DM2 RESEARCH UPDATE

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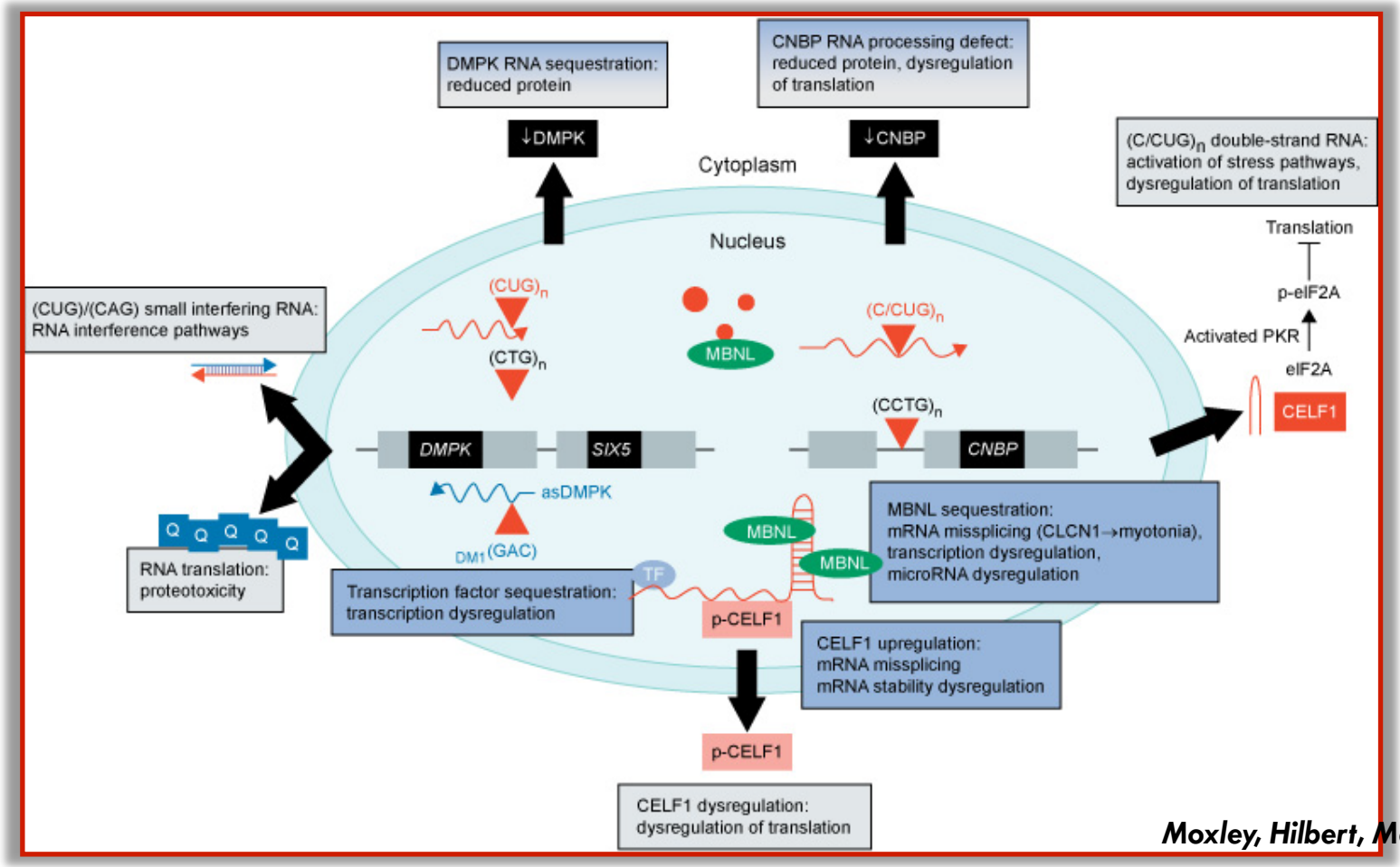
Outline

- Pathogenesis
- Modifier Genes
- Management
- Molecular Therapy
- Take Home Message

Dr Meola has nothing to disclose

Pathogenetic mechanism

Spliceopathy does not fully explain the multisystemic phenotype
thus additional mechanisms may be involved



Moxley, Hilbert, Meola. 2015

DM1 *vs* DM2

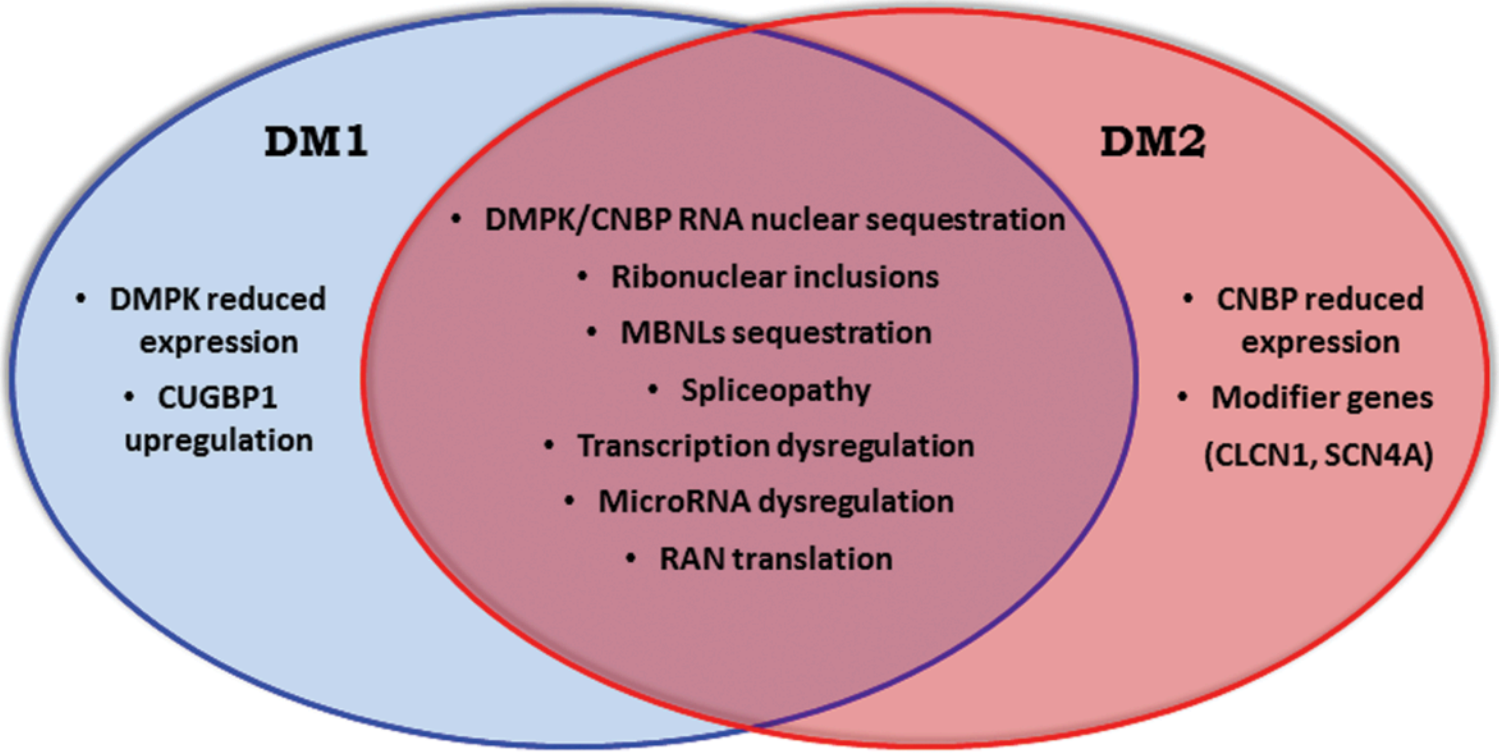
Journal of Neuromuscular Diseases 2 (2015) S59–S71
DOI 10.3233/JND-150088
IOS Press

Research Report

Myotonic Dystrophy Type 2: An Update on Clinical Aspects, Genetic and Pathomolecular Mechanism

Meola and Cardani, 2015

the phenotypic differences between DM1 and DM2 can be explained by other cellular and molecular pathways involved besides the shared toxic-RNA gain of function hypothesized



Alternative splicing

Differences in aberrant expression and splicing of sarcomeric proteins in the myotonic dystrophies DM1 and DM2

Anna Vihola · Linda L. Bachinski · Mario Sirito · Shodimu-Emmanuel Olufemi · Shohrae Hajibashi · Keith A. Baggerly · Olayinka Raheem · Hannu Haapasalo · Tiina Suominen · Jeanette Holmlund-Hampf · Anders Paetau · Rosanna Cardani · Giovanni Meola · Hannu Kalimo · Lars Edström · Ralf Krahe · Bjarne Udd

Vihola et al., 2010

DM1 vs DM2

- **differences in muscle gene expression and splicing: in particular, the aberrant splicing isoform of TNNT3 is twice as frequent in DM2 compared to DM1**

MOREOVER

different protein expression pattern in the highly atrophic fibers has been found between DM1 and DM2

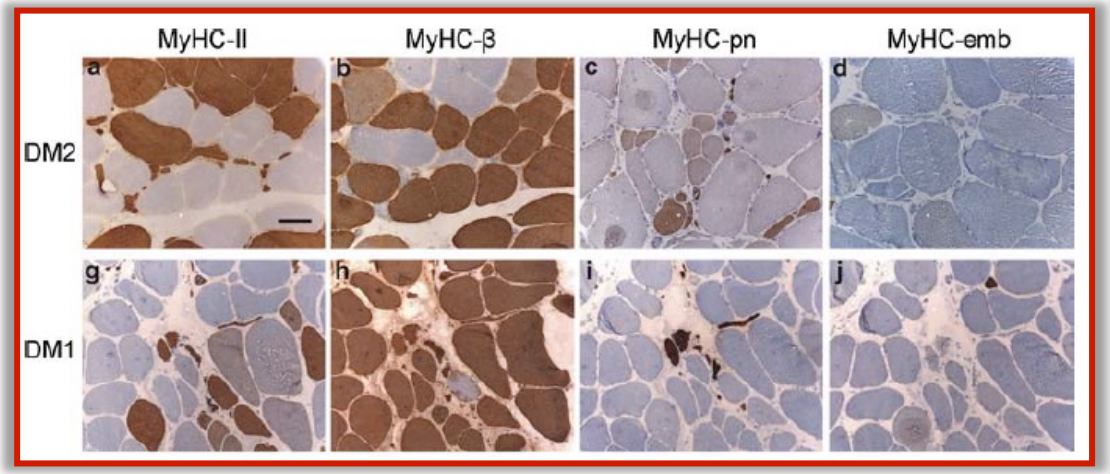
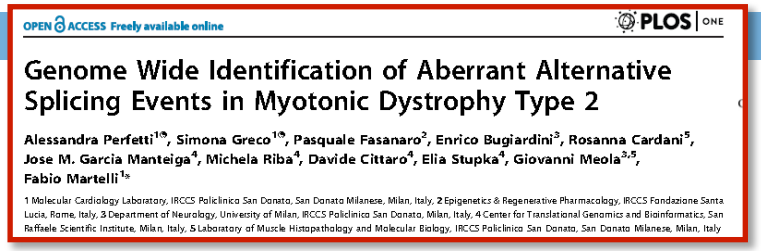


Table 3 Immunohistochemistry results of highly atrophic fibers

Protein	Gene	DM2	DM1
MyHC-IIa	*MYH2*	+++	+++
MyHC-beta	*MYH7*	(+)	+++
MyHC-pn	*MYH8*	+++	+++
MyHC-emb	*MYH3*	(+)	(+)
fTnT	*TNNT3*	++	++
NCAM	*NCAM1*	++	+
Myogenin	*MYOG*	(+)	(+)
Vimentin	*VIM*	(+)	+

Protein expression: (+), in <1% of highly atrophic fibers; +, in 1–10%; ++, in 30–50%; +++, in >75%. The results indicate how many fibers of the highly atrophic fibers pool expressed each given antigen in DM2 ($n = 20$) and DM1 ($n = 5$) muscle biopsies

Alternative splicing



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PLOS ONE

Genome Wide Identification of Aberrant Alternative Splicing Events in Myotonic Dystrophy Type 2

Alessandra Perfetti[1☯], Simona Greco[1☯], Pasquale Fasanaro[2], Enrico Bugiardini[3], Rosanna Cardani[5], Jose M. Garcia Manteiga[4], Michela Riba[4], Davide Cittaro[4], Elia Stupka[4], Giovanni Meola[3,5], Fabio Martelli[1]*

1 Molecular Cardiology Laboratory, IRCCS Policlinico San Donato, San Donato Milanese, Milan, Italy, 2 Epigenetics & Regenerative Pharmacology, IRCCS Fondazione Santa Lucia, Rome, Italy, 3 Department of Neurology, University of Milan, IRCCS Policlinico San Donato, Milan, Italy, 4 Center for Translational Genomics and Bioinformatics, San Raffaele Scientific Institute, Milan, Italy, 5 Laboratory of Muscle Histopathology and Molecular Biology, IRCCS Policlinico San Donato, San Donato Milanese, Milan, Italy

Perfetti et al., 2014

In DM2 muscle biopsies 273 alternative spliced exons in 218 genes were identified

many of these splicing events had been previously described as deregulated either in DM1 or DM2 or both

a subset of alternative splicing events were validated by qPCR in biceps brachii biopsies from 19 DM2 and 15 CTR age and sex matched patients

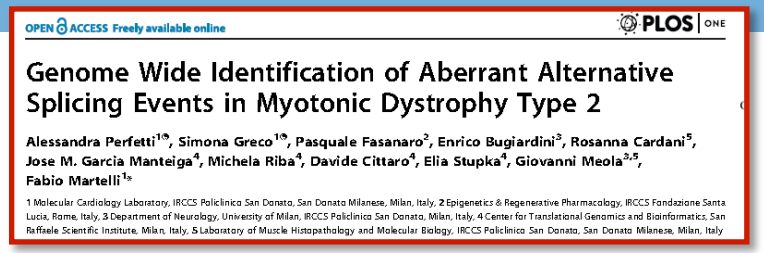
previously described in DM1 and/or DM2

- **PDLIM3**
- **LIMCH1**
- **NDUFV3**
- **CAMK2G**

- **ZMYND11**
- **PDP1**
- **ERI2**
- **VCL**
- **MBOAT7**
- **LAMC2**

not previously described in DM1 and/or DM2

Alternative splicing



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Perfetti et al., 2014

the molecular pathways involving the identified aberrantly spliced genes, were studied by Interactive Pathway Analysis

Table 1. Most significant categories and functions.

DISEASE AND DISORDERS	p value
Immunological disease	3.11E-04 2.13E-02
Neurological disease	3.11E-04 2.30E-02
Skeletal and Muscular Disorders	3.11E-04 1.77E-02
Cancer	9.22E-04 2.46E-02
Reproductive System Disease	9.22E-04 1.77E-02
MOLECULAR AND CELLULAR FUNCTIONS	**p value**
Cell Death and Survival	1.05E-04 2.13E-02
Cellular Development	1.81E-04 1.83E-02
Cell Morphology	2.85E-04 1.77E-02
Cellular Movement	5.35E-04 2.46E-02
Cell To Cell Signaling and Interaction	1.25E-03 2.46E-02
PATHWAYS	**log(p value)**
Lanosterol Biosynthesis	1.73E00
Netrin Signaling	1.73E00
Epithelial Adherens Junction Signaling	1.62E00
Fatty Acid Biosynthesis Initiation II	1.46E00
Palmitate Biosynthesis I (Animals)	1.46E00
Urea Cycle	1.46E00
Calcium Signaling	1.42E00
TOP CARDIOTOXIC FUNCTIONS	**p value**
Increased Levels of Albumin	1.77E-02 1.77E-02
Increased Levels of Alkaline Phosphatase	1.77E-02 6.12E-01
Cardiac Arrythmia	4.07E-03 3.23E-01
Tachycardia	4.07E-03 3.23E-01
Cardiac Dilation	1.77E-02 1.43E-01
Congenital Heart Anomaly	1.77E-02 4.33E-01
Cardiac Hypoplasia	3.95E-02 3.93E-02

doi:10.1371/journal.pone.0093983.t001

The affected genes are involved in numerous pathways and networks important for muscle physio-pathology, suggesting that the identified variants may contribute to DM2 pathogenesis.

of particular interest

Skeletal and Muscular Disorders

Neurological Diseases

Cell Death and Survival

Cellular Development

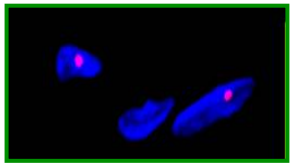
Calcium signaling

Cardiac Arrythmia

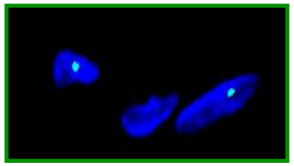
CUGBP1 expression

both in DM1 and DM2

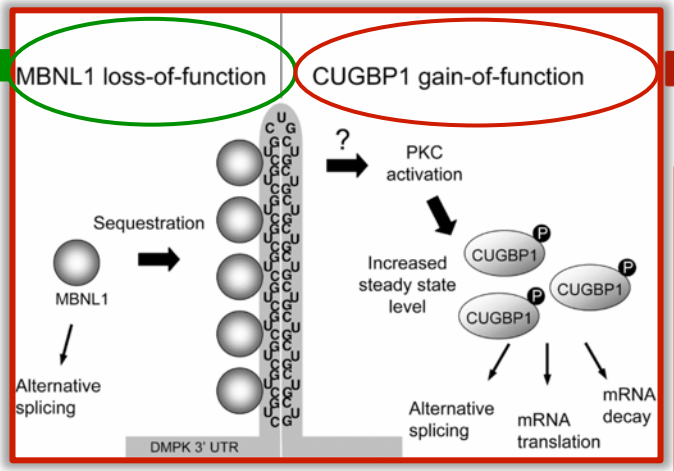
it is clear that MBNL1 is depleted from nucleoplasm through recruitment into ribonuclear inclusions even when clinical symptoms and muscle alterations are very mild



Toxic RNA



MBNL1 foci



CUGBP1 overexpression has been clearly demonstrated in DM1 but not in DM2 muscle

conflicting data have been reported on the expression of CUGBP1 in DM2 human skeletal muscle

CUGBP1

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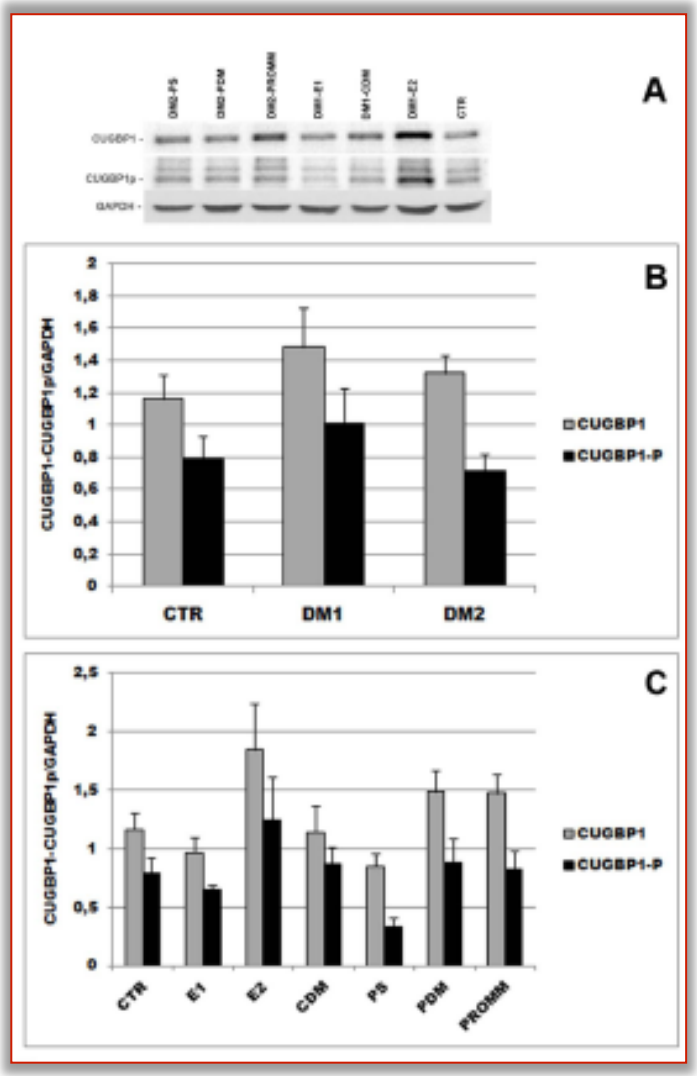
Overexpression of CUGBP1 in Skeletal Muscle from Adult Classic Myotonic Dystrophy Type 1 but Not from Myotonic Dystrophy Type 2

Rosanna Cardani[1☯], Enrico Bugiardini[2☯], Laura V. Renna[3], Giulia Rossi[4], Graziano Colombo[3], Rea Valaperta[5], Giuseppe Novelli[6], Annalisa Botta[4], Giovanni Meola[1,2*]

1 Laboratory of Muscle Histopathology and Molecular Biology, IRCCS Policlinico San Donato, Milan, Italy, 2 Department of Neurology, University of Milan, IRCCS Policlinico San Donato, Milan, Italy, 3 Department of Biosciences, University of Milan, Milan, Italy, 4 Department of Biomedicine and Prevention, Tor Vergata University of Rome, Rome, Italy, 5 Research Laboratories - Molecular Biology, IRCCS Policlinico San Donato, Milan, Italy, 6 IRCCS Neuromed, Pozzilli, Isernia, Italy

Cardani et al., 2013



- **CUGBP1 is overexpressed in DM1 muscle biopsies however the increase is evident only in "classic" DM1 form where CUGBP1 overexpression is accompanied by a parallel increase of the amount of phosphorylated isoform**
- **in DM2 muscle biopsies a slight increase of the CUGBP1 protein levels is observed not related to an increase of protein phosphorylation**

CUGBP1 seems to play a role in classic DM1 more evidently than in DM2

ZNF9/CNBP

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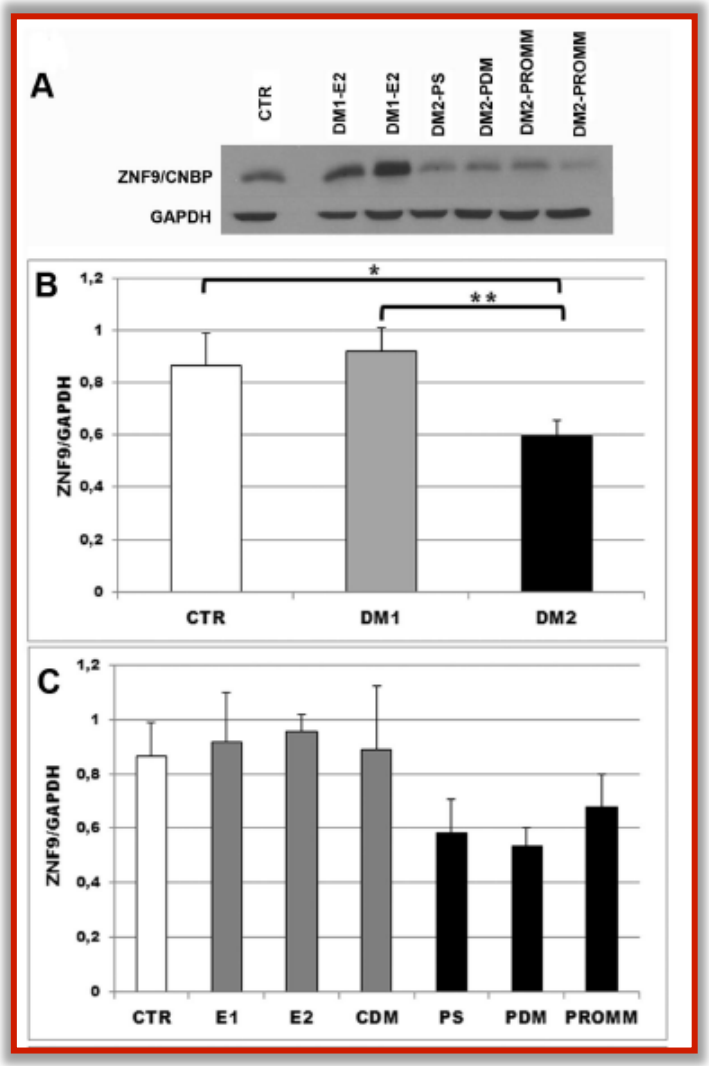
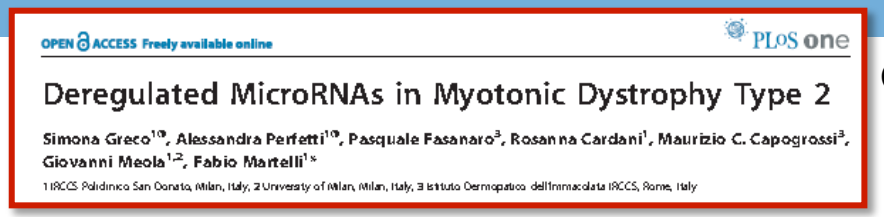
Cardani et al., 2013



ZNF9/CNBP protein levels are significantly reduced in DM2 muscle biopsies compared to DM1 and non-diseased biopsies

ZNF9/CNBP expression might play a role in phenotypic differences between DM1 and DM2

MicroRNA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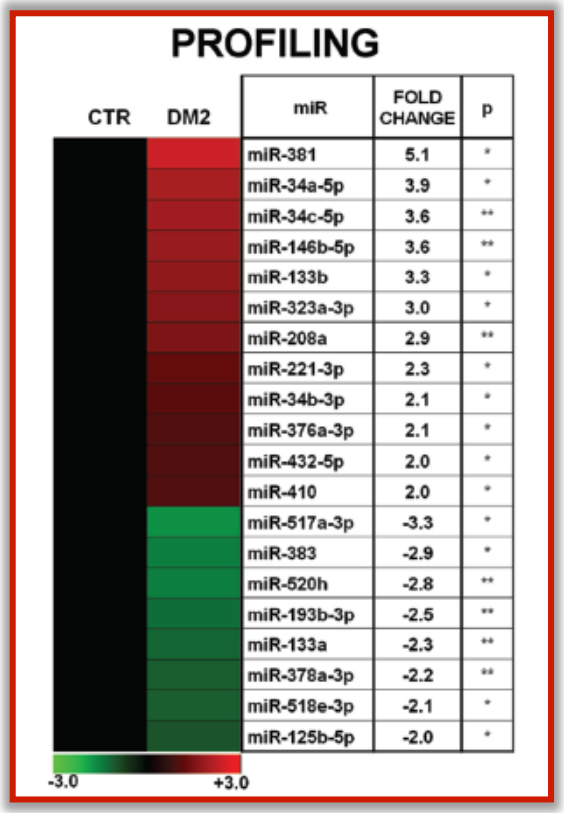
Deregulated MicroRNAs in Myotonic Dystrophy Type 2

Simona Greco[1☯], Alessandra Perfetti[1☯], Pasquale Fasanaro[3], Rosanna Cardani[1], Maurizio C. Capogrossi[3], Giovanni Meola[1,2], Fabio Martelli[1*]

1 IRCCS Policlinico San Donato, Milan, Italy, 2 University of Milan, Milan, Italy, 3 Istituto Dermopatico dell'Immacolata IRCCS, Rome, Italy

Greco et al., 2012

MiRNA profiling identified 20 miRNAs significantly modulated in DM2 muscle compared to CTR

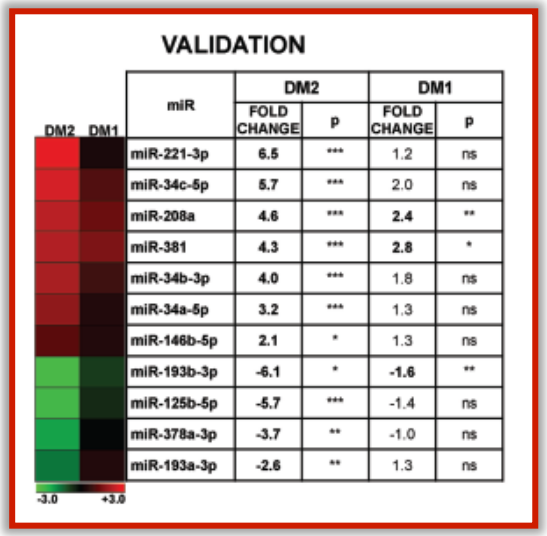


miR	FOLD CHANGE	p
miR-381	5.1	*
miR-34a-5p	3.9	*
miR-34c-5p	3.6	**
miR-146b-5p	3.6	**
miR-133b	3.3	*
miR-323a-3p	3.0	*
miR-208a	2.9	**
miR-221-3p	2.3	*
miR-34b-3p	2.1	*
miR-376a-3p	2.1	*
miR-432-5p	2.0	*
miR-410	2.0	*
miR-517a-3p	-3.3	*
miR-383	-2.9	*
miR-520h	-2.8	**
miR-193b-3p	-2.5	**
miR-133a	-2.3	**
miR-378a-3p	-2.2	**
miR-518e-3p	-2.1	*
miR-125b-5p	-2.0	*

validation by more sensitive and specific qPCR assays identified 11 deregulated miRNAs

⇓

miRNA score allowed to discriminate DM2 patients from CTR with a good sensitivity and specificity.



miR	DM2 FOLD CHANGE	DM2 p	DM1 FOLD CHANGE	DM1 p
miR-221-3p	6.5	***	1.2	ns
miR-34c-5p	5.7	***	2.0	ns
miR-208a	4.6	***	2.4	**
miR-381	4.3	***	2.8	*
miR-34b-3p	4.0	***	1.8	ns
miR-34a-5p	3.2	***	1.3	ns
miR-146b-5p	2.1	*	1.3	ns
miR-193b-3p	-6.1	*	-1.6	**
miR-125b-5p	-5.7	***	-1.4	ns
miR-378a-3p	-3.7	**	-1.0	ns
miR-193a-3p	-2.6	**	1.3	ns

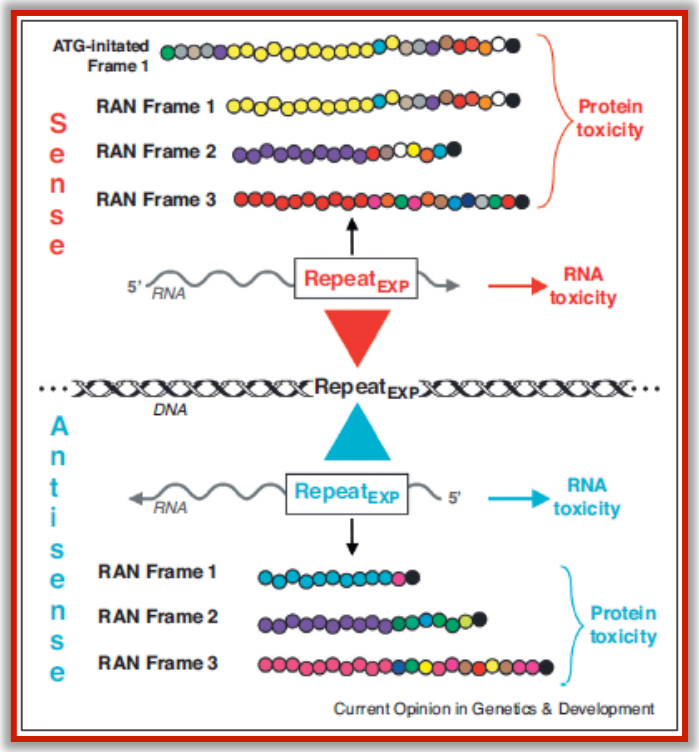
miR-193b-3p, miR-208a and miR-381 showed a similar significant modulation also in DM1 patients

RAN Translation

Non-ATG–initiated translation directed by microsatellite expansions

Tao Zu[a,b,c], Brian Gibbens[a,b,c,1], Noelle S. Doty[a,b,c,1], Mário Gomes-Pereira[d], Aline Huguet[d], Matthew D. Stone[e,f], Jamie Margolis[a,b,c], Mark Peterson[g], Todd W. Markowski[e,f], Melissa A. C. Ingram[a,b,c], Zhenhong Nan[h], Colleen Forster[i], Walter C. Low[h], Benedikt Schoser[i], Nikunj V. Somia[a,b], H. Brent Clark[c,j,k], Stephen Schmechel[l], Peter B. Bitterman[g], Geneviève Gourdon[d], Maurice S. Swanson[l], Melinda Moseley[a,b,c], and Laura P. W. Ranum[a,b,c,2,3]

Zu et al., 2010



a repeat expansion mutation can produce potentially toxic RNA and protein products expressed through a combination of:

- **bidirectional transcription**
- **ATG-initiated translation**
- **repeat associated non-ATG (RAN) translation**

RAN translation of the expanded repeat results in the expression of up to six distinct RAN proteins

Table 1

***In vitro* and *in vivo* evidence for RAN translation**

	Repeat	*In Vitro* evidence of RAN proteins	*In Vivo* evidence of RAN proteins	Reference
SCA8	CAG•CTG	Gln_S[a,b,g], Ala_S[a,b,c,d,f,g], Ser_S[a,b,g] Leu_{AS}[a], Ala_{AS}[a], Cys_{AS}[a]	Ala_S[i,m]	Zu et al. [12••]
DM1	CAG•CTG	Gln_{AS}[a,e,f], Ala_{AS}[a], Ser_{AS}[a]	Gln_{AS}[i,j,l,m]	Zu et al. [12••]
FXTAS	CGG•CCG	Gly_S[a], Ala_S[a,d,g]	Gly_S[h,j,m]	Todd et al. [24••]
C9ORF72 ALS FTD	G_4C_2•G_2C_4	$GlyPro_S$[e], $GlyAla_S$[e]	$GlyPro_{S/AS}$[l], $GlyAla_S$[l], $GlyArg_S$[l] $GlyPro_{S/AS}$[l] $GlyPro_{S/AS}$[k] $GlyAla_S$[l]	Mori et al. [47••] Ash et al. [44••] Almeida et al. [36] Mackenzie et al. [45]
		$GlyPro_{S/AS}$[e], $ProArg_{AS}$[e]	$GlyPro_{S/AS}$[l], $ProArg_{AS}$[l], $ProAla_{AS}$[l] $GlyPro_{S/AS}$[k] $GlyArg_S$[l], $GlyAla$[m] $ProArg_{AS}$[l], $ProAla_{AS}$[l]	Gendron et al. [38•] Donnelly et al. [37•] Mori et al. [46•]
		$GlyPro_S$[a,f], $GlyArg_S$[a,e,f] $GlyAla$[a,f] $GlyPro_{S/AS}$[a,e], $ProArg_{AS}$[a,e,f], $ProAla_{AS}$[a,e,f]	$GlyPro_S$[l,m], $GlyArg_S$[l,m], $GlyAla$[m] $GlyPro_{AS}$[l], $ProArg_{AS}$[l,m], $ProAla_{AS}$[l,m] $GlyArg_S$[l], $GlyAla_S$[l] $GlyPro_{S/AS}$[l], $ProArg_{AS}$[l], $ProAla_{AS}$[l]	Zu et al. [48••] Mann et al. [49]

RAN Translation

Non-ATG–initiated translation directed by microsatellite expansions

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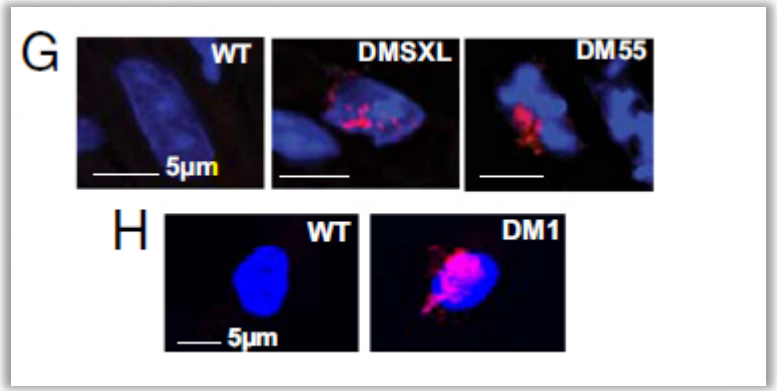
Zu et al., 2010

In DM1 mouse model polyGln nuclear aggregates

- Cardiac myocytes
- leukocytes
- myoblasts
- skeletal muscle

anti- poliGln antibody →



RAN translation has been demonstrated also in DM2

↓

a terta-repeat expansion protein is produced
poly-Leu-Pro-Ala-Cys (LPAC)

anti- poly-Leu-Pro-Ala-Cys (LPAC) antibody →

DM2 brain
poly-Leu-Pro-Ala-Cys (LPAC)
nuclear aggregates in :
neurons, astrocytes and glia of frontal cortex
hippocampus
basal ganglia

Myoblast senescence

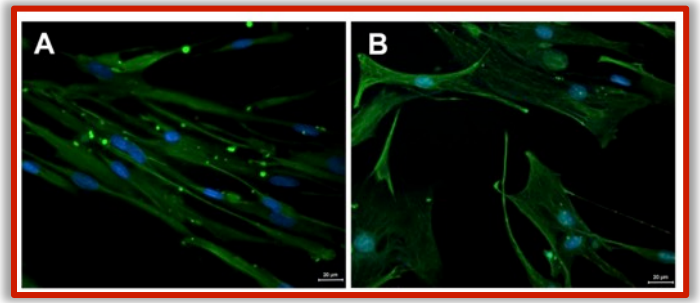
European Journal of Histochemistry

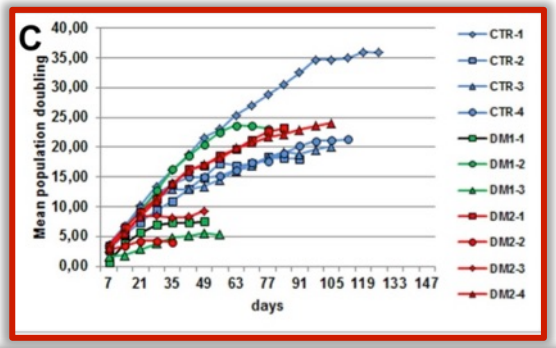
Premature senescence in primary muscle cultures of myotonic dystrophy type 2 is not associated with p16 induction

L.V. Renna,[1] R. Cardani,[2] A. Botta,[3] G. Rossi,[3] B. Fossati,[4] E. Costa,[5,6] G. Meola[2,4]

Renna et al., 2014

DM myoblasts have lower proliferative capability than control myoblasts and reach *in vitro* senescence earlier than controls

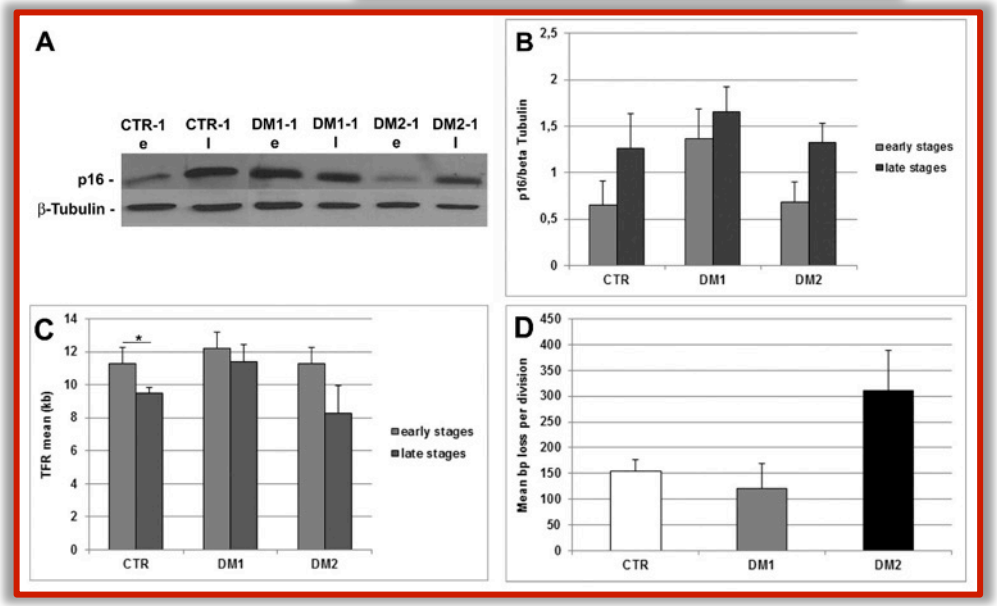




HOWEVER

differentely from DM1, the p16 pathway is not responsible for the premature growth arrest observed in DM2 myoblasts which stop dividing with telomeres shorter than controls

These data could explain the different histological alterations observed between DM1 and DM2 skeletal muscle as for example the selective type 2 fiber atrophy present in DM2 muscle



Modifier genes

Myotonia

In DM2 patients:

- **usually is less severe than in DM1 patients**
- **sometimes may be difficult to reveal even with EMG**

however

in several DM2 patients it can be very severe

in a cohort of 45 genetically confirmed DM2 patients 4/45 patients (8,89%) presented a severe or early onset myotonia.

The genetic analysis of *CLCN1* and *SCN4A* revealed that

- **2 patients showed a recessive mutation in *CLCN1* gene**
- **2 patients showed a mutation in *SCN4A* gene**

Modifier gene: CLCN1

J Neurol
DOI 10.1007/s00415 012 6462 1

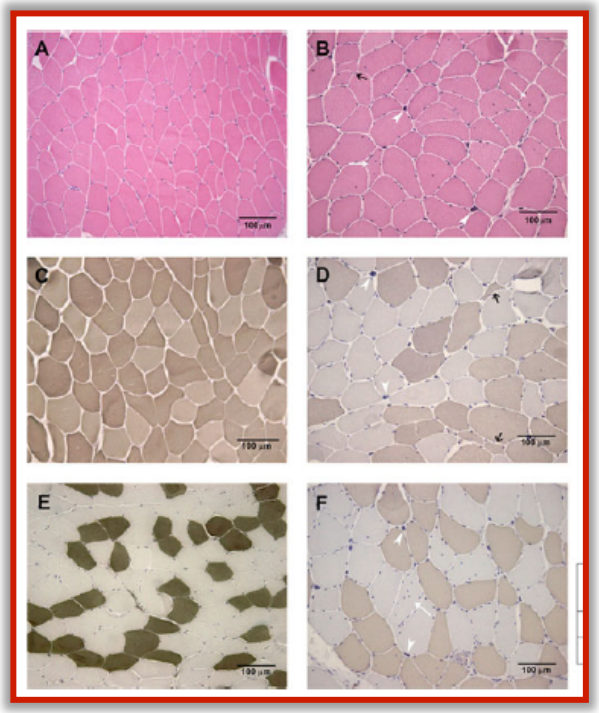
ORIGINAL COMMUNICATION

Co-segregation of DM2 with a recessive CLCN1 mutation in juvenile onset of myotonic dystrophy type 2

Rosanna Cardani · Marzia Giagnacovo · Annalisa Botta · Fabrizio Rinaldi · Alessandra Morgante · Bjarne Udd · Olayinka Raheem · Sini Penttilä · Tiina Suominen · Laura V. Renna · Valeria Sansone · Enrico Bugiardini · Giuseppe Novelli · Giovanni Meola

Cardani et al., 2012

A 15-year-old DM2 patient and her mother were studied to further investigate the unusually young onset in this DM2 family



- **the age at onset was earlier in the daughter than in the mother**
- **the daughter's clinical, histopathological and biomolecular findings did not show greater severity than those observed in her mother**

HOWEVER

daughter presented handgrip myotonia at the age of 14 years.

Direct sequencing CLCN1 gene revealed a heterozygous mutation c.501C>G p.F167L in daughter maternally inherited

the co-segregation of DM2 with a recessive CLCN1 mutation provided the explanation for the unusual clinical findings

Modifier gene: SCN4A

SCN4A mutation as modifying factor of Myotonic Dystrophy Type 2 phenotype

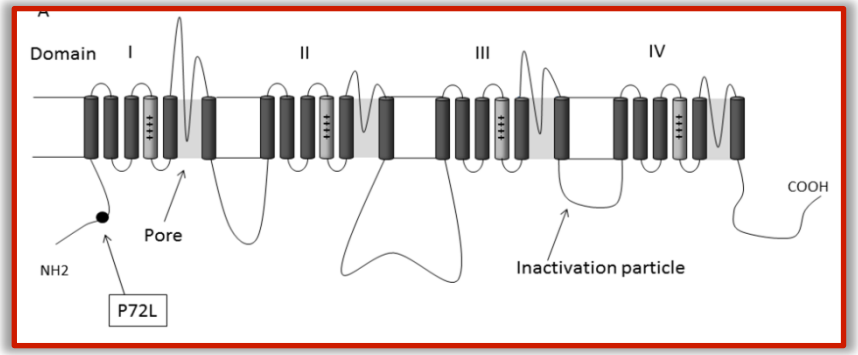
E. Bugiardini [a,1], I. Rivolta [b,1], A. Binda [b], A. Soriano Caminero [c], F. Cirillo [d], A. Cinti [e], R. Giovannoni [e], A. Botta [f], R. Cardani [g], M.P. Wicklund [c], G. Meola [a,g,*]

Bugiardini et al., 2015

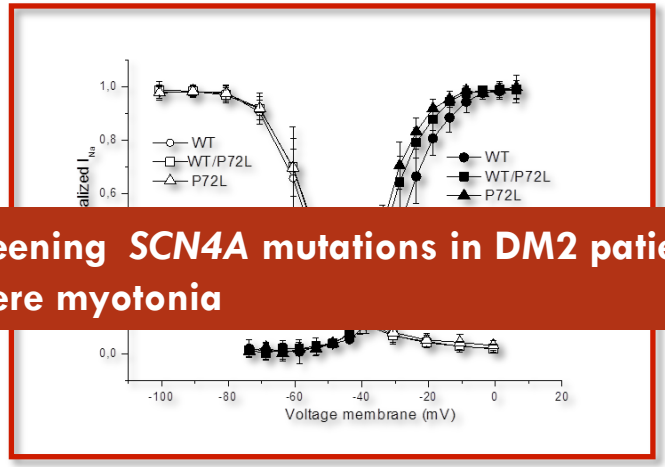
A 26 year old patient complaining of hand cramps and difficulty relaxing her hands after activity was evaluated

Genetic testing was positive:

- **for DM2 (2650 CCTG repeat)**
- **for a variant c.215C>T (p.Pro72Leu) in the *SCN4A* gene**



The variation affects the cytoplasmic N-terminus domain of Nav1.4, where mutations have never been reported



Electrophysiological studies of the P72L variant increase cell excitability

If CLCN1 screening is negative, this case supports for screening *SCN4A* mutations in DM2 patients with atypical cases with severe myotonia

Myotonic dystrophies management

	DM1	DM2
Brain	Psychological, educational, and counseling evaluations as needed Structural imaging as required Routinely assess for sleep disturbances and respiratory insufficiency	Psychological, educational, and other counseling treatment and services CNS medications (for example, stimulants) as necessary under close supervision of care providers
Heart	Yearly electrocardiograms Cardiology consultation for symptomatic patients and long-term follow-up care	Prompt pacemaker placement as needed
Respiratory	Serial monitoring of sitting and supine respiratory function; including forced vital capacity Polysomnography and pulmonary medicine consultation as required	Yearly immunizations Noninvasive or invasive ventilation as required Serial evaluation by pulmonary medicine and sleep consultation as required
Anesthesia	Before elective surgery, have anesthesia consultation and pulmonary medicine evaluation ECG reviewed by cardiology consult Discuss known risks and any previous anesthesia related problems	Use of regional anesthesia over general when appropriate Use of non-depolarizing muscle relaxants Reduce use of opioids In general anesthesia, protection of the airway and minimizing aspiration, careful cardiac monitoring, and extensive postoperative monitoring (at least 24 hours)

Myotonic dystrophies management

	DM1	DM2
Hypersomnia and fatigue	Polysomnograms Metabolic and endocrine screens Psychological, educational, and sleep consultant evaluations	Use of continuous positive airway pressure (CPAP) or bi-level positive airway pressure (BiPAP) Use of CNS stimulants
Endocrine	Symptomatic assessment of testosterone deficiency Yearly lipid profile, thyroid screening, diabetes screening Monitor sleep disturbances	Hormone replacement as required Dietary intervention Medications for lipid and glucose control as needed Treatment for sleep disturbances as required
Gastrointestinal	Occupational and physical therapy consultation (dysphagia) Metabolic and endocrine screens Dietician, gastrointestinal consultations Careful assessment of bloating and signs of pseudo-obstruction	Gastroesophageal reflux may be treated with avoidance of late-night meals, elevation of the head of the bed, and medications Constipation, diarrhea, abdominal pain, and bloating may be treated with modifying the diet to small, low-fat meals Surgery as appropriate for gall bladder disease Use of cholestyramine may help alleviate diarrhea
Pregnancy	Obtain obstetrician and genetic consultation prior to pregnancy as appropriate Discuss possible complications Coordinate monitoring of pregnancy with other care providers, including a neonatal pediatric specialist Closely monitor respiratory function during the third trimester	During delivery, monitor mother's ECG Use regional anesthesia Notify consultants of mother's status and request urgent evaluations as necessary

RNA level: small molecules

Selective inhibition of MBNL1–CCUG interaction by small molecules toward potential therapeutic agents for myotonic dystrophy type 2 (DM2)†

Chun-Ho Wong, Yuan Fu, Sreenivasa Rao Ramisetty, Anne M. Baranger* and Steven C. Zimmerman*

2011

Small Molecules that Target the Toxic RNA in Myotonic Dystrophy Type 2

Lien Nguyen, JuYeon Lee, Chun-Ho Wong, and Steven C. Zimmerman*[a]

2014

Structure of the Myotonic Dystrophy Type 2 RNA and Designed Small Molecules That Reduce Toxicity

2014

Jessica L. Childs-Disney[#a], Ilyas Yildirim[#b], HaJeung Park[a,c], Jeremy R. Lohman[a], Lirui Guan[a], Tuan Tran[a], Partha Sarkar[d], George C. Schatz[b], and Matthew D. Disney[a,*]

Most of the molecules identified resulted to be toxic in cellular assays

Take home message

Take home message

The enormous advances in the understanding of the molecular pathogenesis of DM1 and DM2 has revealed pathways of molecular pathogenesis more complex than previously appreciated

however

the basis for the differences between DM1 and DM2 has not been clarified at the molecular level

important for the development of effective therapies

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……and to patients and their families

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