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SAVOIR & COMPRENDRE
AVANCÉES DE LA RECHERCHE

Advances 2024 in myotonic dystrophy type 2

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This document, published to coincide with the AFM-Téléthon General Meeting 2024, presents myotonic dystrophy type 2 research news from the past year (ongoing studies and clinical trials, scientific and medical publications, etc.).

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Written by
▪ Magali Bichat - Myoinfo, Neuromuscular Disease Information Department, AFM-Téléthon, Évry

Verified by
▪ Nathalie Loux
Directorate of Scientific Operations and Innovation at AFM-Téléthon, Évry

Translated by
Emily Scott

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4 Highlights from the past 12 months

Research closely linked to that carried out in myotonic dystrophy type 1

- The 14th International Myotonic Dystrophy Consortium Meeting (**IDMC-14**) was held in April 2024 in the Netherlands, with the support of AFM-Téléthon, together with the 4th edition of the **Euro-DyMA Pharma's Day.**

Trait d'Union newsletter number 21 – May 2024

- Advances in our understanding of **common mechanisms found in both myotonic dystrophy type 1 (DM1) and myotonic dystrophy type 2 (DM2)** (variations in repeats, interactions between toxic messenger RNA and the MBNL protein, the role of nuclear foci, etc.) were presented as well as **7** drug candidates being trialled in DM1.

The rise of RNA-based drugs

- Drugs using this technology have already been approved to treat other rare diseases (SMA and transthyretin amyloidosis).
- **6** drug candidates in DM1 trials
- including **ATX-01** which targets a mechanism found in both DM1 and DM2.

www.arthexbiotech.com/our-approach-focus#pipeline

A closer look at Euro-DyMA

12 European patient organisations committed to the fight against DM1 and DM2.

→ harmonising good practices and knowledge of these diseases in the European Union.

→ giving patients a voice in clinical trials and studies being conducted or planned in Europe.

2-3 May 2025

Pharma's Day

Organised by Euro-DyMA and the Myotonic Dystrophy Foundation

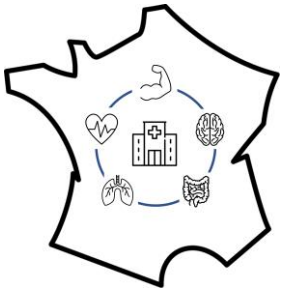
Myotonic dystrophy type 2 — DM2

DM2 mainly affects the muscles but can also impact other organs to a greater or lesser extent. It is very similar to another more common neuromuscular disease called myotonic dystrophy type 1 (DM1).

Common symptoms

- DM2 is a **"multisystem" disorder,** meaning it affects several different organs (muscles, the heart, the digestive system, the nervous system, and, less frequently, the respiratory system).
- Muscles decrease in volume, become weak (**dystrophy**) and have difficulty relaxing after they contract (**myotonia**).
- Symptoms usually **start during adulthood and progress slowly**, but this can vary greatly

Management and treatment



- ☑ **Multidisciplinary treatment** of symptoms at specialist centres.
- ☑ Preventing complications.
- ☑ Improving quality of life.

Diagnosis

Clinical diagnosis

Family history and clinical examination by a doctor:
muscle impairment (myotonia, etc.) which may be associated with hand tremor and early cataracts

Genetic diagnosis

Blood test and muscle biopsy:
abnormally high number of CCTG repeats in the *ZNF9* gene

In numbers

1 to 2 people in every 100,000 have DM2

263 people currently participating in the French DM-Scope registry

However, many individuals with DM2 **have still not received a diagnosis**

What causes it?

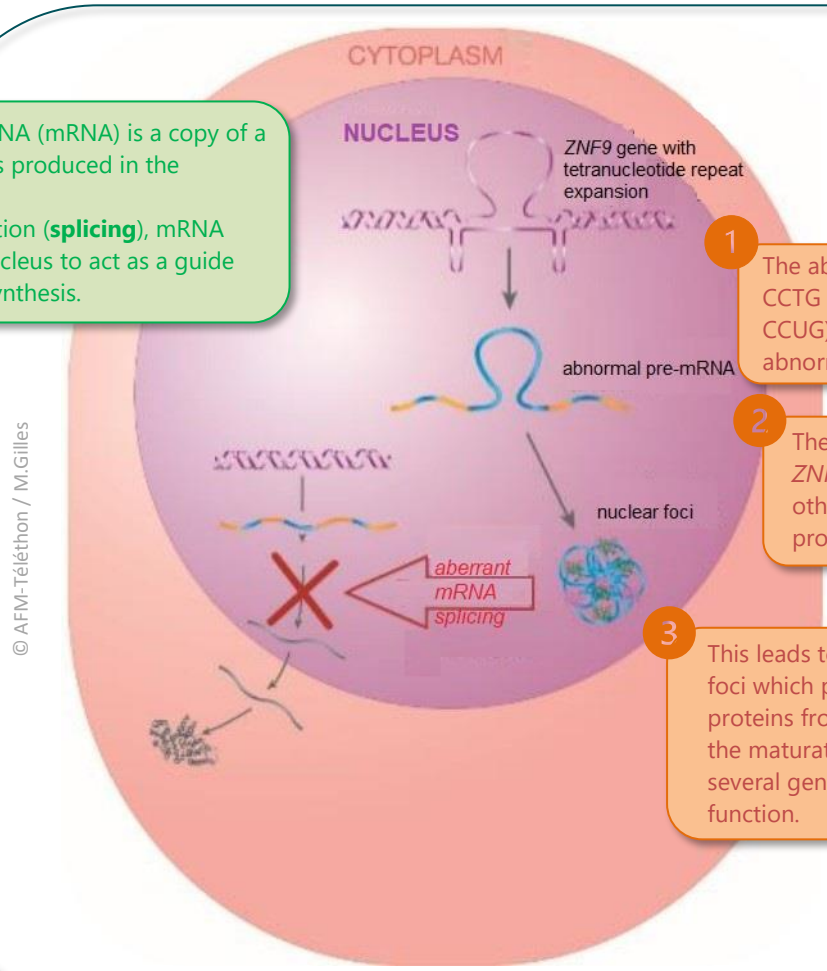
☑ DM2 is caused by a mutation in the ***ZNF9*** (or *CNBP*) **gene** on chromosome 3. This type of mutation is called a repeat expansion and involves a segment of DNA in a gene being repeated more than usual. In DM2, this segment contains four nucleotides and is written as **CCTG** (cytosine, cytosine, thymine and guanine).

Person without DM2
Less than 75 CCTG repeats.

Person with DM2
75 to over 10,000 CCTG repeats

☑ **Autosomal dominant** inheritance: only one copy of the mutated *ZNF9* gene needs to be inherited for myotonic dystrophy type 2 to develop.

Messenger RNA (mRNA) is a copy of a gene which is produced in the nucleus.
After maturation (**splicing**), mRNA leaves the nucleus to act as a guide for protein synthesis.



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1 The abnormally high number of CCTG repeats are transcribed (as CCUG) in *ZNF9* mRNA, producing abnormal mRNA.

2 The CCUG sequences in the abnormal *ZNF9* mRNA tend to bind to each other as well as to nuclear regulatory proteins.

3 This leads to the formation of nuclear foci which prevent these regulatory proteins from carrying out their role in the maturation (splicing) of mRNA from several genes. This disrupts cell function.

For more information on DM2, please visit:
www.afm-telethon.fr/fr/fiches-maladies/dystrophie-myotonique-de-type-2 [page in French]

Clinical tools for future trials

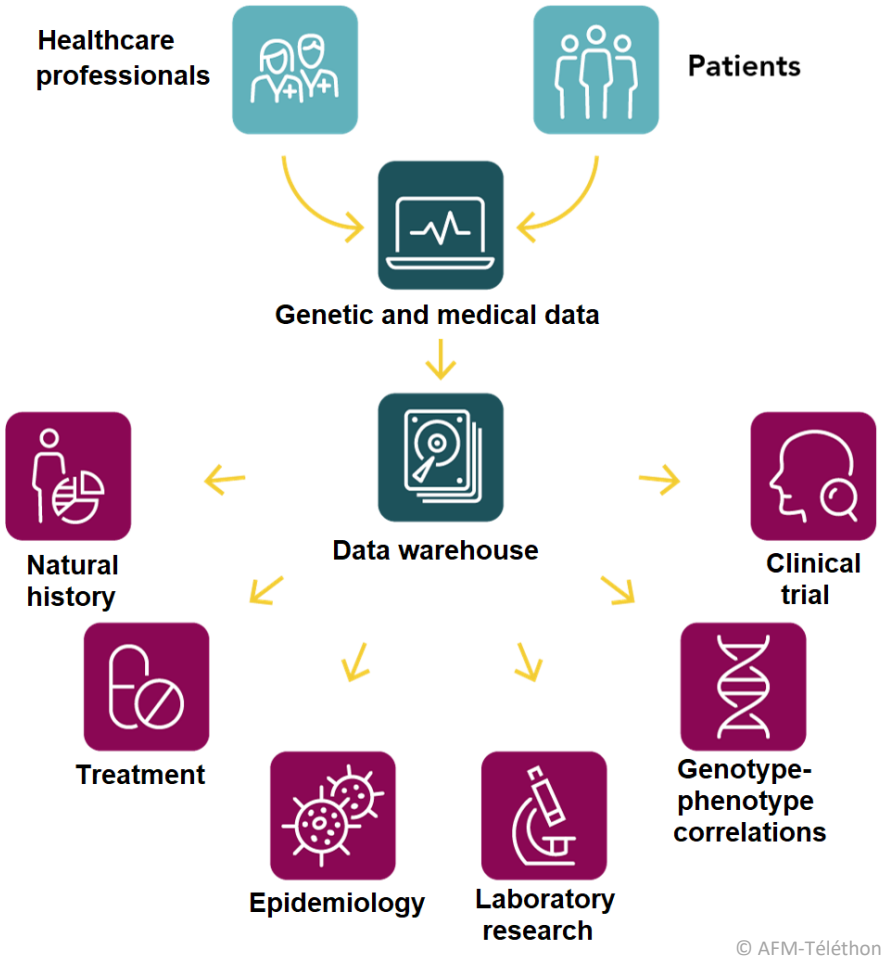
Data warehouses

Developing patient databases makes it possible to carry out censuses (which are exhaustive when conducted in registries) of people with the same disease, determine the natural history of the disease, establish genotype-phenotype correlations and recruit participants to clinical trials.

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

***Genotype-phenotype correlation** studies look for links between genetic characteristics (genotype) and physical characteristics (phenotype, i.e. height, eye colour and shape, hair colour, disease manifestations, etc.).*
They help to identify whether a relationship exists between the presence of a genetic mutation and the manifestations of a genetic disease.

Data warehouse
A data warehouse is a collection of genetic and medical data from people with the same disease (with their consent).



The DM-Scope registry

The DM-Scope registry, supported by AFM-Téléthon, was set up in France in 2008 to collect data from people with myotonic dystrophies and facilitate clinical research in these diseases. It has since become the world's largest myotonic dystrophy database.

- DM-Scope currently collects demographic, clinical and laboratory test data from 3,828 people with myotonic dystrophies (3,551 DM1 patients and 263 DM2 patients).
- In collaboration with 55 specialist neuromuscular disease centres, it has been the foundation for 12 clinical trials (observational studies, basic research, etc.).

www.dmscope.fr/french-registry-of-myotonic-dystrophies/

DM-Scope registry

France | 263 DM2 patients | Recruiting | Created in January 2008

The iDM-Scope project

A French-Québécois consortium called iDM-Scope created an **international platform** for myotonic dystrophies in order to facilitate the implementation of multisite trials, conduct natural history studies, identify biomarkers and develop potential treatments.
Set up in July 2016, it brings together the DM-Scope registry and a Québécois database that covers the Québec City and Saguenay region.

iDM-Scope registry

Canada | 1,410 (DM1/DM2) | Recruiting | Created in 2002

Other registries around the world

Myotonic Dystrophy Family Registry

United States | 2,817 (DM1/DM2) | Recruiting | Created in 2013

https://myotonicregistry.patientcrossroads.org

National Registry for Myotonic Dystrophy & Facioscapulohumeral Dystrophy

United States | 1,151 (DM1/DM2) | Recruiting | Created in 2001

https://www.urmc.rochester.edu/neurology/national-registry.aspx

How does the disease progress?

An update on the 222 DM2 patients enrolled in an American database was provided during the Myotonic Dystrophy Foundation Annual Conference.

- At 40 years old, the probability of having to stop work was 10%.
- At 50 years old, the probability of having to use non-invasive ventilation was 12%.
- At 60 years old, the probability of needing to use a walking frame or wheelchair was 28% and 13% respectively, and 8 to 10% of patients had a pacemaker. The probability of being diagnosed with cancer was 24%.
- The probability of developing diabetes was higher in DM2 (24% at 60 years old) than in DM1.

Hamel J et al. 2023 MDF Annual Conference

Hamel JI et al. Muscle Nerve. 2022 Jul

In search of reliable and sensitive outcome measures

DM2 is a rare disease that progress slowly. Several observational studies are currently underway in order to identify the best endpoints to use in clinical trials. These endpoints need to be effective enough to be able to demonstrate an improvement or stabilisation in the disease over a short period of time (one year) in a small number of patients.

Did you know?

Observation - a driving force for progress

- Observational studies are important for improving our understanding of a disease and anticipating any impairment or problems that may arise. They also help to identify better diagnostic and monitoring tools and are essential in the planning of clinical trials.
- The better a disease is understood, the easier it will be to conclude whether or not a drug candidate is effective at the end of a clinical trial. This also requires having highly-effective tools to monitor the course of the disease.

Four studies currently underway

The Myotonic Dystrophy Foundation website lists myotonic dystrophy trials that are currently taking place.

- The STOPP-DM2 (Study of Pathogenesis and Progression in DM) study is being conducted at the University of Rochester which also coordinates the National Registry for Myotonic Dystrophy & Facioscapulohumeral Dystrophy. Recruitment has been completed and 40 participants have been included.

*A **biological marker** (or **biomarker** for short) is a measurable characteristic that indicates a normal or pathological biological process. Identifying new biomarkers for a disease is very important for monitoring the course of the disease and the efficacy of new treatments. These markers can be physiological (change in blood pressure, heart rate, etc.) or molecular (change in the expression of a protein, etc.).*

A slow but measurable progression

An update on the STOPP-DM2 study was presented during the 2023 Myotonic Dystrophy Foundation Annual Conference. The investigators already had three years' worth of follow-up data for 22 participants. The findings showed that it may be possible to measure significant differences in the strength of muscles most often weakened by the disease (hip, neck and shoulder muscles) after three years, reflecting the disease's progression.

The researchers are also looking at whether splicing changes used in DM1 to show the early effects of a drug candidate in cells could also be used in DM2. Preliminary analyses are encouraging.

Hamel J et al. 2023 MDF Annual Conference

- A natural history study of DM2 is currently taking place at the Kennedy Krieger Institute Center for Genetic Muscle Disorders in Baltimore (United States).
- A study that is looking for biomarkers in myotonic dystrophies (including DM2) is currently recruiting at the Massachusetts General Hospital in Boston (United States).
- This hospital is also currently recruiting for a study that is looking for extracellular RNA biomarkers (able to be measured in blood or urine) that may be able to be used in myotonic dystrophies.

www.myotonic.org/resources/current-studies-and-trials

Clinical advances

The importance of regular multidisciplinary checkups

▪ A literature review of the most recent publications on the treatment and management of DM2 was carried out in Germany. It highlighted the multisystemic nature of DM2. In addition to the muscles, DM2 can also affect the eyes (cataracts), heart (cardiac conduction disorders), nervous system (cognitive impairment), immune system (autoimmune disease), endocrine system (diabetes and hypothyroidism), and, less frequently, the respiratory system.

The authors of this literature review emphasised the importance of multidisciplinary care in enhancing the quality of life of DM2 patients. It also enables any complications to be detected and treated early, particularly heart problems.

For patients who have both DM2 and diabetes (who have a significantly higher risk of cancer), the authors recommended that their moles and thyroids be examined (palpation and blood tests) every year.

Kleefeld F et al. Curr Opin Neurol. 2023

Don't be afraid to share

During your annual follow-up appointments, it is important to mention any problems or discomforts you may be experiencing, even if they don't seem to be related to your disease.

Report any worrying signs to your doctor (unexplained weight loss, presence of blood in your urine, change in the appearance of a mole, etc.).

Mexiletine (Namuscla) to treat myotonia

Mexiletine (Namuscla®) is used to treat myotonia which is characterised by muscle stiffness and difficulty relaxing the muscles. Its use in DM2 is limited as doctors do not have long-term data regarding its safety (particularly with regard to the heart) and efficacy. It is prescribed when myotonia is severe and causes discomfort on a daily basis.

Namuscla® in France

Mexiletine is sold by the pharmaceutical company Lupin under the name Namuscla®. It is available in France as part of the "cadre de prescription compassionnelle" [a French compassionate access scheme] for the treatment of myotonia in myotonic dystrophies in adults. Namuscla® is now available from pharmacies with a prescription from a hospital doctor.

▪ Neurologists and cardiologists from specialist centres in France published an article to help cardiologists monitoring DM1 and DM2 patients decide whether or not to prescribe mexiletine.

Although data from patients with myotonic dystrophies treated with mexiletine published in medical literature is reassuring, its use comes with the need for close cardiac monitoring (cardiac evaluation before starting treatment followed by a yearly checkup).

The onset of any new cardiac symptoms should lead to the benefits of the treatment being reassessed with your cardiologist and neurologist.

Wahbi K et al. Arch Cardiovasc Dis. 2024

▪ The pharmaceutical company Lupin is sponsoring a trial in children and adolescents with myotonic disorders (DM1 and DM2 as well as non-dystrophic myotonias). The trial has two stages. The first stage is currently being conducted in adolescents between the ages of 12 and 17 and will be followed by a second stage (results permitting) in children between the ages of six and 12.

Trial of Namuscla® in myotonic disorders

Phase III
Efficacy

France

12
(6 to 17 years old)

Recruiting

June 2021 – April 2023
56 days of follow-up

2019-003758-97/FR

Understanding and treating pain

In DM2, muscle impairment is proximal
This means that it's the muscles which are closer to the centre of the body (the muscles of the shoulders, upper arms, torso, hips and thighs) that are affected most often.

▪ Over half of people with DM2 suffer from chronic (long-term) lower back pain, according to a Czech study conducted in 40 patients. This pain is likely related to torso muscle weakness (particularly in the lower back) and possibly the severity of myotonia and lack of physical activity.
Vlazna D et al. Front Neurol. 2023

Physical activity
Regularly engaging in moderate physical activity which has been adapted to a patient's physical abilities (swimming, gentle exercise, etc.) improves muscle strength and endurance, reduces feelings of pain and fatigue and has an effect on mental health.
www.afm-telethon.fr/fr/actualites/sport-et-maladie-neuromusculaire-briser-les-idees-recues [page in French]
www.afm-telethon.fr/fr/termes/lactivite-physique-adaptee-une-nouvelle-approche-du-soin-qui-monte-en-puissance [page in French]

Treatment of respiratory problems

Although rare, respiratory problems can develop gradually in DM2 without the patient realising (ineffective cough, recurrent chest infections, headaches or sweating (especially when waking up), difficulty gaining or losing weight, fatigue, etc.).
Regular checkups are able to detect these problems so that non-invasive ventilation (NIV) can be administered. There is currently no consensus on when to start NIV in myotonic dystrophies.

▪ German researchers developed a method to make it easier to detect breathing problems in DM1 and DM2 patients. It involved completing a 27-item checklist (the "Respicheck") together with clinical assessments and lung function tests. A validation study conducted in 172 people (including 72 with DM2) demonstrated that this method was able to identify patients who required ventilation.
Gutschmidt K et al. Neuromuscul Disord. 2023

Central nervous system abnormalities and cognitive impairment

__Cognitive impairment__ is defined as problems with a person's ability to process information (reasoning, memory, attention, language, writing, orientation, spatial reasoning, planning, etc.) and learn. These problems can be present from birth, resulting in delayed psychomotor development. When they present during childhood or adulthood, they can lead to difficulties at school and/or work.

The __central nervous system__ is made up of the brain (the cerebrum, cerebellum and brain stem) and the spinal cord. It is protected by the skeleton (the skull for the brain and the spine for the spinal cord). It analyses sensory information, coordinates movement and orders muscles to contract.

DM2 patients can have impaired planning and organisational skills and impaired visuoconstruction abilities (perceiving spatial relationships between objects, reading a map and choosing the best route to take, etc.) and may struggle with social interactions (recognising the emotions and desires of another person, expressing their feelings, etc.). These difficulties may be linked to central nervous system abnormalities observed on MRIs.

Cognitive assessment

A cognitive assessment performed by a neuropsychologist enables you to identify your strengths and weaknesses so that you can choose which strategies to adopt to compensate for your difficulties and be better prepared in your everyday life.

▪ A study currently taking place in the United States is aiming to better describe the impact of the disease on central nervous system structures using MRI and evaluate how this effects cognitive skills.

Brain structure and clinical data

United States	100 (over 40 years old)	Recruiting	April 2023 – June 2027 1 day of tests

NCT05854433

An increased risk of autoimmune disease

According to several studies, over 20% of DM2 patients may also develop an autoimmune disease (Hashimoto's disease, rheumatoid arthritis, type 1 diabetes, systemic lupus erythematosus, Sjögren's syndrome, psoriasis, etc.).

Immune system disorders

Autoimmune diseases affect 5 to 8% of the general population. Each disease differs from the next in terms of their manifestations but all are caused by a malfunction in the immune system, a network of biological systems which usually protect the body from external threats. In autoimmune diseases, a patient's immune system attacks their own body.
Autoimmune diseases are not genetic. Their treatment consists of drugs used to control the immune response (corticosteroids, immunosuppressants, immunomodulators) and manage pain (painkillers) and inflammation (anti-inflammatories).
www.afm-telethon.fr/fr/termes/maladies-auto-immunes [page in French]

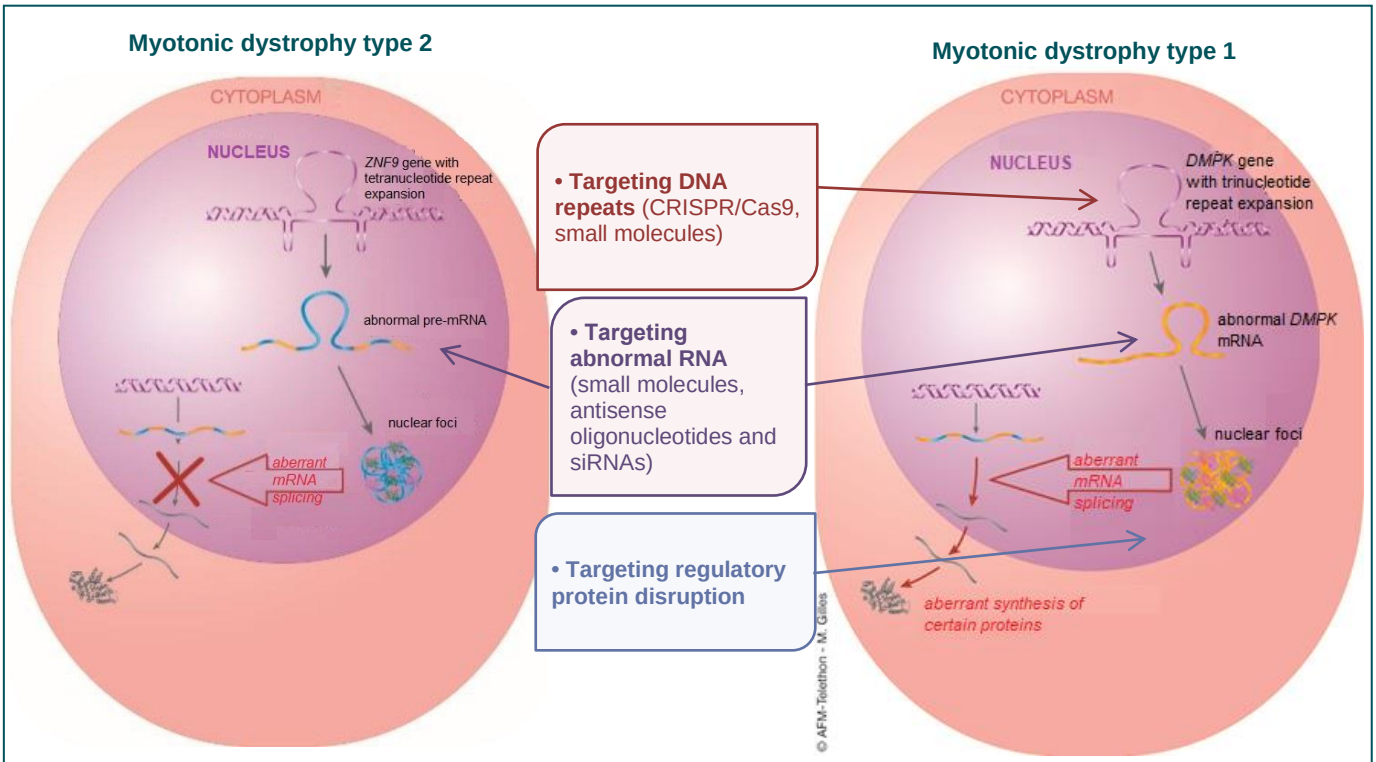
▪ The exact cause is unknown, however, it is specific to DM2 since this association with autoimmune diseases does not exist in DM1.
German researchers have suggested the possible involvement of type I interferons. These proteins are naturally able to recognise genetic material in cells that have been infected by a virus and activate a defence response in the body. These interferons are produced in DM2 even when there is no infection.
Rösing S et al. Nat Commun. 2024

Exploring treatment avenues

Approaches being studied in DM2 are mostly based on mechanisms found in both DM1 and DM2. They involve targeting the abnormally high number of repeats in mRNA in order to release MBNL regulatory proteins which have become trapped in nuclear foci.
This means that DM2 research benefits from progress made in DM1.

▪ These treatment avenues must first be tested and approved in cell and animal models of DM2 before they are allowed to be evaluated in humans in clinical trials.

Two new models to facilitate research
For the first time, a mouse with DM2 was presented at the IDMC-14. In addition, a fly model of DM2 has also been described in literature. These new models will enable critical mechanisms in DM2 to be analysed, suitable therapeutic targets to be identified and potential drug candidates to be evaluated.
Marzullo M et al. Int J Mol Sci. 2023



Treatment avenues being studied in DM2 and/or DM1.

Targeting the genetic mutation

▪ An American team have identified a specific genetic mechanism which is able to reduce the abnormally high number of CCTG repeats in yeast cells.
Papp D et al. G3 (Bethesda). 2023

The future of genetic diagnosis
Repeat expansions are particularly difficult to sequence. New long-read sequencing techniques which have been in development for a few years are able to sequence challenging regions such as the abnormally high number of CCTG repeats in the *ZNF9* gene. Although they are used in research, they still have not been approved to be used as a diagnostic tool in DM2.
Alfano M. et al Elife. 2022 Aug

Studying the roles of mitochondria

Mitochondria are the powerhouses of the cell
Their respiratory chain provides energy for the cell to use. The number of mitochondria in a cell is variable. Muscle fibres, which have a high energy demand, contain several thousand mitochondria.

▪ Mitochondria in DM2 patients have abnormal structures and do not function properly (particularly the respiratory chain proteins). This was shown by an analysis of seven muscle biopsies taken from DM2 patients. However, the link between CCTG repeats and mitochondrial dysfunction has not yet been identified.
Kleefeld F et al. Acta Neuropathol. 2024

▪ Mitochondrial dysfunction may explain the increased incidence of autoimmune diseases in DM2. According to a German study, the accumulation of mutated *ZNF9* RNA induces cellular stress and mitochondrial destruction. Mitochondrial DNA is then released inside cells which activates an abnormal immune response predisposing to autoimmune disease.
Rösing S et al. Nat Commun. 2024

▪ These two articles present mitochondria as a potential therapeutic target in DM2.

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Keep up to date with myotonic dystrophy type 2 research news throughout the year on the AFM-Téléthon website:
www.afm-telethon.fr/en

And via the AFM-Téléthon Groupe d'Intérêt Steinert (DM1 & DM2) blog:
steinert.afm-telethon.fr/ [website in French]