Supplementary Material

Myotonic dystrophy mouse models: towards rational therapy development

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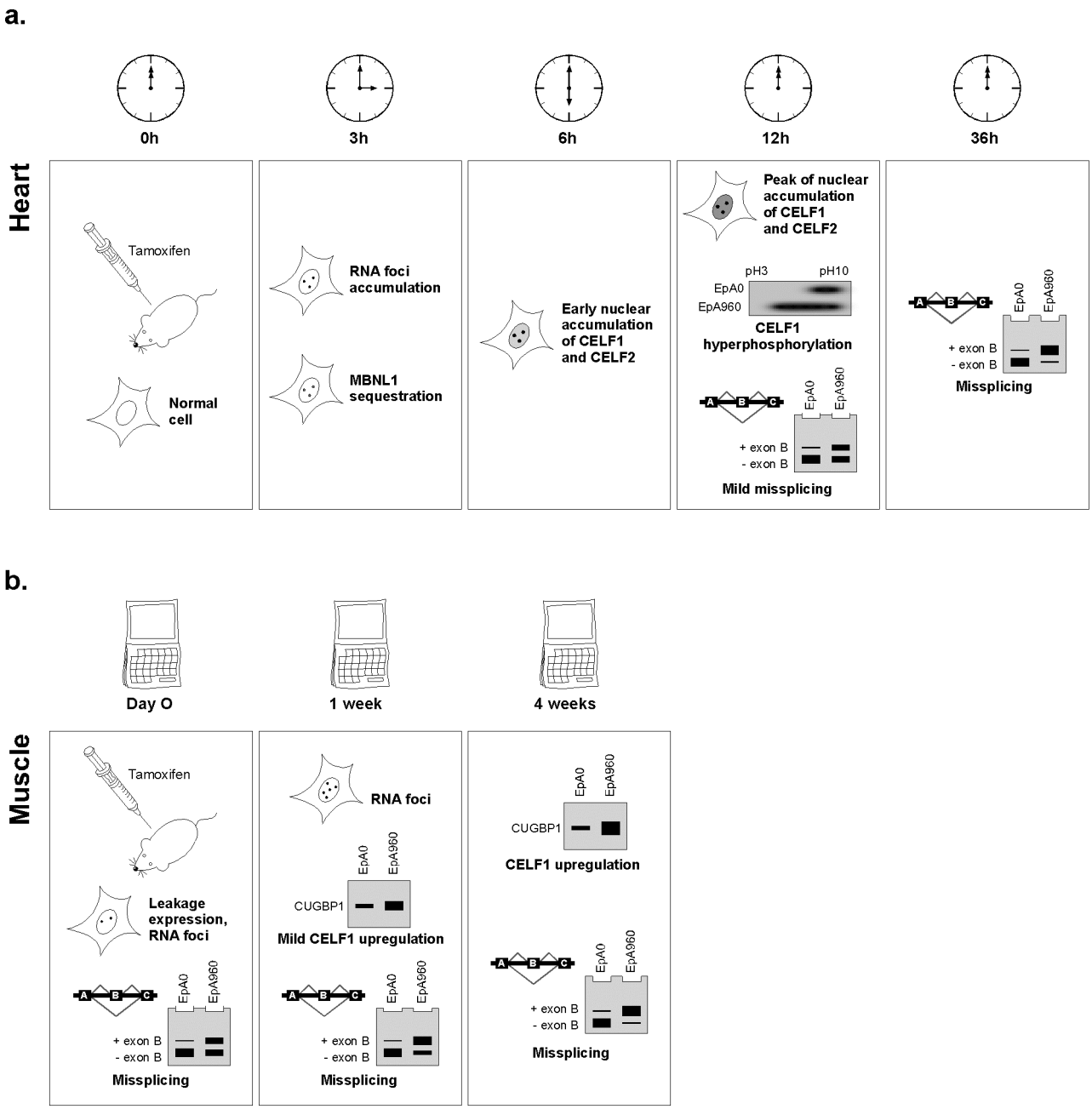

Figure S1. Foci accumulation dynamics and sequence of molecular events following toxic RNA expression. Inducible expression of the transgene allowed a time-course analysis of the molecular events triggered by the expanded CUG repeats in EpA960 heart and skeletal muscle. **(a)** Prior to the induction of transgene expression by tamoxifen administration, mouse heart cells have normal appearance. Three hours following tamoxifen injection CUG-containing RNA foci accumulate in the cell nucleus and sequester muscleblind-like 1 (MBNL1) protein. Increased CUGBP/Elav-like family members 1 (CELF1) and 2 (CELF2) immunofluorescence in the nucleus is first detected six hours following tamoxifen administration and peaks at 12 hours, when CELF1 hyperphosphorylation is detected by two-dimensional electrophoresis. Mild splicing abnormalities are first detected at 12 hours following tamoxifen injection, increasing up to 36 hours. **(b)** Leaky transgene expression in skeletal muscle prior to tamoxifen administration results in foci accumulation and mild splicing defects. CELF1 upregulation is detected one week following tamoxifen injection and increases up to four weeks, paralleling the increasing extent of splicing abnormalities. Splicing abnormalities are detected at four weeks, notably missplicing of CELF1-responsive, but MBNL1-independent transcripts.

Table S1. Abnormal missplicing events described in DM1 patients and transgenic mouse models in skeletal muscles, heart and CNS.

Gene symbol	Gene name	HGNC ID	Entrez gene ID	Target	Refs.
Skeletal muscle					
ATP2A1/ SERCA1	ATPase, Ca++ transporting, cardiac muscle, fast twitch 1	811	487	Exon 22	[S1, 2]
CAPN3	Calpain 3	1480	825	Exon 16	[S2]
CLCN1	Chloride channel 1, skeletal muscle	2019	1180	Intron 2; Exons 7a, 8a	[S3, 4]
DMD	Dystrophin	2928	1756	Exons 71 and 78	[S5]
DTNA	Dystrobrevin, alpha	3057	1837	Exons 11a and 12	[S6]
FHOD1	Formin homology 2 domain containing 1	17905	29109	Exon 11a	[S2]
GFPT1	Glutamine-fructose-6-phosphate transaminase 1	4241	2673	Exon 10	[S2]
INSR	Insulin receptor	6091	3643	Exon 11	[S7]
LDB3/ CYPHER	LIM domain binding 3	15710	11155	Exon 11	[S2]
MBNL1	Muscleblind-like	6923	4154	Exon 7	[S2]
MBNL2	Muscleblind-like	16746	10150	Exon 7	[S2]
MTMR1	Myotubularin related protein 1	7449	8776	Exons 2.1, 2.2	[S8]
NRAP	Nebulin-related anchoring protein	7988	4892	Exon 12	[S2]
PDLIM3	PDZ and LIM domain 3	20767	27295	Exons 5a, 5b	[S2]
RYR1	Ryanodine receptor 1 (skeletal)	10483	6261	Exon 70	[S1]
TNNT3	Troponin T type 3 (skeletal, fast)	11950	7140	Foetal exon	[S9]
TTN	Titin	12403	7273	Z-region Exons 4 and 5; M-line Exon 5	[S2]
Heart					
KCNAB1	Potassium voltage-gated channel, shaker-related subfamily, beta member 1	6228	7881	Exon 2	[S10]
LDB3/ CYPHER	LIM domain binding 3	15710	11155	Exon 11	[S10]
PDLIM3	PDZ and LIM domain 3	20767	27295	Exon 5	[S10]
TNNT2	Troponin T type 2 (cardiac)	11949	7139	Exon 5	[S11]
TTN	Titin			M-line Exon 5	[S10]
Brain					
APP	Amyloid beta (A4) precursor protein	620	351	Exon 7	[S12]
GRIN1	Glutamate receptor, ionotropic, N-methyl D-aspartate 1	4584	2902	Exon 5	[S12]
MAPT/ TAU	Microtubule-associated protein tau	6893	4137	Exons 2, 10	[S12, 13]

Table S2. Histological, molecular and physiological abnormalities found in transgenic mouse models of DM1.

	Histopathology[a]	Molecular phenotype[a]	Physiological and functional phenotype[a]	Repeat dynamics[a]	Refs.
***Dmpk* KO (B. Wieringa)** Transgene expression[b]: Knock-out. Genetic background[b]: 50% C57BL/6 x 129/Ola					
Skeletal muscle	**Late and mild head and neck myopathy.** Clustered small-sized fibres.	Abnormal Ca^{2+} homeostasis.	Normal EMG.	Not applicable	[S14]
***Dmpk* KO (S. Reddy)** Transgene expression: Knock-out. Genetic background: C57BL/6 x 129/Sv					
Skeletal muscle	Late and **progressive myopathy**. **Changes in fibre size.** **Altered mitochondria morphology.** **Myofibre degeneration** and regeneration.	High expression of MyoD and eMHC.	**Decline in force generation.** Abnormal Na^{+} currents.	Not applicable	[S15]
Heart			**Progressive cardiac conduction defects.** **First, second and third degree heart block.** Abnormal Na^{+} currents.		
***Six5* KO (S. Reddy)** Transgene expression: Knock-out. Genetic background: 129/Sv or C57BL/6J x 129/Sv					
Heart			**Mild cardiac conduction defects.**	Not applicable	[S16]
Eye	Lenticular cataracts.	High Atp1a1 expression.			
Testes	**Progressive reduction in testicular mass.** **Leydig cell hyperproliferation.** Spermatogenic cell apoptosis.		**Male sterility.**		
***Six5* KO (S. Tapscott)** Transgene expression: Knock-out. Genetic background: C57BL/6					
Eye	Lenticular cataracts			Not applicable	[S17]
Tg26 (B. Wieringa) Transgene expression: Multisystemic; driven by the human *DMPK* gene promoter. Genetic background: C57BL/6 x 129/Ola					
Skeletal muscle	**Progressive myopathy.** **Centronucleated fibres.** **Changes in fibre size.** **Ringed fibres.** Cytoskeleton disorganisation. **Reduced CLCN1 staining.**		**Deficit in workload tolerance.** **Walking difficulties.** **Myotonic discharges.**	Not reported	[S14, 18]
Heart	**Hyperytophic cardiomyopathy.** Local myocard whorling. Myofibrillar degeneration. **Distorted morphology of mitochondria** and nuclei.	Abnormal Ca^{2+} homeostasis.	Ventricular arrhythmia and dysrhythmia. **Depressed systemic, systolic and diastolic arterial pressure.**		
Other organs and systems			Illness during pregnancy and after delivery.		

Table S2. (continued)

	Histopathology[a]	Molecular phenotype[a]	Physiological and functional phenotype[a]	Repeat dynamics[a]	Refs.
***HSA*^{LR} (C. Thornton)** Transgene expression: Skeletal muscle and neuromuscular junction; driven by the human skeletal actin (HSA) gene promoter. Genetic background: FVB/N					
Skeletal muscle	**Myopathy.** **Centronucleated fibres.** **Ringed fibres.** **Changes in fibre size.** **Reduced CLCN1 immunostaining.**	**Nuclear RNA foci.** **MBNL1 sequestration,** but normal CELF1 levels. **Missplicing** (*e.g. Atp2a1, Atp2a2, Clcn1, Mbnl1, Ttn, Zasp*)	**Myotonia.** **Reduced CLCN1 currents.** High mortality.	Not reported	[S19]
DM300 and/or DMSXL (G. Gourdon) Transgene expression: Multisystemic; driven by the human *DMPK* gene promoter. Genetic background: DM300, C57BL/6; DMSXL: C57BL6/129/Ola/FVB					
Skeletal muscle	**Centronucleated fibres.** **Changes in fibre size and types.** Late **atrophy of muscle.** Abnormalities in diaphragm neuromuscular junctions and phrenic nerves.	**Nuclear RNA foci.** **Missplicing** (*e.g. Insr, Ttn, Ryr1…*)	Mild **myotonia.** **Progressive muscle weakness.** **Reduction of the maximal specific tetanic force in the TA.** **Impaired muscle strength and motor performance** (griptest, wheel test, treadmill test).	**Expansion-biased, tissue-specific, age-dependent somatic mosaicism.**	[S20-24] (unpublished data)
Heart		**Nuclear RNA foci.** **Missplicing** (e.g. *Ldb3, TnnT2*)	**Conduction abnormalities.**		
CNS		**Nuclear RNA foci.** **Missplicing** (*e.g. App, Grin1, Mapt, Mbnl1, Mbnl2*). **Tauopathy.**	**Electrophysiological abnormalities.**		
Other organs and systems		**Nuclear RNA foci and missplicing** (*e.g. Insr*) **in multiple tissues** (*e.g.* pancreas, liver, adipose tissue).	Reduced body size. Increased mortality. Basal hyperglycemia and glucose intolerance. High mortality.	**Expansion-biased, age- and sex-dependent intergenerational instability.**	
EpA960 (T. Cooper) Transgene expression: Conditional and tissue-specific; driven by a CMV enhancer, *ß-actin* gene promoter; and Cre/loxP inducible system; leaky expression. Genetic background: FVB					
Skeletal muscle	**Progressive myopathy.** **Centronucleated fibres.** **Changes in fibre size.** **Fibrosis.** **Myofibre degeneration.** Necrosis. Basophilic fibres.	**Nuclear RNA foci.** **MBNL1 sequestration.** **CELF1 upregulation.** **Missplicing** (*e.g. Atp2a1, Clcn1, Lbd3*)	**Myotonia.** **Muscle wasting.** **Impaired muscle function** (assessed by graded treadmill). High mortality.	Not reported	[S25-27]
Heart	**Dilated cardiomyopathy.** Irregular nuclei. Mitochondria proliferation.	**Nuclear RNA foci.** **MBNL1 sequestration.** **CELF1 hyperphosphorylation and upregulation.** **Missplicing** (*e.g. Tnnt2, Fxr1*). PKC activation.	**Prolonged PR and QRS intervals.** **Heart block.** **Systolic and diastolic dysfunction.** High mortality.	Not reported	

Table S2. (continued)

	Histopathology[a]	Molecular phenotype[a]	Physiological and functional phenotype[a]	Repeat dynamics[a]	Refs.
***GFP-DMPK*-$(CTG)_5$ (M. Mahadevan)** Transgene expression: Conditional, tissue-specific, driven by the *DMPK* gene promoter and tetracycline responsive elements; leaky expression. Genetic background: FVB					
Skeletal muscle	**Myopathy.** **Centronucleated fibres.** Nuclear clustering. **Changes in fibre size.** **Reduced CLCN1 immunostaining.**	Absence of RNA foci. **CELF1 upregulation.** Modest missplicing (*e.g. Clcn1, Tnnt3*). NKX2-5 upregulation.	**Myotonia.**	Not reported	[S28]
Heart	No signs of cardiomyopathy.	Absence of RNA foci. Absence of splicing defects. NKX2-5 upregulation.	**Cardiac conduction defects.** **Prolonged PR intervals.** **Heart block.** High mortality.	Not reported	
***DMPK-GFP*-$(CTG)_{11}$, *DMPK-GFP*-$(CTG)_{91}$ (R. Korneluk)** Transgene expression: Multisyetemic; driven by the human *DMPK* gene promoter. Genetic background: C57BL/6					
Skeletal muscle	**Myofibrillar atrophy.** Developmental defects.			Not reported	[S29]
***Mbnl1*$^{\Delta 3/\Delta 3}$ (M. Swanson)** Transgene expression: Knock-out. Genetic background: 129/Sv					
Skeletal muscle	**Centronucleated fibres.** **Splitting of myofibres.** **Reduced CLCN1 immunostaining.**	**Missplicing** (*e.g. Atp2a1, Clcn1, Lbd3, Mbnl1, Tnnt3*).	**Myotonia.** **Reduced CLCN1 currents.**	Not applicable	[S9, 30]
Heart	**Fibrosis.**	**Missplicing.**	**Cardiac conduction defects.**		
CNS			Apathy and reduced motivation.		
Eye	**Subcapsular *iridescent cataracts.***				
***Mbnl2* KO (F. Chen)** Transgene expression: Knock-out. Genetic background: 129/Ola x C57BL/6J					
Skeletal muscle	**Reduced CLCN1 immunostaining.** **Centronucleated fibres.** **Changes in fibre size.** **Fibrosis.**	**Missplicing.**	**Myotonia.** **Impairment in motor activity.** Spinal curvature and lordosis.	Not applicable	[S31]
***Mbnl2* KO (C. Thornton)** Transgene expression: Knock-out. Genetic background: C57BL/6 x 129					
Skeletal muscle	Normal muscle histology.	Normal splicing.	No myotonia.	Not applicable	[S2]
CUGBP1-TR (L. Timtchenko)[S32] Transgene expression: Multisystemic; driven by human *CELF1* gene promoter and CMV enhancer. Genetic background: FVB					
Skeletal muscle	**Changes in fibre size and content.** **Centronucleated fibres.**	Increased levels of p21 and MEF2A.	**Reduced muscle size.**	Not applicable	
Other organs and systems			Reduction in body weight. High mortality.	Not applicable	

Table S2. (continued)

	Histopathology[a]	Molecular phenotype[a]	Physiological and functional phenotype[a]	Repeat dynamics[a]	Refs.
MCKCUG-BP1 (T. Cooper) Transgene expression: Skeletal muscle and heart; driven by mouse creatine kinase (MCK) gene promoter and enhancer. Genetic background: FVB					
Skeletal muscle	**Centronucleated fibres**. **Changes in fibre size.** Irregular nuclear shape.	**Missplicing** (*e.g. Clcn1, Mtmr1*).		Not applicable	[S33]
Heart	Normal heart histology.	**Missplicing** (*e.g. Mtmr1, Tnnt2*).			
Other organs and systems			Stillborn death.		
TRECUGBP1 (T. Cooper) Transgene expression: Conditional and tissue-specific; driven by minimal CMV promoter and tetracycline-responsive element. Genetic background: FVB					
Skeletal muscle	**Centronucleated fibres.** **Changes in fibre size.** **Myofibre atrophy.**	**Missplicing** (*e.g. Serca1, Ryr1, Mtmr1, Lbd3*).	**Reduction is muscle weight and muscle function** (treadmill assay).	Not applicable	[S34, 35]
Heart	**Hypertrophy.** **Fibre degeneration.** Necrosis. Loss of myocardial fibres.	**Missplicing** (*e.g. Atp2a1, Clcn1, Lbd3*).	**Conduction abnormalities.** **Prolonged PR interval and QRS complex.** **Systolic dysfunction** and ventricular dilation. High mortality within two weeks.		
Other organs and systems			Reduction in body weight. Decreased movement and abnormal gait. Poor grooming.		
***Dmt*-D (D. Monckton)** Transgene expression: Fortuitous expression in multiple tissues; driven by an unidentified mouse gene promoter. Genetic background: FVB					
Kidney Liver Striatum (…)				**Expansion-biased, tissue-specific, age-dependent somatic mosaicism.**	[S36, 37]
Other organs and systems				**Expansion-biased, age- and sex-dependent intergenerational instability.**	
***Dmpk*(CTG)84 (B. Wieringa)** Transgene expression: Multisystemic; driven by the murine *Dmpk* gene promoter. Genetic background: C57BL/6 x 129/Ola; C57BL/6 x 129/Ola x Balb/C; C57BL/6 x 129/Ola x FVB; C57BL/6 x 129/Ola x C3H					
Kidney Stomach Small intestine Brain Eyes (…)				**Expansion-biased, tissue- and cell-specific, age-dependent somatic mosaicism**, influenced by mouse genetic background and genetic polyploidy.	[S38]
Other organs and systems				**Expansion-biased, genetic-background-dependent intergenerational instability.**	

Table S2. (continued)

	Histopathology[a]	Molecular phenotype[a]	Physiological and functional phenotype[a]	Repeat dynamics[a]	Refs.
***Znf9*$^{+/-}$ (Y.-P. Li)** Transgene expression: Knock-out. Genetic background: C57BL/6J					
Skeletal muscle	**Centronucleated fibres. Changes in fibre size.**	Reduced *Clcn1* mRNA levels.	Myotonia.	Not applicable	[S39, 40]
Heart	**Myocardial hypertrophy. Centronucleated fibres. Fibrosis.**		**Conduction abnormalities. Cardiac arrhythmias. Prolonged PR interval.**		
Other organs and systems	Ocular cataracts.		Gait abnormalities.		
DM2-*HSA*tg (R. Krahe) Transgene expression: Driven by the human skeletal actin (HSA) gene promoter.					
Skeletal muscle.	**Myopathy.**	**RNA foci.** Absence of splicing defects.	**Muscle weakness.**	Not reported	[S41] (R. Krahe, unpublished)
Other organs and systems		CELF1 upregulation in liver.			

a. A summary of histopathological findings, molecular abnormalities and physiological phenotypes are described, as well as features of CTG trinucleotide repeat instability. Mouse phenotypes that have closely and consistently mimicked aspects of the human disease are represented in bold.

b. For each DM1 transgenic mouse line a summary of the transgene expression pattern and mouse strain background is presented.

Supplementary references

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