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SAVOIR & COMPRENDRE
AVANCÉES DE LA RECHERCHE

Advances 2024 in Charcot-Marie-Tooth disease

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This document, published to coincide with the AFM-Téléthon General Meeting 2024, presents Charcot-Marie-Tooth disease research news from the past year (international conferences, ongoing studies and clinical trials, scientific and medical publications, etc.).

AFMTÉLÉTHON
CURE THROUGH INNOVATION

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4 Highlights from the past 12 months

Proactive associations behind several conferences

- **The first European conference** dedicated to CMT was held in Paris in June 2023 at the request of the European Charcot-Marie-Tooth Federation and supported by AFM-Téléthon.

www.afm-telethon.fr/fr/actualites/cmt-premier-congres-europeen-consacre-la-maladie [article in French]

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"Together against CMT" - not just a name, but a goal! *A plan of action has been made: diagnoses for all and treatments.*

- **A national CMT conference** organised every year by CMT-France with over 500 participants attending the 2024 digital event.

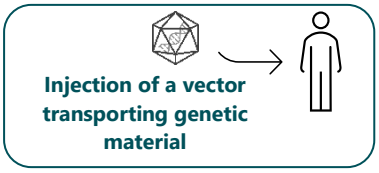
www.youtube.com/@cmtfrance5577 [videos in French]

Increasing interest from the pharmaceutical industry

- Novartis is the **first** major pharmaceutical company to take an interest in CMT with its acquisition of the biotechnology company DTx Pharma and its main drug candidate, a small interfering RNA therapeutic which targets the cause of CMT1A.
- **28** programmes in development which are listed on the CMT-France website.

www.cmt-france.org/Les-essais-et-traitements [website in French]

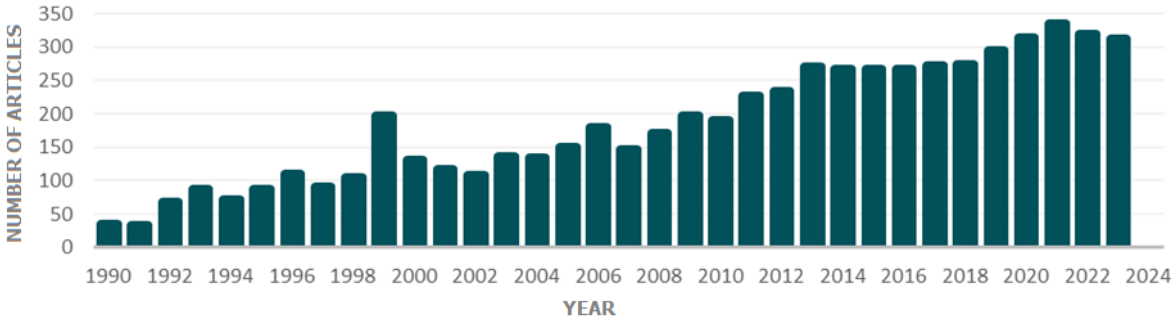
Advances in gene therapy



- **2** clinical trials underway.
- **6** new approaches being studied in various forms of CMT.

Numerous scientific and medical publications

The number of scientific and medical publications on CMT recorded each year demonstrates how active and diverse research in this area is.



Source: PubMed, a bibliographic database in the fields of medicine and biology.

Charcot-Marie-Tooth disease CMT

Charcot-Marie-Tooth disease is a group of genetic diseases that cause damage to the peripheral nerves (nerves that connect the spinal cord to muscles and sensory organs) of the arms and legs (neuropathy). It is also known as hereditary motor and sensory neuropathy (HMSN).

Common symptoms

- Muscle weakness and wasting in the legs (feet and calves) and later in the hands and forearms.
- Balance problems and sensory symptoms in the hands and feet.
- Onset usually occurs during childhood or young adulthood with symptoms such as walking difficulties (stumbling, falling, etc.), a decrease in manual dexterity and foot deformities.

Management and treatment

- Treating the various symptoms, which mainly occur in the muscles and joints, preferably at specialist neuromuscular disease centres.
- Attending physiotherapy and/or occupational therapy sessions in order to maintain or regain ease of movement and reduce the risk of falling.
- Using appropriate devices (available on prescription or to buy) to facilitate everyday activities.
- Engaging in moderate physical activity (swimming, using an exercise bike, etc.) regularly to improve muscle strength and endurance and reduce feelings of pain and fatigue.

Diagnosis

Clinical diagnosis
Clinical examination by a doctor:
to look for motor and sensory signs

Electrophysiological diagnosis
Nerve conduction study:
to measure nerve conduction velocity

Genetic diagnosis
Blood test:
to identify the causative gene

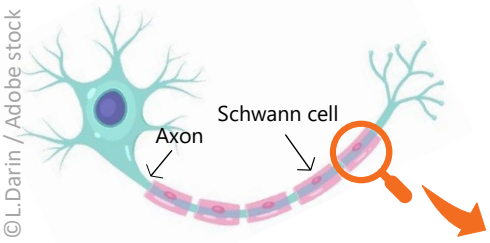
In numbers

9-82 / 100,000

Approximately 40,000 patients
in France

What causes it?

☑ Genetically-determined damage to **peripheral nerves** which send information necessary for movement, perception (touch, pain, etc.), balance, etc.



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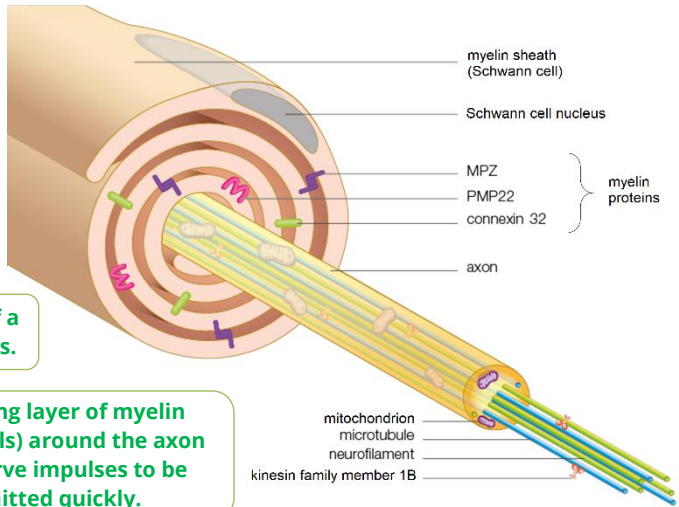
Peripheral nerves connect the body's organs (including muscles) to the central nervous system (spinal cord, brain, etc.).

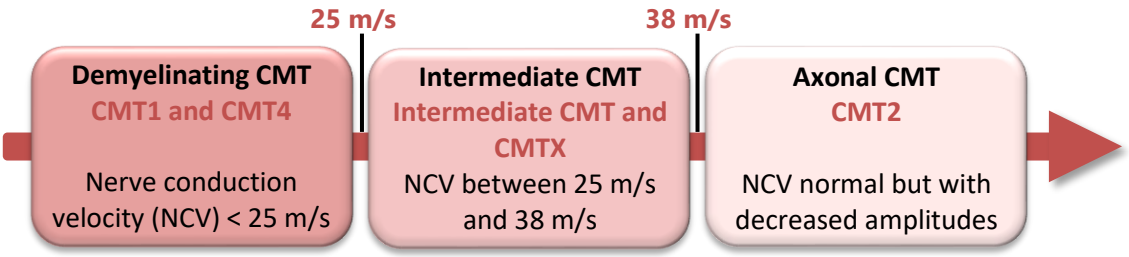


© AFM-Téléthon

An axon is the elongated portion of a nerve that conducts nerve impulses.

An insulating layer of myelin (Schwann cells) around the axon enables nerve impulses to be transmitted quickly.

☑ Slow or weak **nerve impulses**



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☑ **Over 120 genes** that have mutations which cause CMT and associated neuropathies (distal hereditary motor neuropathies (dHMNs) and hereditary sensory neuropathies (HSNs)).

Classic CMT

AARS1, AIFM1, ARHGEF10, ATP1A1, B4GALNT1, CADM3, CNTNAP1, COX6A1, DCTN2, DHTKD1, DGAT2, DNM2, DRP2, EGR2, FBLN5, FGD4, FIG4, GBF1, GDAP1, GJB1, GLA, GNB4, HARS1, HK1, INF2, ITPR3, JAG1, KARS1, KIF1B, KIF5A, LITAF, LMNA, LRSAM1, MARS1, MED25, MME, MORC2, MPV17, MPZ, MTMR2, NAGLU, NDRG1, NEFH, NEFL, PDK3, PLEKHG5, PMP2, PMP22, PNKP, POLR3B, PRPS1, PRX, SBF1, SBF2, SH3TC2, SIGMAR1, SLC25A46, SLC9A3R1, SPG11, SURF1, SYT2, TFG, TRIM2, TRPV4, VCP, YARS1

Form without sensory impairment (dHMN)

ATP7A, BICD2, BSCL2, DCTN1, FBXO38, HSPB3, REEP1, SLC5A7, SPTAN1, VRK, WARS1

CHCHD10, DNAJB2, DYNC1H1, GARS1, HINT1, HSPB1, HSPB8, IGHMBP2, MFN2, MYH14, SETX, SORD, VAPB

DST, RAB7A, SPTLC1

Form without motor impairment (HSN)

ATL1, ATL3, CCT5, CTDP1, DNMT1, ELP1/IKBKAP, KIF1A, NGF, NTRK1, PRDM12, RETREG1/FAM134B, SCN10A, SCN11A, SCN9A, SPTLC2, TECPR2, WNK1

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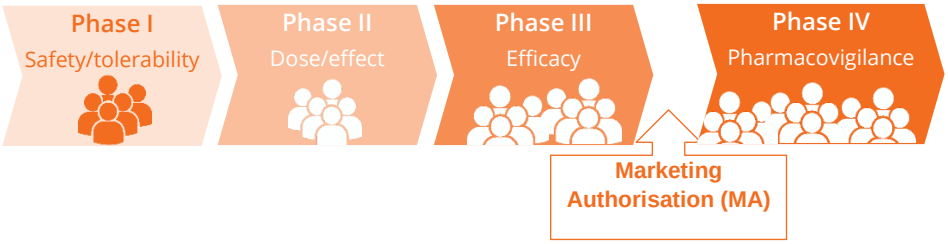
For more information on CMT, please visit:
www.afm-telethon.fr/fr/fiches-maladies/maladie-de-charcot-marie-tooth [page in French]

Clinical trials

Clinical trials consist of assessing a potential treatment (drug candidate, medical device, etc.) in order to ensure that it is well tolerated and effective in treating a disease. The product is tested during successive phases (I, II, III, IV) which each answer specific questions such as, is it well tolerated? What is the optimal dose? Is it effective and according to what criteria (walking ability, motor function, breathing, etc.)? After marketing, the product is then used in real life and continues to be monitored in order to refine knowledge and identify any unexpected or serious side effects that may occur.
www.afm-telethon.fr/fr/vivre-avec-la-maladie/mon-parcours-de-soins/les-essais-cliniques-en-pratique [page in French]



PXT3003 in CMT1A

PXT3003 is a drug candidate which combines three drugs (baclofen, naltrexone and sorbitol) that are already commercially available and have complementary mechanisms of action for limiting PMP22 production. It was developed by the pharmaceutical company Pharnext with the support of AFM-Téléthon during the preclinical stage.

- Pharnext published two press releases in December 2023 detailing the results of the placebo-controlled **PREMIER trial** which evaluated PXT3003 in 387 CMT1A patients who were monitored for 15 months. This international trial took place in France.

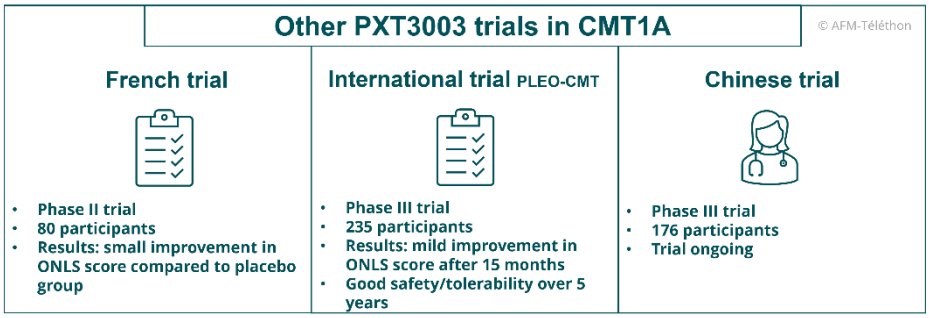
The treatment was well tolerated, a finding consistent with results from two previous trials conducted in over 400 CMT1A patients, some of whom took PXT3003 for six years.

*The **ONLS** (Overall Neuropathy Limitations Scale) assesses the impact of arm and leg muscle impairment on ability to perform daily tasks (difficulty turning a key in a lock, climbing stairs, etc.). The higher the score, the more severe the consequences of the muscle impairment. Therefore, a one-point increase in a patient's ONLS score can mean going from being able to walk without help to having to use crutches to get around.*

The primary endpoint of the PREMIER trial was the ONLS score which assesses a patient's level of disability. The trial did not demonstrate the superiority of PXT3003 over the placebo. Therefore, the PREMIER trial did not confirm the relative efficacy demonstrated during previous trials of the product in CMT1A patients.

The placebo effect in clinical trials
The act of taking part in a clinical trial alone can have a beneficial effect on a patient's symptoms. This is called the placebo effect. In order to obtain reliable clinical trial results, a drug candidate is often compared to a drug that looks identical to the drug candidate but is pharmacologically inactive - the placebo. The placebo effect is very real and has itself become a subject of study, enabling medical practices in both clinical trials and the daily monitoring of patients to improve.

Pharnext plans to refine the analysis of the results of the PREMIER trial and aggregate them with those of previous trials and another trial conducted in China.
Pharnext press release 11 December 2023. *Pharnext press release 19 December 2023.*

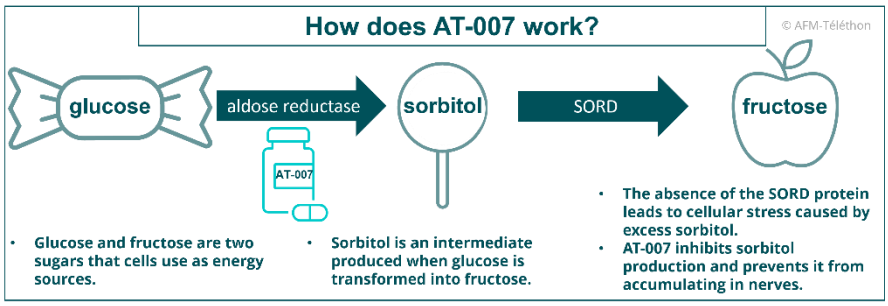


AT-007 in SORD deficiency

SORD deficiency manifests as muscle weakness with or without sensory impairment. It is one of the neuropathies associated with Charcot-Marie-Tooth disease. The disease was only discovered in 2020, however, the first drug candidate, **AT-007 or govorestat,** was quickly identified.

AT-007 is an aldose reductase inhibitor, a type of drug being studied in diabetic neuropathy and other rare disorders such as galactosaemia. It protects nerve cells by limiting the accumulation of sorbitol caused by the absence of the SORD protein.

A clinical trial of AT-007 in SORD deficiency, conducted by Applied Therapeutics, has been running since 2022. The placebo-controlled



INSPIRE trial is evaluating the drug candidate in around 50 patients in Europe (Italy, Czechia and the United Kingdom) and the United States who are being monitored for two years.

Phase III
Efficacy

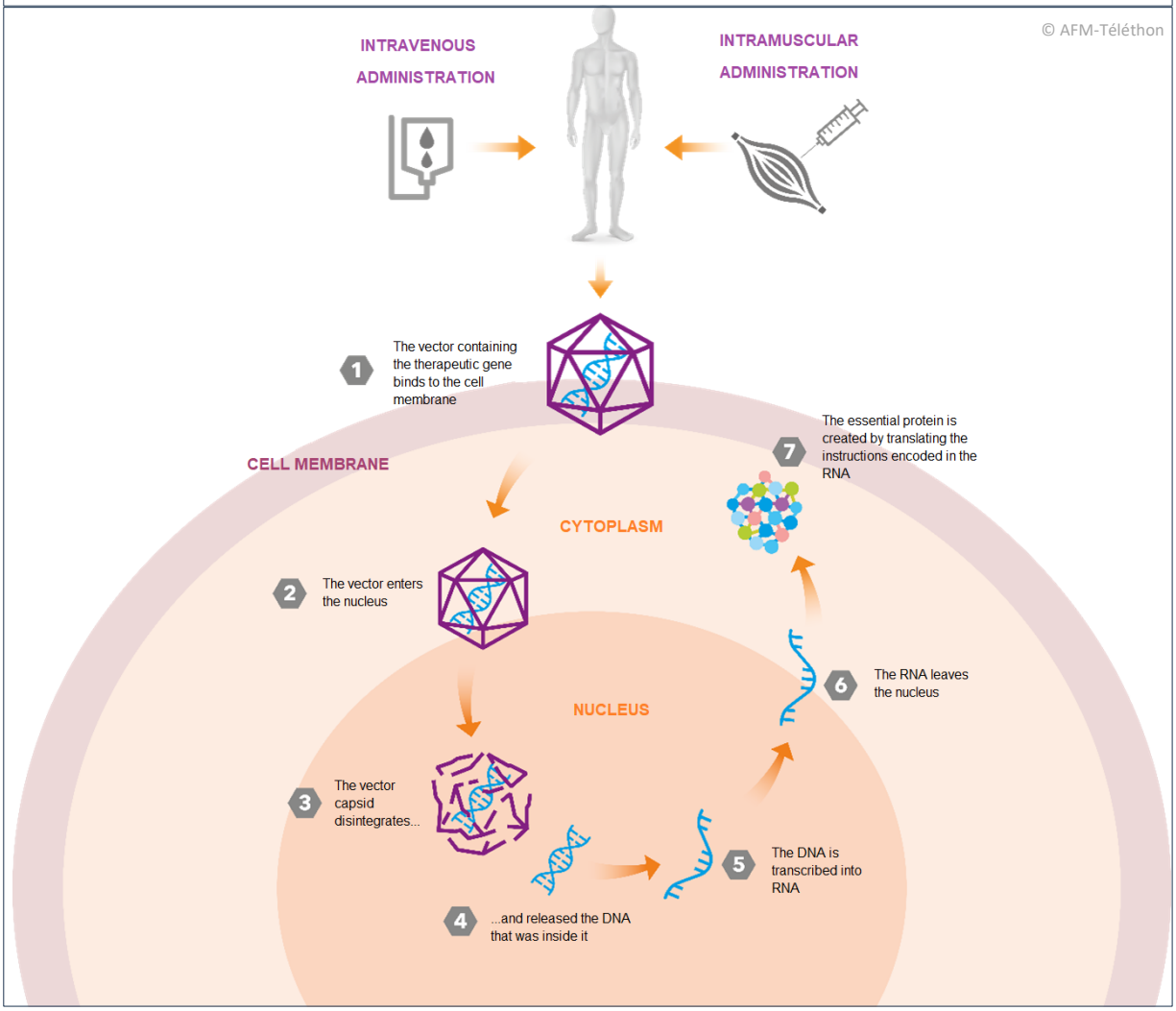
- Interim results after one year showed improved CMT Health Index scores (a questionnaire which evaluates the impact of the disease on daily life and wellbeing) signifying improvements in mobility, fatigue and pain.
The treatment is well tolerated and has not caused any serious side effects.
The trial is still taking place and will run for another year.
Applied Therapeutics press release 15 February 2024

- A Chinese study is currently evaluating the effects of another aldose reductase inhibitor, **epalrestat,** in 30 SORD deficiency patients.

Gene therapy trials

Gene therapy is thriving in the field of neuromuscular diseases, with one drug already available in spinal muscular atrophy (SMA), several clinical trials underway and many drugs being developed.

What is gene therapy?



In giant axonal neuropathy

TSHA-120 is an AAV9-based gene therapy (traditionally used in neurological disorders) containing the *GAN* gene. A total of 14 giant axonal neuropathy patients received a single injection of the drug candidate intrathecally (i.e., as close to the central nervous system as possible). Four escalating doses were evaluated.

One gene, several diseases

Giant axonal neuropathy caused by mutations in the *GAN* gene is usually characterised by abnormalities in the central (intellectual disability, seizures, etc.) and peripheral (gradual loss of muscle strength and sensitivity in the arms and legs) nervous systems starting in early childhood. Milder forms of the disease exist which start in adulthood, do not affect the central nervous system and are similar to axonal Charcot-Marie-Tooth disease.

Results published in a medical journal showed that one year after treatment, the main criterion for evaluating the efficacy of the product had been achieved for one of the doses tested: a slowing of muscle damage, as measured by the 32-item MFM (MFM-32). An improvement in sensory nerve function was also observed in some patients participating in the trial.

Overall, the treatment was well tolerated throughout the trial (up to seven years of follow-up for the first patients included), causing only mild side effects. Although two participants who received the lowest dose died during the study, this was not caused by the drug candidate but by the disease itself according to the principal investigator.

Bharucha-Goebel DX et al. N Engl J Med. 2024

Adeno-associated viruses *(AAVs) are small DNA viruses that can infect humans. However, they do not cause disease but instead trigger a mild immune response. Once inside cells, AAVs do what all viruses do - they incorporate their genes into all of the genes of the infected cells. They are used in genetic engineering as vectors for gene therapy.*

The ***MFM (Mesure de Fonction Motrice [Motor Function Measure])*** *enables motor function in neuromuscular disease patients to be assessed. During an assessment, patients are asked to perform a series of simple movements, and the way in which they perform these movements determines their score.*

Phase I
Safety/tolerability

In *IGHMBP2*-related CMT2S

A gene therapy product which combines the *IGHMBP2* gene with an AAV9 vector is currently undergoing trial in the United States. Mouse model studies have shown encouraging results.

Spinal muscular atrophy or CMT

The *IGHMBP2* gene is involved in CMT2S, but also in a form of spinal muscular atrophy with respiratory distress (SMARD1). SMARD1 mainly affects infants, presenting as severe muscle weakness predominantly in the distal parts of the limbs with respiratory impairment. CMT2S manifests later and does not cause any respiratory problems.

Phase I/II trial for *IGHMBP2*-related diseases

United States

10 (2 months to 14 years old)

Recruiting

November 2021 – November 2028 3 years of follow-up

NCT05152823

Phase I
Safety/tolerability

Phase II
Dose/effect

In CMT1A

A gene therapy trial involving the neurotrophin-3 gene was planned to take place in the United States in three CMT1A patients.

However, due to difficulties in producing the gene therapy product, the trial is currently suspended.

Phase I
Safety/tolerability

Phase II
Dose/effect

Phase I/II CMT1A trial

United States	3 (18 to 35 years old)	Trial suspended	April 2025 – April 2030 3 years of follow-up

NCT03520751

▪ In mouse models of CMT1A, administration of the neurotrophin-3 protein increases axon regeneration. In humans, it has proved to be less effective due to its rapid degradation in blood. Delivering the neurotrophin-3 gene through gene therapy would make it possible to bypass this difficulty as the body would then be able to produce the protein itself.

Biotin in demyelinating neuropathies

Phase II
Dose/effect

Biotin (or vitamin B8) is a food supplement which has been studied in multiple sclerosis, an autoimmune disease which affects the central nervous system.

Administration of high-dose biotin for one year in 15 French patients with autoimmune or genetic demyelinating neuropathies, including five patients with CMT1A or CMT1B, led an improvement in motor and sensory parameters. The treatment was well tolerated.

A placebo-controlled trial in a larger number of patients is still needed in order to more accurately determine the possible benefits of biotin in demyelinating CMT.

Créange A et al. BMC Neurol. 2023

IFB-088 in CMT1A

IFB-088 (or icerguastat) was developed by InFlectis BioScience with the support of AFM-Téléthon. Preclinical trials of IFB-088 in mouse models of CMT1B, CMT1E and CMT1A showed evidence of restored motor function and improved nerve conduction velocities.

▪ *InFlectis BioScience* launched an amyotrophic lateral sclerosis (ALS) clinical trial in December 2022. Enrolment for the trial was completed in January 2024 and the initial results may even be released as early as the end of the year.

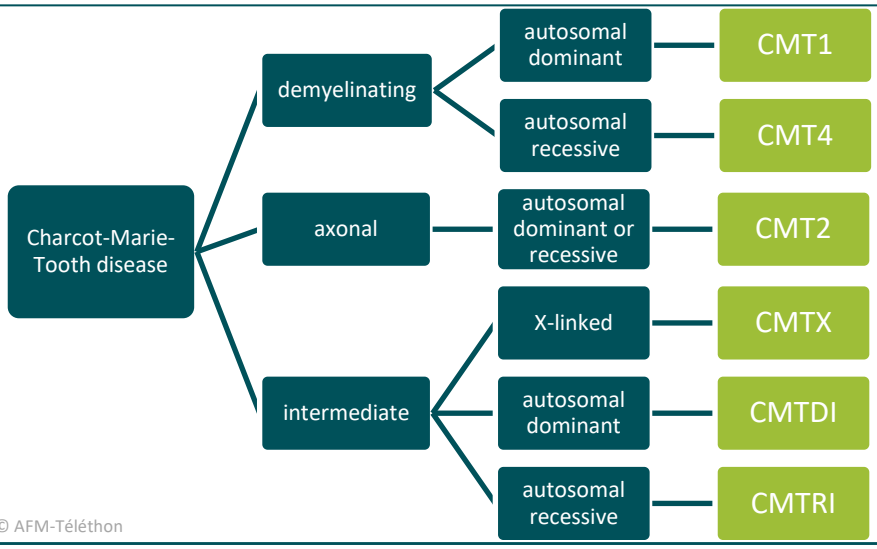
A CMT trial may be considered at a later stage.

InFlectis BioScience press release 31 January 2024

Progress in management and treatment

Databases to help better anticipate the course of the disease

There are many different forms of Charcot-Marie-Tooth disease. These forms can be differentiated by the gene involved in the development of the disease, the mode of inheritance, the age of onset of first symptoms, the course of the disease and the associated signs (hearing loss, respiratory impairment, etc.).



The various different forms of CMT are classified according to type of peripheral nerve damage and mode of inheritance.
Each form (CMT1A, CMT1B, CMT1C, CMT2A, CMT2B, etc.) is caused by a genetic mutation which leads to the production of an abnormal protein. For example, CMT1A is an autosomal dominant demyelinating form caused by the duplication of the PMP22 *gene, while CMT1B is an autosomal dominant demyelinating form caused by mutations in the* P0 *gene.*

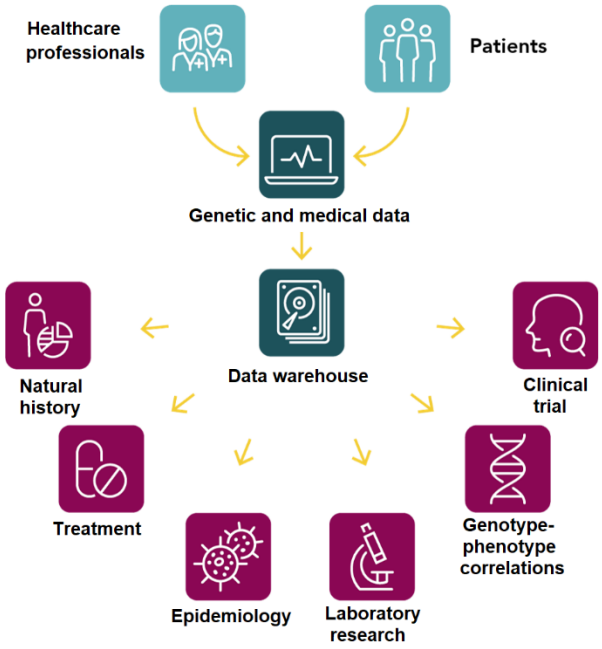
Databases collect medical and genetic data from people with the same disease. Analysing this data helps to determine the natural history of the disease, describe the various different forms, anticipate possible manifestations, establish genotype-phenotype correlations, recruit participants to clinical trials, etc.

Databases and observational studies
These clinical research tools collect data on:
- disease manifestations and the diversity of these manifestations within the same family and between unrelated families (phenotypes),
- genetic testing results (genotypes),
- parameters for monitoring the course of muscle and sensory impairment, which are essential for clinical trials.

Genotype-phenotype correlation *studies look for links between genetic characteristics (genotype) and physical characteristics (phenotype). 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).



National databases

In France, FILNEMUS, a French rare diseases healthcare network, is planning on setting up a database for hereditary neuropathies.

- In Italy, over 1,000 patients participate in a national CMT registry:
  - 66% have demyelinating forms,
  - 25% have axonal forms,
  - and 9% have intermediate forms.

Over 70% of these patients have received a genetic diagnosis.

Analysing the registry data allowed experts to observe that some rare genetic mutations (*HSPB1*, *NEFL* and *SH3TC2* gene mutations) are actually more common than previously thought, discover that certain forms seem to be more severe than others (in particular CMT4A, CMT4C and CMT1E) and better estimate the risk of certain complications (hip dysplasia in earlier forms, scoliosis, etc.). It also helps recruit participants for future clinical trials.

Pisciotta C et al. Eur J Neurol . 2023

*The **FILNEMUS rare neuromuscular diseases healthcare network** hosts, coordinates and encourages interactions between stakeholders involved in the diagnosis, treatment and research of neuromuscular 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 Plan National Maladies Rares [French National Rare Diseases Plan] 2011-2014.*

www.filnemus.fr/

The international INC database

The goal of the Inherited Neuropathies Consortium (INC) database is to help establish the natural history of CMT (the most common forms as well as the rarest forms), develop clinical outcome measures and identify new genes involved in axonal forms of the disease.

▪ Since its creation in 2010, it has collected medical data (clinical and genetic) from over 6,000 people with Charcot-Marie-Tooth disease.

Database for CMT1A, 1B, 2A, 4A, 4C and other forms of CMT

Abroad (outside France) | **Recruiting** | **Created in April 2010**

NCT01193075

www.rarediseasesnetwork.org/cms/inc

Global Registry for Inherited Neuropathies (GRIN)

Created in 2013 by the Hereditary Neuropathy Foundation (HNF), the Global Registry for Inherited Neuropathies (GRIN) was relaunched in 2022. Available in 10 languages, their website enables people with CMT or other inherited peripheral neuropathies to join the registry and share medical and genetic information that could help advance research.

Global Registry for Inherited Neuropathies

Abroad (outside France) | **Recruiting** | **Created in 2013**

Natural history studies currently taking place

Natural history
The natural history of a disease is the description of the different manifestations of a disease and their progression over a specific period of time.

▪ A large-scale cohort study was launched in China in July 2019 (expected to end in 2049). Follow-up will take place over a 20-year period.

Natural history of CMT

China | **500 (all ages)** | **Recruiting** | **20 years of follow-up**

NCT04010188

Two large-scale natural history studies in CMTX1

▪ The Inherited Neuropathies Consortium published results from the largest international natural history study of CMTX1 caused by *GJB1* gene variants to date. The study involved 387 patients who were monitored for several years. A total of 295 families participated in the study and 154 *GJB1* gene variants were analysed.

This form of CMT is linked to the X chromosome. Men are generally affected earlier and more severely than women (53% of the participants were men). CMTX1 manifests as foot deformities (78% of participants) and walking difficulties (75%) which may require orthoses and aids to be used to help stabilise walking, but rarely require the use of a wheelchair (3%). Walking difficulties first start to appear on average around the age of 16 in men and 25 in women.

The study did not identify any signs of central nervous system abnormalities (learning difficulties or "episodes" lasting a few minutes during which the person is unable to speak or move) although several articles mention them in the literature.

For future clinical trials, the authors recommend that the endpoints should involve a combination of biomarkers and CMT-specific clinical outcome measures.
Record CJ et al. Brain. 2023

▪ A second study, conducted in French neuromuscular research centres, described the manifestations of the disease in women in more detail.
The medical team compared the clinical course of CMTX1 in 137 women and 126 men. After the age of 48, 55% of the women in the study had symptoms that were as severe as those seen in the men despite a later onset, and 45% had much milder symptoms or no symptoms at all.
Barbat du Closel L et al. Eur J Neurol. 2023

A very rare proximal form

Hereditary motor and sensory neuropathy with proximal dominant involvement (HMSN-P) is an extremely rare disease caused by mutations in the *TFG* gene. In contrast to CMT, the muscle impairment in this disease is proximal, affecting the upper parts of the arms and legs.

In CMT, muscle impairment is distal
This means that it's the muscles in the lower parts of the arms and legs that are most often affected.
In contrast, proximal impairment manifests in muscles which are closer to the core of the body, i.e. the muscles of the shoulders, upper arms, hips and thighs.

The results of a natural history study involving 16 Japanese patients have been published. Painful abdominal muscle cramps were usually the first sign of the disease, with limb paralysis and respiratory impairment developing after 20 to 30 years of progression.
Shoji H et al. Intractable Rare Dis Res. 2023

Contraindicated drugs

A literature analysis confirmed that two drugs used to treat certain types of cancer (**vincristine and paclitaxel**) may be harmful to CMT patients. Cases of rapid and severe worsening of CMT linked to these products have been reported in several medical articles. They can, however, be prescribed to people suffering from both cancer and CMT as long as the course of the patient's neuropathy is carefully monitored.

According to the authors, these are the only two drugs which have been formally proven to be harmful to CMT patients. Other products may induce milder or rarer effects and should be used with caution. They also feature on the list of treatments not recommended for CMT patients in the Protocole National de Diagnostic et de Soins [French National Diagnosis and Care Protocol] for CMT.
Cavaletti G et al. J Peripher Nerv Syst. 2023
Haute Autorité de Santé [French National Authority for Health] – Protocole National de Diagnostic et de Soins for Charcot-Marie-Tooth disease. April 2020

▪ A group of doctors in the US have highlighted the dangers of misusing **nitrous oxide** as laughing gas. They describe a case of an adolescent with hereditary neuropathy with liability to pressure palsies (HNPP) whose symptoms worsened rapidly and significantly following regular inhalation of this gas.
Castellucci G. et al. Neurohospitalist. 2023 Oct

Poor sleep quality

Over 250 people with Charcot-Marie-Tooth disease completed questionnaires on sleep quality. More than half deemed that their sleep was not restful and almost a quarter felt tired during the day.

Several factors contributed to these results including sleep disorders (such as restless leg syndrome and sleep apnoea), nocturnal cramps and pain, depression and anxiety, etc. Treatment of excessive fatigue in poor sleepers should be multidisciplinary (doctors, physiotherapists, psychologists, etc.).
Bellofatto M et al. J Neurol. 2023

Physical activity

The benefits of physical activity and active physiotherapy in Charcot-Marie-Tooth disease continue to be debated. Regularly engaging in moderate physical activity which has been adapted to a patient's physical abilities (swimming, water aerobics, etc.) improves muscle strength and endurance and reduces feelings of pain and fatigue. High-intensity and/or prolonged muscle exercises on the other hand are bad for muscle fibres.

Finding the sweet spot
When it comes to physical activity, it's better to not "force" anything and avoid going to the point of fatigue or pain. In neuromuscular diseases, this threshold is much lower and is reached even during less intense activities.

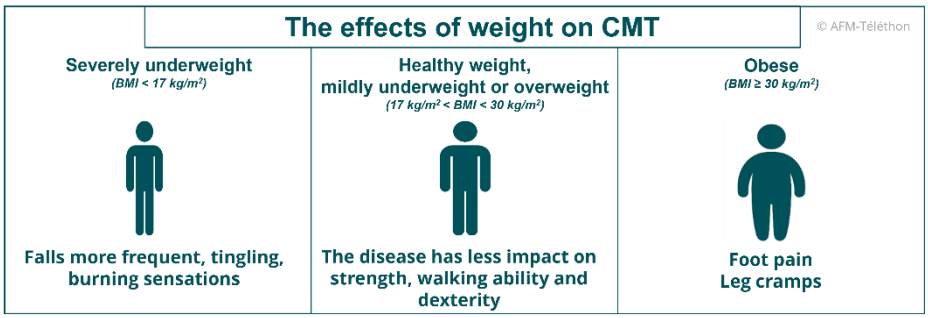
▪ In Italy, 37 patients with CMT (including demyelinating, axonal and intermediate forms) benefited from an intensive physical rehabilitation programme (two to four hours a day, five days a week for three weeks). The programme included strength training, stretching, proprioception exercises (balance training) and endurance exercises, all of which were adapted to their abilities.
The participants saw improvements in their walking ability and balance, as well as in their fatigue, pain and cramps by the end of the programme. However, these effects were not long-lasting and disappeared less than a year after the end of the intensive programme.
Ferraro F et al Neurol Sci. 2023

▪ In the United Kingdom, seven CMT1A patients completed an at-home rehabilitation programme which included regular visits from a physiotherapist. The sessions included exercises which aimed to strengthen their proximal muscles and improve their balance. After three months, they were able to walk more stably compared to seven other patients who did not complete physiotherapy sessions. The London-based medical team who initiated the study emphasised that this safe at-home intervention could easily be implemented, calling for more studies on this approach.
Dudziec MM et al. Muscle Nerve. 2023

Steps to achieve a healthy weight

In 2021, an international study of 477 young people (aged between 3 and 20 years old) with CMT showed that being obese or severely underweight has an impact on health and the manifestations of the disease.

▪ While the majority of the children and adolescents with CMT were a healthy weight (62%), they were three times more likely to be severely underweight (6%) and two times more likely to be obese (7%) than young people of the same age without the disease. This can be explained by the fact that CMT causes muscle wasting (which can cause weight loss) and a decrease in physical activity (which can cause weight gain).



▪ Two years later, a new study conducted on 242 of these young people showed the health benefits of dietary measures and physical activity in maintaining or achieving a healthy weight, even in those who were initially obese or severely underweight.
The authors recommend that patients should seek the help of a doctor who is familiar with CMT when adjusting their diet and physical activity to gain or lose weight. This will help prevent nerves and muscles from being damaged by too strict a diet or overexercising. There are currently no CMT-specific guidelines on this subject, therefore, recommendations are based on those of the World Health Organization for children and adolescents suffering from a disability: limit screen time, engage in moderate physical activity at least one hour a day and more sustained exercise (including muscle strengthening exercises) three times a week.
Donlevy GA et al. Neurology. 2023 Jun

Products to help stabilise walking

Ankle-foot orthoses, insoles and orthopaedic shoes make walking easier and more stable in CMT. However, while many patients benefit from their use, these products are underused, as demonstrated by two studies (a French study of 795 CMT patients and an Italian study of 266 patients).

▪ The vast majority of the French respondents said that they owned orthotic devices (insoles, orthopaedic shoes, ankle-foot orthoses) but over half had stopped using them. The main reasons mentioned were that they were not adjustable, their in-shoe volume, weight, lack of aesthetic appeal, that they caused skin pain, etc.
Blouin C et al. Disabil Rehabil. 2023

▪ The Italian study also showed that half of those who owned orthotic devices had never used them or ended up abandoning them after using them for several years. Around 59% of patients had experienced problems (discomfort or even pain).

The study also showed that adapting and personalising orthotic devices to the needs and expectations of patients can increase their level of acceptance.
Bertini A et al. J Neurol Neurosurg Psychiatry. 2023

Talk to your medical team about your orthotic devices
Especially if you see no improvement, no longer use them or they are causing you pain. This can help you find a more suitable device, both physically and aesthetically.

▪ A team from Toulouse compared the efficacy and acceptability of a new helical-shaped, non-articulated ankle-foot orthosis to that of the traditional posterior ankle-foot orthosis in 20 people with foot drop, two of whom had CMT. After one week of use, walking abilities had improved more with the helical ankle-foot orthosis than with the posterior ankle-foot orthosis or high-top shoes. User satisfaction was significantly higher with the helical ankle-foot orthosis.
Gasq D et al. J Neuroeng Rehabil. 2023

A possible surgery for carpal tunnel syndrome

In neuropathies such as Charcot-Marie-Tooth disease type 1A (CMT1A) and hereditary neuropathy with liability to pressure palsies (HNPP), the presence of thickening along the nerves increases the risk of carpal tunnel syndrome.

A relatively common condition
Compression of a nerve in the wrist (carpal tunnel syndrome) or elbow (cubital tunnel syndrome) manifests as numbness in the fingers and hands. Strength and sensitivity are also reduced.
According to Assurance Maladie (French health insurance system), around 600,000 people suffer from carpal tunnel syndrome every year in France and just over 130,000 undergo surgery.

Traditional treatment may mean surgery. Its benefit in CMT is still poorly understood. There may be a reluctance to undergo surgery when the nerve is already very fragile.

▪ In the first American study on the subject (which included 60 CMT1A patients and 52 HNPP patients), the vast majority of the CMT1A patients saw their symptoms improve after the procedure. These benefits seemed more mixed in the HNPP patients, with a risk of aggravating their symptoms.
Chompoopong P. et al. Muscle Nerve. 2022

▪ A team at a specialist neuromuscular disease centre in Lille published their experience with 18 HNPP patients who had undergone carpal tunnel syndrome surgery. Several years after having the operation, 73% of them were still satisfied with the results.
François T et al. J Hand Surg Eur Vol. 2023

Effects on mental wellbeing

▪ Over 260 adults with CMT responded to an online survey on their mental health and wellbeing which showed that, aside from their physical disabilities, their social life (self-esteem, friendships, emotional support, etc.) also influences their quality of life and life satisfaction.
Experiences of discrimination are common among people with CMT. They are also more likely to suffer from anxiety related to their condition.
The authors of the study suggest that CBT could be beneficial as it encourages patients to engage in enjoyable and rewarding activities to help cope with stigma better and manage their anxiety.
Rule PD et al. Rehabil Psychol. 2023

***Cognitive behavioural therapy (CBT)** is a type of therapy which helps resolve everyday problems by addressing negative attitudes or fears, even phobias, which make these problems worse. This approach can be personalised and adapted to each individual's goals.*

When mental health is affected, counselling can help
Counselling can help patients get through difficult periods (diagnosis, foot surgery, etc.) or certain stages of life (going from childhood to adolescence, wanting children, etc.), or manage feelings of distress when their disease's progression stops them from continuing a physical, professional or leisure activity or impacts their emotional life and relationships.

Pain management

Pain is common in Charcot-Marie-Tooth disease. It can be caused by damage to the nerve itself in neuropathic pain (causing burning sensations, tingling, etc.) or joint deformities and is aggravated by anxiety and fatigue.

Pain and neuromuscular diseases, AFM-Téléthon 2024 [document in French]

▪ A small-scale American study has shown that medicinal cannabis can help reduce pain in CMT. Its prescription is being studied in France on a trial basis in five indications including cancer-related pain and treatment-resistant epilepsy as well as treatment-resistant neuropathic pain which can be seen in CMT patients.
A progress report published by the ANSM [French medicines agency] showed encouraging results. Out of the 3,035 patients included since 2021, over 60% are still being monitored and treated. The ANSM stated that "the data collected during the first two years of the trial show the effectiveness of medical cannabis in the indications included in the trial, which was maintained for several months in some patients." This means that medical cannabis-based drugs may be prescribed for the indications studied in the trial in the future.
Canals PC et al. Am J Hosp Palliat Care. 2023
ANSM news article 20 February 2024

Highly-regulated consumption
Tetrahydrocannabinol (THC) and cannabidiol (CBD) are two of the main active ingredients found in cannabis. In France, the consumption of cannabis or any product containing more than 0.3% THC is banned, however, CBD is allowed to be sold in specialised shops (CBD is not considered to be a narcotic drug). People suffering from a progressive disease such as CMT are advised to consult a healthcare professional if they wish to start using CBD.

Usually only a temporary worsening of symptoms during pregnancy

There are currently no practical recommendations for managing pregnancy in CMT. A British team conducted a survey of 92 mothers with CMT on their experience of pregnancy (171 in total).

An analysis of their responses did not reveal any significant increase in obstetric complications (miscarriages, haemorrhage, etc.) compared to the general population. The type of delivery (vaginal or caesarean section) did not differ significantly either.
Around a third of participants reported a worsening of their symptoms during pregnancy, in particular walking and balance deterioration, mainly during the second and third trimester. Fatigue was also more common and more intense. These symptoms improved after delivery in half of the women questioned.
Skorupinska M et al. Obstet Med. 2023

Cochlear implants for severe hearing loss

People with CMT often have hearing problems which can lead to severe hearing loss. When traditional hearing aids are not able to sufficiently address this, cochlear implants may be offered. Five American patients and two Korean patients were fitted with these devices which, after aural rehabilitation, enabled them to better discern words during conversations, while listening to the radio, etc. These interventions are still rare in CMT but they can improve quality of life.
Song B et al Eur Arch Otorhinolaryngol. 2024
Farber NI et al Ann Otol Rhinol Laryngol. 2024

Coenzyme Q10 in *COQ7*-related CMT

Researchers in Lyon funded by AFM-Téléthon have demonstrated the involvement of the *COQ7* gene in a neuropathy related to CMT (dHMN).

The *COQ7* gene was already known to cause a very severe genetic disease which affects several organs, including the brain, from birth. The protein, called coenzyme Q7 hydroxylase, is involved in the production of coenzyme Q10, a molecule which is essential for cells to produce energy. In the first patients identified, coenzyme Q10 supplementation slowed the progression of the disease. The researchers prescribed this treatment to patients with *COQ7*-related CMT. As the disease progresses slowly, it will undoubtably take several years to see the first significant clinical improvements. However, laboratory tests performed on cells taken from the patients treated with coenzyme Q10 showed promising results.
Jacquier A et al. Brain. 2022

Since then, other similar cases in European, Brazilian, Canadian and Chinese patients have been published.
Rebelo AP Brain. 2023
Zhang XY et al. Brain. 2023

In search of reliable and sensitive biomarkers for clinical trials

It is important to have easy-to-use tools that help to identify the beneficial effects of a drug candidate on a restricted number of patients (since CMT is a rare disease) over a limited period of time (the disease progresses slowly) - usually around one year.
The existence of specific scores, like the CMTNS (CMT Neuropathy Score) and its simplified version, the CMTES (CMT Examination Score), which evaluate the severity and progression of the disease in CMT patients, makes the use of biomarkers such as blood biomarkers (in particular neurofilament light chain) and imaging such as MRI (of muscles or nerves) seem promising.

*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.).*

Essential tools for clinical trials
In order to accelerate the identification and dissemination of relevant biomarkers for CMT clinical trials, AFM-Téléthon has set up a task force on the subject which brings together clinical and scientific experts, industry partners and representatives from patient organisations.

CMT-specific clinical outcome measures

▪ The CMT-FOM (CMT-Functional Outcome Measure) was developed in 2018 to complement measures already in use which have some limitations regarding their use in clinical trials. It's easy to use and evaluates muscle strength, balance, mobility, and arm and leg function. A new publication confirmed the validity of the tool in 214 CMT1A patients aged 18 to 75 years old.
Mandarakas MR et al Neurology. 2024

▪ There are also specific measures for evaluating the impact of CMT on the quality of life of children who have the disease, such as the pCMT-QOL (pediatric CMT-specific QOL outcome measure), developed by experts from the Inherited Neuropathies Consortium (INC).
In May 2023, they released a version of the measure that can be completed by a parent or caregiver.
Wu TT et al J Peripher Nerv Syst. 2023

Medical imaging

Magnetic resonance imaging (MRI)
MRI is useful for detecting abnormalities in nerve fibres and examining muscles. It makes it possible to quantify the degree of muscle fat infiltration (when muscle cells are destroyed, they are replaced by fat cells) in the calves. This is the only confirmed biomarker in CMT.

Several publications show the value of quantitative MRI and measuring the degree of fat infiltration in CMT:

- a French study in 24 CMT1A patients who underwent MRIs that were performed one year apart,
- an international study in children and adolescents (under 20 years old) with CMT1A monitored for one year,
- an international study in 22 patients with CMTX1, 21 with CMT1B and 21 with CMT2A examined one year apart.

Fortanier E et al Neurology. 2024
Doherty CM et al. Ann Neurol. 2024
Doherty CM et al. Ann Clin Transl Neurol. 2024

MRI images can be analysed by artificial intelligence software so that they can be processed quicker, as demonstrated by a British team using data from 20 CMT1A patients.
O'Donnell LF et al J Neurol Neurosurg Psychiatry. 2023

Blood biomarkers

▪ An international consortium of researchers coordinated by a Latvian team measured neurofilament levels in the blood of 73 CMT patients at least twice three years apart. They were unable to establish a correlation between the CMTNS disease severity score and these levels. They therefore concluded that plasma neurofilament concentrations are not a biomarker for CMT progression.
Setlere S et al. Eur J Neurol. 2023

***Neurofilaments** are proteins that are found specifically in neurons. Levels of neurofilament light chain in the blood can be used to measure the degree of neuronal damage.*

▪ A study has been underway in France since September 2021 to better understand how mitofusin 2 abnormalities impact cell function. Supported by AFM-Téléthon, it will ultimately include around 30 CMT2A patients and around 30 healthy subjects.
The researchers will study the lipids and other small molecules from the metabolism using blood and skin samples taken from the CMT2A patients, and will compare them to those of the healthy subjects. Microscopic techniques will enable the organisation and function of important cell structures (cytoskeleton, mitochondria, endoplasmic reticulum, etc.) to be analysed.
This may help to identify biomarkers for monitoring the progression of the disease, in particular during future clinical trials, and therapeutic targets specific to CMT2A.

CMT2A: lipid analysis

France

60 (over 18 years old)

Recruiting

September 2021 – February 2023
1 single visit

NCT04881201

Activity sensors

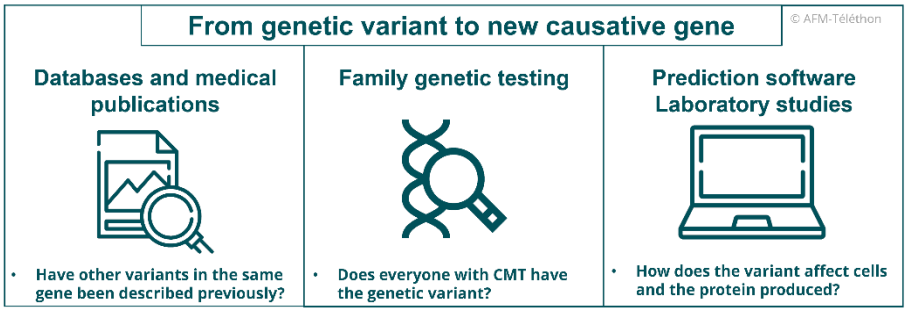
Fifteen CMT1A patients wore small sensors on their chests, thighs and shins to record their movements as they walked. The evaluations were carried out one year apart. Their gaits had several characteristics that were able to be measured by the sensors such as slower walking speed, fatigability, shorter step lengths, greater postural sway, etc. These measurements correlated with the patients' CMT-FOM scores, suggesting that they could be good biomarkers. However, larger studies will be necessary to confirm these findings.
Dinesh K et al. J Peripher Nerv Syst. 2023

Advances in genetics for better diagnoses

Many individuals with CMT still do not have a precise genetic diagnosis, in particular those with axonal forms of CMT. It can be very difficult to identify the genetic mutation (or mutations) responsible for the disease.

▪ In the last few years, new genetic diagnostic techniques have been developed. These "next-generation sequencing" (NGS) techniques make it possible to analyse hundreds of genes simultaneously.

Results need to be interpreted judiciously by experts
Some variations in DNA are harmless, whereas others result in the onset of a genetic disease. These are referred to as **genetic mutations**.
The biggest issue with using next-generation sequencing techniques is that they increase the risk of finding variations in an individual's DNA sequence, called **genetic variants**, which do not cause disease and complicate the analysis of the results.



Analysing the whole genome to reduce time to diagnosis

Given the insufficient diagnostic yield of NGS panels, more and more teams are now turning to "whole-genome sequencing" (WGS).

▪ WGS enabled a genetic diagnosis to be made in 77% of patients in a cohort of 1,515 English patients. However, this percentage varies greatly from one form of CMT to another: from 97% in demyelinating forms and 81% in intermediate forms to under 50% for axonal forms and hereditary motor neuropathy.
Whole-genome sequencing was used to help solve 233 more complex cases. The data was analysed by a team of CMT experts and a diagnosis was achieved in 46 cases (20%).
The identification of new genes involved in CMT as well as technological advances will help to reduce time to diagnosis. However, the authors stress that the genetic complexity of CMT should be taken into account when attempting to solve the most difficult cases. Sometimes, the disease is not monogenic (mutations are present in several genes) or the penetrance of the genetic mutation is incomplete (some members of the same family with the same mutation develop the disease and others do not).
Record CJ et al. Brain. 2024

▪ In South Korea, 72 families underwent whole-genome sequencing (after receiving inconclusive results from NGS panels and *PMP22* gene duplication studies). Fourteen were able to acquire a genetic diagnosis, four of which involved genes that are not typically related to peripheral neuropathies.
Kim YG et al. Brain Commun. 2023

▪ It is sometimes necessary to look beyond the genes that are already known to be involved in CMT and its associated neuropathies. An English publication showed that the study of mitochondrial genes facilitates genetic diagnosis in CMT.
A study of 2,087 patients whose symptoms were suggestive of CMT detected over 1,300 rare variants in 183 genes involved in mitochondrial diseases, of which only 44 were documented enough to conclude that they were the cause of the disease. This enabled 42 patients from 36 families to receive a genetic diagnosis.
Ferreira T et al. J Neurol. 2024

Six new candidate genes

▪ Mutations in the ***DHX9*** gene were detected in 20 people suffering from either axonal CMT or neurodevelopmental disorders. Studies in mice have shown that this gene is involved in regulating the development and maintenance of the nervous system, suggesting a possible link with the symptoms observed.
Calame DG et al Am J Hum Genet. 2023

▪ Mutations in the ***RAB40B*** gene were shown to be involved in axonal CMT in two family members. Studies in flies and zebrafish confirm that these mutations can lead to motor impairment.
Son W et al Exp Neurobiol. 2023

▪ The ***CRYAB*** gene is known to be involved in genetic muscle diseases. Mutations in this gene have also been detected in five people (from two families) who have adult-onset (after the age of 40) axonal CMT with congenital cataracts.
Cortese A et al. Eur J Neurol. 2023

▪ The ***NDUFS6*** gene is a mitochondrial gene which is already known to cause a very severe form of Leigh syndrome, a mitochondrial disease of the central nervous system. This gene appears to be the cause of recessive axonal CMT with associated nystagmus (involuntary movement of the eyes) in five patients from three families.
Armirola-Ricaurte C et al. Genet Med. 2024 Mar

▪ ***INSC*** gene mutations linked to axonal CMT were reported in eight members of an Asian family. Studies in flies confirm the possible involvement of this gene.
Yeh JY et al. EMBO Mol Med.2024

▪ A new aminoacyl-tRNA synthetase gene (***NARS1*** which codes for asparaginyl-tRNA synthetase) has just been found to be involved in a dominant axonal form of CMT thanks to whole exome sequencing performed in three unrelated people.
Beijer D et al. Brain Commun. 2024

In addition, a new case of intermediate CMT related to the *SARS1* gene has been reported, confirming a previous publication on the subject.
Record CJ et al. Ann Neurol. 2023

*An **aminoacyl-tRNA synthetase** is an enzyme that helps attach an amino acid (the building blocks of proteins) to its corresponding transfer RNA. This makes it possible for amino acids to be chained together in the order required to produce a specific protein during protein synthesis.*

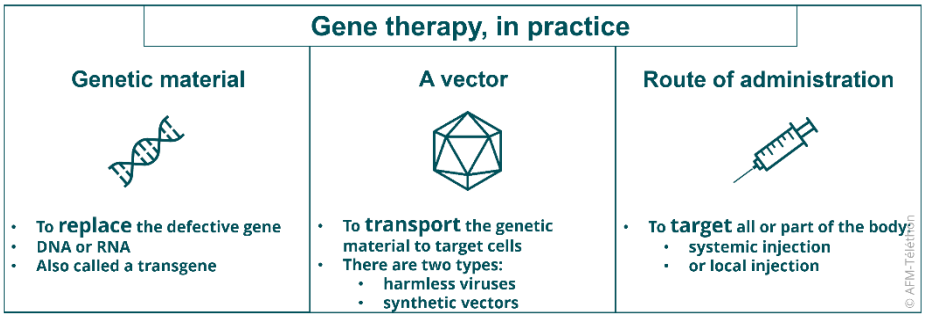
Modifier genes in CMT1A

What is a modifier gene?
Modifier genes are genes whose mutations are able to modify the course of a given genetic disease. They may aggravate or improve symptoms, but cannot cure the disease.

The existence of modifier genes is suspected in CMT1A. To confirm this, teams from the Inherited Neuropathies Consortium (INC) devised a protocol to see which genes could be involved. In order to achieve this, the protocol focused on patients in their database with very severe or very mild phenotypes. This could ultimately lead to new target therapies being identified.

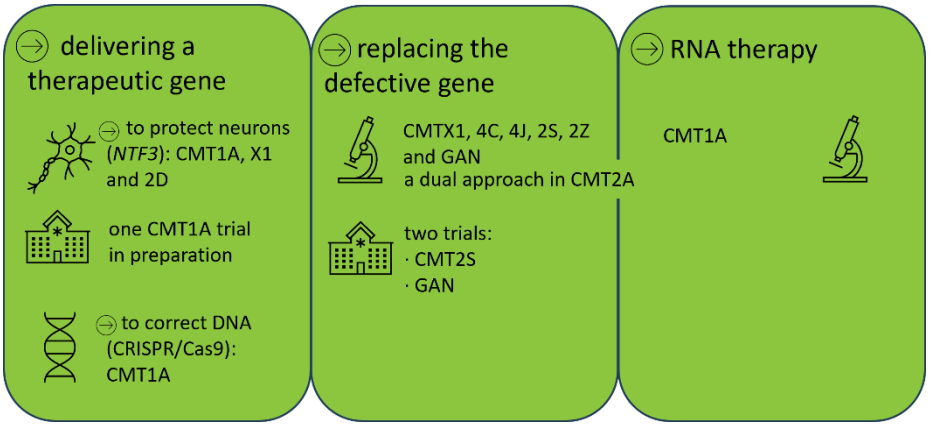
Xu IRL et al. J Peripher Nerv Syst. 2024

Intensification of gene therapy approaches



In its early days, gene therapy consisted solely of replacing a defective gene by delivering a normal gene into the body. Since then, gene therapy techniques have progressed, including those that introduce genetic material such as DNA or RNA (therapeutic genes, antisense oligonucleotides, etc.) into the body for therapeutic purposes.

Approaches used in CMT



In *PMP22*-related CMT1A

▪ The CRISPR/Cas9 system is a new, highly effective tool used to modify genetic information. Japanese researchers have developed a gene therapy approach using the CRISPR/Cas9 system to reduce the number of copies of the *PMP22* gene (CMT1A patients have an extra copy of this gene).
Injection of the gene therapy product into cell models of CMT1A resulted in a 20 to 40% reduction in extra copies of the *PMP22* gene.
Yoshioka Y et al. Commun Med (Lond). 2023

▪ Another approach consists of delivering an interfering RNA to decrease the production of the PMP22 protein which is produced in excess in CMT1A. Several approaches are being studied in CMT1A, two of which are being investigated by French teams:

- a start-up from the Île-de-France (MAAsiRNA) uses a small interfering RNA inside a chemical vector (squalene),
- a biotechnology company in Montpellier (Nervosave Therapeutics) is developing a product which consists of a viral vector expressing an interfering RNA.

For both teams, administration in animals (mice or rats) with the disease showed promising results in terms of muscle strength and nerve conduction velocities.

In *GJB1*-related CMTX1

A team from the Cyprus Institute of Neurology and Genetics, who are very active in CMT gene therapy research, has already developed a gene therapy product based on the *GJB1* gene (which is defective in CMTX1) with promising results seen in a mouse model of CMTX1.

*An **intrathecal injection** involves injecting a product into the cerebrospinal fluid which surrounds the brain and spinal cord. The injection is administered into the lower back between two lumbar vertebrae (like in a lumbar puncture).*

- The product was injected intrathecally into other mice with CMTX1 which had genetic mutations similar to those found in patients (where the protein is present but mutated which risks reducing the efficacy of the connexin 32 produced by gene therapy). This improved their nerve conduction velocities and muscle strength for several months when the treatment was administered before the first signs of the disease (at two months old), but also once the disease was established (after the age of six months), although the benefits were less pronounced.

Kagiava A et al. Mol Ther Methods Clin Dev. 2023

In *SH3TC2*-related CMT4C

- The same team developed a gene therapy product to express the *SH3TC2* gene which was initially delivered using a lentiviral vector but then modified to deliver it using an AAV9 vector.
- Injected intrathecally into mice with CMT4C (whether the disease had already manifested or not), the product improved myelin structure and motor function, and increased nerve conduction velocities.

Georgiou E et al. Mol Ther. 2023

In *MFN2*-related CMT2A

CMT2A is caused by abnormalities in the mitochondrial protein mitofusin 2 (MFN2).

- An Italian team has developed a gene therapy approach which consists of administering RNA interference by AAV9 which inhibits mutated mitofusin 2 by delivering an unmutated copy of the *MFN2* gene on which the RNA interference has no effect.

Their strategy proved effective in restoring the production of a functional MFN2 protein in mouse and cell models of the disease. However, the mouse models only had very mild motor and sensory symptoms and these were not improved by the gene therapy.

Rizzo F et al. Cell Mol Life Sci. 2023

- Cypriot researchers showed that increasing the quantity of mitofusin 1 (*MFN1*) using gene therapy improves mitochondria function in cell models of CMT2A.

Mitofusin 1 is found on the external membrane of mitochondria, like mitofusin 2. Their structures are quite similar but they have distinct properties and functions in mitochondria and cells.

Stavropoulos F et al. J Peripher Nerv Syst. 2023

In *MORC2*-related CMT2Z

South Korean researchers corrected a loss-of-function mutation in the *MORC2* gene by intrathecally injecting a gene therapy product which delivers this gene using an AAV vector. Treated at two months old, six-month-old mice had improved myelination and nerve conduction velocities, and increased muscle mass and strength.
Chung HY et al. Brain. 2024

- Another approach has also been successfully developed and evaluated in *C1orf194l*-deficient mice (the *C1ORF194* gene may be involved in an intermediate form of CMT).
Shen Z et al Neurotherapeutics. 2023

Treatment avenues to pursue

Different strategies are being studied in CMT:

- Developing treatments that are specific to a gene and form of CMT, such as AT-007 in SORD deficiency.
- Researching a mechanism found in several forms which could therefore benefit from the same treatment. This first requires a drug candidate to be developed for a well-known form of the disease before being able to implement it in rarer forms.

For example, drugs developed to treat CMT1A (the most common form) may be useful in other rarer forms of demyelinating CMT.

Main functions of proteins altered in CMT

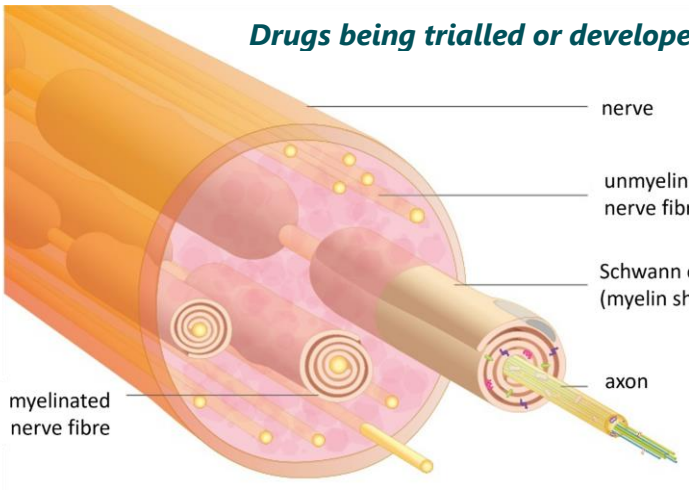
Myelin components
- PMP22
- MPZ
- SH3TC2
- PRX
- GJB1 or Cx32
- PMP2
- DRP2

Aminoacyl-tRNA synthetases (function to be determined):
- GARS1
- AARS1
- MARS1
- HARS1
- YARS1
- KARS1

Regulation of mitochondrial function:
- CHCHD10
- MFN2
- GDAP1
- DHTKD1
- SURF1
- AIFM1
- PDK3
- COX6A1
- SLC25A46

Internal cell transport
- LITAF
- TFG
- GAN
- KIF1B
- KIF1A
- RAB7A
- NEFL
- NEFH
- HSPB1
- DNM2
- DYNC1H1
- SPG11
- MTMR2
- SBF2
- SBF1
- NDRG1
- FGD4
- FIG4
- DCNTN2
- NAGLU
- MORC2

Drugs being trialled or developed in CMT



To target peripheral nerves

Reducing inflammation

CMT1A – Nano-Cur

To target Schwann cells

Improving myelinisation
- CMT1A – TGFβ4; cell therapy
- PXT3003, currently undergoing clinical trials in CMT1A, may improve myelinisation

Preventing the accumulation of toxic molecules
- CMT1A, CMT1B and CMT1E - IFB-088
- CMT1B - inhibiting proteasomes

To target axons

Improving axon function
- CMTDIC and CMT2D: BDNF
- CMT2H: amlexanox

Protecting/repairing axons
- Mitf

Preventing the accumulation of toxic molecules
- SORD deficiency – AT-007

Repairing myelin

▪ A Korean team showed that TGFβ4 increases Schwann cell myelination. Its administration in mice with CMT1A improved their muscle strength and motor function.
Jeon H et al Brain. 2023

▪ Korean researchers injected stem cells into mice with CMT1A. When injected into muscle, these cells promoted muscle and nerve regeneration which led to improved motor function in the mice treated.
Nam YH et al. Biomedicines. 2023 Dec

Reducing nerve inflammation

Macrophages are immune system cells that are present in all tissues of the human body. They play a key role in inflammation, a reaction that enables the body to protect itself from attack (damaged cells, foreign particles, etc.). Several researchers have highlighted the benefit of reducing inflammation via macrophages in lessening nerve damage.

▪ German researchers have shown that macrophages interact and even communicate with Schwann cells. Usually, when an axon is damaged, macrophage activation triggers "debris clearance" (an autophagy mechanism which recycles damaged cells) during which Schwann cells repair the axon.
In demyelinating neuropathies, macrophages are too active and can degrade cells that they shouldn't.
Weiß EM et al J Peripher Nerv Syst. 2023

▪ A French team from the université de Limoges [University of Limoges], with the support of AFM-Téléthon, has developed a new drug called Nano-Cur from curcumin.
When administered daily to rats and mice with CMT1A over an eight-week period, the treatment improved the myelinisation of peripheral nerves, resulting in an increase in muscle strength, endurance and balance in the animals treated.
Nano-Cur inhibits the macrophage response in nerves and reduces oxidative stress.
El Massry M et al Biomater Res. 2024

Oxidative stress
When mitochondrial function is disrupted, toxic molecules called free radicals are produced in excess which damages cell components (DNA, proteins, etc.). Oxidative stress is a situation in which cells are no longer able to control the presence of excessive free radicals.

Removing misfolded proteins

In certain forms of CMT (1A, 1B, etc.), misfolded proteins accumulate in Schwann cells which disrupts the structure and function of the myelin sheath, thus slowing down nerve signal transmission.

Response to misfolded proteins
Proteins are produced in the endoplasmic reticulum. If they are an abnormal shape (mutated, misfolded), they accumulate there. This induces the unfolded protein response (UPR) which generally leads to them being broken down by proteasomes. In the long term, this can cause cell death.

▪ In a literature review, Belgian researchers highlighted the importance of mechanisms that check protein quality and degrade them if necessary in demyelinating forms of CMT.
Libberecht K et al. Biochem Pharmacol. 2023

▪ Researchers have shown that the UPR is disrupted in CMT1B. By inhibiting proteasome activation, they were able to prevent the development of neuropathy in mouse models.
VerPlank JJ et al Life Sci Alliance. 2024

Supplying axons with energy

In order to be able to function properly, axons require a significant amount of energy along their entire lengths. Mitochondria provide this energy. Mitochondria are small structures found in all cells that are able to produce energy for cells to use.

Mitochondria distributed along the entire length of axons
Mitochondria need to be mobile in order to function properly and coordinate their activities. The fusion of several mitochondria into one, alternating with the fission of one mitochondrion into several mitochondria, modulates their activity, number, size and shape.
▪ For cells to function at their best, no region should be devoid of mitochondria (and therefore devoid of energy production).
▪ In nerve cells that are particularly long (some axons can be up to 1 metre long, or even longer), the mitochondria spread themselves out along the entire length of the axon as they move.

▪ Mitochondria are essential to axons, but also to Schwann cells, as demonstrated by a French publication in April 2024. The researchers showed that abnormalities in the mitochondria of Schwann cells in CMT4G caused by a mutation in the *HK1* gene impair myelin sheath maintenance which hinders the transmission of nerve impulses.
Ceprian M et al. Int J Mol Sci. 2024

▪ American researchers showed that delivering BDNF (a neurotrophic factor) to mice with an intermediate form of CMT (CMTDIC) restores axonal transport. Similar results have been reported in CMT2D, which is also caused by an aminoacyl-tRNA synthetase (GARS1).
Rhyme ER et al. Neurobiol Dis. 2024
N Sleigh JN et al. JCI Insight. 2023

▪ It should be noted that in these last two studies, the drug candidate was not injected into the peripheral nerve but into the muscle. This is a route that is being studied more and more in CMT. Muscles and nerves are in close communication with each other and this is capable of producing neurotrophic factors for nerve cells.
Villarroel-Campos D et al. Neural Regen Res. 2024

Repairing axons

American researchers have identified Mitf as a factor produced by Schwann cells to repair axons when they are damaged. It can be produced following injury or in genetic diseases such as CMT4J and CMT4D. Studying this mechanism in more detail will make it possible to explore new therapeutic avenues in CMT.
Daboussi et al., 2023, Cell Reports November 2023

Stop codon readthrough

What is a premature stop codon?
A premature stop codon is a genetic mutation that the cell interprets as a message signalling the end of the translation process. This leads to the production of a protein that is too short, unstable and unable to fulfil its functions.
It is possible for premature stop codons to be ignored in order for a normal protein to be produced. This is called stop codon readthrough.

Given that nonsense mutations are relatively common in the various forms of CMT, French researchers at the université de Limoges evaluated the therapeutic benefits of stop codon readthrough in these genetic diseases. The administration of amlexanox to cells taken from a patient with *GDAP1*-related CMT2H enabled a stable GDAP1 protein to be produced and mitochondrial morphology to be restored.
Benslimane N et al. Pharmaceuticals. 2023

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