignin, C., Davis, I., 2014. DrosophilaSyncrip modulates the expression of mRNAs encoding key synaptic proteins required for morphology at the neuromuscular junction. RNA 20, 1593–1606 doi:10.1261/rna.045849.114.
McNally, E.M., Mestroni, L., 2017. Dilated cardiomyopathy: genetic determinants and mechanisms. Circ. Res. 121, 731–748 doi:10.1161/CIRCRESAHA.116.309396.
Meissner, B., Warner, A., Wong, K., Dube, N., Lorch, A., McKay, S.J., Khattra, J., Rogalski, T., Somasiri, A., Chaudhry, I., Fox, R.M., Miller, D.M., Baillie, D.L., Holt, R.A., Jones, S.J.M., Marra, M.A., Moerman, D.G., 2009. An integrated strategy to study muscle development and myofilament structure in Caenorhabditis elegans. PLoS Genet. 5 e1000537–14. doi:10.1371/journal.pgen.1000537.
Meltzer, M., Long, K., Nie, Y., Gupta, M., Yang, J., Montano, M., 2010. The RNA editor gene ADAR1 is induced in myoblasts by inflammatory ligands and buffers stress response. Clin. Transl. Sci. 3, 73–80 doi:10.1111/j.1752-8062.2010.00199.x.
Meola, G., Cardani, R., 2015a. Myotonic dystrophy type 2: an update on clinical aspects, genetic and pathomolecular mechanism. J. Neuromuscul. Dis. 2, S59–S71 doi:10.3233/JND-150088.
Meola, G., Cardani, R., 2015b. Myotonic dystrophies: an update on clinical aspects, genetic, pathology, and molecular pathomechanisms. Biochim. Biophys. Acta 1852, 594–606. https://doi.org/10.1016/j.bbadis.2014.05.019.
Merkin, J., Russell, C., Chen, P., Burge, C.B., 2012. Evolutionary dynamics of gene and isoform regulation in Mammalian tissues. Science 338, 1593–1599. https://doi.org/10.1126/science.1228186.
Mientjes, E.J., Willemsen, R., Kirkpatrick, L.L., Nieuwenhuizen, I.M., Hoogeveen-Westerveld, M., Verweij, M., Reis, S., Bardoni, B., Hoogeveen, A.T., Oostra, B.A., Nelson, D.L., 2004. Fxr1 knockout mice show a striated muscle phenotype: implications for Fxr1p function in vivo. Hum. Mol. Genet. 13, 1291–1302. https://doi.org/10.1093/hmg/ddh150.
Miller, J.W., Urbinati, C.R., Teng-Umnuay, P., Stenberg, M.G., Byrne, B.J., Thornton, C.A., Swanson, M.S., 2000. Recruitment of human muscleblind proteins to (CUG)(n) expansions associated with myotonic dystrophy. EMBO J. 19, 4439–4448. https://doi.org/10.1093/emboj/19.17.4439.
Miller, B.M., Zhang, S., Suggs, J.A., Swank, D.M., Littlefield, K.P., Knowles, A.F., Bernstein, S.I., 2005. An alternative domain near the nucleotide-binding site of Drosophila muscle myosin affects ATPase kinetics. J. Mol. Biol. 353, 14–25. https://doi.org/10.1016/j.jmb.2005.08.012.
Milne, C.A., Hodgkin, J., 1999. ETR-1, a homologue of a protein linked to myotonic dystrophy, is essential for muscle development in Caenorhabditis elegans. Curr. Biol. 9, 1243–1246.
Miyakawa, I., Konishi, K., 1984. Removal of troponin C and desensitization of myosin B from ascidian smooth muscle by treatment with ethylene diamine tetraacetate. J. Biochem. 95, 57–65.
Miyamoto, S., Hidaka, K., Jin, D., Morisaki, T., 2009. RNA-binding proteins Rbm38 and Rbm24 regulate myogenic differentiation via p21-dependent and -independent regulatory pathways. Genes Cells 14, 1241–1252 doi:10.1111/j.1365-2443.2009.01347.x.
Monferrer, L., Artero, R., 2006. An interspecific functional complementation test in Drosophila for introductory genetics laboratory courses. J. Hered. 97, 67–73. https://doi.org/10.1093/jhered/esj003.
Moore, J.R., Vigoreaux, J.O., Maughan, D.W., 1999. The Drosophila projectin mutant, bentD, has reduced stretch activation and altered indirect flight muscle kinetics. J. Muscle Res. Cell. Motil. 20, 797–806.
Mori, D., Sasagawa, N., Kino, Y., Ishiura, S., 2007. Quantitative analysis of CUG-BP1 binding to RNA repeats. J. Biochem. 143, 377–383. https://doi.org/10.1093/jb/mvm230.
Morriss, G.R., Rajapakshe, K., Huang, S., Coarfa, C., Cooper, T.A., 2018. Mechanisms of skeletal muscle wasting in a mouse model for myotonic dystrophy type 1. Hum. Mol. Genet. 27, 2789–2804. https://doi.org/10.1093/hmg/ddy192.
Mouse Genome Sequencing Consortium, Waterston, R.H., Lindblad-Toh, K., Birney, E., Rogers, J., Abril, J.F., Agarwal, P., Agarwala, R., Ainscough, R., Alexandersson, M., An, P., Antonarakis, S.E., Attwood, J., Baertsch, R., Bailey, J., Barlow, K., Beck, S., Berry, E., Birren, B., Bloom, T., Bork, P., Botcherby, M., Bray, N., Brent, M.R., Brown, D.G., Brown, S.D., Bult, C., Burton, J., Butler, J., Campbell, R.D., Carninci, P., Cawley, S., Chiaromonte, F., Chinwalla, A.T., Church, D.M., Clamp, M., Clee, C., Collins, F.S., Cook, L.L., Copley, R.R., Coulson, A., Couronne, O., Cuff, J., Curwen, V., Cutts, T., Daly, M., David, R., Davies, J., Delehaunty, K.D., Deri, J., Dermitzakis, E.T., Dewey, C., Dickens, N.J., Diekhans, M., Dodge, S., Dubchak, I., Dunn, D.M., Eddy, S.R., Elnitski, L., Emes, R.D., Eswara, P., Eyras, E., Felsenfeld, A., Fewell, G.A., Flicek, P., Foley, K., Frankel, W.N., Fulton, L.A., Fulton, R.S., Furey, T.S., Gage, D., Gibbs, R.A., Glusman, G., Gnerre, S., Goldman, N., Goodstadt, L., Grafham, D., Graves, T.A., Green, E.D., Gregory, S., Guigo, R., Guyer, M., Hardison, R.C., Haussler, D., Hayashizaki, Y., Hillier, L.W., Hinrichs, A., Hlavina, W., Holzer, T., Hsu, F., Hua, A., Hubbard, T., Hunt, A., Jackson, I., Jaffe, D.B., Johnson, L.S., Jones, M., Jones, T.A., Joy, A., Kamal, M., Karlsson, E.K., Karolchik, D., Kasprzyk, A., Kawai, J., Keibler, E., Kells, C., Kent, W.J., Kirby, A., Kolbe, D.L., Korf, I., Kucherlapati, R.S., Kulbokas, E.J., Kulp, D., Landers, T., Leger, J.P., Leonard, S., Letunic, I., Levine, R., Li, J., Li, M., Lloyd, C., Lucas, S., Ma, B., Maglott, D.R., Mardis, E.R., Matthews, L., Mauceli, E., Mayer, J.H., McCarthy, M., McCombie, W.R., McLaren, S., McLay, K., McPherson, J.D., Meldrim, J., Meredith, B., Mesirov, J.P., Miller, W., Miner, T.L., Mongin, E., Montgomery, K.T., Morgan, M., Mott, R., Mullikin, J.C., Muzny, D.M., Nash, W.E., Nelson, J.O., Nhan, M.N., Nicol, R., Ning, Z., Nusbaum, C., O'Connor, M.J., Okazaki, Y., Oliver, K., Overton-Larty, E., Pachter, L., Parra, G., Pepin, K.H., Peterson, J., Pevzner, P., Plumb, R., Pohl, C.S., Poliakov, A., Ponce, T.C., Ponting, C.P., Potter, S., Quail, M., Reymond, A., Roe, B.A., Roskin, K.M., Rubin, E.M., Rust, A.G., Santos, R., Sapojnikov, V., Schultz, B., Schultz, J., Schwartz, M.S., Schwartz, S., Scott, C., Seaman, S., Searle, S., Sharpe, T., Sheridan, A., Shownkeen, R., Sims, S., Singer, J.B., Slater, G., Smit, A., Smith, D.R., Spencer, B., Stabenau, A., Stange-Thomann, N., Sugnet, C., Suyama, M., Tesler, G., Thompson, J., Torrents, D., Trevaskis, E., Tromp, J., Ucla, C., Ureta-Vidal, A., Vinson, J.P., Niederhausern, Von A.C., Wade, C.M., Wall, M., Weber, R.J., Weiss, R.B., Wendl, M.C., West, A.P., Wetterstrand, K., Wheeler, R., Whelan, S., Wierzbowski, J., Willey, D., Williams, S., Wilson, R.K., Winter, E., Worley, K.C., Wyman, D., Yang, S., Yang, S.-P., Zdobnov, E.M., Zody, M.C., Lander, E.S., 2002. Initial sequencing and comparative analysis of the mouse genome. Nature 420, 520–562. https://doi.org/10.1038/nature01262.
Müller, T.J., Kraya, T., Stoltenburg-Didinger, G., Hanisch, F., Kornhuber, M., Stoevesandt, D., Senderek, J., Weis, J., Baum, P., Deschauer, M., Zierz, S., 2014. Phenotype of matrin-3-related distal myopathy in 16 German patients. Ann. Neurol. 76, 669–680. https://doi.org/10.1002/ana.24255.
Munoz-Torres, M., Carbon, S., 2017. Get GO! Retrieving GO data using AmiGO, QuickGO, API, files, and tools. Methods Mol. Biol. 1446, 149–160. https://doi.org/10.1007/978-1-4939-3743-1_11.
Nabel-Rosen, H., Volohonsky, G., Reuveny, A., Zaidel-Bar, R., Zaidel-Bar, R., Volk, T., 2002. Two isoforms of the Drosophila RNA binding protein, how, act in opposing directions to regulate tendon cell differentiation. Dev. Cell 2, 183–193.
Nakahata, S., Kawamoto, S., 2005. Tissue-dependent isoforms of mammalian Fox-1 homologs are associated with tissue-specific splicing activities. Nucleic Acids Res. 33, 2078–2089. https://doi.org/10.1093/nar/gki338.
Nakka, K., Ghigna, C., Gabellini, D., Dilworth, F.J., 2018. Diversification of the muscle proteome through alternative splicing. Skelet. Muscle 8, 8 doi:10.1186/s13395-018-0152-3.
Narici, M., Franchi, M., Maganaris, C., 2016. Muscle structural assembly and functional consequences. J. Exp. Biol. 219, 276–284 doi:10.1242/jeb.128017.
Nash, L.A., Burns, J.K., Chardon, J.W., Kothary, R., Parks, R.J., 2016. Spinal muscular atrophy: more than a disease of motor neurons? Curr. Mol. Med. 16, 779–792 doi:10.2174/1566524016666161128113338.
Nasif, S., Contu, L., Mühlemann, O., 2018. Beyond quality control: the role of nonsense-

mediated mRNA decay (NMD) in regulating gene expression. Semin. Cell Dev. Biol. 75, 78–87. https://doi.org/10.1016/j.semcdb.2017.08.053.
Nezu, Y., Kino, Y., Sasagawa, N., Nishino, I., Ishiura, S., 2007. Expression of MBNL and CELF mRNA transcripts in muscles with myotonic dystrophy. Neuromuscul. Disord. 17, 306–312. https://doi.org/10.1016/j.nmd.2007.01.002.
Nir, R., Grossman, R., Paroush, Z., Volk, T., 2012. Phosphorylation of the Drosophila melanogaster RNA-binding protein HOW by MAPK/ERK enhances its dimerization and activity. PLoS Genet. 8, e1002632 doi:10.1371/journal.pgen.1002632.
Nödl, M.-T., Fossati, S.M., Domingues, P., Sánchez, F.J., Zullo, L., 2015. The making of an octopus arm. Evodevo 6, 19 doi:10.1186/s13227-015-0012-8.
Nongthomba, U., Cummins, M., Clark, S., Vigoreaux, J.O., Sparrow, J.C., 2003. Suppression of muscle hypercontraction by mutations in the myosin heavy chain gene of Drosophila melanogaster. Genetics 164, 209–222.
Nongthomba, U., Ansari, M., Thimmaiya, D., Stark, M., Sparrow, J., 2007. Aberrant splicing of an alternative exon in the Drosophila troponin-T gene affects flight muscle development. Genetics 177, 295–306 doi:10.1534/genetics.106.056812.
Novak, S.M., Joardar, A., Gregorio, C.C., Zarnescu, D.C., 2015. Regulation of heart rate in Drosophila via fragile X Mental retardation protein. PLoS One 10, e0142836 doi:10.1371/journal.pone.0142836.
Nutter, C.A., Jaworski, E.A., Verma, S.K., Deshmukh, V., Wang, Q., Botvinnik, O.B., Lozano, M.J., Abass, I.J., Ijaz, T., Brasier, A.R., Garg, N.J., Wehrens, X.H.T., Yeo, G.W., Kuyumcu-Martinez, M.N., 2016. Dysregulation of RBFOX2 is an early event in cardiac pathogenesis of diabetes. Cell Rep. 15, 2200–2213. https://doi.org/10.1016/j.celrep.2016.05.002.
Oas, S.T., Bryantsev, A.L., Cripps, R.M., 2014. Arrest is a regulator of fiber-specific alternative splicing in the indirect flight muscles of Drosophila. J. Cell Biol. 206, 895–908. https://doi.org/10.1083/jcb.201405058.
Oddo, J.C., Saxena, T., McConnell, O.L., Berglund, J.A., Wang, E.T., 2016. Conservation of context-dependent splicing activity in distant Muscleblind homologs. Nucleic Acids Res. 44, 8352–8362. https://doi.org/10.1093/nar/gkw735.
Ohno, G., Ono, K., Togo, M., Watanabe, Y., Ono, S., Hagiwara, M., Kuroyanagi, H., 2012. Muscle-specific splicing factors ASD-2 and SUP-12 cooperatively switch alternative pre-mRNA processing patterns of the ADF/cofilin gene in Caenorhabditis elegans. PLoS Genet. 8, e1002991 doi:10.1371/journal.pgen.1002991.
Ohtsuka, Y., Okamura, Y., 2007. Voltage-dependent calcium influx mediates maturation of myofibril arrangement in ascidian larval muscle. Dev. Biol. 301, 361–373. https://doi.org/10.1016/j.ydbio.2006.08.013.
Orengo, J.P., Chambon, P., Metzger, D., Mosier, D.R., Snipes, G.J., Cooper, T.A., 2008. Expanded CTG repeats within the DMPK 3' UTR causes severe skeletal muscle wasting in an inducible mouse model for myotonic dystrophy. Proc. Natl. Acad. Sci. U. S. A. 105, 2646–2651. https://doi.org/10.1073/pnas.0708519105.
Orengo, J.P., Ward, A.J., Cooper, T.A., 2011. Alternative splicing dysregulation secondary to skeletal muscle regeneration. Ann. Neurol. 69, 681–690. https://doi.org/10.1002/ana.22278.
Orfanos, Z., Sparrow, J.C., 2013. Myosin isoform switching during assembly of the Drosophila flight muscle thick filament lattice. J. Cell. Sci. 126, 139–148. https://doi.org/10.1242/jcs.110361.
Osborne, R.J., Lin, X., Welle, S., Sobczak, K., O'Rourke, J.R., Swanson, M.S., Thornton, C.A., 2009. Transcriptional and post-transcriptional impact of toxic RNA in myotonic dystrophy. Hum. Mol. Genet. 18, 1471–1481. https://doi.org/10.1093/hmg/ddp058.
Pagliarini, V., La Rosa, P., Sette, C., 2017. Faulty RNA splicing: consequences and therapeutic opportunities in brain and muscle disorders. Hum. Genet. 136, 1215–1235. https://doi.org/10.1007/s00439-017-1802-y.
Palmio, J., Evilä, A., Bashir, A., Norwood, F., Viitaniemi, K., Vihola, A., Huovinen, S., Straub, V., Hackman, P., Hirano, M., Bushby, K., Udd, B., 2016. Re-evaluation of the phenotype caused by the common MATR3 p.Ser85Cys mutation in a new family. J. Neurol. Neurosurg. Psychiatry 87, 448–450 doi:10.1136/jnnp-2014-309349.
Pan, Q., Shai, O., Lee, L.J., Frey, B.J., Blencowe, B.J., 2008. Deep surveying of alternative splicing complexity in the human transcriptome by high-throughput sequencing. Nat. Genet. 40, 1413–1415. https://doi.org/10.1038/ng.259.
Panda, A.C., Abdelmohsen, K., Yoon, J.-H., Martindale, J.L., Yang, X., Curtis, J., Mercken, E.M., Chenette, D.M., Zhang, Y., Schneider, R.J., Becker, K.G., de Cabo, R., Gorospe, M., 2014. RNA-binding protein AUF1 promotes myogenesis by regulating MEF2C expression levels. Mol. Cell. Biol. 34, 3106–3119 doi:10.1128/MCB.00423-14.
Panda, A.C., Abdelmohsen, K., Martindale, J.L., Di Germanio, C., Yang, X., Grammatikakis, I., Noh, J.H., Zhang, Y., Lehrmann, E., Dudekula, D.B., De, S., Becker, K.G., White, E.J., Wilson, G.M., de Cabo, R., Gorospe, M., 2016. Novel RNA-binding activity of MYF5 enhances Ccnd1/Cyclin D1 mRNA translation during myogenesis. Nucleic Acids Res. 44, 2393–2408. https://doi.org/10.1093/nar/gkw023.
Park, J.H., Kang, H.-J., Lee, Y.K., Kang, H., Kim, J., Chung, J.H., Chang, J.S., McPherron, A.C., Lee, S.B., 2015. Inactivation of EWS reduces PGC-1α protein stability and mitochondrial homeostasis. Proc. Natl. Acad. Sci. U. S. A. 112, 6074–6079. https://doi.org/10.1073/pnas.1504391112.
Pascual, M., Vicente, M., Monferrer, L., Artero, R., 2006. The Muscleblind family of proteins: an emerging class of regulators of developmentally programmed alternative splicing. Differentiation 74, 65–80 doi:10.1111/j.1432-0436.2006.00060.x.
Peckham, M., Molloy, J.E., Sparrow, J.C., White, D.C., 1990. Physiological properties of the dorsal longitudinal flight muscle and the tergal depressor of the trochanter muscle of Drosophila melanogaster. J. Muscle Res. Cell. Motil. 11, 203–215.
Pedrotti, S., Giudice, J., Dagnino-Acosta, A., Knoblauch, M., Singh, R.K., Hanna, A., Mo, Q., Hicks, J., Hamilton, S., Cooper, T.A., 2015. The RNA-binding protein Rbfox1 regulates splicing required for skeletal muscle structure and function. Hum. Mol. Genet. 24, 2360–2374. https://doi.org/10.1093/hmg/ddv003.
Perks, K.L., Rossetti, G., Kuznetsova, I., Hughes, L.A., Ermer, J.A., Ferreira, N., Busch, J.D., Rudler, D.L., Spahr, H., Schöndorf, T., Shearwood, A.-M.J., Viola, H.M., Siira, S.J., Hool, L.C., Milenkovic, D., Larsson, N.-G., Rackham, O., Filipovska, A., 2018. PTCD1 is required for 16S rRNA maturation complex stability and mitochondrial ribosome assembly. Cell Rep. 23, 127–142. https://doi.org/10.1016/j.celrep.2018.03.033.
Pettersson, O.J., Aagaard, L., Jensen, T.G., Damgaard, C.K., 2015. Molecular mechanisms in DM1 - a focus on foci. Nucleic Acids Res. 43, 2433–2441. https://doi.org/10.1093/nar/gkv029.
Philips, A.V., Timchenko, L.T., Cooper, T.A., 1998. Disruption of splicing regulated by a CUG-binding protein in myotonic dystrophy. Science 280, 737–741.
Phillips, B.L., Banerjee, A., Sanchez, B.J., Di Marco, S., Gallouzi, I.-E., Pavlath, G.K., Corbett, A.H., 2018. Post-transcriptional regulation of Pabpn1 by the RNA binding protein HuR. Nucleic Acids Res. 46, 7643–7661. https://doi.org/10.1093/nar/gky535.
Picchio, L., Plantié, E., Renaud, Y., Poovthumkadavil, P., Jagla, K., 2013. Novel Drosophila model of myotonic dystrophy type 1: phenotypic characterization and genome-wide view of altered gene expression. Hum. Mol. Genet. 22, 2795–2810. https://doi.org/10.1093/hmg/ddt127.
Picchio, L., Legagneux, V., Deschamps, S., Renaud, Y., Chauveau, S., Paillard, L., Jagla, K., 2018. Bruno-3 regulates sarcomere component expression and contributes to muscle phenotypes of myotonic dystrophy type 1. Dis. Model. Mech. 11 dmm031849. doi:10.1242/dmm.031849.
Pistoni, M., Shiue, L., Cline, M.S., Bortolanza, S., Neguembor, M.V., Xynos, A., Ares, M., Gabellini, D., 2013. Rbfox1 downregulation and altered calpain 3 splicing by FRG1 in a mouse model of facioscapulohumeral muscular dystrophy (FSHD). PLoS Genet. 9, e1003186–16. https://doi.org/10.1371/journal.pgen.1003186.
Poon, K.L., Tan, K.T., Wei, Y.Y., Ng, C.P., Colman, A., Korzh, V., Xu, X.Q., 2012. RNA-binding protein RBM24 is required for sarcomere assembly and heart contractility. Cardiovasc. Res. 94, 418–427. https://doi.org/10.1093/cvr/cvs095.
Poulos, M.G., Batra, R., Li, M., Yuan, Y., Zhang, C., Darnell, R.B., Swanson, M.S., 2013. Progressive impairment of muscle regeneration in muscleblind-like 3 isoform knockout mice. Hum. Mol. Genet. 22, 3547–3558. https://doi.org/10.1093/hmg/ddt209.
Prokopenko, S.N., He, Y., Lu, Y., Bellen, H.J., 2000. Mutations affecting the development of the peripheral nervous system in Drosophila: a molecular screen for novel proteins. Genetics 156, 1691–1715.
Purice, M.D., Taylor, J.P., 2018. Linking hnRNP function to ALS and FTD pathology. Front. Neurosci. 12, 326 doi:10.3389/fnins.2018.00326.
Rajendra, T.K., Gonsalvez, G.B., Walker, M.P., Shpargel, K.B., Salz, H.K., Matera, A.G., 2007. A Drosophila melanogastermodel of spinal muscular atrophy reveals a function for SMN in striated muscle. J. Cell Biol. 176, 831–841. https://doi.org/10.1083/jcb.200610053.
Ramani, A.K., Calarco, J.A., Pan, Q., Mavandadi, S., Wang, Y., Nelson, A.C., Lee, L.J., Morris, Q., Blencowe, B.J., Zhen, M., Fraser, A.G., 2011. Genome-wide analysis of alternative splicing in Caenorhabditis elegans. Genome Res. 21, 342–348 doi:10.1101/gr.114645.110.
Ranum, L.P.W., Cooper, T.A., 2006. RNA-mediated neuromuscular disorders. Annu. Rev. Neurosci. 29, 259–277 doi:10.1146/annurev.neuro.29.051605.113014.
Rau, F., Freyermuth, F., Fugier, C., Villemin, J.-P., Fischer, M.-C., Jost, B., Dembele, D., Gourdon, G., Nicole, A., Duboc, D., Wahbi, K., Day, J.W., Fujimura, H., Takahashi, M.P., Auboeuf, D., Dreumont, N., Furling, D., Charlet-Berguerand, N., 2011. Misregulation of miR-1 processing is associated with heart defects in myotonic dystrophy. Nat. Struct. Mol. Biol. 18, 840–845. https://doi.org/10.1038/nsmb.2067.
Ravel-Chapuis, A., Klein Gunnewiek, A., Bélanger, G., Crawford Parks, T.E., Côté, J., Jasmin, B.J., 2016. Staufen1 impairs stress granule formation in skeletal muscle cells from myotonic dystrophy type 1 patients. Mol. Biol. Cell 27, 1728–1739. https://doi.org/10.1091/mbc.E15-06-0356.
Raz, Y., Raz, V., 2014. Oculopharyngeal muscular dystrophy as a paradigm for muscle aging. Front. Aging Neurosci. 6, 317 doi:10.3389/fnagi.2014.00317.
Renton, A.E., Majounie, E., Waite, A., Simón-Sánchez, J., Rollinson, S., Gibbs, J.R., Schymick, J.C., Laaksovirta, H., van Swieten, J.C., Myllykangas, L., Kalimo, H., Paetau, A., Abramzon, Y., Remes, A.M., Kaganovich, A., Scholz, S.W., Duckworth, J., Ding, J., Harmer, D.W., Hernandez, D.G., Johnson, J.O., Mok, K., Ryten, M., Trabzuni, D., Guerreiro, R.J., Orrell, R.W., Neal, J., Murray, A., Pearson, J., Jansen, I.E., Sondervan, D., Seelaar, H., Blake, D., Young, K., Halliwell, N., Callister, J.B., Toulson, G., Richardson, A., Gerhard, A., Snowden, J., Mann, D., Neary, D., Nalls, M.A., Peuralinna, T., Jansson, L., Isoviita, V.-M., Kaivorinne, A.-L., Hölttä-Vuori, M., Ikonen, E., Sulkava, R., Benatar, M., Wuu, J., Chiò, A., Restagno, G., Borghero, G., Sabatelli, M., ITALSGEN Consortium, Heckerman, D., Rogaeva, E., Zinman, L., Rothstein, J.D., Sendtner, M., Drepper, C., Eichler, E.E., Alkan, C., Abdullaev, Z., Pack, S.D., Dutra, A., Pak, E., Hardy, J., Singleton, A., Williams, N.M., Heutink, P., Pickering-Brown, S., Morris, H.R., Tienari, P.J., Traynor, B.J., 2011. A hexanucleotide repeat expansion in C9ORF72 is the cause of chromosome 9p21-linked ALS-FTD. Neuron 72, 257–268. https://doi.org/10.1016/j.neuron.2011.09.010.
Rexiati, M., Sun, M., Guo, W., 2018. Muscle-specific mis-splicing and heart disease exemplified by RBM20. Genes 9, 18 doi:10.3390/genes9010018.
Rinaldi, F., Terracciano, C., Pisani, V., Massa, R., Loro, E., Vergani, L., Di Girolamo, S., Angelini, C., Gourdon, G., Novelli, G., Botta, A., 2012. Aberrant splicing and expression of the non muscle myosin heavy-chain gene MYH14 in DM1 muscle tissues. Neurobiol. Dis. 45, 264–271. https://doi.org/10.1016/j.nbd.2011.08.010.
Roberts, R., Timchenko, N.A., Miller, J.W., Reddy, S., Caskey, C.T., Swanson, M.S., Timchenko, L.T., 1997. Altered phosphorylation and intracellular distribution of a (CUG) n triplet repeat RNA-binding protein in patients with myotonic dystrophy and in myotonin protein kinase knockout mice. Proc. Natl. Acad. Sci. U. S. A. 94, 13221–13226.
Rohilla, K.J., Gagnon, K.T., 2017. RNA biology of disease-associated microsatellite repeat expansions. Acta Neuropathol. Commun. 5, 63 doi:10.1186/s40478-017-0468-y.
Runfola, V., Sebastian, S., Dilworth, F.J., Gabellini, D., 2015. Rbfox proteins regulate tissue-specific alternative splicing of Mef2D required for muscle differentiation. J. Cell. Sci. 128, 631–637 doi:10.1242/jcs.161059.
Sanger, J.W., Wang, J., Fan, Y., White, J., Mi-Mi, L., Dube, D.K., Sanger, J.M., Pruyne, D., 2017. Assembly and maintenance of myofibrils in striated muscle. Handb. Exp. Pharmacol. 235, 39–75. https://doi.org/10.1007/164_2016_53.
Savkur, R.S., Philips, A.V., Cooper, T.A., 2001. Aberrant regulation of insulin receptor alternative splicing is associated with insulin resistance in myotonic dystrophy. Nat. Genet. 29, 40–47. https://doi.org/10.1038/ng704.
Savkur, R.S., Philips, A.V., Cooper, T.A., Dalton, J.C., Moseley, M.L., Ranum, L.P.W., Day, J.W., 2004. Insulin receptor splicing alteration in myotonic dystrophy type 2. Am. J. Hum. Genet. 74, 1309–1313. https://doi.org/10.1086/421528.
Schiaffino, S., Reggiani, C., 1996. Molecular diversity of myofibrillar proteins: gene regulation and functional significance. Physiol. Rev. 76, 371–423 doi:10.1152/physrev.1996.76.2.371.
Schnorrer, F., Dickson, B.J., 2004. Muscle building; mechanisms of myotube guidance and attachment site selection. Dev. Cell 7, 9–20. https://doi.org/10.1016/j.devcel.2004.06.010.
Schnorrer, F., Schönbauer, C., Langer, C.C.H., Dietzl, G., Novatchkova, M., Schernhuber, K., Fellner, M., Azaryan, A., Radolf, M., Stark, A., Keleman, K., Dickson, B.J., 2010. Systematic genetic analysis of muscle morphogenesis and function in Drosophila. Nature 464, 287–291. https://doi.org/10.1038/nature08799.
Schönbauer, C., Distler, J., Jährling, N., Radolf, M., Dodt, H.-U., Frasch, M., Schnorrer, F.,

2011. Spalt mediates an evolutionarily conserved switch to fibrillar muscle fate in insects. Nature 479, 406–409. https://doi.org/10.1038/nature10559.
Schultz, J., Lee, S.-J., Cole, T., Hoang, H.D., Vibbert, J., Cottee, P.A., Miller, M.A., Han, S.M., 2017. The secreted MSP domain of C. Elegans VAPB homolog VPR-1 patterns the adult striated muscle mitochondrial reticulum via SMN-1. Development 144, 2175–2186 doi:10.1242/dev.152025.
Sebastian, S., Faralli, H., Yao, Z., Rakopoulos, P., Palii, C., Cao, Y., Singh, K., Liu, Q.-C., Chu, A., Aziz, A., Brand, M., Tapscott, S.J., Dilworth, F.J., 2013. Tissue-specific splicing of a ubiquitously expressed transcription factor is essential for muscle differentiation. Genes Dev. 27, 1247–1259 doi:10.1101/gad.215400.113.
Sehnert, A.J., Huq, A., Weinstein, B.M., Walker, C., Fishman, M., Stainier, D.Y.R., 2002. Cardiac troponin T is essential in sarcomere assembly and cardiac contractility. Nat. Genet. 31, 106–110. https://doi.org/10.1038/ng875.
Sellier, C., Cerro-Herreros, E., Blatter, M., Freyermuth, F., Gaucherot, A., Ruffenach, F., Sarkar, P., Puymirat, J., Udd, B., Day, J.W., Meola, G., Bassez, G., Fujimura, H., Takahashi, M.P., Schoser, B., Furling, D., Artero, R., Allain, F.H.T., Llamusi, B., Charlet-Berguerand, N., 2018. rbFOX1/MBNL1 competition for CCUG RNA repeats binding contributes to myotonic dystrophy type 1/type 2 differences. Nat. Commun. 1–15. https://doi.org/10.1038/s41467-018-04370-x.
Shafey, D., Côté, P.D., Kothary, R., 2005. Hypomorphic Smn knockdown C2C12 myoblasts reveal intrinsic defects in myoblast fusion and myotube morphology. Exp. Cell Res. 311, 49–61. https://doi.org/10.1016/j.yexcr.2005.08.019.
Shibata, H., Huynh, D.P., Pulst, S.M., 2000. A novel protein with RNA-binding motifs interacts with ataxin-2. Hum. Mol. Genet. 9, 1303–1313.
Shiels, H.A., White, E., 2008. The Frank-Starling mechanism in vertebrate cardiac myocytes. J. Exp. Biol. 211, 2005–2013 doi:10.1242/jeb.003145.
Shu, P., Fu, H., Zhao, X., Wu, C., Ruan, X., Zeng, Y., Liu, W., Wang, M., Hou, L., Chen, P., Yin, B., Yuan, J., Qiang, B., Peng, X., 2017. MicroRNA-214 modulates neural progenitor cell differentiation by targeting quaking during cerebral cortex development. Sci. Rep. 7, 8014. https://doi.org/10.1038/s41598-017-08450-8.
Siedner, S., Krüger, M., Schroeter, M., Metzler, D., Roell, W., Fleischmann, B.K., Hescheler, J., Pfitzer, G., Stehle, R., 2003. Developmental changes in contractility and sarcomeric proteins from the early embryonic to the adult stage in the mouse heart. J. Physiol. 548, 493–505 doi:10.1113/jphysiol.2002.036509.
Singh, G., 2004. ETR-3 and CELF4 protein domains required for RNA binding and splicing activity in vivo. Nucleic Acids Res. 32, 1232–1241. https://doi.org/10.1093/nar/gkh275.
Singh, R.K., Xia, Z., Bland, C.S., Kalsotra, A., Scavuzzo, M.A., Curk, T., Ule, J., Li, W., Cooper, T.A., 2014. Rbfox2-coordinated alternative splicing of Mef2d and Rock2 controls myoblast fusion during myogenesis. Mol. Cell 55, 592–603. https://doi.org/10.1016/j.molcel.2014.06.035.
Singla, C.L., 1978. Fine structure of the neuromuscular system of Polyorchis penicillatus (Hydromedusae, Cnidaria). Cell Tissue Res. 193, 163–174.
Software, H.W.J.O.S., 2007. Reshaping Data with the Reshape Package. had.co.nZ. n.d.. .
Software, H.W.J.O.S., 2011. The Split-apply-combine Strategy for Data Analysis. n.d.. Citeseer.
Söllner, J.F., Leparc, G., Hildebrandt, T., Klein, H., Thomas, L., Stupka, E., Simon, E., 2017. Data Descriptor: An RNA-Seq Atlas Of Gene Expression In Mouse And Rat Normal Tissues, vol. 4. Nature Publishing Group, pp. 1–11. https://doi.org/10.1038/sdata.2017.185.
Spike, C.A., Shaw, J.E., Herman, R.K., 2001. Analysis of smu-1, a gene that regulates the alternative splicing of unc-52 pre-mRNA in Caenorhabditis elegans. Mol. Cell. Biol. 21, 4985–4995 doi:10.1128/MCB.21.15.4985-4995.2001.
Spilker, K.A., Wang, G.J., Tugizova, M.S., Shen, K., 2012. Caenorhabditis elegans Muscleblind homolog mbl-1 functions in neurons to regulate synapse formation. Neural Dev. 7, 7. https://doi.org/10.1186/1749-8104-7-7.
Spletter, M.L., Schnorrer, F., 2014. Transcriptional regulation and alternative splicing cooperate in muscle fiber-type specification in flies and mammals. Exp. Cell Res. 321, 90–98. https://doi.org/10.1016/j.yexcr.2013.10.007.
Spletter, M.L., Barz, C., Yeroslaviz, A., Schönbauer, C., Ferreira, I.R.S., Sarov, M., Gerlach, D., Stark, A., Habermann, B.H., Schnorrer, F., 2015. The RNA-binding protein Arrest (Bruno) regulates alternative splicing to enable myofibril maturation in Drosophila flight muscle. EMBO Rep. 16, 178–191. https://doi.org/10.15252/embr.201439791.
Spletter, M.L., Barz, C., Yeroslaviz, A., Zhang, X., Lemke, S.B., Bonnard, A., Brunner, E., Cardone, G., Basler, K., Habermann, B.H., Schnorrer, F., 2018. A transcriptomics resource reveals a transcriptional transition during ordered sarcomere morphogenesis in flight muscle. Elife 7, 1361 doi:10.7554/eLife.34058.
Squillace, R.M., Chenault, D.M., Wang, E.H., 2002. Inhibition of muscle differentiation by the novel muscleblind-related protein CHCR. Dev. Biol. 250, 218–230.
Squire, J.M., Paul, D.M., Morris, E.P., 2017. Myosin and actin filaments in muscle: structures and interactions. Subcell. Biochem. 82, 319–371. https://doi.org/10.1007/978-3-319-49674-0_11.
Stallings, N.R., Puttaparthi, K., Dowling, K.J., Luther, C.M., Burns, D.K., Davis, K., Elliott, J.L., 2013. TDP-43, an ALS linked protein, regulates fat deposition and glucose homeostasis. PLoS One 8, e71793 10.1371/journal.pone.0071793.
Stolc, V., Gauhar, Z., Mason, C., Halasz, G., van Batenburg, M.F., Rifkin, S.A., Hua, S., Herreman, T., Tongprasit, W., Barbano, P.E., Bussemaker, H.J., White, K.P., 2004. A gene expression map for the euchromatic genome of Drosophila melanogaster. Science 306, 655–660 doi:10.1126/science.1101312.
Suenaga, K., Lee, K.-Y., Nakamori, M., Tatsumi, Y., Takahashi, M.P., Fujimura, H., Jinnai, K., Yoshikawa, H., Du, H., Ares, M., Swanson, M.S., Kimura, T., 2012. Muscleblind-like 1 knockout mice reveal novel splicing defects in the myotonic dystrophy brain. PLoS One 7, e33218 doi:10.1371/journal.pone.0033218.
Suggs, J.A., Cammarato, A., Kronert, W.A., Nikkhoy, M., Dambacher, C.M., Megighian, A., Bernstein, S.I., 2007. Alternative S2 hinge regions of the myosin rod differentially affect muscle function, myofibril dimensions and Myosin tail length. J. Mol. Biol. 367, 1312–1329. https://doi.org/10.1016/j.jmb.2007.01.045.
Sugnet, C.W., Srinivasan, K., Clark, T.A., O'Brien, G., Cline, M.S., Wang, H., Williams, A., Kulp, D., Blume, J.E., Haussler, D., Ares, M., 2006. Unusual intron conservation near tissue-regulated exons found by splicing microarrays. PLoS Comput. Biol. 2, e4 doi:10.1371/journal.pcbi.0020004.
Sun, C.-Y.J., van Koningsbruggen, S., Long, S.W., Straasheijm, K., Klooster, R., Jones, T.I., Bellini, M., Levesque, L., Brieher, W.M., van der Maarel, S.M., Jones, P.L., 2011. Facioscapulohumeral muscular dystrophy region gene 1 is a dynamic RNA-associated and actin-bundling protein. J. Mol. Biol. 411, 397–416. https://doi.org/10.1016/j.jmb.2011.06.014.
Suzuki, H., Jin, Y., Otani, H., Yasuda, K., Inoue, K., 2002. Regulation of alternative splicing of alpha-actinin transcript by Bruno-like proteins. Genes Cells 7, 133–141.
Swank, D.M., Wells, L., Kronert, W.A., Morrill, G.E., Bernstein, S.I., 2000. Determining structure/function relationships for sarcomeric myosin heavy chain by genetic and transgenic manipulation of Drosophila. Microsc. Res. Technol. 50, 430–442. https://doi.org/10.1002/1097-0029(20000915)50:6<430::AID-JEMT2>3.0.CO;2-E.
Taliaferro, J.M., Vidaki, M., Oliveira, R., Olson, S., Zhan, L., Saxena, T., Wang, E.T., Graveley, B.R., Gertler, F.B., Swanson, M.S., Burge, C.B., 2016. Distal alternative last exons localize mRNAs to neural projections. Mol. Cell 61, 821–833. https://doi.org/10.1016/j.molcel.2016.01.020.
Tamura, K., Stecher, G., Peterson, D., Filipski, A., Kumar, S., 2013. MEGA6: molecular evolutionary genetics analysis version 6.0. Mol. Biol. Evol. 30, 2725–2729. https://doi.org/10.1093/molbev/mst197.
Tan, M.H., Li, Q., Shanmugam, R., Piskol, R., Kohler, J., Young, A.N., Liu, K.I., Zhang, R., Ramaswami, G., Ariyoshi, K., Gupte, A., Keegan, L.P., George, C.X., Ramu, A., Huang, N., Pollina, E.A., Leeman, D.S., Rustighi, A., Goh, Y.P.S., GTEx Consortium, Laboratory, Data Analysis &Coordinating Center (LDACC)—Analysis Working Group, Statistical Methods groups—Analysis Working Group, Enhancing GTEx (eGTEx) groups, NIH Common Fund, NIH/NCI, NIH/NHGRI, NIH/NIMH, NIH/NIDA, Biospecimen Collection Source Site—NDRI, Biospecimen Collection Source Site—RPCI, Biospecimen Core Resource—VARI, Brain Bank Repository—University of Miami Brain Endowment Bank, Leidos Biomedical—Project Management, ELSI Study, Genome Browser Data Integration &Visualization—EBI, Genome Browser Data Integration &Visualization—UCSC Genomics Institute, University of California Santa Cruz, Chawla, A., Del Sal, G., Peltz, G., Brunet, A., Conrad, D.F., Samuel, C.E., O'Connell, M.A., Walkley, C.R., Nishikura, K., Li, J.B., 2017. Dynamic landscape and regulation of RNA editing in mammals. Nature 550, 249–254. https://doi.org/10.1038/nature24041.
Tanaka, M., Yamaguchi, S., Yamazaki, Y., Kinoshita, H., Kuwahara, K., Nakao, K., Jay, P.Y., Noda, T., Nakamura, T., 2015. Somatic chromosomal translocation between Ewsr1 and Fli1 loci leads to dilated cardiomyopathy in a mouse model. Sci. Rep. 5, 7826. https://doi.org/10.1038/srep07826.
Tang, Z.Z., Zheng, S., Nikolic, J., Black, D.L., 2009. Developmental control of CaV1.2 L-type calcium channel splicing by Fox proteins. Mol. Cell. Biol. 29, 4757–4765 doi:10.1128/MCB.00608-09.
Tapial, J., Ha, K.C.H., Sterne-Weiler, T., Gohr, A., Braunschweig, U., Hermoso-Pulido, A., Quesnel-Vallières, M., Permanyer, J., Sodaei, R., Marquez, Y., Cozzuto, L., Wang, X., Gómez-Velázquez, M., Rayon, T., Manzanares, M., Ponomarenko, J., Blencowe, B.J., Irimia, M., 2017. An atlas of alternative splicing profiles and functional associations reveals new regulatory programs and genes that simultaneously express multiple major isoforms. Genome Res. 27, 1759–1768 doi:10.1101/gr.220962.117.
Tawil, R., 2008. Facioscapulohumeral muscular dystrophy. Neurotherapeutics 5, 601–606. https://doi.org/10.1016/j.nurt.2008.07.005.
Tazi, J., Bakkour, N., Stamm, S., 2009. Alternative splicing and disease. Biochim. Biophys. Acta 1792, 14–26. https://doi.org/10.1016/j.bbadis.2008.09.017.
Tews, D.S., Goebel, H.H., Meinck, H.M., 1997. DNA-fragmentation and apoptosis-related proteins of muscle cells in motor neuron disorders. Acta Neurol. Scand. 96, 380–386.
The Gene Ontology Consortium, 2017. Expansion of the Gene Ontology knowledgebase and resources. Nucleic Acids Res. 45, D331–D338. https://doi.org/10.1093/nar/gkw1108.
Thomas, J.D., Sznajder, Ł.J., Bardhi, O., Aslam, F.N., Anastasiadis, Z.P., Scotti, M.M., Nishino, I., Nakamori, M., Wang, E.T., Swanson, M.S., 2017. Disrupted prenatal RNA processing and myogenesis in congenital myotonic dystrophy. Genes Dev. 31, 1122–1133 doi:10.1101/gad.300590.117.
Timchenko, L.T., Miller, J.W., Timchenko, N.A., DeVore, D.R., Datar, K.V., Lin, L., Roberts, R., Caskey, C.T., Swanson, M.S., 1996. Identification of a (CUG)n triplet repeat RNA-binding protein and its expression in myotonic dystrophy. Nucleic Acids Res. 24, 4407–4414.
Timchenko, N.A., Iakova, P., Cai, Z.J., Smith, J.R., Timchenko, L.T., 2001. Molecular basis for impaired muscle differentiation in myotonic dystrophy. Mol. Cell. Biol. 21, 6927–6938 doi:10.1128/MCB.21.20.6927-6938.2001.
Todd, P.K., Ackall, F.Y., Hur, J., Sharma, K., Paulson, H.L., Dowling, J.J., 2014. Transcriptional changes and developmental abnormalities in a zebrafish model of myotonic dystrophy type 1. Dis. Model. Mech. 7, 143–155 doi:10.1242/dmm.012427.
Tortarolo, M., Coco, Lo D., Veglianese, P., Vallarola, A., Giordana, M.T., Marcon, G., Beghi, E., Poloni, M., Strong, M.J., Iyer, A.M., Aronica, E., Bendotti, C., 2017. Amyotrophic lateral sclerosis, a multisystem pathology: insights into the role of TNFα. Mediators Inflamm. 2017 2985051–16. doi:10.1155/2017/2985051.
Tskhovrebova, L., Trinick, J., 2017. Titin and Nebulin in thick and thin filament length regulation. Subcell. Biochem. 82, 285–318. https://doi.org/10.1007/978-3-319-49674-0_10.
Ule, J., Stefani, G., Mele, A., Ruggiu, M., Wang, X., Taneri, B., Gaasterland, T., Blencowe, B.J., Darnell, R.B., 2006. An RNA map predicting Nova-dependent splicing regulation. Nature 444, 580–586. https://doi.org/10.1038/nature05304.
van den Hoogenhof, M.M.G., van der Made, I., de Groot, N.E., Damanafshan, A., van Amersfoorth, S.C.M., Zentilin, L., Giacca, M., Pinto, Y.M., Creemers, E.E., 2018. AAV9-mediated Rbm24 overexpression induces fibrosis in the mouse heart. Sci. Rep. 8, 11696. https://doi.org/10.1038/s41598-018-29552-x.
van der Giessen, K., Di Marco, S., Clair, E., Gallouzi, I.-E., 2003. RNAi-mediated HuR depletion leads to the inhibition of muscle cell differentiation. J. Biol. Chem. 278, 47119–47128. https://doi.org/10.1074/jbc.M308889200.
van der Laan, A.M.A., Vangemert, A.M.C., Dirks, R.W., Noordermeer, J.N., Fradkin, L.G., Tanke, H.J., Jost, C.R., 2012. mRNA cycles through hypoxia-induced stress granules in live Drosophila embryonic muscles. Int. J. Dev. Biol. 56, 701–709 doi:10.1387/ijdb.103172al.
van der Wal, E., Bergsma, A.J., van Gestel, T.J.M., In' t Groen, S.L.M., Zaehres, H., Araúzo-Bravo, M.J., Schöler, H.R., van der Ploeg, A.T., Pijnappel, W.W.M.P., 2017. GAA deficiency in pompe disease is alleviated by exon inclusion in iPSC-Derived skeletal muscle cells. Mol. Ther. Nucleic Acids 7, 101–115. https://doi.org/10.1016/j.omtn.2017.03.002.
Van't Padje, S., Chaudhry, B., Severijnen, L.-A., van der Linde, H.C., Mientjes, E.J., Oostra, B.A., Willemsen, R., 2009. Reduction in fragile X related 1 protein causes cardiomyopathy and muscular dystrophy in zebrafish. J. Exp. Biol. 212, 2564–2570 doi:10.1242/jeb.032532.
Venables, J.P., Tazi, J., Juge, F., 2011. Regulated functional alternative splicing in Drosophila. Nucleic Acids Res. 40, 1–10. https://doi.org/10.1093/nar/gkr648.
Venables, J.P., Vignal, E., Baghdiguian, S., Fort, P., Tazi, J., 2012. Tissue-specific alternative splicing of Tak1 is conserved in deuterostomes. Mol. Biol. Evol. 29, 261–269. https://doi.org/10.1093/molbev/msr193.

Vicente, M., Monferrer, L., Poulos, M.G., Houseley, J., Monckton, D.G., O'dell, K.M.C., Swanson, M.S., Artero, R.D., 2007. Muscleblind isoforms are functionally distinct and regulate? -Actinin splicing. Differentiation 75, 427–440 doi:10.1111/j.1432-0436.2006.00156.x.

Vicente-Crespo, M., Vicente-Crespo, M., Pascual, M., Fernandez-Costa, J.M., Fernandez-Costa, J.M., Garcia-Lopez, A., Garcia-Lopez, A., Monferrer, L., Miranda, M.E., Miranda, M.E., Zhou, L., Zhou, L., Artero, R.D., 2008. Drosophila muscleblind is involved in troponin t alternative splicing and apoptosis. PLoS One 3 doi:10.1371/journal.pone.0001613.

Vieira, N.M., Naslavsky, M.S., Licinio, L., Kok, F., Schlesinger, D., Vainzof, M., Sanchez, N., Kitajima, J.P., Gal, L., Cavaçana, N., Serafini, P.R., Chuartzman, S., Vasquez, C., Mimbacas, A., Nigro, V., Pavanello, R.C., Schuldiner, M., Kunkel, L.M., Zatz, M., 2014. A defect in the RNA-processing protein HNRPDL causes limb-girdle muscular dystrophy 1G (LGMD1G). Hum. Mol. Genet. 23, 4103–4110. https://doi.org/10.1093/hmg/ddu127.

Vuong, C.K., Black, D.L., Zheng, S., 2016. The neurogenetics of alternative splicing. Nat. Rev. Neurosci. 17, 265–281. https://doi.org/10.1038/nrn.2016.27.

Wächter, N., Storch, A., Hermann, A., 2015. Human TDP-43 and FUS selectively affect motor neuron maturation and survival in a murine cell model of ALS by non-cell-autonomous mechanisms. Amyotroph. Lateral Scler. Frontotemporal Degener. 16, 431–441 doi:10.3109/21678421.2015.1055275.

Wang, G.-S., Cooper, T.A., 2007. Splicing in disease: disruption of the splicing code and the decoding machinery. Nat. Rev. Genet. 8, 749–761. https://doi.org/10.1038/nrg2164.

Wang, Z., Xiao, X., Van Nostrand, E., Burge, C.B., 2006. General and specific functions of exonic splicing silencers in splicing control. Mol. Cell 23, 61–70. https://doi.org/10.1016/j.molcel.2006.05.018.

Wang, G.-S., Kearney, D.L., De Biasi, M., Taffet, G., Cooper, T.A., 2007. Elevation of RNA-binding protein CUGBP1 is an early event in an inducible heart-specific mouse model of myotonic dystrophy. J. Clin. Invest. 117, 2802–2811 doi:10.1172/JCI32308.

Wang, E.T., Sandberg, R., Luo, S., Khrebtukova, I., Zhang, L., Mayr, C., Kingsmore, S.F., Schroth, G.P., Burge, C.B., 2008a. Alternative isoform regulation in human tissue transcriptomes. Nature 456, 470–476. https://doi.org/10.1038/nature07509.

Wang, L.-C., Hung, W.-T., Pan, H., Chen, K.-Y., Wu, Y.-C., Liu, Y.-F., Hsiao, K.-M., 2008b. Growth-dependent effect of muscleblind knockdown on Caenorhabditis elegans. Biochem. Biophys. Res. Commun. 366, 705–709. https://doi.org/10.1016/j.bbrc.2007.12.024.

Wang, Z., Glenn, H., Brown, C., Valavanis, C., Liu, J.-X., Seth, A., Thomas, J.E., Karlstrom, R.O., Schwartz, L.M., 2009. Regulation of muscle differentiation and survival by Acheron. Mech. Dev. 126, 700–709. https://doi.org/10.1016/j.mod.2009.05.003.

Wang, E.T., Cody, N.A.L., Jog, S., Biancolella, M., Wang, T.T., Treacy, D.J., Luo, S., Schroth, G.P., Housman, D.E., Reddy, S., Lécuyer, E., Burge, C.B., 2012. Transcriptome-wide regulation of pre-mRNA splicing and mRNA localization by muscleblind proteins. Cell 150, 710–724. https://doi.org/10.1016/j.cell.2012.06.041.

Wang, E.T., Ward, A.J., Cherone, J.M., Giudice, J., Wang, T.T., Treacy, D.J., Lambert, N.J., Freese, P., Saxena, T., Cooper, T.A., Burge, C.B., 2015. Antagonistic regulation of mRNA expression and splicing by CELF and MBNL proteins. Genome Res. 25, 858–871 doi:10.1101/gr.184390.114.

Wang, F., Minakhina, S., Tran, H., Changela, N., Kramer, J., Steward, R., 2018. Tet protein function during Drosophila development. PLoS One 13, e0190367 doi:10.1371/journal.pone.0190367.

Watts, G.D.J., Wymer, J., Kovach, M.J., Mehta, S.G., Mumm, S., Darvish, D., Pestronk, A., Whyte, M.P., Kimonis, V.E., 2004. Inclusion body myopathy associated with Paget disease of bone and frontotemporal dementia is caused by mutant valosin-containing protein. Nat. Genet. 36, 377–381. https://doi.org/10.1038/ng1332.

Weeland, C.J., van den Hoogenhof, M.M., Beqqali, A., Creemers, E.E., 2015. Insights into alternative splicing of sarcomeric genes in the heart. J. Mol. Cell. Cardiol. 81, 107–113. https://doi.org/10.1016/j.yjmcc.2015.02.008.

Wei, C., Qiu, J., Zhou, Y., Xue, Y., Hu, J., Ouyang, K., Banerjee, I., Zhang, C., Chen, B., Li, H., Chen, J., Song, L.-S., Fu, X.-D., 2015. Repression of the central splicing regulator RBFox2 is functionally linked to pressure overload-induced heart failure. Cell Rep. 10, 1521–1533. https://doi.org/10.1016/j.celrep.2015.02.013.

Weitkunat, M., Schnorrer, F., 2014. A guide to study Drosophila muscle biology. Methods 68, 2–14. https://doi.org/10.1016/j.ymeth.2014.02.037.

Wells, L., Edwards, K.A., Bernstein, S.I., 1996. Myosin heavy chain isoforms regulate muscle function but not myofibril assembly. EMBO J. 15, 4454–4459.

Weyn-Vanhentenryck, S.M., Mele, A., Yan, Q., Sun, S., Farny, N., Zhang, Z., Xue, C., Herre, M., Silver, P.A., Zhang, M.Q., Krainer, A.R., Darnell, R.B., Zhang, C., 2014. HITS-CLIP and integrative modeling define the Rbfox splicing-regulatory network linked to brain development and autism. Cell Rep. 6, 1139–1152. https://doi.org/10.1016/j.celrep.2014.02.005.

Weyn-Vanhentenryck, S.M., Feng, H., Ustianenko, D., Duffié, R., Yan, Q., Jacko, M., Martinez, J.C., Goodwin, M., Zhang, X., Hengst, U., Lomvardas, S., Swanson, M.S., Zhang, C., 2018. Precise temporal regulation of alternative splicing during neural development. Nat. Commun. 9, 2189. https://doi.org/10.1038/s41467-018-04559-0.

Wheeler, T.M., 2008. Myotonic dystrophy: therapeutic strategies for the future. Neurotherapeutics 5, 592–600. https://doi.org/10.1016/j.nurt.2008.08.001.

Wickham, H., 2011. ggplot2. Wiley Interdisciplinary Reviews: Computational Statistics 3. pp. 180–185. https://doi.org/10.1002/wics.147.

Wilkie, G.S., Zimyanin, V., Kirby, R., Korey, C., Francis-Lang, H., Van Vactor, D., Davis, I., 2001. Small bristles, the Drosophila ortholog of NXF-1, is essential for mRNA export throughout development. RNA 7, 1781–1792.

Will, C.L., Lührmann, R., 2011. Spliceosome structure and function. Cold Spring Harb. Perspect. Biol. 3 a003707–a003707. doi:10.1101/cshperspect.a003707.

Wong, M., Martin, L.J., 2010. Skeletal muscle-restricted expression of human SOD1 causes motor neuron degeneration in transgenic mice. Hum. Mol. Genet. 19, 2284–2302. https://doi.org/10.1093/hmg/ddq106.

Worthington, M.T., Amann, B.T., Nathans, D., Berg, J.M., 1996. Metal binding properties and secondary structure of the zinc-binding domain of Nup475. Proc. Natl. Acad. Sci. U. S. A. 93, 13754–13759.

Xie, N., Chen, M., Dai, R., Zhang, Y., Zhao, H., Song, Z., Zhang, L., Li, Z., Feng, Y., Gao, H., Wang, L., Zhang, T., Xiao, R.-P., Wu, J., Cao, C.-M., 2017. SRSF1 promotes vascular smooth muscle cell proliferation through a Δ133p53/EGR1/KLF5 pathway. Nat. Commun. 8, 16016. https://doi.org/10.1038/ncomms16016.

Xu, F., Ackerley, C., Maj, M.C., Addis, J.B.L., Levandovskiy, V., Lee, J., Mackay, N., Cameron, J.M., Robinson, B.H., 2008. Disruption of a mitochondrial RNA-binding protein gene results in decreased cytochrome b expression and a marked reduction in ubiquinol-cytochrome c reductase activity in mouse heart mitochondria. Biochem. J. 416, 15–26. https://doi.org/10.1042/BJ20080847.

Yamaguchi, Y., Oohinata, R., Naiki, T., Irie, K., 2008. Stau1 negatively regulates myogenic differentiation in C2C12 cells. Genes Cells 13, 583–592 doi:10.1111/j.1365-2443.2008.01189.x.

Yang, C., Ramanath, S., Kronert, W.A., Bernstein, S.I., Maughan, D.W., Swank, D.M., 2008. Alternative versions of the myosin relay domain differentially respond to load to influence Drosophila muscle kinetics. Biophys. J. 95, 5228–5237 doi:10.1529/biophysj.108.136192.

Yang, C., Kaplan, C.N., Thatcher, M.L., Swank, D.M., 2010. The influence of myosin converter and relay domains on cross-bridge kinetics of Drosophila Indirect flight muscle. Biophys. J. 99, 1546–1555. https://doi.org/10.1016/j.bpj.2010.06.047.

Ye, J., Beetz, N., O'Keeffe, S., Tapia, J.C., Macpherson, L., Chen, W.V., Bassel-Duby, R., Olson, E.N., Maniatis, T., 2015. hnRNP U protein is required for normal pre-mRNA splicing and postnatal heart development and function. Proc. Natl. Acad. Sci. U. S. A. 112, E3020–9. https://doi.org/10.1073/pnas.1508461112.

Yin, Z., Ren, J., Guo, W., 2015. Sarcomeric protein isoform transitions in cardiac muscle: a journey to heart failure. Biochim. Biophys. Acta 1852, 47–52. https://doi.org/10.1016/j.bbadis.2014.11.003.

Zaffran, S., Astier, M., Gratecos, D., Sémériva, M., 1997. The held out wings (how) Drosophila gene encodes a putative RNA-binding protein involved in the control of muscular and cardiac activity. Development 124, 2087–2098.

Zanetta, C., Nizzardo, M., Simone, C., Monguzzi, E., Bresolin, N., Comi, G.P., Corti, S., 2014. Molecular therapeutic strategies for spinal muscular atrophies: current and future clinical trials. Clin. Ther. 36, 128–140. https://doi.org/10.1016/j.clinthera.2013.11.006.

Zhang, Wenqing, Liu, H., Han, K., Grabowski, P.J., 2002. Region-specific alternative splicing in the nervous system: implications for regulation by the RNA-binding protein NAPOR. RNA 8, 671–685.

Zhang, Libin, Lee, J.E., Wilusz, J., Wilusz, C.J., 2008a. The RNA-binding protein CUGBP1 regulates stability of tumor necrosis factor mRNA in muscle cells: implications for myotonic dystrophy. J. Biol. Chem. 283, 22457–22463. https://doi.org/10.1074/jbc.M802803200.

Zhang, Zhenxi, Lotti, F., Dittmar, K., Younis, I., Wan, L., Kasim, M., Dreyfuss, G., 2008b. SMN deficiency causes tissue-specific perturbations in the repertoire of snRNAs and widespread defects in splicing. Cell 133, 585–600. https://doi.org/10.1016/j.cell.2008.03.031.

Zhang, Zhenxi, Pinto, A.M., Wan, L., Wang, W., Berg, M.G., Oliva, I., Singh, L.N., Dengler, C., Wei, Z., Dreyfuss, G., 2013. Dysregulation of synaptogenesis genes antecedes motor neuron pathology in spinal muscular atrophy. Proc. Natl. Acad. Sci. U. S. A. 110, 19348–19353. https://doi.org/10.1073/pnas.1319280110.

Zhang, Xu, Koolhaas, W.H., Schnorrer, F., 2014. A versatile two-step CRISPR- and RMCE-based strategy for efficient genome engineering in Drosophila. G3 (Bethesda) 4, 2409–2418 doi:10.1534/g3.114.013979.

Zhang, Yunjiao, Si, Y., Ma, N., Mei, J., 2015. The RNA-binding protein PCBP2 inhibits Ang II-induced hypertrophy of cardiomyocytes though promoting GPR56 mRNA degeneration. Biochem. Biophys. Res. Commun. 464, 679–684. https://doi.org/10.1016/j.bbrc.2015.06.139.

Zhang, Linlin, Yang, Y., Li, B., Scott, I.C., Lou, X., 2018. The DEAD-box RNA helicase Ddx39ab is essential for myocyte and lens development in zebrafish. Development 145https://doi.org/10.1242/dev.161018. dev161018.

Zheng, X., Reho, J.J., Wirth, B., Fisher, S.A., 2015. TRA2β controls Mypt1 exon 24 splicing in the developmental maturation of mouse mesenteric artery smooth muscle. Am. J. Physiol., Cell Physiol. 308, C289–96 doi:10.1152/ajpcell.00304.2014.

Zhou, X., Li, M., Huang, H., Chen, K., Yuan, Z., Zhang, Y., Nie, Y., Chen, H., Zhang, X., Chen, L., Chen, Y., Mo, D., 2016. HMGB2 regulates satellite-cell-mediated skeletal muscle regeneration through IGF2BP2. J. Cell. Sci. 129, 4305–4316 doi:10.1242/jcs.189944.

Zullo, L., Fossati, S.M., Imperadore, P., Nödl, M.-T., 2017. Molecular determinants of cephalopod muscles and their implication in muscle regeneration. Front. Cell Dev. Biol. 5, 53 doi:10.3389/fcell.2017.00053.