JUNE 2020

SAVOIR & COMPRENDRE
AVANCÉES DE LA RECHERCHE

ADVANCES in myotonic dystrophy type 2

> DM2
>proximal myotonic myopathy
> PROMM

Myotonic dystrophy type 2 or PROMM (Proximal Myotonic Myopathy) is a rare disease of genetic origin. It affects the muscles, which become weak (dystrophy) and difficult to relax after contraction (myotonia). It can also affect other organs (heart, eyes, etc.). It manifests in adulthood and progresses slowly. This disease has many similarities with another, much more common neuromuscular disease, Steinert's disease (or myotonic dystrophy type 1).

This document has been translated into English form *"Les Avancées dans la dystrophie myotonique de type 2"*, published by the French Muscular Dystrophy Assocation (AFM-Téléthon). It presents news from the past year about research into myotonic dystrophy type 2: international symposia, ongoing clinical trials or studies, scientific and medical publications, etc.

It can be downloaded from the English version of the AFM-Téléthon website we, where other information can also be found regarding AFM-Téléthon projects to develop treatments for rare diseases.

WEB www.afm-telethon.com

AFMTÉLÉTHON
INNOVER POUR GUÉRIR

Drafted by
▪ Myoinfo,
Neuromuscular Disease Information Department, AFM-Téléthon, Évry

French version validation
▪ Guillaume Bassez
Myology Research Centre, Institute of Myology, Pitié-Salpêtrière Hospital, Paris
▪ Denis Furling
Myology Research Centre, Institute of Myology, Pitié-Salpêtrière Hospital, Paris.
▪ Geneviève Gourdon
Myology Research Centre, Institute of Myology, Pitié-Salpêtrière Hospital, Paris
▪ Nathalie Loux
Project Manager
Scientific Department, AFM-Téléthon, Evry.

English version validation
▪ Jon Andoni Urtizberea,
Institute of Myology, Pitié-Salpêtrière Hospital, Paris

Acknowledgments
▪ We would like to thank all the individuals affected by this disease who have taken the time to review or amend all or part of this document.

Table of Contents

*
* *

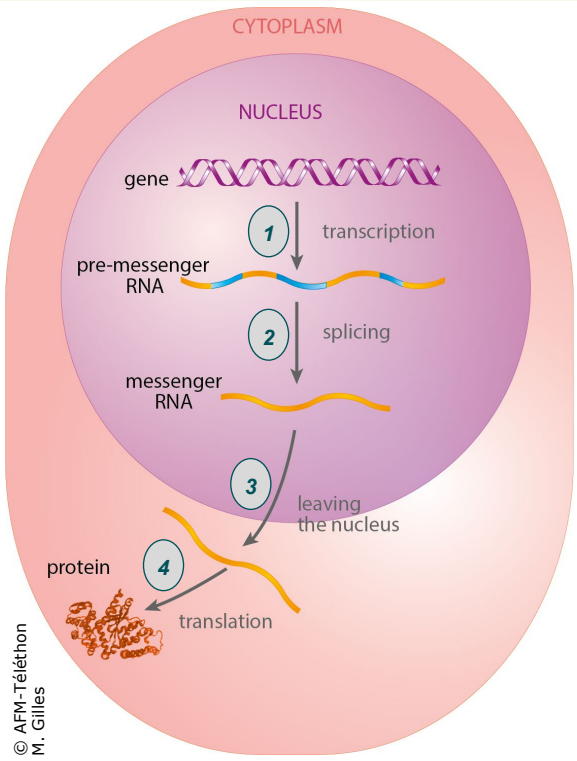
Genetic diseases *are diseases resulting from abnormalities in an individual's DNA, i.e. the information that determines how the body functions biologically. This information is contained in our cells in the form of chromosomes. We inherit this information from our parents and our children inherit it from us. This is why genetic diseases are often familial, i.e. several members of the same family may be affected by the same genetic disease.*

Myotonic dystrophy type 2 (DM2), also known as Proximal Myotonic Myopathy (PROMM) is a rare neuromuscular disease of genetic origin.
It is caused by abnormal repeats of a small DNA sequence (CCTG nucleotide quadruplet), in the *ZNF9* (also known as *CNBP*) gene on chromosome 3.
Usually, up to 75 CCTG repeats are present on the *ZNF9* gene. In DM2, the number of CCTG repeats is abnormally high, ranging from 75 up to more than 10,000 repeats.

Abnormal messenger RNA disrupts normal muscle cell function.

Assembly instructions are needed to produce the ZNF9 protein. This is the role of the *ZNF9* messenger RNA.
It is produced in the nucleus by copying the *ZNF9* gene (transcription).
After maturation (splicing), the *ZNF9* messenger RNA leaves the nucleus to serve as a guide in the production of the ZNF9 protein.

The role of messenger RNA in protein synthesis

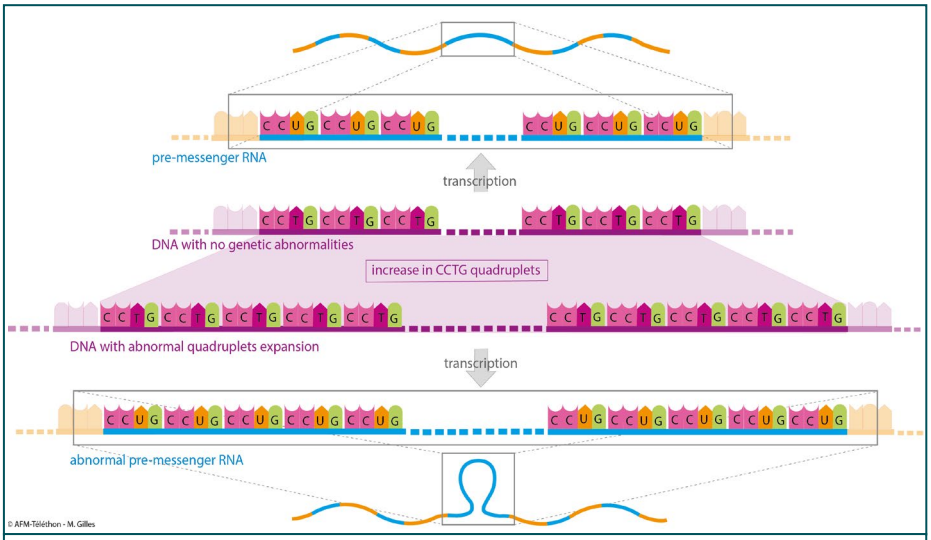


Messenger RNA is a copy of a gene. It contains the information needed to produce a protein.

***1.** Pre-messenger RNA is produced in the nucleus from the DNA sequence (transcription).*
***2.** It undergoes a maturation process (splicing), resulting in messenger RNA that can be used to synthesise a protein.*
***3.** Messenger RNA leaves the nucleus, heading into the cytoplasm where protein synthesis takes place.*
***4.** It is used as a 'template' by the cell machinery to produce a protein (translation).*
Each of these steps is controlled by so-called 'regulatory' proteins.

*The **nucleotide** is the base unit of the DNA molecule and comes in 4 different types (A, T, G and C). Each combination of 3 nucleotides (triplet or trinucleotide) on the gene corresponds to an amino acid in the protein.*

▪ In DM2, abnormal CCTG quadruplet repeats are also copied into the *ZNF9* messenger RNA.

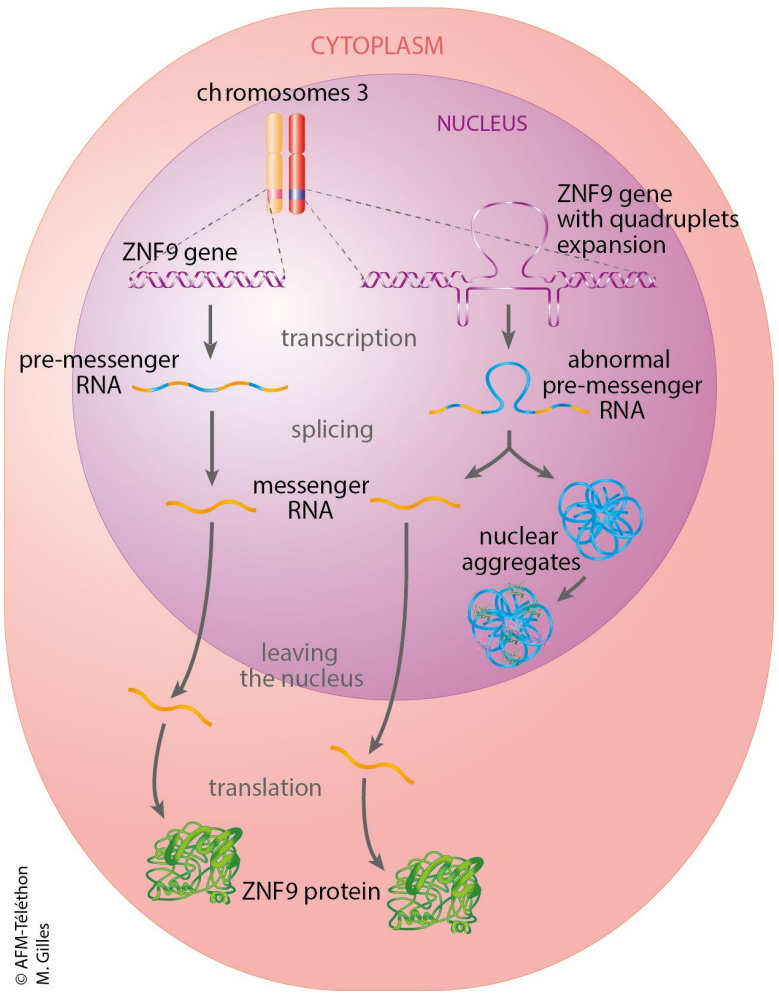


Expansion of CCTG quadruplets in DM2

DM2 is caused by a significant increase in the number of repeats of a small DNA sequence composed of 4 nucleotides (quadruplet) in the ZNF9 gene.
During the production of the ZNF9 messenger RNA, this repeated sequence is copied.
The ZNF9 messenger RNA has a long CCUG chain that has a tendency to fold back onto itself and form stem-loops with other ZNF9 messenger RNAs.

The *ZNF9* RNA containing CCUG expansions form abnormal stem-loops that accumulate in the nucleus and generate nuclear aggregates, which in turn cause the sequestration of regulatory proteins of the MBNL (Muscleblind-like) family, such as MBNL1, MBNL2 and MBNL3.

These regulatory proteins are involved in the maturation of numerous messenger RNAs (other than *ZNF9* messenger RNA). The sequestration of MBNL regulatory proteins causes, by extension, significant cell disruption.



Formation of aggregates in the nucleus

- The CCTG expansion is transcribed into CCUG in the ZNF9 messenger RNA, forming abnormal messenger RNA.

- The CCUG sequences in the abnormal ZNF9 messenger RNA have a tendency to bind to each other and to nuclear regulatory proteins.

- They form aggregates that prevent these regulatory proteins from fulfilling their role in the maturation (splicing) of messenger RNA for numerous genes.

- This disrupts normal cell function.

***Splicing** is one of the steps in protein synthesis. In the first step, namely 'transcription', the gene message is transcribed into messenger RNA (a bit like a photocopy of the part of the DNA carrying the gene). In the second step, namely 'splicing', the messenger RNA is spliced: certain parts (the introns) are cut and the remaining pieces (the exons) are recombined into a single mature messenger RNA strand that contains only the information needed to guide protein synthesis.*

Key events

REDs, an enhanced team to combat myotonic dystrophy

Since 2019, four teams have come together, led respectively by Denis Furling, an expert in myotonic dystrophy, Geneviève Gourdon, a specialist in CTG triplet repeats, Arnaud Ferry, a specialist in muscle physiology, and Guillaume Bassez, a neurologist and clinician/researcher who coordinates the DM-Scope registry. These complementary teams now make up the Repeat Expansions & Myotonic Dystrophy (REDs) team, thus pooling efforts to combat this disease, accelerating research and generating new therapeutic avenues.

WEB https://www.institut-myologie.org/recherche/myologie-centre-de-recherche/equipe-4-denis-furling/

Uniting the European myotonic dystrophy associations

The year 2019 saw the birth of a new patient association called Euro-DyMA (European Myotonic Dystrophy Association) exclusively dedicated to myotonic dystrophies type 1 and type 2, and uniting the European patient associations involved in combating these diseases.

The Institute of Myology hosts the headquarters of this association, a very short distance from the new REDs team. AFM-Téléthon is, obviously, represented within Euro-DyMA, in particular via the Steinert's disease (DM1/DM2) Interest Group.

WEB http://euro-dyma.eu/

Euro-DyMA: the European myotonic dystrophy association
Trait d'union - The Steinert's disease (DM1/DM2) Interest Group Newsletter 2020 (Jan)

Medical/scientific conferences and workshops

There are several conferences dedicated to myotonic dystrophy, allowing researchers and clinicians engaged in this disease to exchange information regarding the progress of their research projects and to establish new collaborations.

The International Myotonic Dystrophy Consortium, IDMC-12

The International Myotonic Dystrophy Consortium (IDMC) meets every two years. Its 12th edition (**IDMC-12**) took place between the 10th and the 14th of June 2019 in Gothenburg, Sweden. It received financial support from AFM-Téléthon.

Experts in this disease from around the world exchanged information regarding scientific advances in molecular mechanisms, animal models, databases, therapeutic avenues and clinical trials in myotonic dystrophy. A review of ongoing projects has confirmed that the pharmaceutical industry has a growing interest in myotonic dystrophy, with more than a dozen different pharmaceutical companies involved, mostly in programmes that are still at the pre-clinical stage.

WEB https://idmc12.org/

The *Myotonic* annual conference

▪ The annual conference of the American *Myotonic* association saw a gathering, over a 3-day period in September 2019, of over 450 individuals, including 160 professionals involved in researching and treating myotonic dystrophy. Among them were 45 representatives from pharmaceutical

companies, demonstrating the level of involvement of the pharmaceutical industry in research on Steinert's disease, and also DM2.
WEB https://www.myotonic.org/2019-myotonic-annual-conference

The time for clinical trials has returned, in the United States primarily…
Trait d'union - The Steinert's disease (DM1/DM2) Interest Group Newsletter 2019 (Jan)

▪ A pipeline of drug candidates currently in development in myotonic dystrophy and arising from academic or pharmaceutical research, is available online on the *Myotonic* association's website. Three pharmaceutical companies currently have ongoing projects in DM2.
WEB https://www.myotonic.org/sites/default/files/pages/files/Myotonic-Dystrophy-Drug-Development-Pipeline-as-of-19-May-2020-Full.pdf

*The **central nervous system** consists of the brain (cerebrum, cerebellum and brainstem) and its extension, the spinal cord. It is protected by a bone structure (the neurocranium for the brain and the spinal column for the spinal cord). It analyses sensory information, coordinates movement and transmits commands for the muscles to contract.*

A workshop on central nervous system impairment in myotonic dystrophy

▪ A workshop on central nervous system impairment has been organised by the American *Myotonic* association, as part of its annual conference in September 2019.
WEB https://www.myotonic.org/sites/default/files/pages/files/Myotonic-CNSWorkshopAgenda-FNL-2019-08-22.pdf

This topic is regularly addressed during Myotonic conferences, and was the subject of a dedicated session in 2017 aimed at individuals suffering from myotonic dystophy and their close caregivers. This meeting, which involved almost 350 participants, provided a description of the signs of nervous system impairment and their impact on quality of life. While it is most commonly described in DM1, central nervous system impairment is also seen in DM2.
As with muscle weakness, the families are awaiting an effective treatment for central nervous system impairment, first and foremost for memory lapses and for feelings of "confused" thoughts. This requires, inter alia, a determination of which assessment tools are reliable and relevant in measuring cognitive impairment and its progression, particularly in the context of a clinical trial.

Patient Input to Inform the Development of Central Nervous System Outcome Measures in Myotonic Dystrophy.
White M.
Ther Innov Regul Sci. 2020 (Jan)

The ENMC Workshop

▪ A workshop entitled: "Myotonic dystrophies, molecular approaches for clinical purposes. Framing a European molecular research network", organised by the ENMC in October 2019 at Hoofddorp (the Netherlands) brought together almost 30 participants (researchers, geneticists, molecular biologists, clinicians, patient associations including AFM-Téléthon, etc.), with the aim of identifying obstacles slowing down the development of new therapies in myotonic dystrophy and offering solutions.
Steinert's disease, and to a lesser degree myotonic dystrophy type 2, are characterised by a very diverse range of symptoms, even within a single family with several members affected. The mechanisms involved in the appearance of a specific symptom are not all known. Broader sharing of knowledge and expertise, and also research tools, would help to better understand the disease mechanisms and identify new therapeutic targets. The various participants would like to see the establishment of a European consortium to strengthen their interactions.

*The **European Neuromuscular Centre** (ENMC) is an international organisation that aims to support research in the field of neuromuscular disease. It regularly organises international meetings bringing together scientists and clinicians on a specific topic.*
WEB www.enmc.org/

WEB https://www.enmc.org/download/myotonic-dystrophies-molecular-approaches-for-clinical-purposes-framing-a-european-molecular-research-network/

248th ENMC International Workshop: Myotonic dystrophies: Molecular approaches for clinical purposes, framing a European molecular research network, Hoofddorp, the Netherlands, 11-13 October 2019.
Wansink DG, Gourdon G, van Engelen BGM *et al.*
Neuromuscul Disord 2020 (Apr)

National and international congresses on neuromuscular disease

The topic of myotonic dystrophy is also regularly addressed at French and international congresses dedicated to neuromuscular disease, such as the *Myology 2019* international congress (organised by AFM-Téléthon in March 2019 in Bordeaux), the annual meeting of the French Myology Society (organised in November 2019 in Marseille), or the International Congress of the *World Muscle Society* (October 2019 in Copenhagen, Denmark).

2020, a singular year

The COVID-19 pandemic has had an impact on myotonic dystrophy research: many teams have put their laboratory work on pause, certain clinical trials have been discontinued provisionally, and congresses have been cancelled or postponed.

In response to the health crisis, healthcare professionals and patient associations have mobilised.

▪ The FILNEMUS rare neuromuscular diseases network, which acts as coordinator and host for French centres of expertise, has stimulated a great deal of action from the very beginning of the pandemic, and is adapting this action through biweekly e-meetings, in which doctors from AFM-Téléthon participate.
Thus, it has issued recommendations for doctors and patients, posted on its website frequently asked questions & answers and self-rehabilitation materials to mitigate the closure of physiotherapy practices, and issued alerts regarding the risks associated with administering hydroxychloroquine. It has also developed a national operational strategy for reference centres and centres of expertise, in order to ensure patients receive optimal and consistent treatment across France.
FILNEMUS has surveyed more than 90 neuromuscular patients affected by COVID-19 in France:

▪ A survey organised by FILNEMUS, in collaboration with AFM-Téléthon, among individuals affected by neuromuscular disease, will help to assess the impact of the pandemic (psychological impact, impact on home care, etc.).

WEB http://www.filnemus.fr/
WEB https://www.afm-telethon.fr/coronavirus

▪ The AFM-Téléthon Steinert's disease (DM1/DM2) Interest Group published an issue of its newsletter on COVID-19, including several interviews with myotonic dystrophy specialists.

WEB Steinert's disease and COVID
WEB Trait d'union - The Steinert's disease (DM1/DM2) Interest Group Newsletter 2019 (May)

▪ On the international stage, the American *Myotonic* association published recommendations on the respiratory care of patients with myotonic dystrophy during the pandemic. These were translated into French by the Neuromuscular Disease Network for Canada (NMD4C).

*The **FILNEMUS rare neuromuscular diseases healthcare network** is hosting, coordinating and encouraging interactions between participants in the diagnosis, treatment and research of new muscular diseases (reference centres and centres of expertise, diagnostic laboratories, research teams, associations for individuals affected by these conditions, etc.). It was created in February 2014, as part of the second Rare Diseases French National Plan, 2011-2014.*
WEB www.filnemus.fr

WEB https://www.myotonic.org/respiratory-care-recommendations-myotonic-dystrophy-patients-during-covid-19-pandemic

The publication of international recommendations

In order to ensure that every individual with myotonic dystrophy (DM) benefits from the best possible care, the American patient association, *Myotonic,* is encouraging recommendations to be produced that can be referred to by care teams who are not (or not very) used to diagnosing and treating these diseases.

▪ Thus, in the last year, *Myotonic* has published the first consensus-based care recommendations for adults with DM2 and recommendations regarding cardiological care in DM1 and DM2.

All these recommendations come from working groups involving a combination of clinicians and researchers from North America and Europe (including France), and are based mainly on expert opinions and on the results of the few controlled available clinical. For each topic, the authors review all aspects of treatment, from the diagnostic stage to follow-up methods.

Consensus-based care recommendations for adults with myotonic dystrophy type 2.
Schoser B, Montagnese F, Bassez G *et al.*
Neurol Clin Pract. 2019 (Aug)

Clinical Care Recommendations for Cardiologists Treating Adults With Myotonic Dystrophy.
McNally EM, Mann DL, Pinto Y *et al.*
J Am Heart Assoc. 2020 (Feb)

▪ These reference documents are available in several languages on the *Myotonic* website.
WEB https://www.myotonic.org/toolkits-publications

▪ *Genereview*, a reference medical journal on genetic diseases, has updated an article dedicated to DM2.

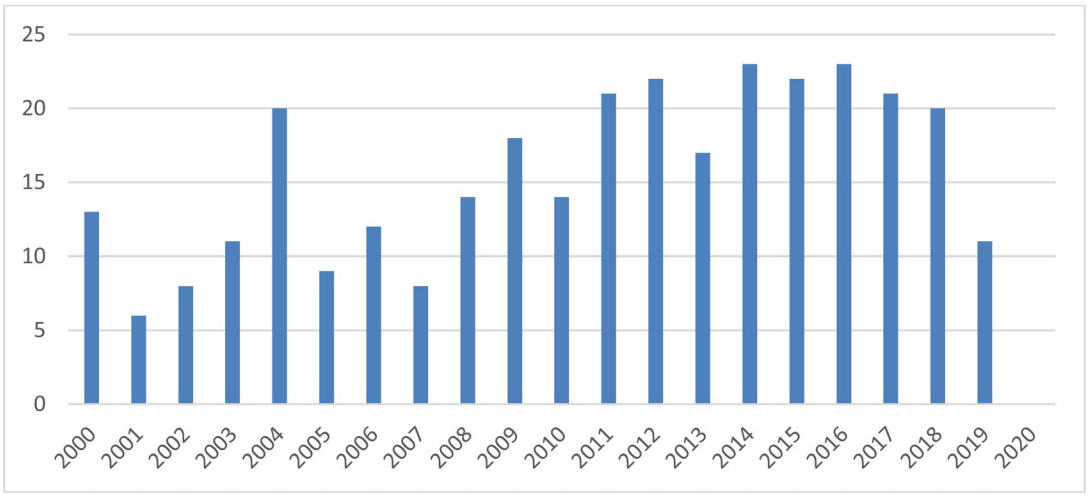
Myotonic Dystrophy Type 2.
Schoser B
GeneReviews (March 2020 update)

*"**Myotonic**" (the new name for the Myotonic Dystrophy Foundation – MDF) is an American not-for-profit organisation dedicated to myotonic dystrophy. Its mission is to contribute towards improving the quality of life of patients with myotonic dystrophy and to support research into a treatment for this condition.*
WEB www.myotonic.org

Scientific publications

It is through articles published in specialist journals that researchers working on myotonic dystrophy type 2 (DM2) communicate to the scientific and medical community their work and the conclusions or hypotheses they are able to draw from this work. The number of publications recorded each year on DM2 demonstrates that there is continuing interest in this disease, which was first described in 1994.

▪ Several major areas of research stand out:
- gaining a better clinical understanding of DM2 (the consequences of this disease on the body, what medical examinations are used most often for follow-up, in daily practice or during clinical trials, etc.);
- suggesting and evaluating different treatments and drug candidates in clinical trials;
- studying the disease mechanisms involved in the onset of the disease and suggesting new therapeutic avenues.



Number of medical/scientific publications on DM2 each year since 2000.

Patient Databases

The development of patient databases makes it possible to perform a survey (an exhaustive one in the case of a registry) of patients suffering from a particular disease, to clarify the natural history of the disease, to establish genotype/phenotype correlations and to help recruit patients into clinical trials.

***Genotype/phenotype correlation** studies investigate the existence of a relationship between genetic characteristics, the genotype, and characteristics expressing themselves in an observable manner, the phenotype (height, eye colour and shape, hair colour, disease manifestation, etc.). This makes it possible to identify a (more or less) close relationship between the presence of genetic abnormalities and the manifestations of a genetic disease.*

The DM-Scope Observatory

The DM-Scope is a patient database, supported by AFM-Téléthon which was established in France in 2008 for the purpose of collecting data relating to patients with myotonic dystrophy and supporting clinical research among these patients. It has become the largest database in the world for myotonic dystrophy.

▪ DM-Scope contains demographic, clinical and laboratory data for 3,359 patients with myotonic dystrophy: 185 patients with DM2 (1 child and 184 adults) and 3,174 patients with DM1 (363 children at the time of inclusion and 2,811 adults).

DM-Scope French Observatory for myotonic dystrophy

Studying the natural history of the disease, improving treatment, and promoting clinical research and the development of new therapies.

(supported by AFM-Téléthon)

Status	Country	Date created
Recruitment is ongoing	France	January 2008

As of June 2020: 185 patients with myotonic dystrophy type 2 have been included in the DM-Scope Observatory.

▪ In an article published in June 2019, a Franco-Québec consortium headed by researchers from the Institute of Myology in Paris presented a report on the status of this database.

Thanks to close cooperation between 55 neuromuscular reference centres or centres of expertise, DM-Scope is the most significant database in the world dedicated to myotonic dystrophy. It is responsible for 12 clinical studies in myotonic dystrophy (observational studies, fundamental research, recruitment of patients for clinical trials, etc.), including one aimed at better describing hearing disorders in DM2 (study currently underway).

The DM-scope registry: a rare disease innovative framework bridging the gap between research and medical care.

De Antonio M, Dogan C, Daidj F *et al.*

Orphanet J Rare Dis. 2019 (Jun)

WEB http://www.dmscope.fr/

***Neuromuscular disease reference centres** provide specialist consultations in the field of neuromuscular disease that are approved by the French Ministry of Health. Besides the medical follow up of patients with neuromuscular diseases, reference centre consultations can be requested for their expertise in the area of diagnosis or treatment, for complex medical situations. They contribute to the conduct of clinical trials and to the improvement of professional*

The I-DM-Scope project

The objective of the French/Québec consortium called iDM-Scope is to create an **international platform** for myotonic dystrophy in order to facilitate the setting up of multicentre studies, conduct natural history studies, identify biological markers, develop potential treatments, etc. First established in July 2016, it combines the DM-Scope Observatory and the Q-DMR Québec database that encompasses the Québec and Saguenay regions.

The Q-DMR Québec myotonic dystrophy registry Better understanding DM, facilitating the participation of patients in research projects and clinical trials		
Status	**Country**	**Date created**
Recruitment is ongoing	Canada	2002
As of April 2018: 1410 patients had been included in this database.		

Other registries worldwide

The MDFR (Myotonic Dystrophy Family Registry) is an online database launched in 2013 by the American patient association, *Myotonic*. It collects medical and demographic information about patients with myotonic dystrophy (DM), to help researchers develop effective new treatments and to identify participants for potential research studies. The goal is to collect data for 3000 patients aged 11 to 17 years, followed up over a 5-year period (due to end in February 2021).

Myotonic Dystrophy Family Registry (MDFR) Online collection of data on myotonic dystrophy (DM) [NCT02398786] (Sponsor: *Myotonic Dystrophy Foundation*)		
Status	**Country**	**Date created**
Recruitment is ongoing	United States	February 2013

WEB https://myotonicregistry.patientcrossroads.org

Other countries have also set up national databases, including the United States and the United Kingdom.

United States myotonic dystrophy database Connecting patients suffering from DM with research teams, collecting patient genetic and demographic characteristics. (Sponsor: *University of Rochester*)		
Status	**Country**	**Date created**
Recruitment is ongoing	United States	2000
As of August 2017, 180 patients with DM2 had been included in the database.		

British myotonic dystrophy database Collecting genetic and demographic patient characteristics, facilitating the enrolment of patients in clinical trials. (Sponsor: *John Walton Muscular Dystrophy Research Centre*)		
Status	**Country**	**Date created**
Recruitment is ongoing	United Kingdom	2012
As of June 2020, 782 patients with DM1 or DM2 had been included in the database.		

Clinical advances

Observational studies help to better understand a disease, identify better diagnostic or monitoring tools, evaluate the effect of a treatment in the longer term, etc. They are essential in being able to plan clinical trials.

In search of reliable and sensitive measurement tools

Several observational studies are currently underway in myotonic dystrophy type 2 (DM2) to identify the best outcome measures to use in a clinical trial.

DM2 is a rare disease that progresses slowly. The measured parameters must make it possible to identify disease improvement or stabilisation, over a short period of time (one year) and with a small number of patients.

The COMEDY-2 study

In Germany, the COMEDY-2 observational study followed up 66 patients with DM2 over a one-year period. A battery of medical tests was performed twice, at one year's interval, to measure muscle strength, endurance, motor skills, myotonia, pain, fatigue, daily activity levels, gait disorders and balance disorders, etc.

Their results show that muscle impairment manifests as muscle weakness, which increases with age and which can be evaluated using a manual muscle test and a portable dynamometer.

The MBS (myotonia behavior scale) score is used to evaluate myotonia severity. In this study, more than 75% of participants presented only moderate and temporary myotonia episodes and muscle stiffness, or even no muscle stiffness at all.

The authors also recommend, during clinical trials, that one should use: questionnaires to evaluate muscle pain (myalgia); the 6-minute walk test (measuring the distance walked during 6 minutes, often performed during clinical trials involving neuromuscular disease) to evaluate endurance; and the QMFT (Quick Motor Function Test) test to evaluate motor function as a whole (the movements that the patient is able to perform).

Validation of Motor Outcome Measures in Myotonic Dystrophy Type 2.
Montagnese F, Rastelli E, Khizanishvili N *et al.*
Front Neurol. 2020 (Apr)

__Myotonia__ is a muscle fibre relaxation defect: after contraction, the muscle does not quickly return to its initial resting state. This phenomenon gives a sensation of stiffness due to the slow relaxation of the muscles after contraction. It has a tendency to improve after movement repetition. Myotonia is generally not painful (in contrast to cramp, for example), but it can be bothersome for certain tasks of daily life (opening a pot of jam, changing a light bulb, handling certain objects, etc.). During a clinical examination, the doctor can trigger it by striking the fleshy part of the muscle with a reflex hammer.

The __manual muscle test__ is a manual method for evaluating the strength of each muscle group: the contraction of the muscle whose strength is being measured occurs against the resistance exerted by the hand of the person performing the test. The measurement is expressed using a graduated scale from 0 (no strength) to 5 (normal muscle strength).

The ASCEND-DM study

The ASCEND-DM study expects to recruit up to 180 participants: 120 patients with DM1 and 60 patients with DM2, to be followed up over a 2-year period.

The ASCEND-DM observational study
Evaluating clinical parameters and biomarkers in myotonic dystrophy type 1 (n=120) and type 2 (n=60) [NCT03867435]
(Sponsor: *National Institute of Neurological Disorders and Stroke (NINDS)*)

Status	Number of participants (age)	Country	Follow-up period	Start – End
Recruitment currently underway	180 (aged 11 to 70 years)	United States	2 years	February 2020–July 2027

Other observational studies currently underway

On its website, the American *Myotonic* patient association identifies trials that are currently underway in myotonic dystrophy. Three studies in DM2 are cited as currently underway in the United States:

- The STOPP-DM2 (Study of Pathogenesis and Progression in DM2) study, conducted at the University of Rochester, which also coordinates the American myotonic dystrophy database. This trial is expected to include 50 patients with DM2 (recruitment is currently underway).
- A natural history study is currently underway at the Centre for Genetic Muscle Disorders at the Kennedy Krieger Institute, in Baltimore.
- Recruitment for a study investigating biomarkers in neuromuscular disease, including DM2, is currently underway, at the Boston Medical Center (USA).

WEB https://www.myotonic.org/current-studies-and-trials

Blood biomarkers

Based on work conducted in mice, and blood samples collected from 6 patients with DM2, American researchers have identified a set of changes in splicing, measurable in the blood and characteristic of DM2. This could represent a good biomarker for the disease.

Loss of MBNL1 induces RNA misprocessing in the thymus and peripheral blood.
Sznajder ŁJ, Scotti MM, Shin J *et al.*
Nat Commun. 2020 (Apr)

*The so-called **natural history of a disease**, as doctors refer to it, is the description of different manifestations of that disease and their progression over time without the use of a treatment.*

*A **biological marker**, also referred to as a biomarker, is a measurable characteristic that indicates a normal or pathological biological process. The identification of new biological markers for a disease is very important in monitoring the progression of the disease and the efficacy of new treatments, whether these markers are physiological (change in blood pressure, heart rate, etc.) or molecular (change in the expression of a protein, etc.).*

Therapeutic cannabis and myotonia

The symptomatic treatment of myotonia, which can be accompanied by myalgia, especially in DM2, is based on a few therapeutic drugs used over the long term: mexiletine, lamotrigine, carbamazepine and phenytoin. However, this does not always give satisfactory results.

- In an article published in October 2019, German clinicians reported the results of an open-label pilot study conducted among 6 participants, 4 with DM1 or DM2, and 2 with myotonia congenital involving an abnormality of the gene coding the chloride channel.

Over a period of four weeks, the study participants took an oil with increasing doses of CBD (cannabidiol) and THC (tetrahydrocannabinol), the two active ingredients in cannabis used for therapeutic purposes. The analysis of the clinical parameters, with respect to myotonia and also muscle pain, tends to support the fact that the product has a positive effect. The authors recommend new trials, this time randomised and involving a larger number of patients.

A role for cannabinoids in the treatment of myotonia? Report of compassionate use in a small cohort of patients.
Montagnese F, Stahl K, Wenninger S, Schoser B.
J Neurol. 2019 (Oct)

Gait disturbance, falls

A study lasting 100 days, among 42 patients with DM2 and 102 patients with DM1, showed that these patients fell 7 to 8 times more frequently than normal: 17% of patients with DM2 had at least two falls during the study. These usually occurred indoors, hence the importance of adapting the environment to reduce the risk of falls at home (installing anti-slip mats and handrails, removing any potential obstacles, etc.). The patients most at risk

of falling are the most elderly, the least active and those with the greatest muscle weakness.

High incidence of falls in patients with myotonic dystrophy type 1 and 2: A prospective study.
Berends J, Tieleman AA, Horlings CGC *et al.*
Neuromuscul Disord. 2019 (Aug)

Bone fragility

▪ A study involving 13 patients with DM2 has shown greater bone fragility, due to hormone and muscle impairment resulting from the disease: among these DM2 patients, 7 had experienced fractures related to bone fragility and 6 showed a reduction in hip bone mineral density (osteopenia).

Fragility fractures and bone mineral density in male patients affected by type 1 and type 2 myotonic dystrophy.
Passeri E, Sansone VA, Sconfienza LM *et al.*
Neuromuscul Disord. 2019 (Nov)

Exploring therapeutic avenues

Advances in our knowledge of molecular mechanisms in myotonic dystrophy type 2 (DM2) allow us to consider different possible therapeutic avenues. DM2 can also benefit, in the long-term, from progress made in Steinert's disease (DM1), since the two diseases share certain pathological mechanisms.
Before they can be validated in humans as part of clinical trials, these therapeutic avenues must first be tested on cell and animal models.

▪ Therapeutic avenues currently being investigated in DM2 target abnormal *ZNF9* messenger RNA. They are based on the use of:
- either RNA (antisense oligonucleotides or microRNA) capable of binding to the abnormally repeated CCUG RNA sequence on the mutated *ZNF9* messenger RNA,
- or small molecules capable of binding to the structure in the shape of stem-loops formed by the *ZNF9* messenger RNA CCUG repeats.

Micro-RNAs *(miRNAs) are small RNA molecules produced by the cell that are not translated into protein. Their role is to regulate the expression of genes by blocking the translation of the messenger RNA of these genes into protein. The expression of these miRNAs varies depending on the situation. In neuromuscular disease, certain miRNAs are expressed and not others, and the combination of miRNAs expressed differs depending on the neuromuscular disease and is specific to each disease.*

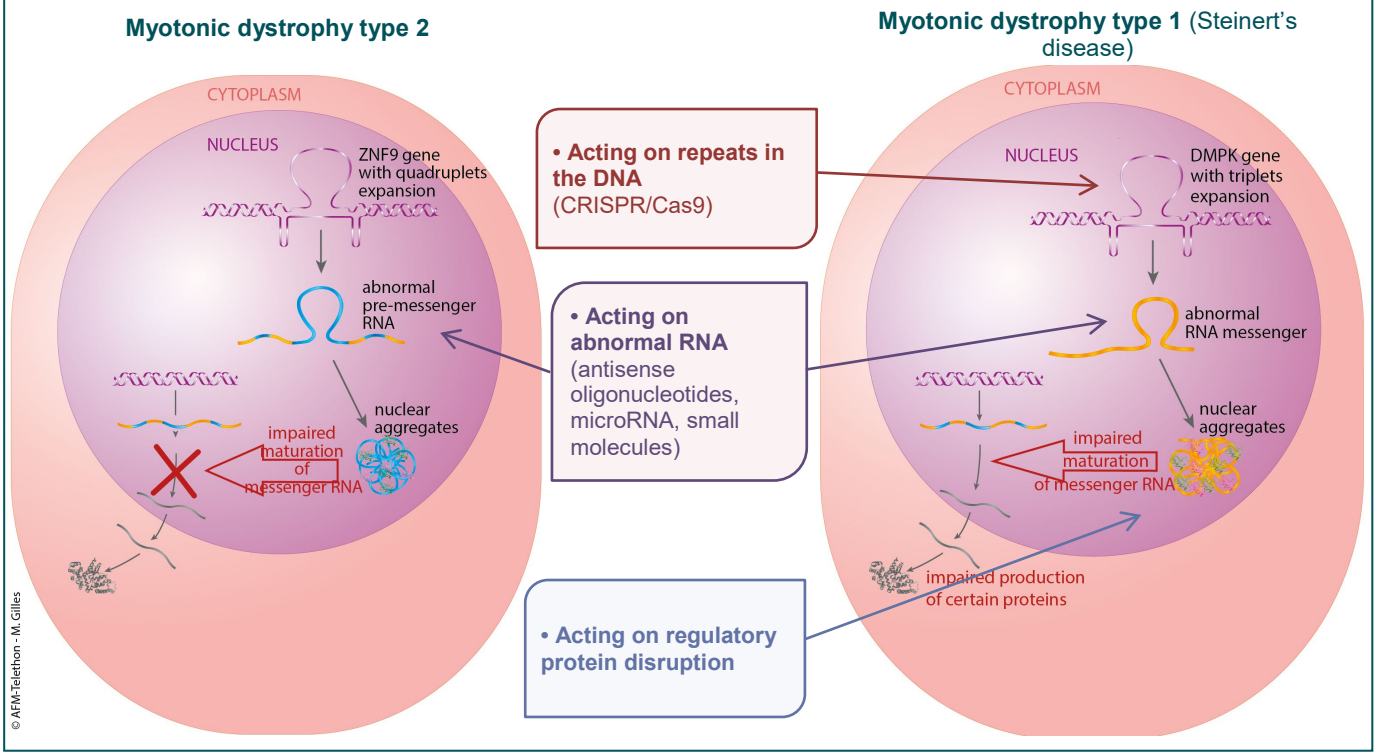
▪ Two literature reviews have focused on the use of microRNA or small molecules in myotonic dystrophy types 1 and 2.
▪ While research on microRNA in fly models or mouse models of Steinert's disease appear to be promising, knowledge about disrupted microRNA in DM2 is still very limited. Further research is needed to identify one or more potential therapeutic targets in DM2.

MicroRNA-Based Therapeutic Perspectives in Myotonic Dystrophy.
López Castel A, Overby SJ, Artero R.
Int J Mol Sci. 2019 (Nov)

▪ The majority of small molecules currently in development are being studied in Steinert's disease. Only 2 molecules being tested on DM2 cell models are presented.
However, the mechanisms that these approaches are based on are common to DM1 and DM2: they involve targeting the abnormal repeats in the messenger RNA in order to free the MBNL regulatory proteins trapped in the nuclear aggregates. The search, in DM2, for small molecules targeting *ZNF9* RNA will, indeed, benefit from advances made in DM1.

Mitigating RNA Toxicity in Myotonic Dystrophy using Small Molecules.
Reddy K, Jenquin JR, Cleary JD, Berglund JA.
Int J Mol Sci. 2019 (Aug)

Therapeutic avenues being investigated in DM2 and/or DM1.



▪ In the United States, Matthew Disney's team is searching for a compound capable of specifically degrading the abnormal *ZNF9* messenger RNA. It has developed and tested several candidate molecules on cells collected from patients with DM2.

This team has shown that the use of antisense oligonucleotides in DM2 could be toxic. These can bind to a short repeated CCTG sequence present on *MBNL1*, which causes degradation of the MBNL1 regulatory protein and increases the disruption observed in DM2 cells.

This work also helps to better understand the effects of the increase in CCTG repeats on the *ZNF9* messenger RNA. The MBNL1 protein, by binding to the mutated *ZNF9* messenger RNA, causes an impairment in the splicing of the *ZNF9* RNA itself.

Structure-Specific Cleavage of an RNA Repeat Expansion with a Dimeric Small Molecule Is Advantageous over Sequence-Specific Recognition by an Oligonucleotide.
Benhamou RI, Angelbello AJ, Andrews RJ *et al.*
ACS Chem Biol. 2020 (Jan)

A Toxic RNA Catalyzes the Cellular Synthesis of Its Own Inhibitor, Shunting It to Endogenous Decay Pathways.
Benhamou RI, Angelbello AJ, Wang ET, Disney MD.
Cell Chem Biol. 2020 (Jan)

*An **antisense oligonucleotide** is an RNA fragment, generally laboratory-synthesised, that can bind specifically to a natural messenger RNA: the antisense oligonucleotide nucleotide sequence (its chemical formula) is complementary to that of the messenger RNA it is targeting. Thus, it can modify the messenger RNA (exon skipping or incorporation) by intervening at its maturation stage (splicing).*

*
* *