MARCH 2023 | 9TH EDITION

SAVOIR & COMPRENDRE
DATA SHEET

OVERVIEW OF NEURO-MUSCULAR diseases

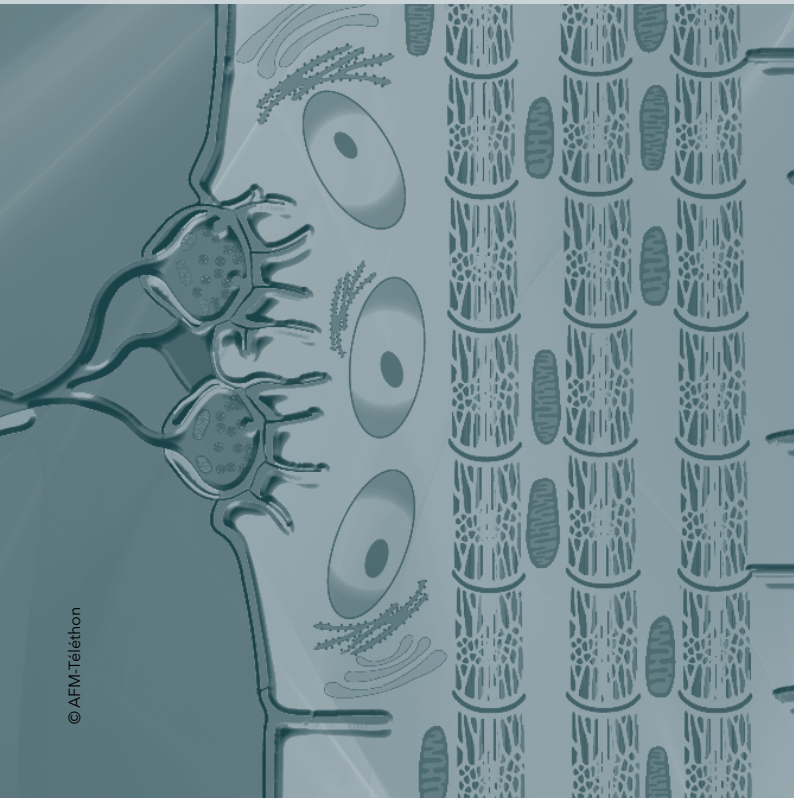
After a brief reminder of the structure of the motor unit and the various modes of inheritance, this document provides short descriptions of the neuromuscular diseases that are part of our scope at AFM-Téléthon, as well as how to manage and treat them.

For each group of diseases, as well as in the motor unit section and some other sections, the proteins involved are depicted in an illustration.

The ORPHAcodes (Orphanet) and OMIM® codes (*Online Mendelian Inheritance In Man®*) for the diseases are provided where they exist.

The groups of neuromuscular diseases are presented in alphabetical order.

There is an index at the end of the document that provides an alphabetical list of the neuromuscular diseases covered in this data sheet, with the associated proteins and genes listed in separate indexes.



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Prevalence of neuromuscular diseases

• In epidemiology, incidence refers to the number of newly diagnosed cases of a disease within a particular time period. Prevalence is generally expressed as "the number of cases per 100,000 people per year", which allows comparisons to be made between populations and over time.

• The prevalence figures for Europe published in this "Savoir & Comprendre data sheet" are taken from: "Orphanet Report Series - Rare Diseases Collection - Prevalence and incidence of rare diseases: Bibliographic data" (January 2022). Orphanet conducted a systematic literature review in order to estimate the prevalence of rare diseases in Europe. These estimations provide some insight into the prevalence of these diseases but should not be assumed to be 100% accurate. Prevalence has been estimated for:
- diseases that are present at birth: prevalence = prevalence at birth x (patient life expectancy/general population life expectancy).
- other diseases: prevalence = incidence x mean duration of the disease.

NEUROMUSCULAR DISEASES
are caused by motor unit impairment

Neuromuscular diseases can be primary or secondary, and can occur alone or together with another condition. Only primary neuromuscular diseases (disorders caused by direct motor unit abnormalities) are covered by this data sheet, therefore, secondary neuromuscular diseases (disorders caused by another condition such as endocrine issues, harmful substances, medication, etc.) will not be discussed. Clinical presentations where symptomatic central nervous system impairment is the most prominent sign will also not be covered. That said, the lines between these classifications are often blurry. Most primary neuromuscular diseases are genetic, while some are autoimmune conditions.

Muscular dystrophy *vs* myopathy

- **Muscular dystrophies:** a group of genetic diseases that cause degeneration of muscle tissue. Muscular dystrophies affect muscles which have reached structural maturity. Necrosis destroys the muscle fibres of these muscles. Muscle regeneration mechanisms then try to restore the anatomic and physiological integrity of the affected tissue.
- **Myopathy:** general term that refers to diseases that affect muscle tissue.

While the clinical approach is still essential, the definitive diagnosis of most neuromuscular diseases relies on increasingly sophisticated molecular biology techniques such as those that involve analysing the protein whose deficiency or absence is responsible for the disease, next-generation sequencing (NGS) technologies which are capable of analysing entire genomes at a low cost in just a few days, and those that involve identifying the causative genetic mutation in DNA or RNA. Genetic counselling makes it possible to assess the risk of a genetic disease recurring in a family and may allow a prenatal diagnosis to be made.

The vast majority of neuromuscular diseases currently have no cure. However, treating and managing the symptoms and secondary conditions (contractures, orthopaedic deformities, respiratory insufficiency, heart failure, swallowing difficulties, bowel problems, pain, immune disorders, etc.) can improve the quality of life of people affected by these diseases. Early, regular and personalised treatment can limit impairment and improve life expectancy. The use of assistive technology to mitigate motor impairment helps ensure that patients are able to communicate and live as independently as possible.

Recently, treatments based on innovative therapies developed from our knowledge of causative genetic mechanisms have been created for a small number of diseases (spinal muscular atrophies, Duchenne muscular dystrophy), some of which are already on the market.

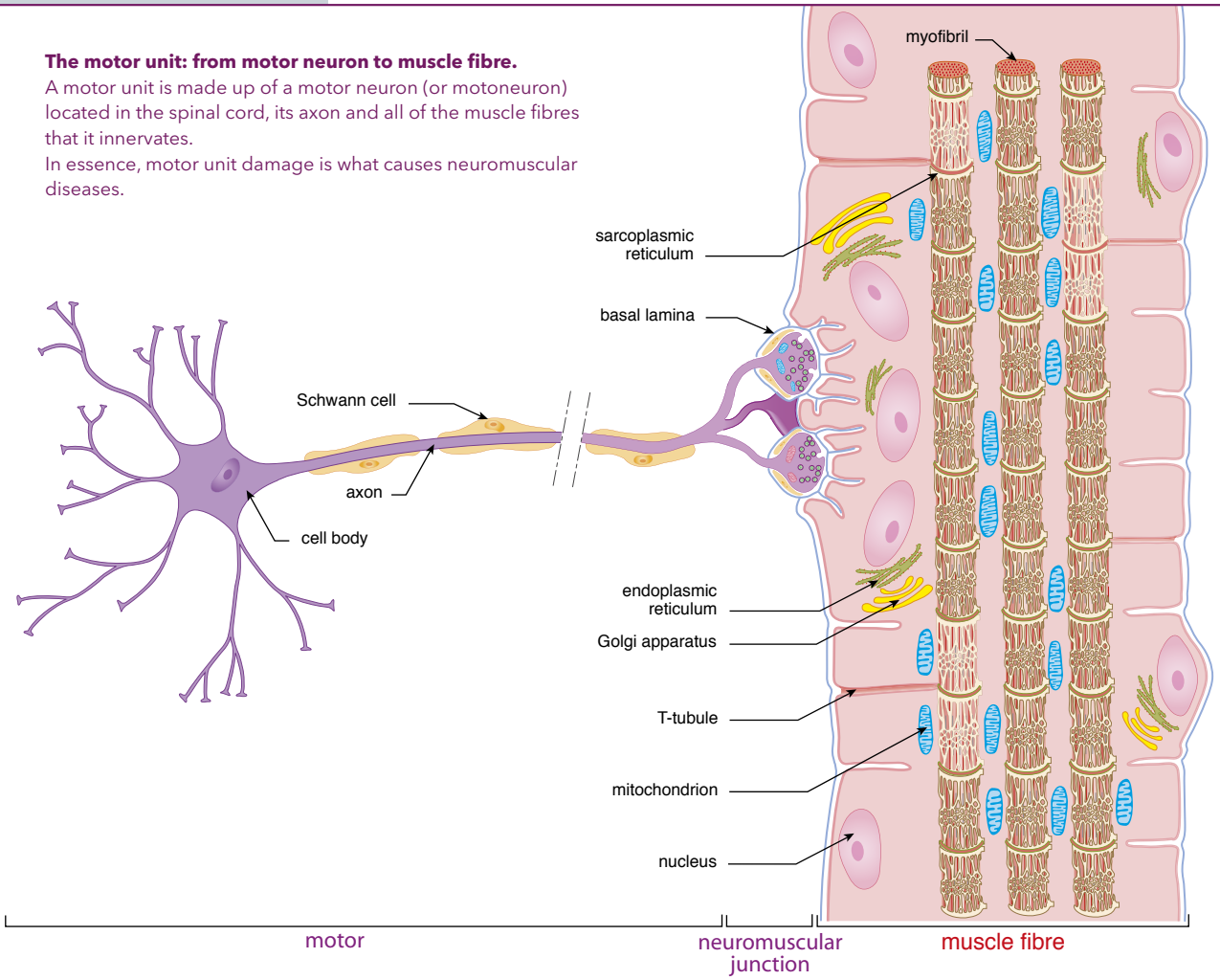
The motor unit

A motor unit consists of a motor neurone and all of the muscle fibres that it innervates. The number of muscle fibres in a motor unit varies depending on the size of the muscle (for example, there are 3 to 6 muscle fibres per motor unit in extraocular muscles and several thousand muscle fibres per motor unit in limb muscles). In the biceps, a single motor neuron innervates and synchronously activates around one hundred muscle fibres. Motor units are the basic functional units of muscle contraction. During movement, the force generated by a muscle corresponds to the number of motor units contracting. The higher the number of motor units contracting simultaneously, the greater the force generated.

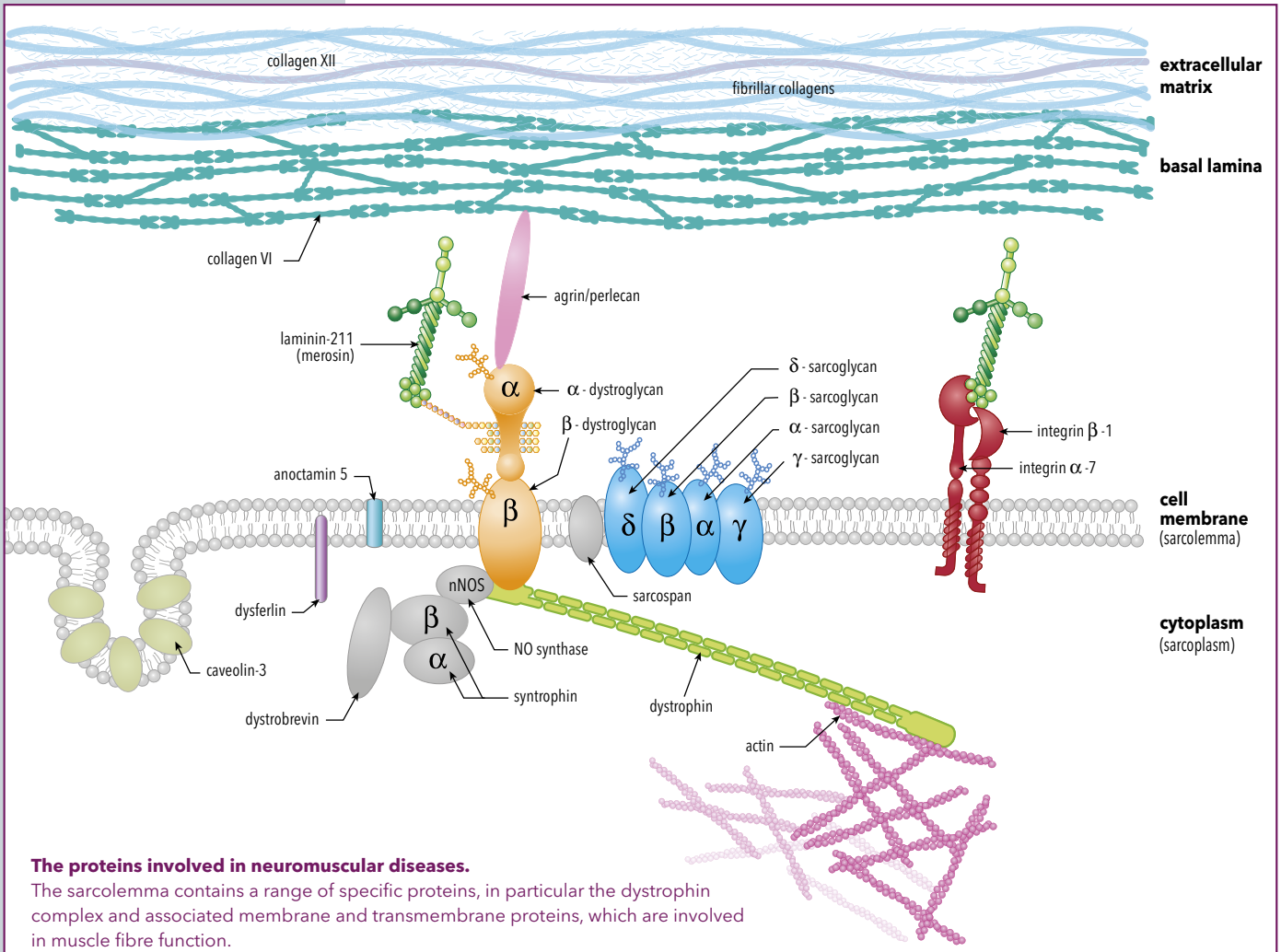
The proteins involved in neuromuscular diseases

Each muscle fibre (or muscle cell) is made up of numerous myofibrils. These myofibrils extend in parallel columns along the entire length of the muscle fibre. Various different protein complexes connect these myofibrils to the sarcolemma (the plasma membrane of the muscle cell) and the extracellular matrix.
Extracellular matrix proteins include laminin α2 and collagen VI while α-, β-, δ- and γ-sarcoglycans, integrins, dysferlin and caveolin-3 are found in the sarcolemma.

The motor unit: from motor neuron to muscle fibre.
A motor unit is made up of a motor neuron (or motoneuron) located in the spinal cord, its axon and all of the muscle fibres that it innervates.
In essence, motor unit damage is what causes neuromuscular diseases.



Dystrophin is a subsarcolemmal protein that forms a complex with other proteins (dystroglycans, dystrobrevin, syntrophins) that connects the exterior of the muscle fibre (extracellular matrix) to the interior (cytoskeleton) through the sarcolemma.
Myofibrils contain actin, tropomyosin, troponin (thin filaments) and myosin (thick filaments). Other proteins are involved in sarcomere stability such as telethonin, myotilin, desmin, titin and nebulin. Myofibrils are joined together by desmin filaments. Desmin also links myofibrils to the sarcolemma and the outer nuclear membrane.
Fukutin and other proteins such as FKRP, POMGNT1, POMT1, POMT2 and LARGE are found in the Golgi apparatus and are involved in the glycosylation of α-dystroglycan.
Certain selenoproteins are found in the endoplasmic reticulum.
Emerin and lamin A and C are found in the nuclear envelope. These proteins enable chromatin and the nuclear envelope to interact with each other.



The proteins involved in neuromuscular diseases.
The sarcolemma contains a range of specific proteins, in particular the dystrophin complex and associated membrane and transmembrane proteins, which are involved in muscle fibre function.

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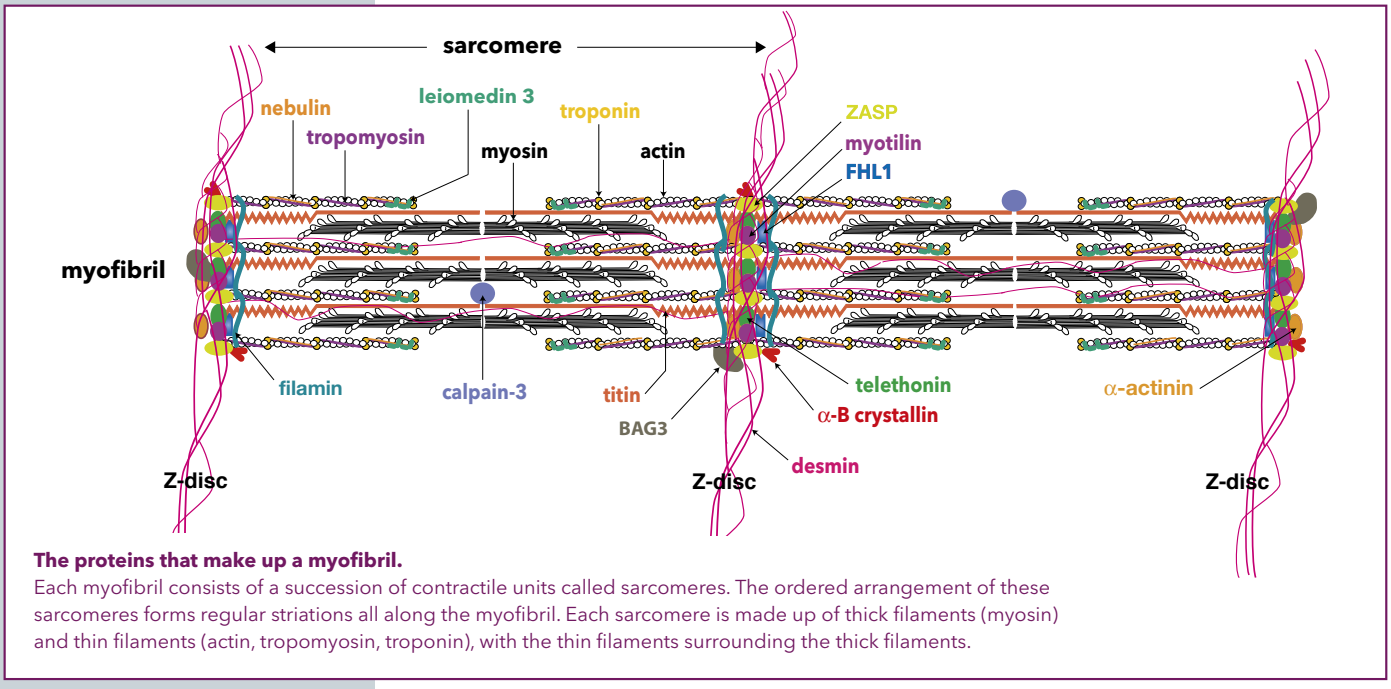

The proteins that make up a myofibril.
Each myofibril consists of a succession of contractile units called sarcomeres. The ordered arrangement of these sarcomeres forms regular striations all along the myofibril. Each sarcomere is made up of thick filaments (myosin) and thin filaments (actin, tropomyosin, troponin), with the thin filaments surrounding the thick filaments.

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Modes **OF INHERITANCE**

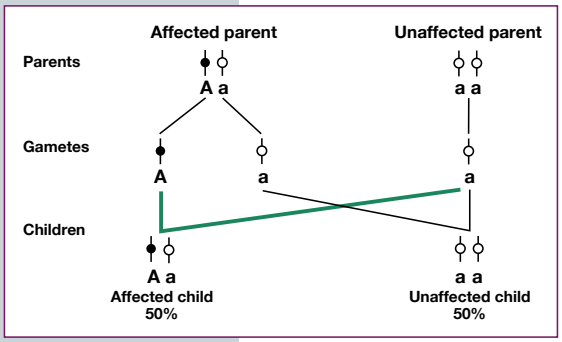
The risk of inheriting a genetic disease depending on its mode of inheritance.

Mendelian inheritance

Some genetic neuromuscular diseases are caused by mutations in a single gene they are monogenic.

The gene that causes the disease is carried by one of the 23 pairs of chromosomes found in the nucleus of cells.

Both chromosomes in a pair are identical (same size, same shape, etc.), one coming from the father, the other from the mother. Only the 23rd pair of chromosomes differs depending on whether you are male or female. Women have two X chromosomes (XX) while men have one X chromosome and one Y chromosome (XY). These are referred to as the "sex chromosomes". The other 22 pairs of chromosomes, which look the same in both males and females, are called "autosomes". Monogenic neuromuscular diseases are generally passed down through families according to Mendel's laws of inheritance. When the genetic mutation is located on one of the 22 pairs of autosomes, this is called "autosomal inheritance". When the genetic mutation is located on the X chromosome, this is referred to as "X-linked inheritance". X-linked diseases are usually recessive and are mainly expressed in males given that they only have one X chromosome.



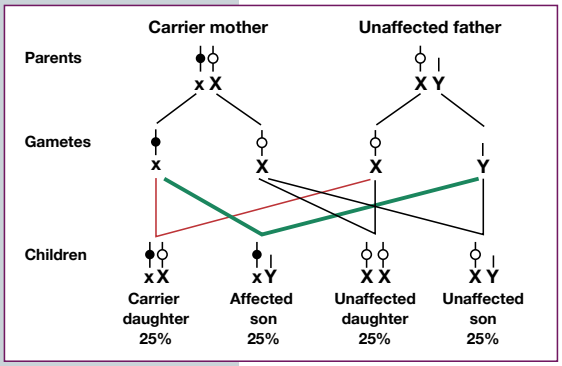
Autosomal dominant inheritance.

The affected child inherits a chromosome carrying the genetic mutation from the affected parent (mother or father). If one of the two parents has the disease, there will be a 50% chance of it being passed on with every pregnancy.

If the child does not inherit the disease, inheritance stops in this branch of the family.

Chromosome carrying the gene responsible for the disease

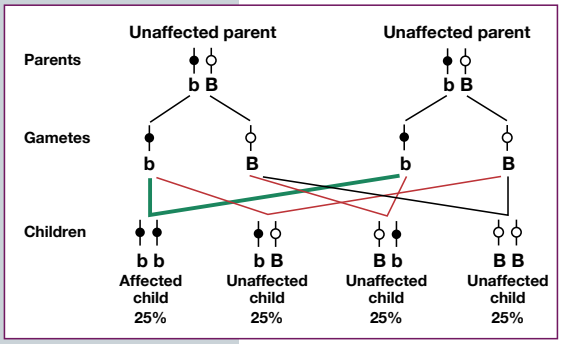
Chromosome carrying the normal gene



X-linked recessive inheritance.

The disease only manifests if the mutation is present on both X chromosomes in women and on the single X chromosome in men.

If a woman only has one X chromosome carrying the genetic mutation, she will not be affected by the disease but she can still pass it on to her children. Each of her sons will have a 50% chance of being affected and each of her daughters will have a 50% chance of being a carrier.



Autosomal recessive inheritance.

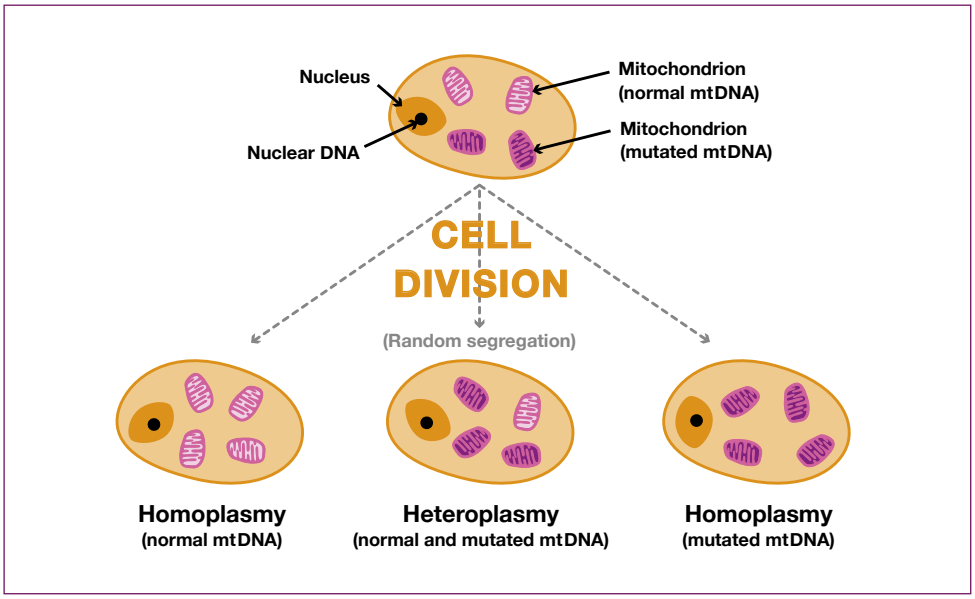
The affected child inherits two chromosomes carrying the genetic mutation - one from their father and one from their mother. For these parents, the chance of passing on the autosomal recessive disease is 25% (1 in 4) in each pregnancy.

Children who only inherit one chromosome carrying the genetic mutation, from their father or their mother, are not affected by the disease.

Maternal inheritance

Not all mitochondrial diseases are passed down according to Mendel's laws of inheritance, which only apply to genes carried by the chromosomes found in cell nuclei (nuclear DNA).

Mitochondria have their own DNA called mitochondrial DNA (mtDNA) which contains 37 genes coding for 22 transfer RNAs, 2 ribosomal RNAs and proteins involved in the composition of the mitochondrial respiratory chain. Children inherit their mitochondria, and therefore their mitochondrial DNA, exclusively from their mother, so when a mutated gene is found in mitochondrial DNA, the mitochondrial disease is said to be "maternally inherited".

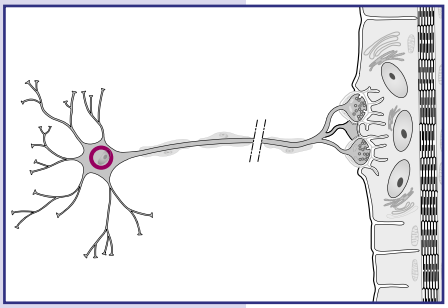


Maternal inheritance.

When there is a mutation in mitochondrial DNA, it only affects some of the cell's mitochondria (heteroplasmy). Each cell contains varying quantities of mitochondria with normal mtDNA and mitochondria whose mtDNA carries the genetic mutation (mutated mtDNA). As the cells divide, the mutated mitochondria are randomly segregated.

SPINAL MUSCULAR ATROPHIES (SMA)

ORPHA 70



Autosomal recessive degenerative motor neuron diseases caused by a survival motor neuron (SMN) protein (coded for by the *SMN1* gene located on chromosome 5) deficiency. Annual incidence estimated at around one new case in every 5,000 births and prevalence estimated at 3/100,000.

• Degeneration of motor neurons in the spinal cord meaning that the command to contract no longer reaches the muscle fibres • Linked to the *SMN1* gene located on chromosome 5 • Mainly affect proximal muscles; occasionally referred to as "proximal" spinal muscular atrophies, these diseases are distinct from so-called "distal" spinal muscular atrophies which are linked to other genes • Clinical diagnosis usually confirmed by genetic testing • Genetic counselling for patient's siblings and partner possible (testing for heterozygosity) • Prenatal diagnosis possible • Several types of SMA depend on the age of onset of clinical signs and performance criteria • The later the onset, the less severe the progression • Severity is partly determined by the number of copies of an almost identical gene called *SMN2* • Other genes and modifying factors are likely also involved.

Participate in the Registre SMA France [French SMA registry] to help improve our understanding of spinal muscular atrophies: http://www.urcpo.pifo.uvsq.fr/SMA/ [page in French]

Spinal muscular atrophy type 1 (SMA type 1 or Werdnig-Hoffmann disease)

ORPHA 83330 - OMIM 253300

• Onset within the first six months of life • Unable to sit unsupported • Type 1A and 1B: unable to support or lift their head • Type 1C: able to support and lift their head • Severe, generalised hypotonia ("floppy" baby) • Muscle weakness in all four limbs • Tongue fasciculations • Respiratory muscle weakness (stomach breathing and so-called "paradoxical" breathing, risk of early-onset chest wall deformity) • Very severe respiratory impairment • Without treatment, the vast majority of patients die before the age of two • Prolonged survival is possible with ventilation and/or nutritional support (gastrostomy) • Incidence: 0.26/100,000.

Spinal muscular atrophy type 2 (SMA type 2)

ORPHA 83418 - OMIM 253550

• Onset after the child can sit without support but before they can stand or walk independently (between six and 18 months old) • Symmetrical trunk and proximal muscle weakness • Able to sit without support • Levels of paralysis (mainly in the lower limbs) vary from child to child • Poor and unstable walking ability achieved in very few cases • Controlled head movements • Motor function in the upper limbs • Somewhat significant intercostal muscle weakness • Weak cough • Scoliosis, joint contractures • Prevalence at birth: 2/100,000.

Spinal muscular atrophy type 3 (SMA type 3 or Kugelberg-Welander disease)

ORPHA 83419 – OMIM 253400

• Onset between the child learning to walk and run (i.e. after they are 18 months old) and the end of adolescence • Symmetrical proximal muscle weakness, mainly in the lower limbs, which causes a waddling gait • Difficulty getting up from the floor and climbing stairs • Myopathy-like symptoms common • Frequent falls • Abnormal

fatigability • Respiratory and orthopaedic complications such as scoliosis and joint contractures • Progression can be slow (several years) or rapid (a few months) with loss of ambulation • 10% of all spinal muscular atrophies are type 3.

Spinal muscular atrophy type 4 (SMA type 4)
ORPHA 83420 - OMIM 271150
• Adult-onset: clinical manifestations start after the age of 18 • Slowly progressive muscle weakness mainly affecting the proximal muscles of the limbs • Waddling gait • Progression can vary, leading to increasing difficulties in running then walking • Inconsistent and generally late loss of ambulation • 1% of all spinal muscular atrophies are type 4.

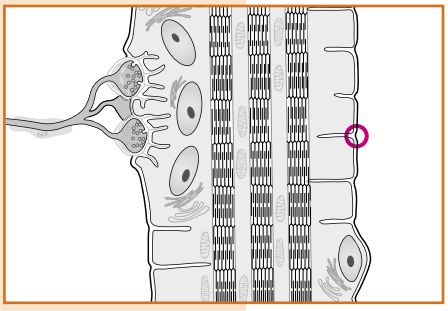
Management and treatment

• Disease-modifying therapies for types 1, 2 and 3: prescription subject to approval by a FILNEMUS [the French rare neuromuscular diseases healthcare network] multidisciplinary meeting • Spinraza® (nusinersen), an antisense oligonucleotide which increases the production of the SMN protein from the *SMN2* gene: intrathecal administration every four months, SMA type 1, 2 or 3 • Evrysdi® (risdiplam) increases the production of SMN, oral administration, indicated to treat patients from two months old, SMA type 1, 2 or 3, or one to four copies of the *SMN2* gene • Zolgensma® (onasemnogene abeparvovec), gene therapy, intravenous infusion, babies and young children weighing less than 21 kg, SMA type 1 or with a biallelic *SMN1* gene mutation and three copies of the *SMN2* gene maximum • Genetic counselling • Adapted physiotherapy (massages, mobilisation, postures, intermittent positive-pressure breathing, mucus clearance) and devices used to mitigate joint contractures and limb, spinal and rib cage deformities • Ventilation • Spinal surgery • Assistive technology (electric wheelchair, computer, etc.) to ensure the highest level of independence possible.

• For more information, please consult the Protocole National de Diagnostic et de Soins [French National Diagnosis and Care Protocol] (25 March 2021): https://www.has-sante.fr/jcms/p_3245042/fr/amyotrophie-spinale-infantile [document in French]

MUSCLE CHANNELOPATHIES

Periodic paralyses



Rare genetic diseases, usually autosomal dominant. Linked to mutations in muscle membrane ion channels which modify the excitability of muscle cells, resulting in attacks of extreme muscle weakness (during which muscles are not excitable and therefore do not contract) or delayed muscle relaxation (myotonia). The prevalence of hyperkalaemic periodic paralyses is estimated at 0.5/100,000, and 1/100,000 for hypokalaemic periodic paralyses.

• Autosomal dominant genetic diseases • Affect less than one person in every 100,000 • Brief but frequent attacks of extreme muscle weakness which usually resolve spontaneously and first occur at an early age (first decade) • During an attack, extreme muscle weakness starts at the extremities and gradual spreads; triggered by sudden rest after exercise, a very salty and/or sugary meal, exposure to cold, fever, or physical or psychological trauma • Often associated with myotonia • Muscle strength generally returns to normal between attacks • Improvement with age (attacks disappear around 40-50 years old) • Occasional onset of muscle weakness after several years of attacks.

Hyperkalaemic periodic paralysis

ORPHA 682 - OMIM 170500

• Caused by a mutation in the muscle sodium channel α-subunit **gene *(SCN4A)*** located on chromosome 17.

Hypokalaemic periodic paralysis type 2

ORPHA 681 - OMIM 613345

• Caused by a mutation in the muscle sodium channel α-subunit **gene *(SCN4A)*** located on chromosome 17.

Hypokalaemic periodic paralysis type 1

ORPHA 681 - OMIM 170400

• Caused by a mutation in the CACNA1S gene located on chromosome 1 which codes for the α-subunit of the dihydropyridine receptor, an ion channel which allows calcium ions to pass through the muscle cell membrane.

Andersen-Tawil syndrome

ORPHA 37553 - OMIM 170390

• Caused by a deficiency in the alpha subunit of the potassium channel Kir2.1 ***(KCNJ2* gene,** located on chromosome 17) in 60% of cases • Attacks of extreme muscle weakness associated with a prolonged QT interval, various ventricular arrhythmias (risk of sudden death) and characteristic physical features (short stature, scoliosis, low-set ears, hypertelorism, broad nasal root, micrognathia, clinodactyly, brachydactyly and syndactyly).

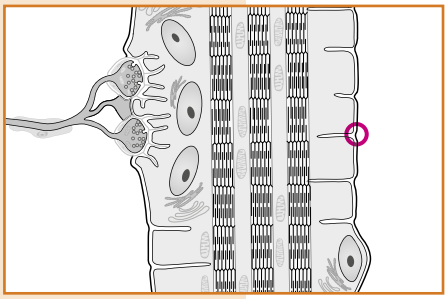
Management and treatment

• Genetic counselling • Treatment of attacks • Lifestyle habits: light muscle exercise without stopping abruptly, avoiding the cold • Diet and drugs can help to prevent attacks or reduce their frequency • Andersen-Tawil syndrome: drug contraindications (risk of torsades de pointes).

• For more information, please visit the Centre de Référence des Canalopathies Musculaires [Specialist Muscle Channelopathy Centre] website: https://pitiesalpetriere.aphp.fr/centre-de-reference-des-canalopathies-musculaires/ [website in French]

MUSCLE CHANNELOPATHIES

Non-dystrophic myotonias



Rare autosomal dominant or recessive genetic diseases. Linked to mutations in muscle membrane ion channels which modify the excitability of muscle cells, resulting in abnormally slow muscle relaxation felt as muscle stiffness (myotonia). Affect less than one person in every 100,000 on average. Prevalence of autosomal recessive myotonia congenita and autosomal dominant myotonia congenita: 1/100,000.

Autosomal recessive myotonia congenita (Becker disease)

ORPHA 614 – OMIM 255700

• Autosomal recessive • Caused by recessive mutations in the CLCN1 gene (located on chromosome 7) which codes for a muscle chloride channel that allows chloride ions to cross the muscle cell membrane • Onset usually during the first or

even second decade, rarely during early childhood • Muscle stiffness usually occurs after rest but improves with continued activity ("warm-up phenomenon") • Muscle weakness is more intense in the upper limbs while stiffness is mainly felt in the lower limbs • Hypertrophy of hip and lower limb muscles.

Autosomal dominant myotonia congenita (Thomsen disease)

ORPHA 614 - OMIM 160800

• Autosomal dominant • Caused by dominant mutations in the ***CLCN1* gene** (located on chromosome 7) which codes for a muscle chloride channel that allows chloride ions to cross the muscle cell membrane • Onset at birth or during early childhood • Muscle stiffness usually occurs after rest but improves with continued activity ("warm-up phenomenon") • Myotonia fluctuates little throughout life • No worsening • Muscle hypertrophy common.

Paramyotonia congenita (Eulenberg disease)

ORPHA 684 - OMIM 168300

• Autosomal dominant • Caused by a mutation in the muscle sodium channel α-subunit **gene *(SCN4A)*** located on chromosome 17 • Affects less than one person in every 100,000 • Early childhood onset • Characterised by "paradoxical" myotonia, called as such as it worsens with repeated muscle contractions • Feeling of stiffness caused by difficulty of muscles to relax after movement (myotonia) which persists with exercise, worsens significantly in the cold and is associated with muscle weakness • Episodes of weakness usually resolve quickly and spontaneously (a few minutes to a few hours) • Polyuria possible after an episode of myotonia • Symptoms are stable allowing patients to lead a normal social and work life.

Potassium-aggravated myotonia (including myotonia fluctuans, myotonia permanens and acetazolamide-responsive myotonia)

ORPHA 612 - OMIM 608390

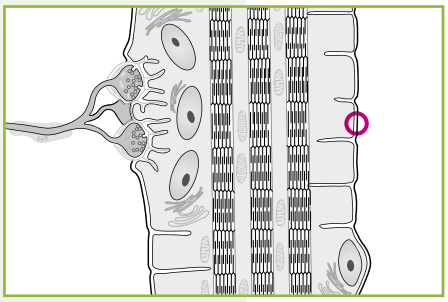
• Autosomal dominant • Caused by a missense mutation in the ***SCN4A* gene** (located on chromosome 17) which codes for the α subunit of the muscle sodium channel Nav1.4 • Very rare • Onset during childhood or adolescence • Myotonia is aggravated by potassium ingestion • In myotonia fluctuans, muscle stiffness occurs during rest after exercise • In myotonia permanens, muscle stiffness is continuous and severe • Painful muscle stiffness is caused by fasting in acetazolamide-responsive myotonia • Few or no episodes of weakness • Not or only mildly progressive • Respiratory problems due to myotonia are possible in permanent myotonia.

Management and treatment

• Avoiding exposure to the cold • Gentle physiotherapy (deep tissue massage) • Adapted muscle exercises • Special diet • Certain drugs (mexiletine or carbamazepine, acetazolamide, etc.) can improve symptoms • Anaesthetic considerations to avoid worsening myotonia • Orthopaedic care.

• For more information, please visit the Centre de Référence des Canalopathies Musculaires web-site: https://pitiesalpetriere.aphp.fr/centre-de-reference-des-canalopathies-musculaires/ [website in French]

CONGENITAL MUSCULAR DYSTROPHIES (CMDs)



Heterogeneous group of neuromuscular diseases with autosomal recessive inheritance in the vast majority of cases. Over 30 genes are currently known to be involved in CMDs. The majority of CMDs can be classified as either collagenopathies (*COL6A1, COL6A2, COL6A3* genes), dystroglycanopathies (18 genes, the ones most often involved being *POMT1, POMT2, POMGNT1, ISPD, FKRP, FKTN* and *LARGE*) or merosinopathies (*LAMA2* gene). They start at birth or within the first few months of life with generally quite severe predominant muscle weakness. They are the second most common cause of congenital muscular hypotonia after congenital myopathies. Their prevalence is estimated to be between 0.6 and 0.9 people in every 100,000.

• Three criteria must be met to diagnose an infant with CMD: neonatal hypotonia, increase in creatine kinase (CK) levels (often very marked) and a dystrophic pattern on muscle biopsy • Immunostaining for three extracellular matrix proteins (merosin, alpha-dystroglycan and collagen VI) used during initial screening to identify the subtype of CMD • Skin biopsy sometimes necessary, either to study merosin or to prepare a fibroblast culture used to look for morphological collagen network abnormalities • Routine brain imaging (MRI) to look for white matter and/or supratentorial and infratentorial abnormalities) • Routine eye examination • Muscle imaging, in particular whole-body musculoskeletal MRI, is often used to show the pattern of muscles involved • Most common forms: *COL6*-related CMDs (12 to 19% of CMDs), dystroglycanopathies (12 to 25%), *LAMA2*-related CMDs (10 to 37%) and *SELENON*-related CMDs (11.65%).

Classification of congenital muscular dystrophies

• **CMDs linked to abnormalities in the extracellular matrix** such as a form linked to mutations in the *COL6* genes (Ullrich CMD) and a form linked to the *LAMA2* gene (merosin-deficient CMD (MDC1A)), which are the most common; CMDs caused by mutations in the *ITGA7* gene (CMD with integrin alpha-7 deficiency) or *COL12A1* gene (CMD with collagen XII deficiency) are extremely rare;

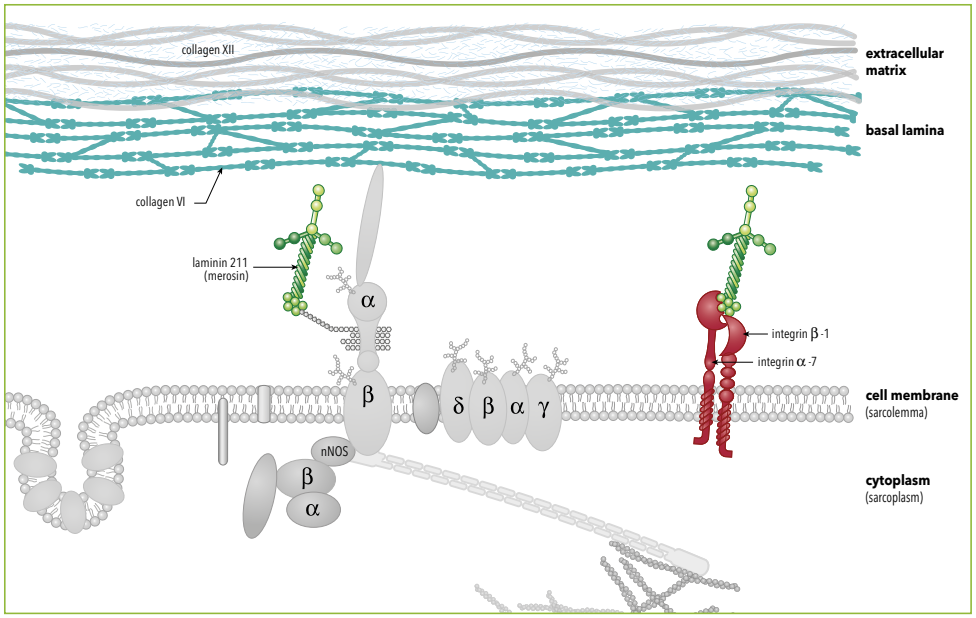
• **Dystroglycanopathies (also called α-dystroglycanopathies)** are linked to abnormalities in α-dystroglycan, a key muscle cell surface protein, and involve 18 different genes, the majority of which play a role in the glycosylation of α-dystroglycan;

• **CMDs linked to abnormalities in endoplasmic reticulum proteins** such as rigid spine muscular dystrophy 1 (selenoprotein N deficiency) linked to mutations in the *SELENON* gene (formerly *SEPN1*); or a form with early cataracts and mild intellectual disability linked to mutations in the *INPP5K* gene;

• **CMDs linked to abnormalities in the transport of vesicles between the endoplasmic reticulum and Golgi apparatus:** forms linked to mutations in the *TRAPPC11, GOSR2* or *BET1* gene;

• **CMDs linked to abnormalities in the nuclear envelope** such as a severe form (L-CMD) linked to sporadic mutations in the *LMNA* gene, which codes for lamin A and C; or a very rare form linked to mutations in the *SYNE1* gene, which codes for nesprin-1;

• **Megaconial-type CMD** is linked to mitochondrial abnormalities caused by mutations in the *CHKB* gene which codes for choline kinase β.



Do not confuse congenital muscular dystrophies with congenital myopathies

• Muscular dystrophies affect muscles that have reached structural maturity. Necrosis destroys the affected muscles' muscle fibres. Muscle regeneration mechanisms then try to restore the anatomic and physiological integrity of the affected tissue • Congenital myopathies are caused by muscle tissue development problems which usually affect the cytoskeleton. There is no tissue necrosis or regeneration involved.

CMDs linked to abnormalities in the extracellular matrix

Ullrich congenital muscular dystrophy (UCMD)

ORPHA 75840 – OMIM 254090/ OMIM 616470

• The most common CMD in Europe • Allelic disorder: Bethlem myopathy • Caused by mutations in one of the three genes coding for collagen VI: ***COL6A1, COL6A2*** (located on chromosome 21) or ***COL6A3*** (located on chromosome 2) which code for the α-1, α-2 and α-3 subunits of collagen VI respectively • The forms caused by de novo mutations and autosomal dominant inheritance are common • Collagen VI is a component of the extracellular matrix where it forms a very strong mesh that supports the muscle fibre • Very rare form caused by mutations in the gene which codes for the α-1 subunit of collagen XII: ***COL12A1*** (located on chromosome 6), autosomal recessive • Muscular weakness with proximal joint contractures, axial stiffness and distal joint hypermobility (fingers, ankles) • Congenital hip dislocation common • Congenital torticollis or kyphosis possible at birth • Skin hyperextensibility • Hyperkeratosis and superficial folliculitis (grainy skin) • Keloid scars • Normal CK levels • Walking ability variable: unable to walk (early severe form), delay in learning to walk followed by gradual loss of ambulation (mild progressive form), able to walk until adulthood (milder stable form also seen in Bethlem myopathy) • Limiting respiratory insufficiency starting during childhood • Ventilatory support (NIV) required around the age of eleven years old on average • Scoliosis • Orthodontic problems • Increased risk of spontaneous pneumothorax • Slowly progressive with worsening of muscular and respiratory symptoms.

Merosin-deficient congenital muscular dystrophy (congenital muscular dystrophy type 1A or MDC1A)

ORPHA 258 - OMIM 607855

• Caused by a deficiency in merosin, also called laminin α-2 (***LAMA2* gene** located on chromosome 6), one of the major components of the basement membrane of skeletal muscle cells • Hypotonia in early infancy ("floppy" baby) with marked trunk muscle weakness (axial hypotonia) associated with limb muscle weakness • Muscle contractures from the first few months of life (which can sometimes give rise to arthrogryposis) • White matter signal abnormalities with no intellectual disability or major brain malformations • Good psychological development contrasted by delayed motor development • Poor walking ability only achieved in very few cases • Very high CK levels • Severe course linked to the severity of spine and chest deformities as well as respiratory complications • Cardiac involvement common starting in adolescence • Epileptic manifestations in 30% of cases • Merosin deficiency seen on muscle or skin biopsy.

Congenital muscular dystrophy with integrin alpha-7 deficiency

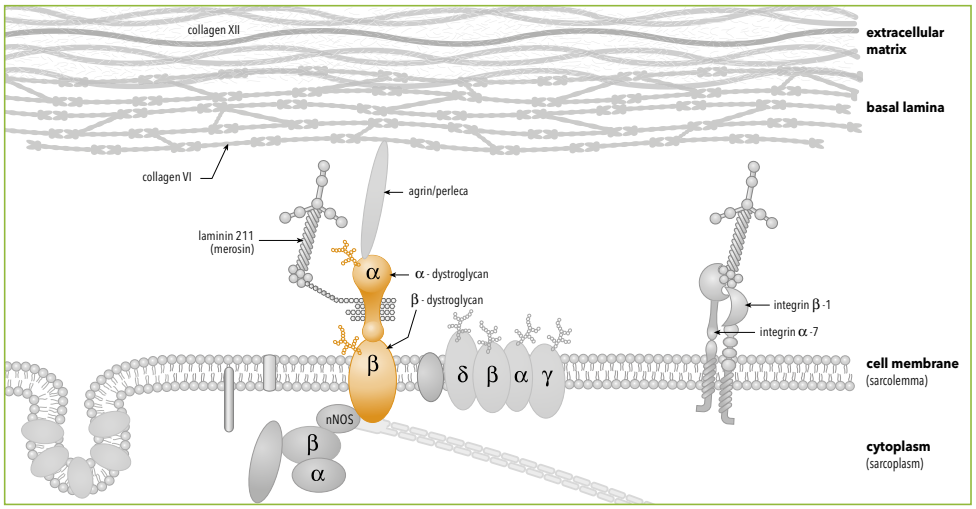
ORPHA 34520 - OMIM 613204

• Caused by mutations in the ***ITGA7* gene** (located on chromosome 12) which codes for integrin α-7, a cellular receptor for laminin 2, which is involved in interactions between cells and the extracellular matrix, as well as in cell-to-cell interactions, cell migration and differentiation during development • Hypotonia at birth, torticollis occasionally • Delayed motor development (learning to walk around two to three years old).

Dystroglycanopathies

ORPHA 370953

Autosomal recessive genetic diseases • Onset at birth or during the first few months of life • Somewhat marked muscle weakness associated with central nervous system abnormalities • Quite rare in France • Caused by primary or secondary defects in the glycosylation of α-dystroglycan, a protein that acts as a bridge between the extracellular matrix and dystrophin • If α-dystroglycan is not glycosylated correctly, it can no longer bind to extracellular matrix proteins • Brain and/or eye abnormalities as well as intellectual disability of varying severity, suggesting an associated neuronal migration disorder • Very high CK levels • Wide spectrum of clinical forms of varying severities, ranging from Walker-Warburg syndrome and muscle-eye-brain disease (MEB) to limb-girdle forms (LGMD) and classic forms of CMD.



Dystroglycans are glycoproteins that form part of the dystrophin-associated protein complex. The dystroglycan complex is comprised of two subunits called α-dystroglycan and β-dystroglycan which are encoded by a single messenger RNA molecule. α-dystroglycan is an extracellular protein. One end binds to the α2 subunit of laminin in the basement membrane of the muscle cell, while the other end binds to β-dystroglycan which is a transmembrane protein. The intracellular part of β-dystroglycan binds to dystrophin.
Outside the cell, α-dystroglycan binds directly to components of the extracellular matrix - laminin 1, laminin 2, perlecan and agrin. Dystroglycans can interact with other transmembrane proteins (sarcoglycan complex, sarcospan) which stabilise the bond between α-dystroglycan and the cell surface.

The eighteen genes involved in dystroglycanopathies

Genes that code for proteins that transfer sugar molecules to α-dystroglycan:

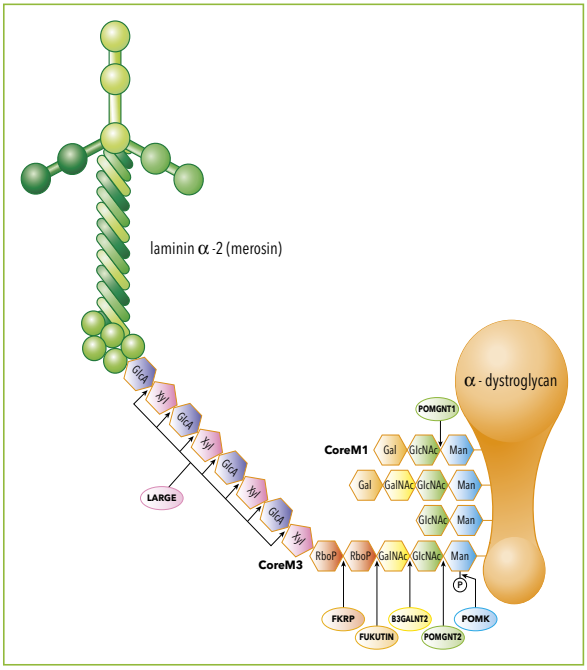
- *POMT1* (chromosome 9)
- *POMT2* (chromosome 14)
- *POMGNT1* (chromosome 1)
- *FKTN* (chromosome 9)
- *FKRP* (chromosome 19)
- *LARGE* (chromosome 22)
- *POMGNT2* (chromosome 3)
- *B3GALNT2* (chromosome 1)
- *B4GAT2* (chromosome 11)
- *POMK/SGK196* (chromosome 8)
- *RXYLY1/TMEM5* (chromosome 12)

Genes involved in making sugar precursors:

- *GMPPB* (chromosome 3)
- *DPM1* (chromosome 4)
- *DMP2* (chromosome 9)
- *DMP3* (chromosome 1)
- *DOLK* (chromosome 9)
- *CRPPA/ISPD* (chromosome 7)

Gene that codes for α- and β-dystroglycan:

- *DAG1* (chromosome 3)



The glycosylation of α-dystroglycan

This process entails successively adding sugar molecules and involves around 20 enzymes.
It allows α-dystroglycan to fulfil its key role as a link between the intracellular cytoskeleton and the extracellular matrix, which protects the muscle fibre membrane from damage caused by the repeated contraction and relaxation of the muscle fibre.

Fukuyama congenital muscular dystrophy

ORPHA 272 – OMIM 253800

• Caused by mutations in the ***FKTN* gene** (located on chromosome 9) which codes for fukutin, a Golgi apparatus enzyme involved in the glycosylation of α-dystroglycan • Found all over the world but prevalent in Japan • Severe intellectual disability and seizures associated with significant face and limb muscle weakness and hypotonia in early infancy • Often fatal in childhood or adolescence • Milder forms resemble limb-girdle muscular dystrophies (LGMD2M).

Muscle-eye-brain disease (MEB)

ORPHA 588 – OMIM 253280 / 253800 / 613153 / 613150

• First described in Finland • Caused by mutations in the ***POMGNT1* gene** (located on chromosome 1) which codes for O-mannose beta-1,2-N-acetylglucosaminyltransferase • This Golgi apparatus protein is an enzyme that participates in transforming proteins into glycoproteins (glycans) by adding a specific sugar (O-mannose) to them • Mutations in the *FKTN, FKRP* and *POMT2* genes may also be involved • Mild or severe muscle weakness (hypotonia) associated with brain abnormalities (leading to intellectual disability and myoclonic epilepsy) as well as eye abnormalities (severe myopia, retinal hypoplasia, strabismus, congenital glaucoma).

Walker-Warburg syndrome

ORPHA 899 – OMIM 236670 / 615181 / 236670 / 614643/ 616538 / 608799 / 615042 / 613153 / 253800 / 615350/ 613154 / 615249 / 613150 / 253280 / 614830 / 615041.

• A genetically very heterogeneous disorder • Initially linked to mutations in the ***POMT1* gene** (located on chromosome 9) which codes for protein O-mannosyltransferase 1, another enzyme that participates in transforming proteins into glycoproteins (glycans) by adding a specific sugar (O-mannose) to them • Mutations in the *B3GALNT2, B4GAT1, CRPPA, DAG1, DMP1, DPM2, FKRP, FKTN, GMPPB, LARGE1, POMK, POMT2, POMGNT1, POMGNT2* and *TMEM5* genes can also cause Walker-Warburg syndrome • Muscle weakness generally masked by complex abnormalities in brain and eye development • Encephalopathy with epilepsy • Poor prognosis with most patients dying within the first year of life.

Congenital muscular dystrophy type 1D (MDC1D)

ORPHA 98894 - OMIM 608840

• Caused by mutations in the LARGE gene (located on chromosome 22) which codes for an acetylglucosaminyltransferase-like protein, another enzyme which is involved in the glycosylation of alpha-dystroglycan • Neurological phenotype more severe than muscular • Profound intellectual disability • Muscle weakness mainly affecting the limb-girdle muscles, occasionally associated with retinopathy.

CMDs linked to abnormalities in endoplasmic reticulum proteins

Rigid spine muscular dystrophy 1 (RSMD1)

ORPHA 97244 - OMIM 602771

• Caused by mutations in the ***SELENON*** (**formerly *SEPN1***) gene (located on chromosome 1) which codes for selenoprotein N, an endoplasmic reticulum membrane protein that adjusts the quantity of calcium stored in the endoplasmic reticulum using a redox mechanism • Axial myopathy with stiff back and early (before the age of 15) restrictive respiratory syndrome • Cervical and axial stiffness ("rigid spine") with or without scoliosis • Facial weakness common • Nasal voice • Not very progressive mild limb muscle weakness with patients able to walk • No major limb contractures • Normal CK levels • Right heart involvement with pulmonary hypertension beginning around the age of 20 in 15% of cases.

CMDs linked to abnormalities in the nuclear envelope

LMNA-related congenital muscular dystrophy (L-CMD)

ORPHA 157973 – OMIM 613205

• Caused by mutations in the ***LMNA* gene** (located on chromosome 1) which codes for lamin A and C, proteins whose 3D structure plays an important role in the architecture of the nuclear envelope. These proteins are also involved in chromatin organisation and the regulation of DNA transcription and replication.

• Two clinical presentations with different severities • Very few spontaneous movements at birth and very limited postural and motor development • Almost normal postural and motor development with independent walking achieved in

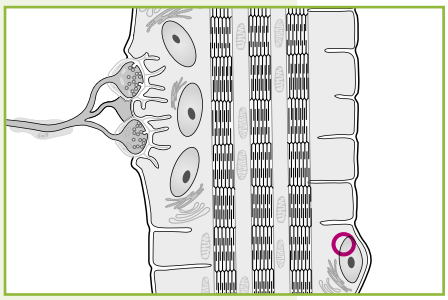
some cases; slow progression during the first decade marked by the axial weakness spreading (thoracic and lumbar lordosis) • Proximal weakness in the upper limbs and distal weakness in the lower limbs • Stiffness of the spine • Contractures mainly in the lower limbs, in particular the Achilles tendons • Heart rhythm and conduction disturbances, cardiomyopathy • Poor head control ("dropped head") is a characteristic sign • Mildly increased CK levels.

Management and treatment

• Genetic counselling • Physiotherapy and devices used to mitigate contractures and deformities in the limbs, spine and rib cage • Ventilation • Spinal surgery if necessary • Assessment of cardiac function (ECG, Holter monitor, echocardiogram) at least every two years and treatment if necessary (especially in CMDs caused by LAMA2, FKRP or LMNA gene mutations) • Epilepsy medication (if epilepsy is present) • Monitoring of central nervous system damage (brain MRI) • Assistive technology (electric wheelchair, computer) to ensure the highest level of independence possible.
• Management of any potential learning difficulties.
• For more information, please consult the Protocole National de Diagnostic et de Soins for collagen VI-related myopathies: https://www.has-sante.fr/jcms/p_3376221/fr/myopathies-reliees-au-collagene-vi [document in French]

Emery-Dreifuss
MUSCULAR DYSTROPHIES

ORPHA 261 - OMIM 310300 / 181350 / 612998 / 612999



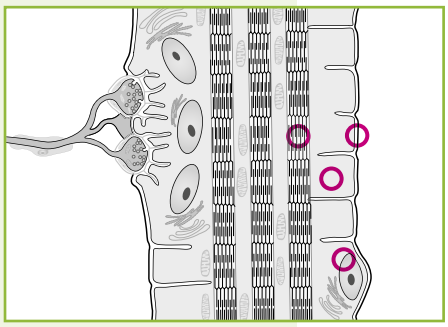
Rare autosomal recessive, autosomal dominant or X-linked recessive genetic diseases caused by a deficiency in a nuclear envelope protein (emerin or lamin A and C). Their prevalence in Europe is estimated at 0.3/100,000.

• The X-linked recessive forms are caused by an absence of emerin, a protein anchored to the inner nuclear membrane of muscle fibres (***EMD* gene** located on the X chromosome), or the FHL1 protein (***FHL1* gene** on the X chromosome) • The autosomal forms (dominant and recessive) are caused by an absence of lamin A and C, proteins which form a fibrous network that lines the inner nuclear membrane of cells (***LMNA* gene** located on chromosome 1) • Uncoupling of the nucleoskeleton and cytoskeleton caused by disruption in the interactions between emerin, lamin and nesprin proteins • Significant inter- and intrafamilial variability • No obvious genotype-phenotype correlation • Childhood onset (around eight to 10 years old) • Joint contractures (elbows, Achilles tendons and cervical spine) • Slow progression with setting in of muscle weakness and atrophy in the shoulders, arms and legs • Cardiac involvement: heart rhythm disturbances (with risk of sudden death) and ultimately a risk of heart failure.

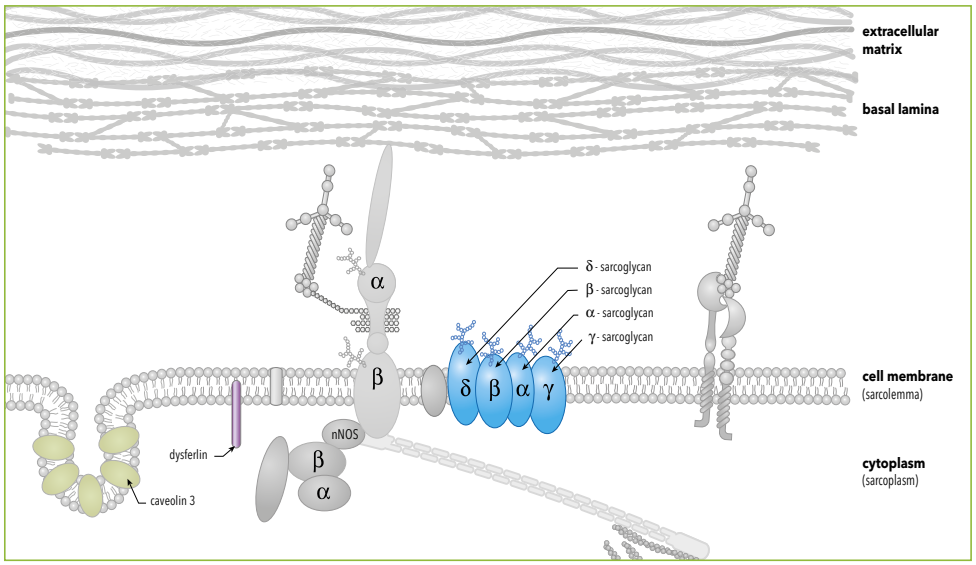
Management and treatment

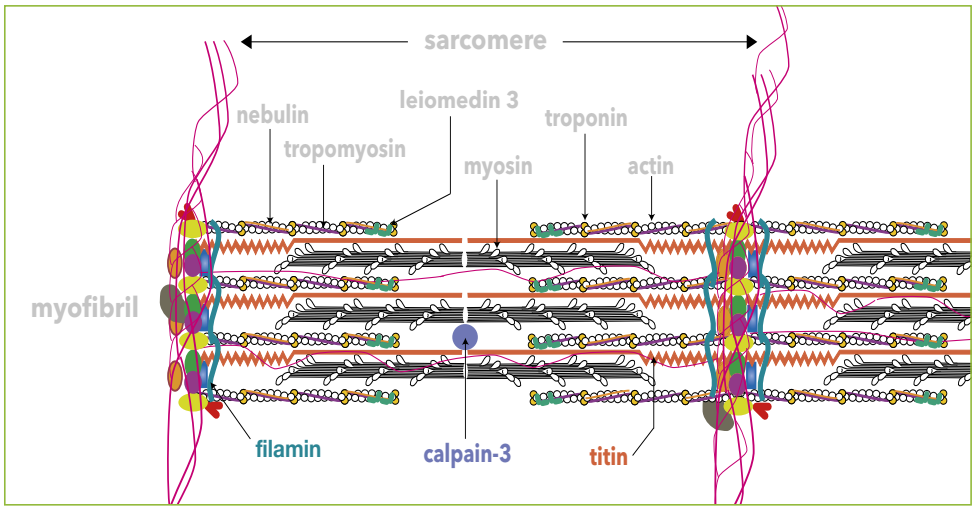
• Genetic counselling • Monitoring of cardiac function and treatment (implantation of an implantable cardioverter defibrillator is essential in "laminopathies") • Physiotherapy to help manage contractures • Surgery sometimes necessary to correct lower limb deformities.

Limb Girdle **MUSCULAR DYSTROPHIES** (LGMD)



Limb-girdle muscular dystrophies are a heterogenous group of autosomal dominant (LGMD D or type 1) and autosomal recessive (LGMD R or type 2) genetic diseases. Their prevalence is estimated to be between 0.8 and 6 people in every 100,000.
Recessive limb-girdle muscular dystrophies are by far the most common. There are 27 subtypes which are distinguished on a molecular level (LGMD R1 to LGMD R27).
Dominant subtypes are much rarer (LGMD D1 to LGMD D5).





New nomenclature since 2018

- LGMD "R" and LGMD "D" refer to the autosomal recessive and autosomal dominant forms of the disease respectively.
- The number indicates the chronological order in which these forms were discovered. For example, LGMD R1 refers to a recessive form whose causative gene was the first to be described.

• Limb-girdle muscular dystrophies are characterised by progressive muscle weakness mainly affecting the shoulder and pelvic girdle muscles • Muscle fibre deterioration caused by a primary defect in an extracellular matrix, sarcolemma, sarcomere, endoplasmic reticulum, nuclear envelope or cytoskeleton protein (whose function is usually structural, sometimes enzymatic) • Clinical diagnosis confirmed by muscle biopsy (essential in most cases), muscle MRI, and molecular and genetic studies • Progressive muscular dystrophies with very variable onsets • Weakness in pelvic (pelvic girdle) and shoulder (shoulder girdle) muscles with or without atrophy • Dystrophic pattern on muscle biopsy • Variable muscle enzyme (CK) elevation • Respiratory involvement possible • Cardiac involvement uncommon with some exceptions (LGMD1D, LGMD2G, LGMD2I) • Great clinical variability: severe forms with progressive worsening leading to loss of ambulation; mild forms characterised by persistent significant fatigability • Clinical courses vary greatly.

Calpain-3-related limb-girdle muscular dystrophy R1 or calpainopathy (LGMD2A)

ORPHA 267 - OMIM 253600

• The most common type of autosomal recessive LGMD in Europe • Caused by an absence of or a defect in calpain-3, a skeletal muscle-specific enzyme (***CAPN3* gene** located on chromosome 15) which plays a key role in the renewal of sarcomere proteins and the maintenance of sarcomere integrity • Symmetrical muscle weakness and atrophy mainly affecting the axial muscles of the trunk and the proximal muscles of the four limbs • Onset of signs starting in the second decade • Difficulty running and climbing stairs • Later axial (lordosis) and scapular symptoms (scapular winging, difficulty raising the arms) • Selective muscle weakness and atrophy (posterior compartment of the thigh affected more than the anterior compartment, hip adductors, axial muscles) • Mild contractures (Achilles tendon) • Loss of ambulation during the first fifteen years after onset of the disease on average • Cardiac and respiratory complications rarely reported • Initial working diagnosis even more likely if the patient is of Basque, Réunionese, Slavic or Amish origin • Prevalence estimated to be between 1 and 7 people in every 100,000.

Dysferlin-related limb-girdle muscular dystrophy R2 (LGMD2B)

ORPHA 268 - OMIM 253601

• Second most common type of autosomal recessive LGMD in Europe • Caused by a deficiency in dysferlin (***DYSF* gene** located on chromosome 2), a protein found in the membrane of muscle fibres which is involved in the skeletal muscle membrane repair process • Mutations in the *DYSF* gene also cause Miyoshi myopathy and distal myopathy with anterior tibial onset (DMAT), which are now referred to as "dysferlinopathies" • Various different dysferlinopathies (Miyoshi myopathy, LGMD2B, DMAT) can be present in the same family • Weakness and atrophy of the limb-girdle muscles (mainly the pelvic girdle muscles compared to the fixator muscles of the scapula) • Early involvement of the calves • Onset around the age of 20 with ability to walk lost within a few years • Cardiomyopathy rare but possible • Respiratory impairment which generally does not require ventilation • Proximal muscle weakness which can spread to the distal muscles over time • Forms with limb-girdle involvement and forms with distal involvement can occur in the same family • Prevalence: 0.1 - 0.9/100,000.

Sarcoglycanopathies: α-sarcoglycan-related limb-girdle muscular dystrophy R3 (LGMD2D), β-sarcoglycan-related limb-girdle muscular dystrophy R4 (LGMD2E), γ-sarcoglycan-related limb-girdle muscular dystrophy R5 (LGMD2C) and δ-sarcoglycan-related limb-girdle muscular dystrophy R6 (LGMD2F)

ORPHA 62 / 119 / 353 / 219 - OMIM 608099 / 604286 / 253700 / 601287

• Fourth most common type of autosomal recessive LGMD in Europe • Caused by abnormalities in one of the sarcoglycans, transmembrane glycoproteins which are part of the dystrophin-associated glycoprotein complex - the dystrophin-glycoprotein complex (the ***SGCA* gene** codes for α-sarcoglycan located on chromosome 17, the ***SGCB* gene** codes for β-sarcoglycan located on chromosome 4, the ***SGCG* gene** codes for γ-sarcoglycan located on chromosome 13 and the SGCD gene codes for δ-sarcoglycan located on chromosome 5) • By ensuring the stability of the muscle fibre membrane, the dystrophin-glycoprotein complex and dystrophin protect the muscle cell from damage caused by muscle contraction • Variable age of onset, usually during childhood • Symmetrical limb-girdle muscle weakness and atrophy • Clinically similar with some differences in disease progression • Only a combination of immunostaining and genetic testing makes it possible to differentiate between the different types • Calf hypertrophy • Macroglossia • Scapular winging • Very high CK levels • Significant risk of dilated cardiomyopathy, especially in γ- and β-sarcoglycanopathies (nearly half of patients) • Variable respiratory involvement • Certain mutations are seen most often in specific groups or populations (North African, Gypsy, Amish) • Around 400 people in France have a genetically-confirmed sarcoglycanopathy.

Telethonin-related limb-girdle muscular dystrophy R7 (LGMD2G)

ORPHA 34514 - OMIM 601954

• Autosomal recessive • Caused by a deficiency in a sarcomere protein called telethonin (***TCAP* gene** located on chromosome 17) • Proximal muscle weakness and atrophy starting in the second decade, with distal muscle weakness and atrophy which causes steppage gait • Age of onset: adolescence • Cardiomyopathy possible • 18 cases published.

TRIM32-related limb-girdle muscular dystrophy R8 (LGMD2H)

ORPHA 1878 - OMIM 254110

• Autosomal recessive • Caused by a deficiency in the TRIM32 protein which functions as an E3 ubiquitin ligase and is involved in protein degradation and the stabilisation of costameres which connect sarcomeres to the extracellular matrix (TRIM32 gene located on chromosome 9) • Age of onset: adult • Quadriceps and pelvic girdle muscle weakness • Respiratory weakness rare • No cardiomyopathy • Slowly progressive • Ability to walk retained beyond the age of 50 • Common in Canadian Hutterites.

FKRP-related limb-girdle muscular dystrophy R9 (LGMD2I)

ORPHA 34515 - OMIM 607155

• Autosomal recessive • Caused by mutations in the ***FKRP* gene** (located on chromosome 19) which codes for an enzyme in the fukutin family called FKRP (fukutin-related protein) that participates in the glycosylation of α-dystroglycan • Secondary α-dystroglycan and laminin α2 deficiencies less marked than in the congenital form • α-dystroglycan is a laminin receptor that connects laminin (an extracellular matrix protein) to the cytoskeleton of the muscle cell • Variable muscular phenotype • Age of onset: middle or late childhood • Slowly progressive proximal muscle weakness mainly affecting the lower limbs • Muscle pseudohyper trophy (calves, tongue) common • Cramps, muscle pain • Elevated CK levels • Respiratory insufficiency, which may precede loss of ambulation, requiring nocturnal non-invasive ventilation in 25 to 50% of cases • High risk of dilated cardiomyopathy (30 to 50% of cases) which is not related to the severity of the patient's motor deficit • Prevalence in Europe: 1/100,000.

Titin-related limb-girdle muscular dystrophy R10 (LGMD2J)

ORPHA 140922 - OMIM 608807

• Autosomal recessive • Caused by mutations in the ***TTN* gene** (located on chromosome 2) which codes for titin, a giant sarcomere protein which maintains myosin filaments and contributes to muscle elasticity • Age of onset: young adulthood • Proximal and distal symptoms • Ability to walk generally loss around 20 years after onset of the disease • Cardiomyopathy rarely observed • Initially described in Finland in a large family which had both limb-girdle and distal forms • Around 15 cases published.

POMT1-related limb-girdle muscular dystrophy R11 (LGMD2K)

ORPHA 86812 - OMIM 609308

• Autosomal recessive • Caused by mutations in the ***POMT1* gene** (located on chromosome 9) which codes for protein O-mannosyltransferase 1, an enzyme involved in the glycosylation of α-dystroglycan • Onset in childhood or adolescence, before the age of 30 • Difficulty climbing stairs and running • Intellectual disability • A few cases of dilated cardiomyopathy • A dozen cases published.

Anoctamin-5-related limb-girdle muscular dystrophy R12 (LGMD2L)

ORPHA 206549 - OMIM 611307

• Third most common type of LGMD in Europe • Autosomal recessive • Caused by mutations in the ***ANO5* gene** (located on chromosome 11) which codes for anoctamin 5, a transmembrane protein involved in membrane repair (plugging holes, regulating the entry of calcium into the endoplasmic reticulum) • Variable age of onset, usually between 30 and 50 years old • Discomfort when walking, poor performance in sports • Exercise-induced muscle pain, burning sensation in the calf muscles • Proximal muscle weakness and atrophy mainly affecting the lower limbs, usually asymmetric • Cardiomyopathy, arrhythmia • No respiratory involvement • Slowly progressive with ability to walk retained • In addition to LGMD2L, mutations in the ***ANO5* gene** also cause Miyoshi myopathy 3, pseudometabolic myopathies and asymptomatic elevated CK levels.

Fukutin-related limb-girdle muscular dystrophy R13 (LGMD2M)

ORPHA 206554 - OMIM 611588

• Autosomal recessive • Caused by mutations in the ***FKTN* gene** (located on chromosome 9) which codes for fukutin, a protein involved in the glycosylation of α-dystroglycan • Age of onset: early childhood or later • Axial muscle weakness and proximal muscle weakness (more marked in the lower limbs), improved with corticosteroids • Cardiomyopathy possible • Intellectual disability in the most severe forms • A dozen cases published.

POMT2-related limb-girdle muscular dystrophy R14 (LGMD2N)

ORPHA 206559 - OMIM 613158

• Autosomal recessive • Caused by mutations in the ***POMT2* gene** (located on chromosome 14) which codes for protein O-mannosyltransferase 2, an endoplasmic reticulum enzyme involved in the glycosylation of α-dystroglycan • Early childhood onset • Difficulty running • Calf hypertrophy • Scapular winging • Cognitive impairment variable • Cardiomyopathy rarely observed • Less than 25 cases published.

POMGNT1-related limb-girdle muscular dystrophy R15 (LGMD2O)

ORPHA 206564 - OMIM 613157

• Autosomal recessive • Caused by mutations in the ***POMGNT1* gene** (located on chromosome 1) which codes for an enzyme involved in the glycosylation of α-dystroglycan • Onset in childhood or adolescence • Difficulty running • Calf hypertrophy • No cardiomyopathy • Two cases published.

α-dystroglycan-related limb-girdle muscular dystrophy R16 (LGMD2P)

ORPHA 280333 - OMIM 613818

• Autosomal recessive • Caused by mutations in the ***DAG1* gene** (located on chromosome 3) which codes for dystroglycan • Age of onset: childhood • Increased CK levels • Calf pseudohypertrophy • Difficulty walking and climbing stairs • Intellectual disability possible • No cardiomyopathy • Two cases published.

Plectin-related limb-girdle muscular dystrophy R17 (LGMD2Q)

ORPHA 254361 - OMIM 613723

• Autosomal recessive • Caused by mutations in the ***PLEC1* gene** (located on chromosome 8) which codes for plectin-1, a membrane protein that anchors the cytoskeleton • Age of onset: early childhood • Delay in learning to walk • Difficulty climbing stairs • Associated epidermolysis bullosa simplex possible • No respiratory involvement • No cardiac involvement • Loss of ambulation during adulthood • Cases from three families published.

TRAPPC11-related limb-girdle muscular dystrophy R18 (LGMD2S)

ORPHA 369840 - OMIM 615356

• Autosomal recessive • Caused by mutations in the ***TRAPPC11* gene** (located on chromosome 4) which codes for a protein that is essential for membrane fusion through its interaction with other TRAPP (TRAnsport Protein Particle) proteins: the TRAPP complex is involved in transport between the Golgi apparatus and the endoplasmic reticulum, and in the formation and/or movement of endosomes/lysosomes • Age of onset: young adulthood • Progressive proximal muscle weakness which leads to walking difficulties • Impairment more severe in the hip muscles than in the shoulder girdle muscles • Scoliosis, hip dysplasia • Respiratory involvement • Abnormal movements (ataxia), intellectual disability, cataracts and seizures possible • Cases from seven families published.

GMPPB-related limb-girdle muscular dystrophy R19 (LGMD2T)

ORPHA 363623 - OMIM 615352

• Autosomal recessive • Caused by mutations in the ***GMPPB* gene** (located on chromosome 3) which codes for the beta subunit of GDP-mannose pyrophosphorylase, an enzyme associated with the glycosylation of α-dystroglycan • Age of onset: early childhood/young adulthood • Hypotonia • Microcephaly • Mild intellectual disability possible • Seizures • Difficulty climbing stairs and running • Cataracts • Nystagmus • Cardiomyopathy possible • Respiratory insufficiency • Normal brain MRIs • Muscle biopsy: hypoglycosylation of α-dystroglycan • Less than 15 cases published.

ISPD-related limb-girdle muscular dystrophy R20 (LGMD2U)

ORPHA 352479 - OMIM 616052

• Autosomal recessive • Caused by mutations in the ***CRPPA* gene** (located on chromosome 7) which codes for CDP-L-ribitol pyrophosphorylase A, also called isoprenoid synthase domain-containing protein (ISPD), which is necessary for the glycosylation of α-dystroglycan • Age of onset: childhood • Hypotonia • Walking difficulties • Slowly progressive • Loss of ambulation possible at various ages • Earlier form with cerebellar abnormalities, myopia and oculomotor apraxia • Mild cardiomyopathy possible • Only a few cases published.

POGLUT1-related limb-girdle muscular dystrophy R21 (LGMD2Z)

ORPHA 480682 - OMIM 617232

• Autosomal recessive • Caused by mutations in the ***POGLUT1* gene** (located on chromosome 3) which codes for the POGLUT1 enzyme (or protein O-glucosyltransferase 1), an endoplasmic reticulum protein necessary for the glycosylation of α-dystroglycan • Onset usually during young adulthood, but can

also be at birth or during childhood • Slowly progressive proximal muscle weakness and atrophy which mainly affects the lower limbs (quadriceps) • Scapular winging • Loss of ambulation possible between the ages of 30 and 60 • Respiratory impairment possible (generally mild) • No cardiac involvement • Muscle MRI: fatty muscle degeneration starting at the centre and spreading to the peripheries of the muscles involved • 15 cases published.

Limb-girdle muscular dystrophy R22 collagen VI-related dystrophy (Bethlem myopathy)

ORPHA 610 - OMIM 158810

• Autosomal recessive (10% of Bethlem myopathies) • Allelic disorder: Ullrich congenital muscular dystrophy • Caused by mutations in one of the three genes coding for collagen VI: ***COL6A1, COL6A2*** (located on chromosome 21) or ***COL6A3*** (located on chromosome 2) which code for the α-1, α-2 and α-3 subunits of collagen VI respectively • Variable age of onset: early childhood, adolescence, adulthood • Hypotonia and delayed motor development in early childhood • Proximal muscle weakness mainly affecting the extensor muscles • Contractures of the wrists, elbows, hips, knees and Achilles tendons • Distal joint hypermobility, particularly in the proximal and distal interphalangeal joints • Gradual worsening of contractures • Scoliosis, spinal rigidity • Decline in muscle strength after the age of 40 • Over two thirds of patients over the age of 50 retain their ability to walk independently • No cardiac involvement • Inconsistent respiratory involvement • Keloid scars • Thin, grainy skin (keratosis pilaris) • Muscle MRI: fatty degeneration starting at the peripheries of muscles ("target" sign) • Intermediate form between Ullrich congenital muscular dystrophy and Bethlem myopathy: loss of ambulation around the age of 19 on average, respiratory insufficiency requiring non-invasive ventilation around the age of 20 • Form characterised in particular by contractures ("myosclerosis") caused by certain recessive mutations in the *COL6A2* gene; severe and progressive contractures of the ankles, knees, elbows, finger flexors, shoulders, neck and masseter muscles • Great intrafamilial variability.

Laminin subunit α2-related limb-girdle muscular dystrophy R23

ORPHA 565837 - OMIM 618138

• Autosomal recessive • Caused by mutations in the ***LAMA2* gene** (located on chromosome 6) which result in a partial deficiency in the protein that it codes for - laminin α2 (or merosin) • Age of onset: childhood, adolescence, adulthood • Slight delay in learning to walk (18 months old on average) • Proximal weakness and/or fatigability • Difficulty running and jumping • Joint contractures • Seizures (febrile or epileptic) in 30% of cases • White matter abnormalities without impaired intellectual development • Respiratory involvement possible • Cardiac involvement in 25% of cases, usually after the age of 40 • Sensorimotor neuropathy possible • 10 times less common than the congenital form • Less than 50 cases published.

POMGNT2-related limb-girdle muscular dystrophy R24

ORPHA 565899 - OMIM 618135

• Autosomal recessive • Caused by mutations in the ***POMGNT2* gene** (located on chromosome 3) which codes for protein O-mannose beta-1,4-N-acetylglucosaminyltransferase 2 (POMGNT2), a protein that contributes to the glycosylation of α-dystroglycan • Highly variable severity • Some patients may be clinically asymptomatic • Delayed motor development • Delayed speech • Impaired intellectual development • Proximal muscle weakness • Calf hypertrophy • Increased CK levels • Less than 10 cases published.

BVES-related limb-girdle muscular dystrophy R25 (LGMD2X)

ORPHA 476084 - OMIM 616812

• Autosomal recessive • Caused by mutations in the ***BVES (POPDC1)* gene** (located

on chromosome 6) which codes for Popeye domain-containing protein 1, a membrane protein involved in skeletal muscle membrane trafficking, heart rate, and the survival of cardiomyocytes following a myocardial infarction • Variable age of onset (adolescence to adulthood) • Atrioventricular block (sometimes isolated) • Slowly progressive proximal muscle weakness and atrophy • Difficulty walking • Increased CK levels • Around 15 cases published.

Autosomal recessive limb-girdle muscular dystrophy-26 (LGMD R26)

OMIM 618848

• Autosomal recessive • Caused by mutations in the ***POPDC3* gene** (located on chromosome 6) which codes for Popeye domain-containing protein 3, a cAMP effector protein involved in skeletal muscle membrane trafficking • Onset: adolescence to adulthood • Proximal muscle weakness and atrophy starting in the lower limbs • Calf hypertrophy • Increased CK levels • No cardiac involvement • Seven cases published.

Autosomal recessive limb-girdle muscular dystrophy-27 (LGMD R27)

OMIM 619566

• Autosomal recessive • Caused by mutations in the ***JAG2* gene** (located on chromosome 14) which codes for Jagged-2, a protein that binds to a Notch membrane receptor that plays an essential role in the establishment and maintenance of a reserve pool of satellite cells • Weakness in the neck and limb flexors, mainly affecting the proximal muscles of the lower limbs • Muscle weakness usually slowly progressive • Loss of ambulation possible • Occasional scoliosis, rigid spine • Facial muscle weakness, ptosis rare • Cardiac involvement possible • Mild respiratory involvement • 23 cases published.

DNAJB6-related limb-girdle muscular dystrophy D1 (LGMD1D)

ORPHA 34516 - OMIM 603511

• Autosomal dominant • Caused by a mutation in the G/F domain of the ***DNAJB6* gene** (located on chromosome 7) which codes for a chaperone protein • Age of onset variable (25-50 years old, sometimes earlier) • Proximal and/or distal muscle weakness and atrophy (difficulty walking on tiptoes) • Dysphagia uncommon • Respiratory difficulties possible • No cardiac involvement • Slowly progressive, occasionally more severe • Ability to walk retained until old age • Around 40 cases published.

TNP03-related limb-girdle muscular dystrophy D2 (LGMD1F)

ORPHA 55595 - OMIM 608423

• Autosomal dominant • Caused by mutations in the ***TNPO3* gene** (located on chromosome 7) which codes for transportin 3 (TNPO3), an essential precursor-mRNA splicing factor and nuclear import receptor for serine/arginine-rich (SR) proteins • Variable age of onset, usually during childhood • Muscle weakness initially affecting the pelvic girdle muscles, followed by the axial and shoulder girdle muscles • Scapular winging • Arachnodactyly possible • Normal or mildly increased CK levels • Dysphagia, respiratory insufficiency uncommon • No cardiac involvement • Variable progression • No early loss of ambulation • Around 60 cases published (three families and two sporadic cases).

HNRNPDL-related limb-girdle muscular dystrophy D3 (LGMD1G)

ORPHA 55596 - OMIM 609115

• Autosomal dominant • Caused by mutations in the ***HNRNPDL* gene** (located on chromosome 4) which codes for proteins that bind to pre-mRNA and function in splicing and nuclear export • Adult onset • Proximal muscle weakness usually starting in the pelvic girdle muscles, sometimes in the shoulder girdle muscles or scapuloperoneal weakness • Limited finger and toe flexion • Scapular winging

• Early cataracts common • Asymmetric diaphragm involvement possible • No cardiac involvement • Slowly progressive • Cases from seven families (Brazil, Uruguay, China, Argentina, Spain and Italy) published.

Calpain-3-related limb-girdle muscular dystrophy D4 (LGMD1I)

ORPHA 565909 - OMIM 618129

• Autosomal dominant • Caused by an absence of or a defect in calpain-3, a skeletal muscle-specific enzyme (***CAPN3* gene** located on chromosome 15) which plays a key role in the renewal of sarcomere proteins and the maintenance of sarcomere integrity • Later and milder than the autosomal recessive form (LGMD2A) • Onset usually during young adulthood • Difficulty walking • Scapular winging • Increased CK levels, which is sometimes the only abnormality detected • Paraspinal muscle, gluteal muscle, hamstring and medial gastrocnemius involvement • Abdominal wall weakness, lordosis • Camptocormia, which is sometimes the only clinical sign • Highly variable clinical severity, even within the same family • Cases from around 15 families published as well as over 30 sporadic cases.

Limb-girdle muscular dystrophy D5 collagen VI-related dystrophy (Bethlem myopathy)

ORPHA 610 - OMIM 158810

• Autosomal dominant (90% of Bethlem myopathies) • Caused by mutations in one of the three genes coding for collagen VI: ***COL6A1, COL6A2*** (located on chromosome 21) or ***COL6A3*** (located on chromosome 2) which code for the α-1,α-2 and α-3 subunits of collagen VI respectively • Hypotonia and delayed motor development in early childhood • Proximal muscle weakness mainly affecting the extensor muscles • Contractures of the wrists, elbows, hips, knees and Achilles tendons • Distal joint hypermobility, particularly in the proximal and distal interphalangeal joints • Gradual worsening of contractures • Scoliosis, spinal rigidity • Decline in muscle strength after the age of 40 • Over two thirds of patients over the age of 50 retain their ability to walk independently • Normal or mildly increased CK levels • Thin, grainy skin (keratosis pilaris) • Keloid scars • Muscle MRI: fatty degeneration starting at the peripheries of muscles ("target" sign) • No cardiac involvement • Later respiratory involvement possible • Intermediate form between Ullrich congenital muscular dystrophy and Bethlem myopathy: loss of ambulation around the age of 19 on average, respiratory insufficiency requiring non-invasive ventilation around the age of 20 • Form characterised in particular by contractures ("myosclerosis") caused by certain recessive mutations in the COL6A2 gene; severe and progressive contractures of the ankles, knees, elbows, finger flexors, shoulders, neck and masseter muscles • Great intrafamilial variability • Prevalence: 0.5 - 0.77/100,000.

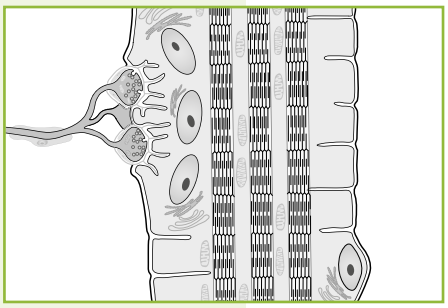
Management and treatment

• Genetic counselling • Adapted physiotherapy • Assistive mobility devices • Monitoring of respiratory function and NIV if necessary • Monitoring of cardiac function and treatment if necessary • Mitigation of motor impairment using assistive technology to ensure the highest level of independence possible (walking stick, electric wheelchair, computer, etc.) • Management of learning difficulties in the event of intellectual disability • Development of innovative treatments (gene therapy, pharmacogenetics, etc.) for calpainopathies, dysferlinopathies, several forms of sarcoglycanopathies and FKRP deficiencies.

• For more information, please consult the Protocole National de Diagnostic et de Soins for collagen VI-related myopathies: https://www.has-sante.fr/jcms/p_3376221/fr/myopathies-reliees-au-collagene-vi [document in French]

Facioscapulohumeral MUSCULAR DYSTROPHY (FSHD)

ORPHA 269 - OMIM 158900 / 158901 / 619477 / 619478



Autosomal dominant genetic disease caused by chromatin decompaction and hypomethylated DNA in the D4Z4 region of chromosome 4.
FSHD1, which accounts for 95% of all FSHD cases, is caused by a decrease in the number of repeats in the D4Z4 region (containing one to 10 repeats instead of the usual 11 to 100 repeats) on chromosome 4.
FSHD2, which accounts for 5% of all FSHD cases, is caused by mutations in the *SMCHD1* gene located on chromosome 18. A small number of patients have mutations in the *LRIF1* gene located on chromosome 1 (FSHD3) or mutations in the *DNMT3B* gene located on chromosome 20 (FSHD4).
The different types of facioscapulohumeral muscular dystrophy only differ genetically.
The generally accepted prevalence figure for Europe is 4.5 people in every 100,000. Around 3,000 people have FSHD in France.

• Progressive muscular dystrophy with a very variable age of onset • Symptoms typically start between the ages of 10 and 20, however, there are infantile forms which can have a very early onset (and are therefore more severe) and forms whose symptoms begin after the age of 50 • Facioscapulohumeral muscular dystrophy is named after the muscles that are affected most often: those of the face (facio), shoulder blades (scapulo) and upper arms (humeral) • Weakness often asymmetric • Muscle pain • Weakness in the fixator muscles of the scapula making it difficult to raise the arms above the head • Decreased facial expression (expressionless, eyes not closing completely while asleep, horizontal or lopsided smile) • Inability to whistle or puff out cheeks • Lower lip often everted • Involvement of the gluteal muscles (in almost half of cases) and dorsiflexors of the feet leading to difficulty getting up from a sitting position, waddling gait and steppage gait • Abdominal wall weakness causing lordosis • Distal involvement of the extensor muscles of the hands and fingers possible • Respiratory insufficiency secondary to chest deformities • Cochlea and retina may be affected (often asymptomatic) • Very slow progression, often with periods of relative stability • Life expectancy unaffected despite functional disability which can be severe • Significant clinical variability, even within the same family • The diagnosis of the most common type (FSHD1) can be confirmed by a routine but complex DNA test (pulsed-field gel electrophoresis and/or molecular combing).

The French FSHD registry

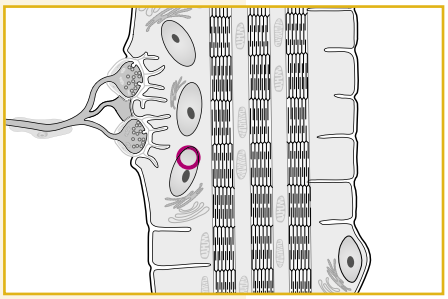
The Observatoire National Français des patients atteints de DMFSH [French National Registry for patients with FSHD] was created in June 2013.
Funded by AFM-Téléthon, this data warehouse aims to gather genetic and clinical information from as many people as possible with FSHD in order to improve our understanding of the disease and accelerate the development of drugs.
www.fshd.fr [document in French]

Management and treatment

• Genetic counselling • Adapted physiotherapy • Regular appropriate physical activity • Monitoring of vision and hearing • Monitoring of respiratory function • Cardiac assessment (basic monitoring) • Patients may benefit from scapular fixation surgery • Mitigation of motor impairment to ensure the highest level of independence possible (foot drop support, walking stick, lifting seat, wheelchair, etc.) • Specific management of severe infantile forms.
• For more information, please consult the Protocole National de Diagnostic et de Soins (21 January 2022): https://www.has-sante.fr/jcms/p_3310328/fr/dystrophie-musculaire-facio-scapulo-humerale [document in French]

Oculopharyngeal MUSCULAR DYSTROPHY (OPMD)

ORPHA 270 - OMIM 164300



Autosomal dominant genetic disease caused by expanded polyalanine tracts (coded for by GCN trinucleotide repeats) in the PABPN1 protein (PABPN1 gene located on chromosome 14). Rare in France (1 to 9 people in every 100,000), more common in Quebec.

• Progressive muscular dystrophy mainly affecting the muscles of the upper eyelids and throat • Clinical onset during adulthood (40 to 60 years old) • Ptosis • Dysphagia, occasionally severe swallowing difficulties which can lead to complications (aspiration pneumonia or cachexia) • Mainly proximal limb muscle weakness (shoulder and pelvic girdle muscles), therefore walking and certain arm movements can become difficult • Slowly progressive with gradual worsening of oculopharyngeal muscle weakness • Swallowing difficulties can be life threatening • Earlier form caused by frameshift mutations in the ***HNRNPA2B1* gene** (located on chromosome 7) which codes for two proteins, HNRNPA2 and HNRNPB1, which are involved in alternative splicing and cytoplasmic RNA trafficking, translation and stabilisation.

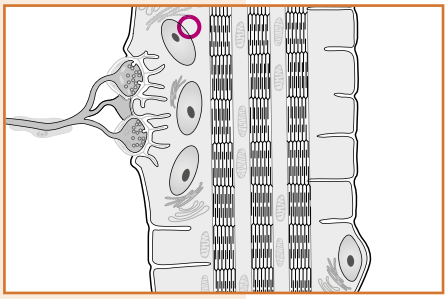
Management and treatment

• Genetic counselling • Special diet • Rehabilitation, surgery (cricopharyngeal myotomy) • Gastrostomy or jejunostomy to administer nutrition in the event of severe swallowing difficulties • Monitoring of respiratory function • Wearing special glasses that hold up the eyelids, or even ptosis surgery • Mitigation of impairments to ensure the highest level of independence possible (walking stick, lifting seat, wheelchair, etc.).

• For more information, please consult the Protocole National de Diagnostic et de Soins (September 2022): https://www.has-sante.fr/jcms/p_3374041/fr/dystrophie-musculaire-oculopharyngee [document in French]

MYOTONIC DYSTROPHIES

ORPHA 206647

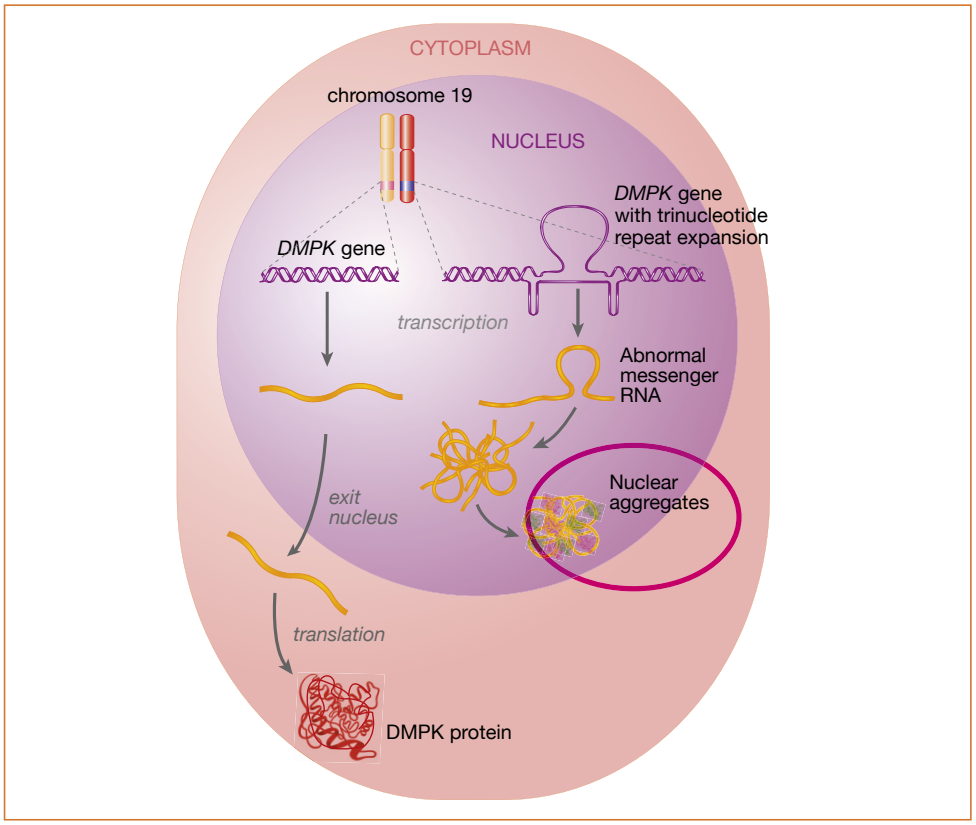


Autosomal dominant genetic diseases caused by a significant increase in the number of repeats of a DNA sequence composed of three nucleotides in the *DMPK* gene for myotonic dystrophy type 1 (DM1) or four nucleotides in the CNBP (formerly ZNF9) gene for myotonic dystrophy type 2 (DM2). In Europe, 8.78 people in every 100,000 have myotonic dystrophy.

• The accumulation of mutated messenger RNA molecules with the abnormal expanded triplet or quadruplet repeats in cell nuclei disrupts the expression and activity of cell proteins by sequestering other messenger RNA molecules and splicing proteins
• Multisystem diseases that affect the muscles, eyes, nervous system, heart, lungs, gastrointestinal system and endocrine glands.

Myotonic dystrophy type 1 (DM1) or Steinert's disease

ORPHA 273 – OMIM 160900



The molecular mechanism of Steinert's disease.
One of the two copies of the DMPK gene in people with Steinert's disease contains a genetic mutation. The messenger RNA molecules produced from this mutated copy are abnormally long and tend to bind to nuclear proteins to form aggregates. The presence of these aggregates disrupts cell function.

• Caused by the expansion of a CTG trinucleotide repeat (50 to 3,000 CTG repeats instead of the usual five to 37) in the ***DMPK* gene** (located on chromosome 19) which codes for myotonin protein kinase, a protein involved in the transfer of energy in cells • The greater the number of CTG repeats, the more severe the disease • Clinical onset can occur at any age • Generally, the earlier the onset, the more severe the disease

• Difficulty relaxing muscles after they contract (myotonia), particularly those of the hands (those of the tongue and the masseter muscles less often) • Myotonia may be minimal, not present at all or disappear over time • Early baldness in men • Bilateral early cataracts (before the age of 50) are indicative of the disease • Excessive daytime sleepiness • Cognitive, mood and behavioural problems • Heart rhythm and conduction disturbances • Respiratory difficulties • Weakness and atrophy of the face, neck, pharynx, forearm, hand, dorsiflexor, abdominal, intercostal and diaphragm muscles • Steppage gait sometimes noted by the patient as the first symptom • Bowel problems (constipation/diarrhoea, partial obstruction, megacolon) • Swallowing difficulties • Gallstones • Elevated GGT levels • Sleep disorders, depression • Infertility/reduced fertility • Endocrine disorders: hypothyroidism, insulin resistance • Variable impairment and progression which can reach a stage of severe disability 15 to 20 years after onset (loss of ambulation and intellectual disability of varying severity) • Genetic counselling difficult due to the instability of the repeats and the genetic anticipation of the disease (signs and symptoms appear at an earlier age and/or become more severe as the disease is passed down over the generations) which varies depending on the sex of the carrier parent • Presymptomatic and prenatal testing possible (including preimplantation genetic diagnosis) • Prevalence: 5/100,000.

- **Late-onset form** • Onset after the age of 40 • Symptoms limited to cataracts and baldness in men.
- **Adult-onset form** • Onset between the ages of 20 and 40 • Myotonia mainly affecting the hands (difficulty unclenching a fist) • Distal muscle atrophy and weakness • Occasional dysphonia and swallowing difficulties.
- **Childhood- or juvenile-onset form** • Onset between the ages of 10 and 20 • More marked myotonia • Mild cognitive impairment • Cardiac involvement.
- **Infantile form** • Onset between the ages of one month and 10 years old • Learning difficulties are sometimes the only sign of the disease, apart from muscular manifestations (myotonia or weakness).
- **Congenital form** • Onset at birth • Severe neonatal hypotonia • Respiratory distress • Clubfoot • Suckling and swallowing difficulties • Generally poor prognosis.

Myotonic dystrophy type 2 (DM2 or PROMM)

ORPHA 606 – OMIM 602668

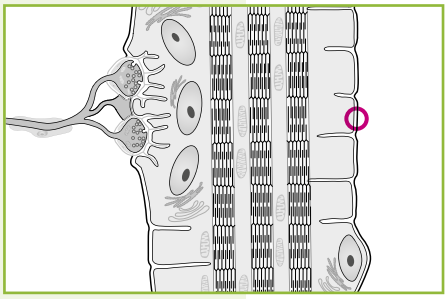
• Another form of autosomal dominant myotonic dystrophy • Caused by a quadruplet of nucleotides (CCTG) repeated 75 to over 11,000 times in the ***CNBP*** (formerly ***ZNF9***) **gene** (located on chromosome 3) which codes for a "zinc finger" nucleic acid-binding protein • Childhood or adulthood onset with myotonia, muscle atrophy and gradual loss of strength in the proximal muscles of the limbs often associated with muscle pain • Cataracts and baldness common • Cardiac involvement (heart rhythm disturbances) less common and abnormalities in other organs are much milder than in myotonic dystrophy type 1 • No genetic anticipation or congenital forms observed to date • Clinical course generally more favourable than that of myotonic dystrophy type 1 • Prevalence: 1 - 9/100,000.

Management and treatment

• Genetic counselling • Adapted physiotherapy • Annual routine monitoring of cardiac function, implantation of a pacemaker if necessary • Monitoring of respiratory function (PFT, ABG) • Cataract surgery • Anaesthetic considerations • Nutritional support • Drugs to help treat myotonic symptoms, pain, hypersomnia and mood disorders • Assistive technology to mitigate motor impairment and ensure the highest level of independence possible (walking stick, wheelchair electric).

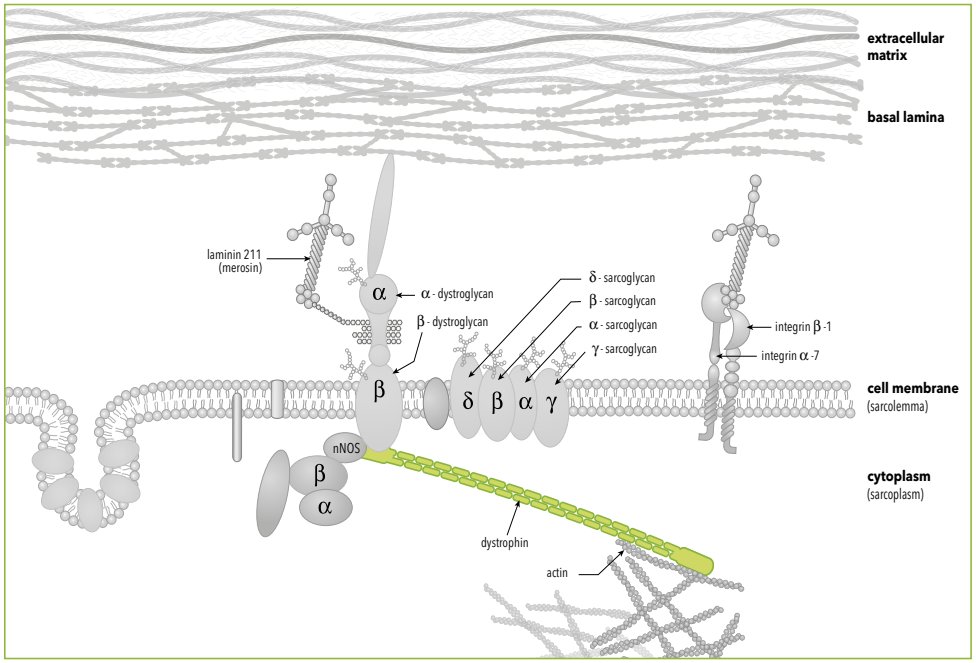
DYSTROPHINOPATHIES

ORPHA 207085



X-linked recessive genetic diseases caused by mutations in the *DMD* gene which codes for dystrophin. One newborn boy in every 3,500 is born with Duchenne muscular dystrophy (150 new cases/year). Female carriers are sometimes symptomatic (cramps, fatigue, cardiomyopathy). De novo mutations in one third of cases.

• Dystrophin is a protein localised to the muscle cell membrane • It binds the actin of the cytoskeleton to the glycoproteins of the sarcolemma: dystroglycans (α, β) and sarcoglycans (α, β, γ, δ) • α-dystroglycan binds to laminin α2 of the extracellular matrix • As a result, the dystrophin-associated protein complex creates a link between the cytoskeleton of the muscle fibre and the extracellular matrix (in particular the basement membrane) • Molecular abnormalities in dystrophin cause the membrane of muscle fibres to weaken.



Duchenne muscular dystrophy (DMD)

ORPHA 98896 – OMIM 310200

• Walking difficulties usually start around two to three years old • Weakening of the hip and pelvic muscles (pelvic girdle muscles) • Waddling gait on tiptoes, chest sways back (lumbar lordosis) • Difficulty climbing stairs • Enlargement of the calves • Worsening and generalisation of muscle damage (lower and upper limb, trunk, heart and smooth muscles) • Loss of ambulation around the ages of 10 - 12 • Spinal deformity (kyphosis and scoliosis during pubertal growth spurts) • Respiratory involvement (restrictive lung disease) • Cardiac involvement (dilated cardiomyopathy) • Impaired verbal skills and working memory possible (one third of cases) • Autistic-like forms with communication problems • Prenatal and preimplantation genetic diagnosis possible • The definitive diagnosis of DMD is made based on molecular criteria • Prevalence at birth: 9.9/100,000.

Becker muscular dystrophy (BMD)

ORPHA 98895 – OMIM 300376

• Six times less common than Duchenne muscular dystrophy • Symptoms similar to Duchenne muscular dystrophy but less marked and with later onset • Slower progression and normal or near normal life expectancy in the absence of severe and progressive cardiac involvement • Loss of ambulation inconsistent • Cognitive impairment rare but possible • Incidence: 3.22 - 5.5/100,000 newborn boys • Prevalence in Europe: 2/100,000.

Women with dystrophinopathies

• Approximately 5 to 22% of women and girls with a ***DMD* gene** mutation manifest symptoms • Symptoms vary greatly from one person to another • In rare cases, girls are affected by a form of Duchenne muscular dystrophy that is identical to the one that occurs in boys • Female carriers of DMD are usually asymptomatic • Fatigue, cramps, muscle pain • Muscle weakness often asymmetric • Somewhat manifest and progressive cardiomyopathy, including in women who have no muscle symptoms • Learning difficulties and behavioural issues possible.

Mild dystrophinopathies

• Cramps, muscle pain on exertion, asymptomatic elevated CK levels • Mild forms with no loss of ambulation.

Management and treatment

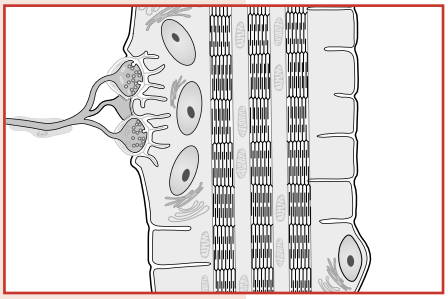
• Genetic counselling • Prevention of joint contractures through adapted physiotherapy • Equipment • Monitoring of respiratory and cardiac function • Spinal surgery • Ventilation • Mitigation of functional disabilities using assistive technology (electric wheelchair, IT solutions, new technologies, etc.) to ensure the highest level of independence possible • Drugs: corticosteroids; ACE inhibitors to prevent heart failure • Ataluren (Translarna®): innovative stop codon readthrough treatment (used in patients with nonsense mutations in the *DMD* gene - about 10% of DMD patients) • Management of cognitive or behavioural issues.

• For more information, please consult the Protocole National de Diagnostic et de Soins for Duchenne muscular dystrophy (27 November 2019): https://www.has-sante.fr/jcms/p_3121365/fr/dystrophie-musculaire-de-duchenne [document in French]

• For more information, please consult the Protocole National de Diagnostic et de Soins for Becker muscular dystrophy (28 January 2020): https://www.has-sante.fr/jcms/p_3121203/fr/dystrophie-musculaire-de-becker [document in French]

FIBRODYSPLASIA ossificans progressiva (FOP)

ORPHA 337 - OMIM 135100



Autosomal dominant or sporadic genetic disease caused by a mutation in the *ACVR1* gene (located on chromosome 2) which codes for a receptor involved in osteogenesis. Very rare: just under 90 cases recorded in France. Prevalence: 0.06 - 0.14/100,000.

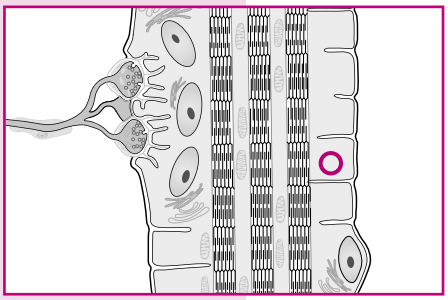
• Childhood onset • Painful flare-ups followed by the ossification of muscles which become "rock hard" • Malformed toes and/or thumb present at birth (microdactyly, bunions) • Progressive ankylosis (joint stiffening) and deformities • Unpredictable course with flare-ups occurring at various intervals throughout life • Spontaneous, or very often post-traumatic, flare-ups even after minimal trauma (in particular intramuscular injections).

Management and treatment

• Genetic counselling • Prevention of muscle trauma (even minimal) • Avoiding surgical procedures (including muscle biopsies) and intramuscular injections (vaccines, local anaesthetic including at the dentist's) as much as possible • Gentle physiotherapy • Fall prevention • Long-term pain relief • Diagnosing flare-ups early makes it possible to start treatment which can prevent secondary ossification of the muscles.

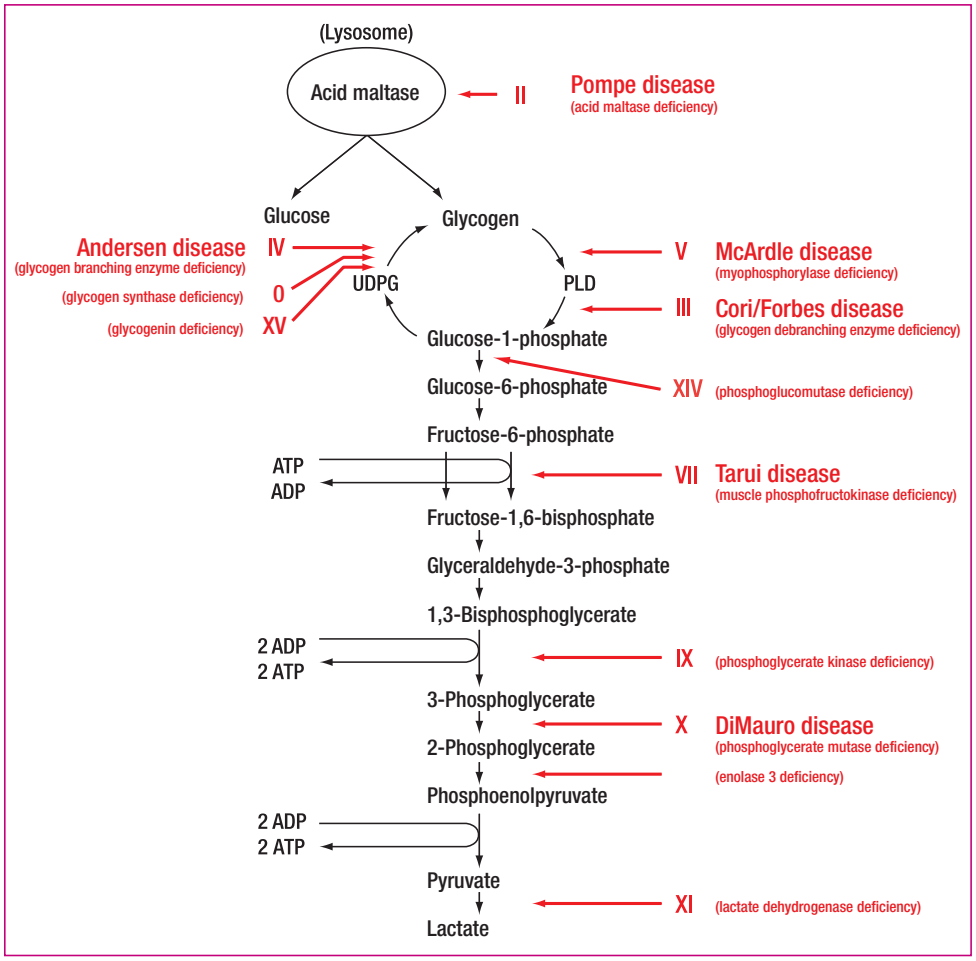
GLYCOGEN STORAGE DISEASES

ORPHA 206959



Autosomal recessive genetic carbohydrate metabolism diseases. They are caused by a defect in the chain of chemical reactions that transform sugars provided by food into the energy (ATP) used by muscles. During physical exercise, glycogen is not able to be transformed into glucose to provide the energy necessary for muscle cells to function properly. This leads to excessive amounts of unused glycogen accumulating in the cells of various organs.

• There are several types of glycogen storage diseases which are classified based on the deficient enzyme involved • They affect muscle and/or other organs (brain, liver, heart) • Onset at any age (from childhood to adulthood), most often in the form of exercise intolerance • Muscle fatigue and pain on exertion, cramps and/or progressive muscle weakness and atrophy • Other possibly associated manifestations: myoglobinuria, hepatic involvement, cardiac involvement • Course varies depending on the type.



Glycogen storage disease type II (Pompe disease)

ORPHA 365 – OMIM 232300

• Simultaneously a metabolic muscle disease and a lysosomal storage disease, Pompe disease is caused by a deficiency in α-1,4-glucosidase or acid maltase (***GAA* gene** located on chromosome 17) which prevents the degradation of glycogen into glucose within lysosomes • Gradual accumulation of glycogen in multiple organs • Autosomal recessive inheritance • Three clinical forms classified according to residual enzyme activity • Prevalence at birth: 0.8/100,000 • Prevalence: 3/100,000 • In 2019, just under 250 cases of Pompe disease were recorded in France.

Infantile form: most severe • Onset before the age of three months • "Floppy" baby (hypotonia) • Suckling and swallowing difficulties • Early hypertrophic cardiomyopathy• Hepatomegaly • Respiratory problems caused by diaphragmatic weakness • Detection of acid maltase deficiency: dried blood spot test which must be confirmed by another technique (biochemical assays, genetic testing) • Reference diagnosis made using cultured fibroblasts and muscle biopsy• Without treatment, the prognosis is poor with most patients dying between the ages of one and two years old • Treatment with early enzyme replacement therapy can lead to a regression or even disappearance of cardiomyopathy, longer life expectancy, achievement of functional and motor milestones with a risk of secondary complications (particularly neurological) after several years of treatment.

Juvenile form: onset during late childhood or early adolescence • Myopathy with or without cardiomyopathy • Motor and respiratory problems • Without treatment, this form can progress towards severe respiratory insufficiency around the ages of 15 to 20.

Adult form: onset after the age of 20 • Mild muscle weakness • Respiratory impairment often the most prominent manifestation • Heart disease rare • Frequently misdiagnosed • Slow progression resulting in longer life expectancy.

Glycogen storage disease type III (Cori disease or Forbes disease)

ORPHA 366 - OMIM 232400

• Caused by a defect in one or both of the debranching enzyme's active sites (***AGL* gene** located on chromosome 1) • The debranching enzyme is responsible for breaking down branching points during glycogen catabolism • Normally, the successive actions of the debranching enzyme's two active sites (a glucosidase site and a transferase site) transform glycogen into glucose in the liver and muscles and then makes it usable in the body • In glycogen storage disease type III, abnormal glycogen (abnormal structure comprised of numerous branching points and short peripheral chains) accumulates in organs and tissue • The different types of glycogen storage disease type III are classified according to the active site(s) and organ affected • Incidence estimated at 1/100,000 births.

Glycogen storage disease type IIIa: the enzyme's two active sites are defective in both the muscles and the liver • Most common form of the disease (85% of cases) • Onset in early childhood • Hypoglycaemia even after short fasts • Early-onset hepatomegaly with liver size usually returning to normal during adulthood • Growth retardation (short stature) and delayed psychomotor development • Mild proximal muscle weakness (fatigability) common • Increased CK levels • Improvement of hepatic symptoms and worsening of muscle weakness after puberty • Improvement in tolerance to fasting • Cirrhosis in 15% of cases • Cardiac involvement possible.

Glycogen storage disease type IIIb: the enzyme's two active sites are only defective in the liver • 15% of cases • Liver involvement only (the heart and muscles are unaffected).

Glycogen storage disease type IV (Andersen disease)

ORPHA 367 - OMIM 232500

• Caused by a deficiency in the glycogen branching enzyme (***GBE1* gene** located on chromosome 3) which leads to abnormal glycogen (fewer branching points with an amylopectin-like structure, also known as polyglucosan) being stored in various organs • Common in the Ashkenazi community • Extremely heterogeneous clinical presentation with hepatic and/or neuromuscular involvement • Age of onset of the neuromuscular form: from the foetal period to adulthood.

Fatal perinatal type (most severe form): reduced or no foetal movements, arthrogryposis, pulmonary hypoplasia and perinatal death.

Congenital types: severe hypotonia, cardiomyopathy, respiratory failure, associated nervous system involvement.

Milder types: late onset, muscle weakness or cardiomyopathy with heart failure • Prenatal diagnosis possible.

Glycogen storage disease type V (McArdle disease)

ORPHA 368 - OMIM 232600

• Caused by a deficiency in myophosphorylase (coded for by the ***PYGM* gene** located on chromosome 11) • Inability to break down glycogen into glucose • Mainly seen in males • No obvious genotype-phenotype correlation • Variable age of onset, usually during the first decade• Exercise intolerance with muscle pain and cramps • Symptoms triggered by stress, cold and alcohol • Temporary muscle swelling • Painful fatigue during exercise (sustained or sudden burst) forcing the patient to stop • "Second wind" phenomenon (ability to gradually return to exercise after a few minutes of rest through the use of lipids and oxidative phosphorylation) • Risk (50% of cases) of acute rhabdomyolysis (extremely elevated CK levels and myoglobinuria) which can result in acute kidney injury • Course usually stable and occasionally severe • Proximal weakness can develop in elderly patients after everal years of progression (25% of cases) Proximal muscle atrophy (arms, thighs) • Ischaemic forearm exercise test important for diagnosis (painful cramping in the forearm from repeatedly opening and closing the hand for less than a minute) • There are currently no effective treatments for glycogen storage disease type V

but a high-protein diet, exercise/lifestyle changes and creatine use can help manage the symptoms.

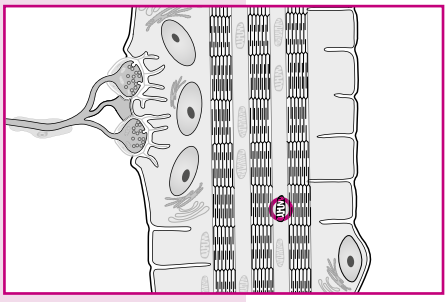
Glycogen storage disease type VII (Tarui disease)
ORPHA 371 – OMIM 232800
• Very rare disease; only around one hundred cases worldwide (found mainly in Japanese and Ashkenazi populations) • Only a few people in France have this disease • Caused by a deficiency in muscle phosphofructokinase (***PFKM* gene** located on chromosome 12) which prevents the breakdown of glycogen into glucose • Exercise intolerance starting in childhood (pain and cramps during exercise) with recovery after rest • Myoglobinuria rare except in the event of strenuous exercise • Permanent muscle weakness possible • Course usually stable and occasionally severe.

Management and treatment

• Appropriate dietary management according to the type of glycogen storage disease • High-protein diet • Breaking up meals into small, frequent snacks • Carbohydrate consumption should match the level of physical activity envisaged • In the event of hypoglycaemia, continuous nocturnal gastric drip feeding may be necessary • Avoiding intense physical activity • Allowing rest periods • Controlled workout sessions to improve physical performance • Physiotherapy and ventilation if necessary • Ensuring the highest level of independence possible • Enzyme replacement therapy in glycogen storage disease type II.
• For more information, please consult the Protocole National de Diagnostic et de Soins for glycogen storage disease type II (8 August 2016): https://www.has-sante.fr/jcms/c_2659919/fr/maladie-de-pompe [document in French]
• For more information, please consult the Protocole National de Diagnostic et de Soins for glycogen storage disease type III (16 February 2021): https://www.has-sante.fr/jcms/p_3237036/fr/glycogenose-de-type-iii-gsd-iii-pour-glycogen-storage-disease-type-iii [document in French]
• For more information, please consult the Protocole National de Diagnostic et de Soins for glycogen storage disease type V (17 June 2019): https://www.has-sante.fr/jcms/p_3076463/fr/glycogenose-de-type-v-maladie-de-mc-ardle [document in French]

LIPID STORAGE MYOPATHIES

ORPHA 206953



Autosomal recessive genetic diseases. Myopathies related to lipid metabolism which usually manifest during fasting, stress and/or exercise.

• Lipid storage myopathies are caused by a defect in the chain of chemical reactions that transform fats provided by food into the energy used by the body (fatty acid beta-oxidation, a degradation pathway which takes place in mitochondria (except the first step which takes place in the cytoplasm) and in other cellular organelles such as peroxisomes) • Fats accumulate in muscle cells and cannot be used • Exercise intolerance characterised by muscle pain occurring during or after exercise • Possibly associated manifestations: impaired consciousness, cardiac involvement, myoglobinuria, hypoglycaemia following exercise • Onset can occur during the neonatal period, childhood or adulthood depending on the type of lipid storage

myopathy • Extremely variable clinical course • Certain lipid storage myopathies only manifest themselves through the body's lack of adaptation to exercise and fasting • There are several types of lipid storage myopathies which are distinguished according to the enzyme deficiency involved.

Systemic primary carnitine deficiency

ORPHA 158 - OMIM 212140

• Caused by a deficiency in a carnitine transporter (***SLC22A5* gene** located on chromosome 5) • The main role of carnitine is to control the entry of long-chain fatty acids (> 14 carbons) into the mitochondria and to intervene in the formation of acylcarnitines from medium- and short-chain fatty acids in the mitochondrial matrix • Progressive proximal muscle weakness with episodes of hypoglycaemia • Associated heart disease possible • Young children may present with episodes of encephalopathy linked to episodes of hypoglycaemia • Treatable with appropriate therapies.

Carnitine palmitoyltransferase II (CPT II) deficiency

ORPHA 228302 - OMIM 255110

• ***CPT2* gene** located on chromosome 1 • The CPT II enzyme, localised to the inner mitochondrial membrane, catalyses the transport of long- or very long-chain fatty acids by allowing them to cross the mitochondrial membranes, the first step in fatty acid beta-oxidation • There are three subtypes of CPT II deficiency: a lethal neonatal form, a severe infantile hepatocardiomuscular form and a myopathic form • Lethal neonatal form: generalised disease with onset a few days after birth • Severe infantile hepatocardiomuscular form: generalised disease with onset within the first year of life • Myopathic form: onset during the second or third decade, sometimes later • Muscle weakness• Cardiac involvement (cardiomyopathy, heart rhythm disturbances) • Hepatic involvement • Treatable with appropriate therapies • Over 300 cases published.

Partial CPT II deficiency

• Intense, prolonged, paroxysmal muscle cramps and myoglobinuria triggered by exercise • Muscle pain can be permanent • Usually no signs or symptoms of the condition between attacks.

Short chain acyl-CoA dehydrogenase deficiency

ORPHA 26792 - OMIM 201470

• Caused by mutations in the ***ACADS* gene** (located on chromosome 12) which codes for an acyl-CoA dehydrogenase necessary for the beta-oxidation of short chain fatty acids in mitochondria • Usually asymptomatic • Failure to thrive in very few cases • Hypotonia • Seizures • Progressive myopathy.

Very long chain acyl-CoA dehydrogenase deficiency

ORPHA 26793 - OMIM 201475

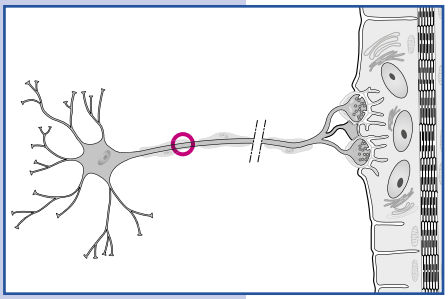
• Caused by mutations in the ***ACADVL* gene** (located on chromosome 17) which codes for an acyl-CoA dehydrogenase necessary for the beta-oxidation of very long-chain fatty acids in mitochondria • Heterogeneous clinical presentation with manifestations ranging from fatal cardiomyopathy to myopathy starting during adolescence.

Management and treatment

• Exercise restriction, planning rest periods, diet monitoring • Carnitine and CPT II deficiencies: carnitine, avoiding prolonged exercise, diet low in fat and rich in carbohydrates, avoiding skipping meals • Acyl-CoA dehydrogenase deficiencies: occasionally responsive to riboflavin (vitamin B2).

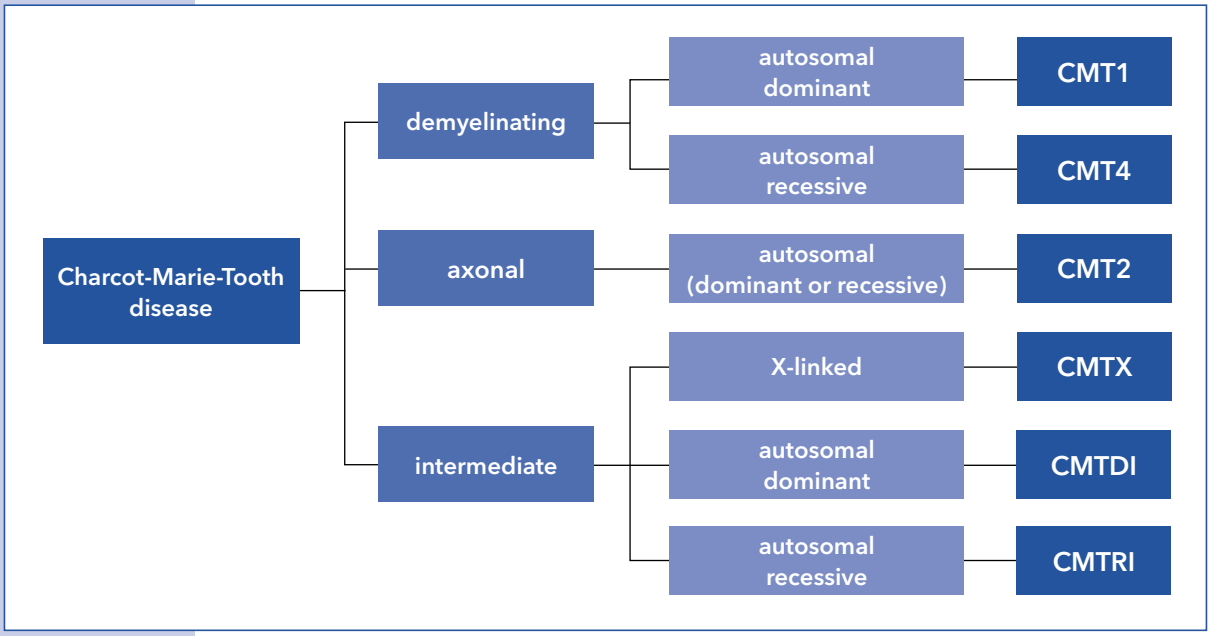
CHARCOT-MARIE-TOOTH (CMT) diseases

ORPHA 166



Autosomal dominant, autosomal recessive or X-linked dominant genetic diseases. Peripheral nerve impairment initially caused by damage to either the myelin sheath (CMT1 and CMT4), axons (CMT2), or the myelin sheath and axons (X-linked (CMTX) and autosomal dominant intermediate (CMTDI) forms).
Prevalence : 9.7 - 82.3/100,000 (around 30,000 people in France).

• Hereditary motor and sensory neuropathies (HMSN) • Type depends on the location of the nerve damage: CMT types 1 and 4 (initial damage to the myelin sheath with reduced nerve conduction velocities) and CMT type 2 (axonal degeneration with substantially normal nerve conduction velocities) • "Intermediate CMT" in 10% of cases, with damage to both the myelin sheath and axons • Age of onset very variable, most often in the first two decades • Distal motor deficit and sensory impairment • Pes cavus • Distal muscle atrophy, particularly in the calves, thighs, forearms and hands • Impairment generally bilateral • Gradual development of steppage gait causing falls and sprains and making it difficult to run • Reduced walking distance • Joint contractures causing lesser toe deformities • Occasional hand involvement, generally after several years of progression: decreased muscle strength, tasks requiring manual dexterity difficult to perform, "claw hand", possible loss of pincer grasp • Fatigability • Cramping common, especially during periods of disease progression • Generally decreased or absent deep tendon reflexes • Deep sensory impairment common • Pain • Severity of the disease varies greatly from patient to patient, even within the same family • Progression unpredictable • Level of disability ranges from experiencing discomfort when walking to having to use a wheelchair (around 10% of cases) • Rare phrenic nerve involvement causing somewhat significant respiratory insufficiency • Generally slowly progressive • Diagnosis based on electromyography (EMG) results, mode of inheritance and genetic testing • Nerve biopsies are only performed in exceptional circumstances • To date, over 80 genes have been implicated in CMT, and 46 are implicated in neuropathies associated with CMT (distal hereditary motor neuropathy (dHMN) and hereditary sensory and autonomic neuropathy (HSAN)) • Only 40% of patients



currently have a genetic diagnosis, the three most common forms being CMT1A (accounting for approximately half of all CMT cases), CMTX1 and CMT2A.

Charcot-Marie-Tooth disease type 1 (CMT1)

• Autosomal dominant, demyelinating • Caused by mutations:
- in the ***PMP22* gene** (located on chromosome 17) which codes for peripheral myelin protein-22 (PMP22) (**CMT1A,** ORPHA 101081 – OMIM 118220; **CMT1E,** ORPHA 90658 – OMIM 118300) • Onset before the age of 20 in 70% of cases • Asymptomatic in 25% of cases • Ataxic gait • Nerves enlarged on palpation • Pes cavus • Great variability, even within the same family;
- in the ***MPZ* gene** (located on chromosome 1) which codes for myelin glycoprotein P0, a Schwann cell membrane protein which makes up nearly 50% of myelin sheath protein components in the peripheral nervous system (**CMT1B,** ORPHA 101082 - OMIM 118200) • Up to 25% of these mutations are de novo mutations;
- in the ***LITAF* gene** (located on chromosome 16) which codes for a factor involved in protein degradation (**CMT1C,** ORPHA 101083 - OMIM 601098) • 1.6% of all CMT1 cases in France • Onset during the second decade • Decreased deep tendon reflexes • Inconsistent motor deficit;
- in the ***EGR2* gene** (located on chromosome 10) which codes for a transcription factor (**CMT1D,** ORPHA 101084 - OMIM 607678) • 1% of all CMT1 cases • Severe distal motor deficit • Ptosis • Areflexia;
- in the ***NEFL* gene** (located on chromosome 8) which codes for a neurofilament light chain polypeptide which is a major component of intermediate filaments and plays an important role in the assembly and maintenance of the axonal cytoskeleton (**CMT1F,** ORPHA 101085 - OMIM 607734);
- in the ***FBLN5* gene** (located on chromosome 14) which codes for fibulin 5, an extracellular matrix glycoprotein which regulates the development and maintenance of tissues rich in elastic fibres • Associated with age-related macular degeneration and skin hyperelasticity (ORPHA 280598 - OMIM 608895).
- in the ***GJB3* gene** (located on chromosome 1) which codes for connexin 31, an essential component of gap junctions found in the skin, cochlea and Schwann cells • Demyelinating neuropathy with hearing impairment and skin ulcers (ORPHA 139512).

Charcot-Marie-Tooth disease type 4 (CMT4)

• Autosomal recessive, demyelinating • Rare, only found in isolated families or populations with high consanguinity rates • Early onset: birth, early childhood • Delayed motor development • Severe distal motor deficit • Muscle atrophy • Areflexia • Sensory impairment • Pes cavus • Scoliosis • Caused by mutations:
- in the ***GDAP1* gene** (located on chromosome 8) which codes for a protein involved in neuronal development (**CMT4A,** ORPHA 99948 - OMIM 214400) • Delayed motor development in the second year of life • Severe predominantly motor neuropathy • Proximal involvement at the end of the first decade • Foot deformities and scoliosis common • Hand muscle atrophy occurs later;
- in the ***MTMR2* gene** (located on chromosome 11) which codes for a myotubularin-related phosphatase (**CMT4B1,** ORPHA 99955, OMIM 601382) • Childhood onset • Distal and proximal muscle weakness in the lower limbs • Clubfoot • Scoliosis • Possible initial vocal cord paresis • Occasional diaphragmatic, facial and bulbar weakness • Ability to walk independently lost during the third decade;
- in the ***SBF2* gene** (located on chromosome 11) which codes for MTMR13, a myotubularin-related pseudophosphatase (**CMT4B2,** ORPHA 99956 - OMIM 604563) • Childhood onset • Severe progression • Early-onset glaucoma common;
- in the ***SBF1* gene** (located on chromosome 22) which codes for MTMR5, a myotubularin-related protein (**CMT4B3,** ORPHA 363981 - OMIM 615284);
- in the ***SH3TC2* gene** (located on chromosome 5) which codes for a protein with SH3

domains and TPR motifs (**CMT4C,** ORPHA 99949, OMIM 601596) • 16% of all Caucasian forms • Great clinical variability • Delay in learning to walk with respiratory and cranial nerve involvement • Milder form with scoliosis and foot deformities • Scoliosis • Hypoacusis, tongue atrophy and facial weakness possible;
- in the ***NDRG1* gene** (located on chromosome 8) which codes for a signalling protein which plays a role in cell differentiation (**CMT4D,** ORPHA 99950 - OMIM 601455) • Generally found in the gypsy population • Associated with deafness • Tongue atrophy possible;
- in the ***EGR2* gene** (located on chromosome 10) which codes for a transcription factor (**CMT4E,** ORPHA 99951 - OMIM 605253) • Wide spectrum of phenotypes • Slowly progressive neuropathy • Congenital hypomyelinating neuropathy with respiratory and cranial nerve involvement;
- in the ***PRX* gene** (located on chromosome 19) which codes for periaxin, a protein which stabilises the axon-Schwann cell unit (**CMT4F,** ORPHA 99952 - OMIM 614895) • Early childhood onset • Delay in learning to walk (after 18 months old) • Severe distal lower limb muscle atrophy • Early-onset scoliosis • Possible neuropathic pain • Occasional eye problems, hearing loss and respiratory insufficiency;
- in the ***HK1* gene** (located on chromosome 10) which codes for hexokinase, an enzyme which transforms glucose into glucose-6-phosphate (**CMT4G,** formerly known as **hereditary motor and sensory neuropathy, Russe type,** ORPHA 99953 - OMIM 605285) • Childhood onset • Distal muscle weakness in the lower limbs • Weakness in the upper limbs occurs later • Severe sensory impairment;
- in the ***FGD4* gene** (located on chromosome 12) which codes for frabin, a Rho GTPase activation factor (**CMT4H,** ORPHA 99954 - OMIM 609311) • Delay in learning to walk • Severe scoliosis • Occasionally a milder form;
- in the ***FIG4* gene** (located on chromosome 6) which codes for a phosphatase (**CMT4J,** ORPHA 139515 - OMIM 611228) • Clinical variability • Severe impairment beginning in early childhood • Onset ranges from early childhood to the sixth decade • Proximal and distal (sometimes asymmetric) muscle weakness.

Charcot-Marie-Tooth disease type 2 (CMT2)

• Axonal, autosomal dominant or recessive • Makes up nearly 30% of all CMT cases • Weakness and atrophy of the distal muscles in the lower limbs • Atrophy of the intrinsic muscles of the hands less common and occurs later • Decreased deep tendon reflexes • Mild sensory impairment, often less severe than in CMT1 • Deafness common • Slowly progressive • Caused by mutations:
- in the ***SORD* gene** (located on chromosome 15) which codes for sorbitol dehydrogenase, an enzyme that converts sorbitol into fructose (OMIM 618912) • Identified in 2020 • May be one of the most common axonal forms • Autosomal recessive (common sporadic form) • Weakness mainly affecting the lower limbs • Sensory impairment absent in half of all cases;
- in the ***KIF1B* gene** (located on chromosome 1) which codes for kinesin family member 1B, a protein involved in axonal transport (**CMT2A1,** ORPHA 99946 - OMIM 118210) • Autosomal dominant;
- in the ***MFN2* gene** (located on chromosome 1) which codes for mitofusin 2, a mitochondrial fusion protein (**CMT2A2,** ORPHA 99947 - OMIM 609260) • The most common axonal form • Autosomal dominant or recessive;
- in the ***RAB7* gene** (located on chromosome 3) which codes for a protein involved in endocytosis (**CMT2B,** ORPHA 99936 - OMIM 600882) • Autosomal dominant;
- in the ***LMNA* gene** (located on chromosome 1) which codes for lamin A and lamin C, proteins associated with the nuclear membrane (**CMT2B1,** ORPHA 98856 - OMIM 605588) • Autosomal recessive;
- in the ***PNKP* gene** (located on chromosome 19) which codes for a polynucleotide kinase 3-prime phosphatase involved in DNA repair (**CMT2B2,** ORPHA 101101 - OMIM 605589) • Autosomal recessive;
- in the ***TRPV4* gene** (located on chromosome 12) which codes for a calcium-

permeable cation channel (**CMT2C,** ORPHA 99937 - OMIM 606071) • Scapuloperoneal atrophy • Vocal cord paresis (laryngeal dyspnoea) • Stridor • Diaphragm paresis • Autosomal dominant;
- in the ***GARS1* gene** (located on chromosome 7) which codes for glycyl-tRNA synthetase, an enzyme that is essential in protein synthesis (**CMT2D,** ORPHA 99938 - OMIM 601472)
• Weakness predominantly in the hands • Wasting of the thenar and 1st dorsal interosseous muscles • Autosomal dominant;
- in the ***NEFL* gene** (located on chromosome 8) which codes for a light neurofilament protein (**CMT2E,** ORPHA 99939 - OMIM 607684) • Autosomal dominant;
- in the ***HSPB1* gene** (located on chromosome 7) which codes for a heat-shock protein (**CMT2F,** ORPHA 99940 - OMIM 606595) • Autosomal dominant;
- in the ***CADM3* gene** (located on chromosome 1) which codes for a cell-cell adhesion protein at the interface between axons and Schwann cells (**CMT2FF,** OMIM 619519) • Marked involvement of the upper limbs • Described in three families • Autosomal dominant;
- in the ***LRSAM1* gene** (located on chromosome 9) which codes for a protein that selectively regulates cell adhesion molecules (**CMT2P** (formerly CMT2G), ORPHA 300319 - OMIM 614436) • Autosomal dominant or recessive;
- in the ***GDAP1* gene** (located on chromosome 8) which codes for a protein involved in neuronal development (**CMT2H,** ORPHA 101102 - OMIM 607731/CMT2K, ORPHA 99944 - OMIM 607831) • Autosomal recessive or dominant;
- in the ***MPZ* gene** (located on chromosome 1) which codes for a Schwann cell membrane protein (**CMT2I,** ORPHA 99942 - OMIM 607677) • Autosomal dominant;
- in the ***MPZ* gene** (located on chromosome 1) which codes for a Schwann cell membrane protein (**CMT2J,** ORPHA 99943 - OMIM 607736) • Pupillary abnormalities • Deafness • Autosomal dominant;
- in the ***HSPB8* gene** (located on chromosome 12) which codes for a heat-shock protein (**CMT2L,** ORPHA 99945 - OMIM 608673) • Autosomal dominant;
- in the ***DNM2* gene** (located on chromosome 19) which codes for dynamin 2, a protein involved in axonal transport (**CMT2M,** ORPHA 228179 - OMIM 606482) • Autosomal dominant;
- in the ***AARS1* gene** (located on chromosome 16) which codes for alanyl-tRNA synthetase (**CMT2N,** ORPHA 228174 - OMIM 613287) • Autosomal dominant;
- in the ***DYNC1H1* gene** (located on chromosome 14) which codes for cytoplasmic dynein heavy chain 1 which is involved in axonal transport (**CMT2O,** ORPHA 284232 - OMIM 614228) • Autosomal dominant;
- in the ***DHTKD1* gene** (located on chromosome 10) which codes for dehydrogenase E1 and transketolase domains-containing protein 1 (**CMT2Q,** ORPHA 329258 - OMIM 615025) • Autosomal dominant;
- in the ***TRIM2* gene** (located on chromosome 4) which codes for a neuroprotective protein involved in protein degradation (**CMT2R,** ORPHA 397968 - OMIM 615490) • Autosomal recessive;
- in the ***IGHMBP2* gene** (located on chromosome 11) which codes for immunoglobulin mu-binding protein 2 (**CMT2S,** ORPHA 443073 - OMIM 616155) • Autosomal recessive;
- in the ***MME* gene** (located on chromosome 3) which codes for a membrane metalloendopeptidase protein (**CMT2T,** ORPHA 495274 - OMIM 617017) • Autosomal dominant or recessive;
- in the ***MARS* gene** (located on chromosome 12) which codes for a methionyl-tRNA synthetase protein involved in binding methionine to its transfer RNA (**CMT2U,** ORPHA 397735 - OMIM 616280) • Autosomal dominant;
- in the ***NAGLU* gene** (located on chromosome 17) which codes for alpha-N-acetylglucosaminidase, a protein involved in the hydrolysis of terminal N-acetyl-D-glucosamine residues (**CMT2V,** ORPHA 447964 - OMIM 616491) • Autosomal dominant;
- in the ***HARS1* gene** (located on chromosome 5) which codes for histidyl-tRNA

synthetase, a protein involved in binding histidine to its transfer RNA (**CMT2W,** ORPHA 488333 - OMIM 616625) • Autosomal dominant;
- in the ***SPG11* gene** (located on chromosome 15) which codes for spatacsin, a protein involved in the maintenance of axonal integrity (**CMT2X,** ORPHA 466775 - OMIM 616668) • Autosomal recessive;
- in the ***VCP* gene** (located on chromosome 9) which codes for a valosin-containing protein (**CMT2Y,** ORPHA 435387 - OMIM 616687) • Autosomal dominant;
- in the ***MORC2* gene** (located on chromosome 22) which codes for a protein that facilitates the repair of double-strand DNA breaks (**CMT2Z,** ORPHA 466768 - OMIM 616688) • Autosomal dominant;
- in the ***NEFH* gene** (located on chromosome 22) which codes for heavy neurofilament subunit (**CMT2CC,** OMIM 616924) • Autosomal dominant;
- in the ***ATP1A1* gene** (located on chromosome 1) which codes for the α-1 subunit of Na+/K+ ATPase, a membrane protein responsible for establishing and maintaining the transmembrane electrochemical gradient of Na+ and K+ ions (**CMT2DD,** ORPHA 521414 - OMIM 618036) • Autosomal dominant;
- in the ***HINT1* gene** (located on chromosome 5) which codes for the purine phosphoramidase HINT1 (**axonal neuropathy with neuromyotonia,** ORPHA 324442 - OMIM 137200) • Onset usually occurs at the end of the first decade • Motor deficit of the dorsiflexors of the feet and toes • Myotonia • Increased CK levels • Autosomal recessive.

Charcot-Marie-Tooth disease type X (CMTX)

• 10% of all CMT cases • Caused by mutations:
- in the ***GJB1* gene** (located on the X chromosome) which codes for connexin 32 (**CMTX1,** ORPHA 101075 - OMIM 302800) • Second most common form of CMT • 90% of all X-linked CMT cases • Onset in the second decade • Earlier and more severe neuropathy in men: motor deficit, impaired proprioception, foot deformities, areflexia, demyelinating or intermediate neuropathy on EMG • In women: axonal neuropathy on EMG • Temporary episodes of CNS impairment (hearing loss, confusion, aphasia, dysphagia, focal paralysis) may occur which can l ast a few hours to a few days;
- in the ***PRPS1* gene** (located on the X chromosome) which codes for an enzyme involved in purine metabolism (**CMTX5,** ORPHA 99014 - OMIM 311070).
- in the ***AIFM1* gene** (located on the X chromosome) which codes for a mitochondrial factor involved in oxidative phosphorylation and redox control (**CMTX4,** ORPHA 101078 - OMIM 310490);
- in the ***PDK3* gene** (located on the X chromosome) which codes for a mitochondrial enzyme involved in the phosphorylation of the alpha subunit of the E1 component of the mitochondrial PDH complex (**CMTX6,** ORPHA 352675 - OMIM 300905).

Dominant intermediate Charcot-Marie-Tooth disease (CMTDI)

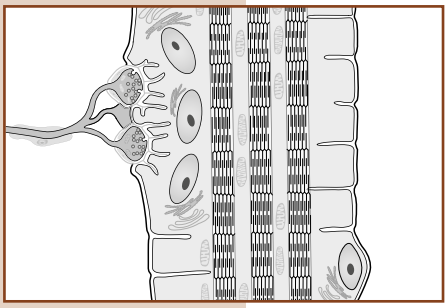
• Autosomal dominant, demyelinating and axonal • Caused by mutations:
- in the ***DNM2* gene** (located on chromosome 19) which codes for dynamin 2, a protein involved in axonal transport (**CMTDIB,** ORPHA 100044 - OMIM 606482), 37 cases;
- in the ***YARS1* gene** (located on chromosome 1) which codes for an enzyme involved in the synthesis of transfer RNA (**CMTDIC,** ORPHA 100045 - OMIM 608323), 35 cases;
- in the ***MPZ* gene** (located on chromosome 1) which codes for a Schwann cell membrane protein (**CMTDID,** ORPHA 100046 - OMIM 607791), 12 cases;
- in the ***KARS1* gene** (located on chromosome 16) which codes for a protein involved in binding lysine to its transfer RNA (**CMTRIB,** ORPHA 254334 - OMIM 613641), 1 case;
- in the ***PLEKHG5* gene** (located on chromosome 1) which codes for pleckstrin homology domain containing, family G member 5, a protein that activates the nuclear

factor kappa B signalling pathway (**CMTRIC,** ORPHA 369867 - OMIM 615376), 3 cases;
- in the ***COX6A1* gene** (located on chromosome 12) which codes for subunit 6A1 of cytochrome c oxidase (**CMTRID,** ORPHA 435998 - OMIM 616039).

Management and treatment

• Genetic counselling • Physiotherapy to mitigate joint contractures • Orthoses (foot drop supports, splints, braces, orthopaedic shoes, etc.) • Orthopaedic surgery to correct foot deformities • Assistive technology to help those who have difficulty with tasks involving manual dexterity • Walking aids (crutches, electric wheelchair, etc.).
• For more information, please consult the Protocole National de Diagnostic et de Soins (20 April 2020) : https://www.has-sante.fr/jcms/p_3168018/fr/neuropathies-hereditaires-sensitivomotrice-de-charcot-marie-tooth [document in French]

INFLAMMATORY MYOPATHIES



Non-hereditary autoimmune diseases. Types of inflammatory myopathies, also known as idiopathic inflammatory myopathies, include dermatomyositis, inclusion body myositis, immune-mediated necrotising myopathy, overlap myositis and polymyositis.

Dermatomyositis

ORPHA 221

• Microangiopathy (damage to the endothelium of small blood vessels in the dermis and muscle) associated with an abnormal accumulation of complement, mediated by type I interferons • Subacute or insidious onset at any age • Symmetrical, proximal motor deficit (shoulder and pelvic girdle muscles, neck muscles) • Skin manifestations: reddish-purple rash on the upper eyelids, reddish-purple bumps on the backs of the hands and fingers, and red swollen areas around the fingernails • Additional tests: testing for specific autoantibodies (such as anti-SAE, anti-MDA5, anti-TIF1-γ, anti-NXP-2 and anti-Mi-2 autoantibodies), perivascular inflammatory infiltrate, perifascicular atrophy • Variable progression: usually rapid and severe without appropriate treatment, can be slower or even chronic • Associated with an increased risk of cancer (ovarian, lung, pancreatic, lymphoma, stomach, bowel, etc.) • Prevalence in Europe: 6/100,000.

Inclusion body myositis

ORPHA 611

• Deposits of abnormal toxic proteins (beta-amyloid, phosphorylated tau, etc.) in muscle and presence of CD8+ T cells in certain muscle fibres • Insidious onset later in life (usually after the age of 50) • Primarily affects men (male-to-female ratio of 2:1) • Very frequently misdiagnosed • Associated with other autoimmune conditions (lupus, Sjögren's syndrome, sarcoidosis, etc.) in 15% of patients • No increased risk of cancer • Frequent associated with certain autoantibodies (antinuclear, anti-Ro52/60, anti-RNP) • Monoclonal gammopathy in 23% of cases • Testing for antibodies against cN1A is used to help diagnose the disease • Initial signs: weakness in the quadriceps. (difficulty getting up from a squatting position and climbing stairs, falls caused by

knees giving way, etc.) or finger flexors (difficulty gripping, lifting and using tools) • Distal and asymmetric muscle weakness and atrophy with weakness in at least one of the following: tibialis anterior muscles, quadriceps, forearm muscles • Camptocormia possible • Swallowing difficulties common in the advanced stage of the disease • Slowly progressive • Diagnosis confirmed by muscle biopsy: presence of rimmed vacuoles, and endomysial and perinecrotic inflammatory infiltrates • Resistance to treatments usually used to treat inflammatory myopathies (corticosteroids, immunosuppressants) • Prevalence in Europe: 0.5/100,000

Immune-mediated necrotising myopathy
ORPHA 206569
• Associated with myositis-specific autoantibodies in approximately 60% of cases: anti-HMGCR (anti-3-hydroxy-3-methylglutaryl-CoA reductase)/anti-SRP (anti-signal recognition particle) autoantibodies • Makes up 10% of all idiopathic inflammatory myopathy cases • Onset usually between the ages of 30 and 70 • Clinical and histological signs are sometimes indistinguishable from those of muscular dystrophy with muscle necrosis and very high CK levels • Weakness in the upper and lower limbs • Difficulty getting up from a sitting position, climbing stairs or lifting objects • Diagnosed by testing for autoantibodies • The use of statins has frequently been found to cause immune-mediated necrotising myopathy (adult forms) • Paediatric forms recently recognised • Treatment with immunosuppressants leads to dramatic recovery in some cases • Prevalence: 2.4 - 33.8/100,000.

Overlap myositis
ORPHA 206572
• Defined as myositis with one clinical and/or autoantibody overlap feature. Some possible clinical overlap features include extramuscular or extracutaneous manifestations of polyarthritis, Raynaud's phenomenon, sclerodactyly, scleroderma (proximal), interstitial lung disease and/or signs of systemic lupus erythematosus (SLE). Overlap autoantibodies include those observed in some inflammatory myopathies such as anti-synthetase syndrome.

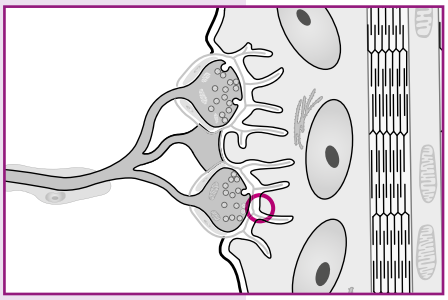
Polymyositis
ORPHA 732
• Muscle fibres damaged by cytotoxic CD8+ T cells • Gradual, symmetrical, proximal muscle weakness (shoulder girdle, pelvic girdle and neck muscles) • No skin involvement • Diagnosis confirmed by muscle biopsy (endomysial inflammatory infiltrates, perinecrotic infiltrates, invasion of muscle fibres) • Prevalence in Europe: 7.1/100,000.

Management and treatment

• Long-term symptomatic (pain medication) and immune-targeted treatments (corticosteroids, immunosuppressants, polyvalent immunoglobulins, plasmapheresis) which are generally effective except in inclusion body myositis • Adapted physiotherapy and strength training (not during flare-ups) • Prevention of lung infections • Tests (depending on the context) to screen for cancer (dermatomyositis): chest CT scan, mammogram, tumour marker tests, bronchoscopy, colonoscopy, gastroscopy, etc.
• For more information, please consult the Protocole National de Diagnostic et de Soins for adult and juvenile dermatomyositis (September 2016): https://www.has-sante.fr/jcms/c_2666858/fr/dermatomyosite-de-l-enfant-et-de-l-adulte [document in French]
• For more information, please consult the Protocole National de Diagnostic et de Soins for inclusion body myositis (November 2021): https://www.has-sante.fr/jcms/p_3295071/fr/myosite-a-inclusions-sporadique [document in French)

MYASTHENIA GRAVIS

ORPHA 589



Non-hereditary autoimmune disease. Most people with myasthenia gravis make autoantibodies that bind to acetylcholine receptors located at the neuromuscular junction. Myasthenia gravis (MG) affects 20 people in every 100,000.

Contraindicated drugs

Drugs to avoid

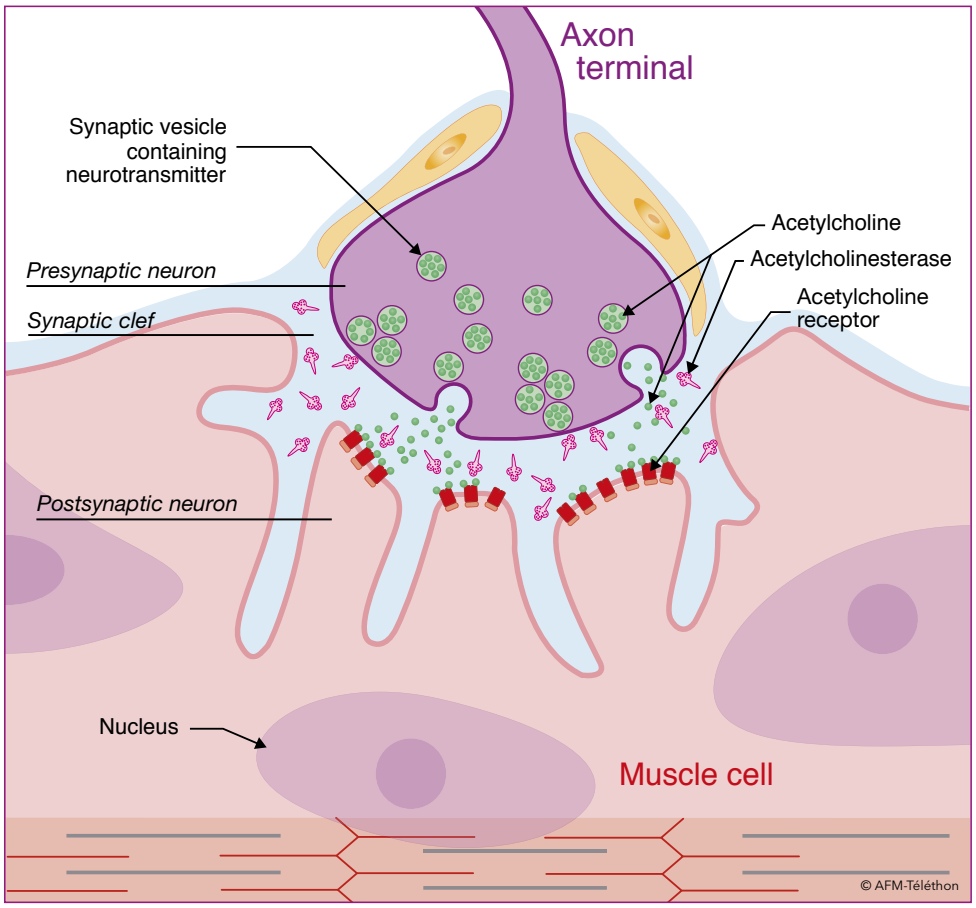
- Aminoglycosides, colistin, polymyxin B, telithromycin, injectable cyclins, macrolides, fluoroquinolones
- Quinine, quinidine, hydroxychloroquine, procainamide
- Beta blockers (even eye drops)
- Phenytoin, trimethadione
- Dantrolene
- D-penicillamine
- Magnesium

Drugs to be used with caution

- Neuromuscular blocking agents: rapidly degrading non-depolarising drugs, such as atracurium, can be used with close monitoring
- Benzodiazepines
- Antipsychotics (phenothiazine)
- Carbamazepine
- Lithium

• Intravenous iodinated contrast media used in imaging can induce acute decompensation of the disease and are not recommended for use during a flare-up.
• Polio, tetanus and flu vaccinations do not aggravate myasthenia gravis when it is well controlled.
• Live vaccines (such as the oral polio vaccine) are absolutely contraindicated in patients who are on corticosteroids or immunosuppressants.
• The use of nicotine patches to help quit smoking can aggravate myasthenia gravis.
• Interferon alpha and beta can aggravate or even induce myasthenia gravis.

Protocole National de Diagnostic et de Soins for myasthenia gravis, Centre de References de pathologie neuro- musculaire Paris Est [East Paris Specialist Neuromuscular Disease Centre], July 2015.



• Disease linked to a T cell-dependent humoral immune response which is directed against the motor end plate of the postsynaptic membrane • The type of myasthenia gravis in which the body makes autoantibodies directed against acetylcholine receptors (**anti-AChR** autoantibodies) is by far the most common • There are also types (which are a little different clinically) in which the body makes autoantibodies directed against the MuSK protein, a muscle-specific tyrosine kinase receptor (**anti-MuSK** autoantibodies), autoantibodies directed against the LRP4 protein or "low-density lipoprotein receptor-related protein 4" (**anti-LRP4** autoantibodies), a protein that has been identified as an agrin receptor; the interaction between LRP4 and agrin activates MuSK • Neuromuscular junction disorder which can start at any age: most often between the ages of 20 and 30 in women and between 40 and 60 in men • Muscle weakness and fatigability of varying intensity and duration that can affect any muscle • Worsening on exertion and/or with repetitive movements • In general, the muscle weakness is less significant in the morning, worsens during the day and improves with rest • Fluctuating ptosis (or diplopia, or even ophthalmoplegia), characteristic symptom of the disease • Risk of thymoma • The

course of myasthenia gravis is variable and can include flare-ups of varying severity, somewhat complete remissions or unpredictable exacerbations, resulting in a disability that varies greatly between individuals • Risk of decompensation of the disease during pregnancy, childbirth or the postpartum period • Diagnosis can be confirmed using various different methods: pharmacological test (neostigmine) which demonstrates a significant improvement in muscle strength; detection of anti-AChR, anti-MuSK or anti-LPR4 autoantibodies in serum • Electrophysiological studies such as repetitive nerve stimulation and/or single-fibre electromyography (SFEMG) • Warning symptoms of a myasthenic crisis may include breathing difficulties, severe dysphagia and rapid worsening of the symptoms of the disease.

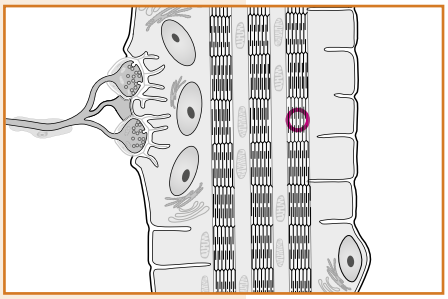
Management and treatment

• Initial chest CT scan when myasthenia gravis is first detected to look for thymoma • Consider that patients may have another autoimmune disease during their follow-up • Anticholinesterases • Corticosteroid therapy • Immunosuppressants • Neonatal Fc receptor blockers • Thymectomy • In the event of an acute flare-up: ventilation • Anaesthetic considerations • Certain drugs are contraindicated (see box) • Live attenuated vaccines (oral polio, rubella, etc.) are contraindicated in patients who are on immunosuppressants.

• For more information, please consult the Protocole National de Diagnostic et de Soins (24 july 2015) : https://www.has-sante.fr/jcms/c_2048406/fr/myasthenie-autoimmune

CONGENITAL MYOPATHIES

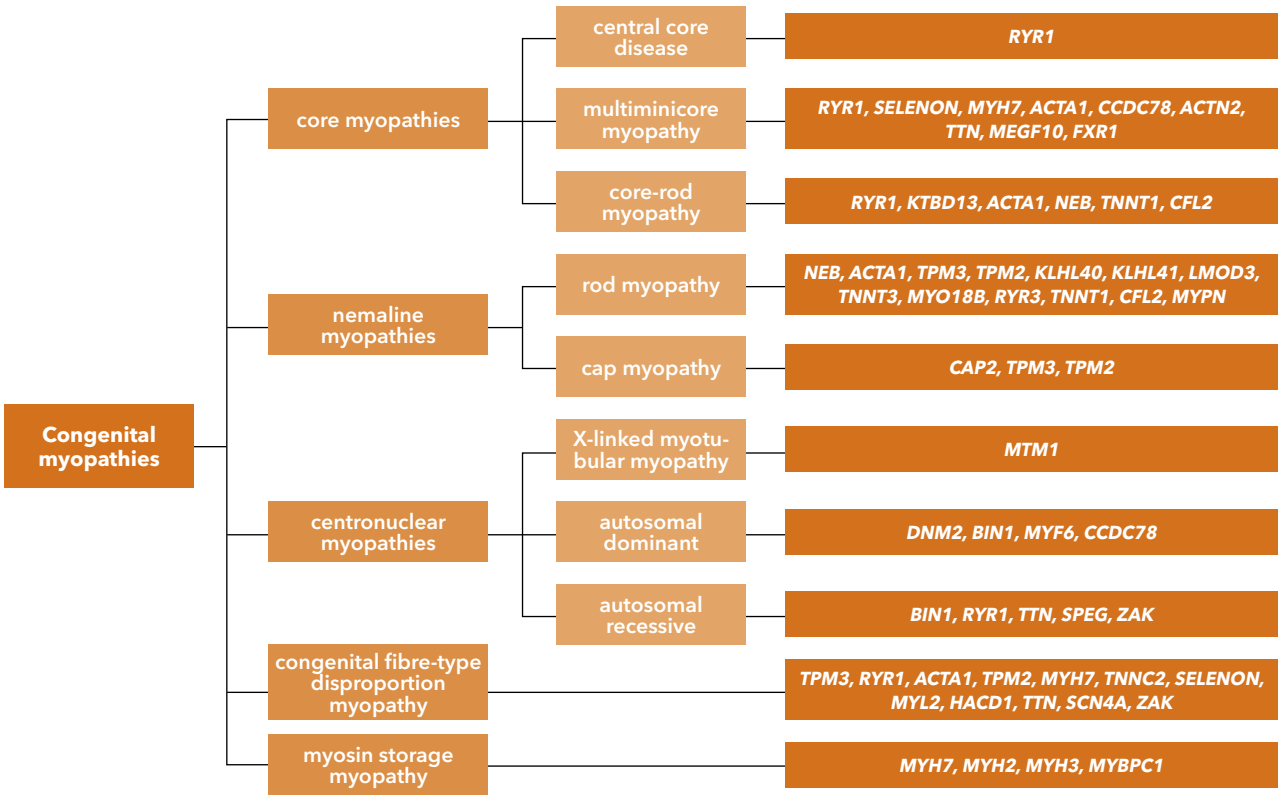
ORPHA 97245



Heterogeneous group of rare, autosomal dominant, autosomal recessive or X-linked recessive genetic diseases. Onset typically early. Prevalence estimated at 1.5/100,000 in the general population and 2.73/100,000 in the paediatric population.

• Onset typically early (from birth to six months/one year old, sometimes older) • Later onset possible depending on the type • Generally not progressive • Congenital disorders which affect the structure of muscle fibres in a non-degenerative way • In general, the earlier the onset, the more life-threatening the disease will be, especially if there is respiratory muscle involvement, however, the possibility of an improvement cannot be ruled out • In older children and adults, congenital myopathies are generally much less debilitating and patients can usually walk independently • Those related to ryanodine receptor 1 (RyR1) dysfunction are among the most common types of congenital myopathy • The various different types are classified according to the histological abnormalities involved.

Main types of congenital myopathies



Central core disease

ORPHA 597 - OMIM 117000

• Autosomal dominant or recessive genetic disease • Caused by a defect in ryanodine receptor 1 (RyR1), a calcium channel which plays a major role in muscle contraction during the excitation-contraction coupling of muscle fibres (***RYR1* gene** located on

Core myopathies - the most common type of congenital myopathy

The prevalence of core myopathies is 0.37/100,000. Under a microscope, they are characterised by regions in muscle cells which are not coloured by certain stains. These regions are called "cores". Cores are disorganised areas, devoid of mitochondria, where proteins such as desmin, αB-crystallin, filamin C, myotilin, RyR1, triadin and dihydropyridine receptors (DHPR) accumulate in an abnormal manner. The size and location of these cores (central, small, spread out, etc.) are what is used to distinguish different types of congenital myopathies.

chromosome19) • The *RYR1* gene is also one of the genes that causes malignant hyperthermia (ORPHA 423 - OMIM 145600) • Different manifestations depending on the age of onset of the disease • Degree of severity varies greatly among affected individuals within the same family who have the same genetic mutation • Often detected during childhood and sometimes at birth • Onset may occur later, even during adulthood • May be discovered due to an episode of malignant hyperthermia (a severe reaction to certain anaesthetic drugs characterised by generalised muscle contractions and an increase in body temperature).

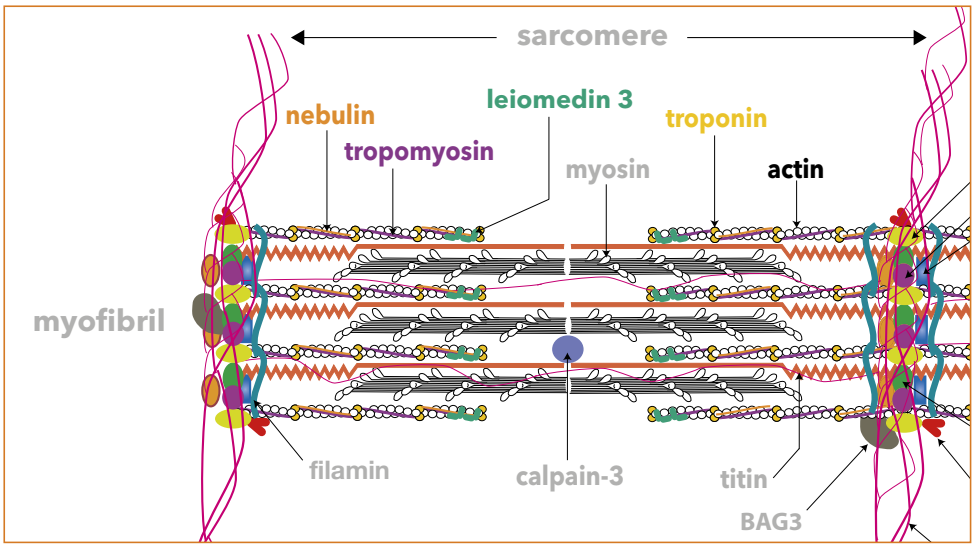
• **In children:** generalised hypotonia ("floppy" baby), delay in learning to walk • Orthopaedic complications (hip dislocation, chest and/or foot deformities) • Respiratory insufficiency.

• **In adults:** diffuse muscle weakness, occasionally with orthopaedic deformities • Nonprogressive disease, usually mildly debilitating • Patients generally able to participate in normal school and social activities • In certain severe forms: ability to walk impaired, ventilation may be required • The variability of clinical expression and the spectrum of morphological abnormalities associated with the approximately 250 *RYR1* gene mutations described to date suggest the existence of a clinical and histological continuum between central core disease and multiminicore myopathy.

Multiminicore myopathy

ORPHA 324604 - OMIM 602771

• Autosomal dominant or recessive genetic disease usually caused by mutations in the ***SELENON* gene** (located on chromosome 1) which codes for selenoprotein N (SEPN1), an endoplasmic reticulum calcium sensor that adjusts the quantity of calcium stored in the terminal cisternae of the endoplasmic reticulum using a redox mechanism • Neonatal hypotonia • Swallowing difficulties, facial muscle weakness • Associated diaphragmatic and cardiac involvement common • Delay in learning to walk, diffuse muscle weakness • Marked spinal contractures (rigid spine) • Normal CK levels • A severe form of the disease with ophthalmoplegia exists which is caused by mutations in the ***RYR1* gene** (ORPHA 598 - OMIM 255320) • Very variable clinical course.



Nemaline myopathies

ORPHA 607

• Heterogeneous group of genetic skeletal muscle diseases characterised by the presence of small rod-like structures in muscle fibres (rod myopathies) or cap-like structures at the periphery of muscle fibres (cap myopathy) • Present from birth or may appear later, even in adulthood • The most severe forms manifest from birth with generalised diffuse hypotonia ("floppy" baby), muscle weakness in the hands, feet,

trunk and face, contractures, significant joint deformities, swallowing difficulties and impaired respiratory function • In forms with later onset: foot and spinal deformities (kyphosis and scoliosis), poor performance in sports • In older children and adults: non-progressive weakness and generally only mildly debilitating • There are several forms classified according to the mode of inheritance and age of onset of the disease • Fifteen genes which code for thin filament proteins or proteins that regulate the stability or renewal of thin filaments have been identified • Prevalence: 0.20/100,000.

- **NEM1** (ORPHA 171439 – OMIM 609284): **tropomyosin 3 deficiency** (***TPM3* gene** located on chromosome 1 which codes for slow muscle alpha-tropomyosin), autosomal dominant (mild intermediate forms, childhood onset) or autosomal recessive (severe congenital form);
- **NEM2** (ORPHA 171436 / 171439 / 171430 – OMIM 256030): **nebulin deficiency** (***NEB* gene** located on chromosome 2), autosomal recessive (mild typical congenital forms and severe congenital form), most common type of nemaline myopathy;
- **NEM3** (ORPHA 171430 / 171436 – OMIM 161800) and cap myopathy: **skeletal muscle α-actin deficiency** (***ACTA1* gene** located on chromosome 1), autosomal dominant (mild and severe forms), de novo autosomal dominant (mild and severe forms), autosomal recessive (severe congenital form, or form with excess of thin filaments), germline mosaic (mild and severe forms), second most common type of nemaline myopathy;
- **NEM4** (ORPHA 171436 / 171439 – OMIM 609285): **beta-tropomyosin deficiency** (***TPM2* gene** located on chromosome 9), autosomal dominant (typical congenital form);
- **NEM5** (ORPHA 98902 - OMIM 605355): **slow skeletal muscle troponin T deficiency** (***TNNT1* gene** located on chromosome 19), autosomal recessive (congenital form reported exclusively in the Amish community);
- **NEM6** (ORPHA 171439 - OMIM 609273): **BTB/Kelch deficiency** (***KBTBD13* gene** located on chromosome 15 which codes for a protein from the BTB/Kelch family); this protein modulates muscle relaxation kinetics, autosomal dominant (mild form with slow muscle relaxation);
- **NEM7** (ORPHA 171436 – OMIM 610687): **cofilin-2 deficiency** (***CFL2* gene** located on chromosome 14), autosomal recessive (typical congenital form);
- **NEM8** (ORPHA 171430 – OMIM 615348): **KLHL40 ("kelch-like family member 40") protein deficiency** (***KLHL40* gene** located on chromosome 3), autosomal recessive (severe congenital form);
- **NEM9** (ORPHA 171436 / 171439 / 171430 – OMIM 615731): **KLHL41 ("kelch-like family member 41") protein deficiency** (***KLHL41* gene** located on chromosome 2), autosomal recessive (severe congenital form with distal form during childhood);
- **NEM10** (ORPHA 171436 / 171430 – OMIM 616165): **leiomodin 3 deficiency** (***LMOD3* gene** located on chromosome 3), autosomal recessive (severe congenital form, milder stable form with ability to walk retained into young adulthood);
- **Klippel-Feil syndrome 4** (ORPHA 447974 – OMIM 616549): **myosin XVIIIB deficiency** (***MYO18B* gene** located on chromosome 22), autosomal recessive, associated with severe nemaline myopathy and facial dysmorphism;
- **NEM11** (ORPHA 171439 – OMIM 617336) and cap myopathy: **myopalladin deficiency** (***MYPN* gene** located on chromosome 10), autosomal recessive (onset of proximal muscle weakness and atrophy in the lower limbs and neck in the first decade, slowly progressive);
- ***CAP2*-related nemaline myopathy: cyclase-associated protein 2 deficiency** (***CAP2* gene** located on chromosome 6), sporadic (neonatal hypotonia, very severe dilated cardiomyopathy);
- **Cap myopathy 1** (ORPHA 171881 - OMIM 609284): **tropomyosin 3 deficiency** (***TPM3* gene** located on chromosome 1 which codes for slow muscle alpha-tropomyosin), autosomal dominant;
- **Cap myopathy 2** (ORPHA 171881 - OMIM 609285): **beta-tropomyosin deficiency** (***TPM2* gene** located on chromosome 9), autosomal dominant.

X-linked myotubular myopathy

ORPHA 596 - OMIM 310400

• X-linked recessive genetic disease caused by mutations in the ***MTM1* gene** (located on the X chromosome) which codes for myotubularin, an enzyme that regulates the sorting and trafficking of intracellular vesicles • Decreased foetal movements common, associated with the presence of polyhydramnios • At birth: neonatal hypotonia and severe respiratory problems, swallowing difficulties, facial muscle paralysis (facial diplegia), ptosis, ophthalmoplegia, chest and foot deformities often associated • Progression usually rapid and fatal • Increased risk of hepatic cholestasis and/or peliosis hepatis (10 to 17% of cases) • In the event that respiratory support enables a patient to survive beyond the neonatal stage, there will likely be a delay in them learning how to sit, stand and walk • Very marked muscle weakness • Ophthalmoplegia • Cognitive development normal.

• Over half of female carriers (ORPHA 604680) have muscle weakness which is usually mild (able to walk independently) or moderate (able to walk with assistance) • Severe muscle weakness with loss of ambulation in 3% of cases • Fatigue (70% of cases) • Exercise intolerance (nearly 50% of cases) • Pain, limitations in activities of daily living, reduced quality of life.

Centronuclear myopathy

• Nuclei in a chain at the centre of muscle cells • Autosomal dominant (ORPHA 169189) or recessive (ORPHA 169186) genetic disease • Clinically similar to X-linked myotubular myopathy with which it has long been confused • The classic form is passed down through autosomal dominant inheritance • Many cases are sporadic • Prevalence: 0.08/100,000.

• Half of the autosomal dominant forms are caused by mutations in the ***DNM2* gene** (located on chromosome 19) which codes for dynamin 2 (OMIM 160150), while the rest are caused by mutations in the ***BIN1* gene** (located on chromosome 2) which codes for amphiphysin 2, and the ***CCDC78* gene** (located on chromosome 16) which codes for the CCDC78 protein (OMIM 614807).

• The autosomal recessive forms are caused by mutations in the ***BIN1* gene** (located on chromosome 2) which codes for amphiphysin 2 (OMIM 255200), the ***SPEG* gene** (located on chromosome 2) which codes for the SPEG protein (OMIM 615959), the ***RYR1* gene** (located on chromosome 19) which codes for RyR1 (King-Denborough syndrome, OMIM 619542) or the ***TTN* gene** (located on chromosome 2) which codes for titin (Salih myopathy, OMIM 611705).

• Early childhood onset with a delay in learning to walk • Onset can occur later, including in adulthood, with falls and difficulty walking • Muscle weakness in the lower limbs • Facial muscle weakness • Extraocular muscle involvement with limited movement of the eyes (ophthalmoplegia) and drooping of the upper eyelids (ptosis) • Chewing and/or swallowing difficulties possible • The disease is somewhat debilitating and its course can vary depending on the muscle weakness and orthopaedic deformities experienced by the patient • Often slowly progressive • Occasional loss of ability to walk independently.

Centronuclear myopathy genetics

- Centronuclear myopathies are most often caused by mutations in the *MTM1, DNM2, BIN1, RYR1* and *TTN* genes. *MTM1, DNM2,* and *BIN1* code for proteins which interact with each other and are involved in membrane remodelling and trafficking, while RyR1 plays a role in excitation-contraction coupling and titin in the assembly of sarcomeres.

- Mutations are also found in the *SPEG1, MYF6* and *ZAK (MAP3K20)* genes, but these are less common.

- The genetic mutations that cause centronuclear myopathies remain unknown in around 16% of cases.

Congenital fibre-type disproportion myopathy

ORPHA 2020

• Autosomal dominant or recessive genetic disease • Neonatal hypotonia • Predominantly proximal muscle weakness • Bulbar weakness • Not or only mildly progressive, except for in severe forms (25% of cases, with contractures, scoliosis and respiratory problems) • Smaller type I muscle fibres compared to type II muscle fibres • Prevalence: 0.23/100,000 • Caused by:

- dominant mutations in the ***TPM3* gene** (located on chromosome 1) which codes for slow muscle alpha-tropomyosin or tropomyosin 3 (OMIM 255310) • The most common cause.

- recessive mutations in the ***RYR1* gene** (located on chromosome 19) which codes for ryanodine receptor 1 • The cause in 20% of cases.
- dominant mutations in the ***ACTA1* gene** (located on chromosome 1) which codes for skeletal muscle α-actin (OMIM 620278 / 161800) • The cause in 5% of cases.
- dominant mutations in the ***TPM2* gene** (located on chromosome 9) which codes for β-tropomyosin, ***MYH7* gene** (located on chromosome 14) which codes for a sarcomere protein called beta myosin heavy chain, and ***TNNC2* gene** (located on the chromosome 20) which codes for troponin C (fast skeletal troponin).
- recessive mutations in the ***SELENON* gene** (located on chromosome 1) which codes for selenoprotein N (SEPN1) (OMIM 602771), ***MYL2* gene** (located on chromosome 12) which codes for myosin light chain-2, ***HACD1* gene** (located on chromosome 10) which codes for an enzyme involved in very long chain fatty acid synthesis, ***TTN* gene** (located on chromosome 2) which codes for titin, ***SCN4A* gene** (located on chromosome 17) which codes for the alpha subunit of the muscle sodium channel Nav1.4, or the ***ZAK* gene** (located on chromosome 2) which codes for an enzyme from the MAP kinase family.

Myosin storage myopathy

ORPHA 53698

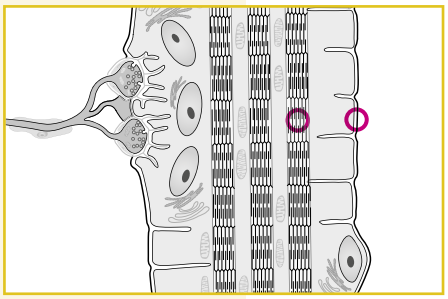
• Autosomal genetic disease characterised by the presence of protein clumps, which contain abnormal myosin, within muscle fibres • Caused by:
- dominant mutations in the ***MYH7* gene** (ORPHA 79091, OMIM 605637) which is located on chromosome 14 and codes for the beta myosin heavy chain, a sarcomere protein • Childhood or adult onset • Scapuloperoneal weakness and atrophy • Beta myosin heavy chain aggregates • Slowly progressive • Great clinical variability.
- dominant mutations in the ***MYH2* gene** (ORPHA 2053, OMIM 605637) which is located on chromosome 17 and codes for myosin heavy chain IIa • Variable age at onset • Proximal weakness in all four limbs • Facial weakness • External ophthalmoplegia, ptosis • High-arched palate • Not or only mildly progressive.
- dominant mutations in the ***MYH3* gene** which is located on chromosome 17 and codes for the embryonic myosin heavy chain • Characterised by distal arthrogryposis with mild muscle weakness.
- dominant or recessive mutations in the ***MYBPC1* gene** (located on chromosome 12) which codes for myosin-binding protein C • Neonatal hypotonia • Lip and/or tongue tremor • Predominantly proximal muscle weakness • Scoliosis, lordosis, rigid spine • High-frequency resting and intentional tremor • No cognitive impairment • Slow progression during childhood, stable during adolescence and adulthood.

Management and treatment

• Genetic counselling • Adapted physiotherapy (joint mobilisation, hyperinsufflation, etc.) and devices used to mitigate contractures in the limbs, spine and rib cage • Scoliosis surgery • Intensive respiratory care (nasal ventilation, tracheostomy, etc.) in severe forms • Nutritional support (dietary changes, enteral nutrition, etc.) • Cardiac monitoring • Assistive technology (electric wheelchair, computer, etc.) to ensure the highest level of independence possible.

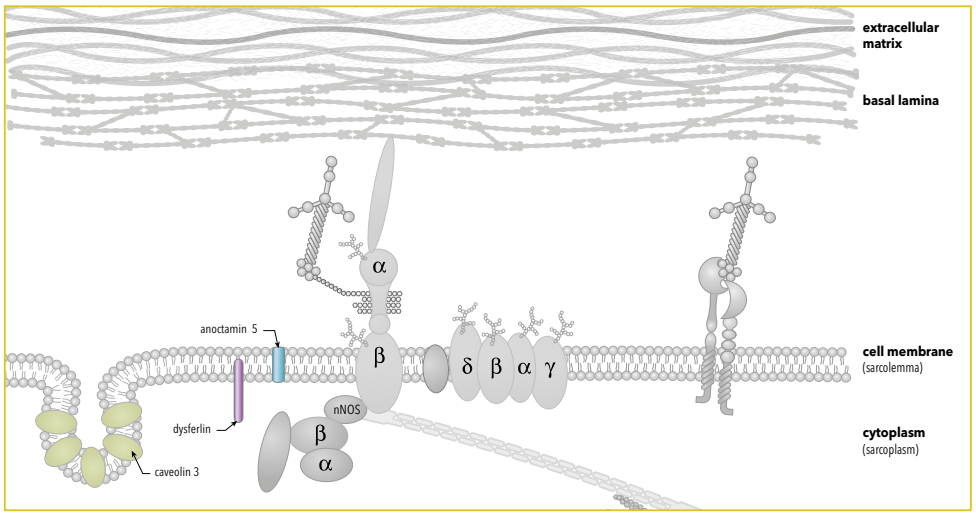
DISTAL MYOPATHIES

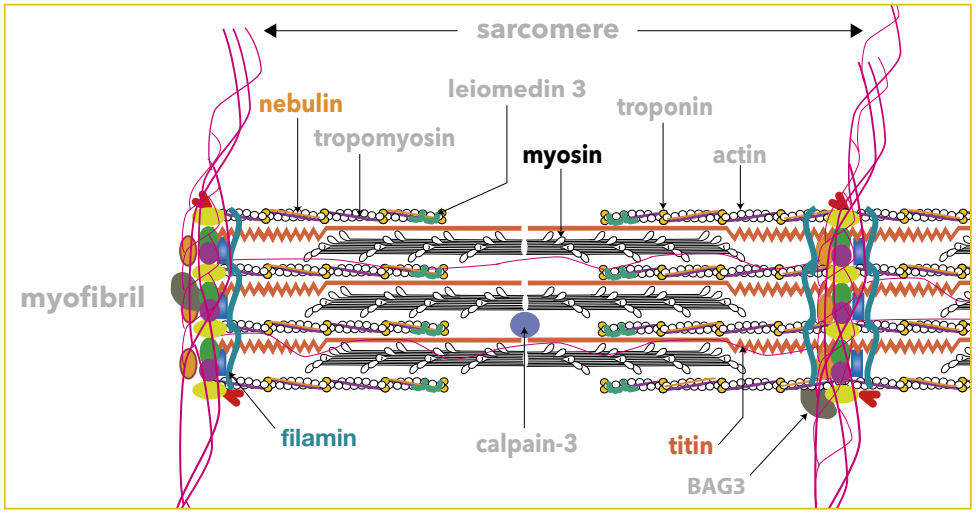
ORPHA 599



Heterogeneous group of autosomal dominant or recessive genetic diseases which mainly affect the distal parts of the limbs (lower legs, feet, forearms and hands).

• Weakness and atrophy of the distal muscles of the limbs (lower legs, feet, forearms, hands) which may spread to the proximal muscles • Onset during adolescence or adulthood • Relatively mild course depending on the type.





Autosomal recessive distal myopathies

- GNE myopathy (Nonaka myopathy)
- Miyoshi myopathy 1
- Miyoshi myopathy 3
- Early-onset distal myopathy with nebulin defect

Miyoshi myopathy

ORPHA 45448

• Autosomal recessive disease • Most common distal myopathy in France • Onset in young adulthood (between 15 and 30 years old) • Difficulty standing on tip toes, climbing stairs, running and jumping • Weakness and atrophy of the calf muscles (sometimes asymmetric initially) • Intrinsic hand muscles spared • CK levels almost

constantly very high • Often rapidly progressive and marked by pelvic girdle muscle weakness leading to patients being unable to walk (in a third of cases after 10 to 15 years of progression on average) • Later progression to the muscles of the upper limbs and shoulders • Forms are sometimes severe and very rapidly progressive • No associated cardiac or respiratory impairment • Makes up approximately a third of all distal myopathies • Prevalence: 0.26/100,000.

Miyoshi myopathy 1
ORPHA 45448 - OMIM 254130
• Dysferlin (***DYSF* gene** on chromosome 2) is localised to the membrane of muscle fibres • It is involved in membrane fusion and repair • Dysferlin interacts with membrane-localised proteins such as annexin A1 and A2 • Mutations in the *DYSF* gene also cause one of the recessive forms of limb-girdle muscular dystrophy (LGMD2B) and distal myopathy with anterior tibial onset (DMAT), which are now referred to as "dysferlinopathies" • Various different dysferlinopathies (Miyoshi myopathy, LGMD2B, DMAT) can be present in the same family.

Miyoshi myopathy 3
ORPHA 45448 - OMIM 613319
• Anoctamin 5 (***ANO5* gene** located on chromosome 11) is a transmembrane protein involved in membrane repair (plugging holes, regulating the entry of calcium into the endoplasmic reticulum) • In addition to Miyoshi myopathy 3, mutations in the *ANO5* gene also cause LGMD2L, pseudometabolic myopathies and asymptomatic elevated CK levels.

GNE myopathy (Nonaka myopathy)
ORPHA 602 - OMIM 605820
• Autosomal recessive disease caused by mutations in the ***GNE* gene** (located on chromosome 9) which codes for UDP-N-acetylglucosamine 2-epimerase, an enzyme that plays an essential role in protein sialylation • Rare, mainly found in the Middle East and Asia (Japan, China) • Onset in young adulthood (during the second or third decade) with weakness in the muscles of the anterior compartment of the lower legs (foot drop and steppage gait) • Later involvement of the posterior compartment of the lower legs, the proximal muscles and the upper limbs (shoulders, wrist extensors, hands) • Quadriceps spared even in advanced stages of the disease • Wheelchair-bound on average 10 to 15 years after onset • Joint deformities • Prevalence: 0.1/100,000.

Early-onset distal myopathy with nebulin defect
• Autosomal recessive disease • Caused by mutations in the ***NEB* gene** (located on chromosome 2) which codes for nebulin, a protein associated with the thin filaments of striated muscle • Predominant weakness in the dorsiflexor muscles, extensor muscles of the fingers and the neck flexors • Later proximal weakness • Facial muscle weakness possible • Asymmetric weakness possible (50% of cases) • Respiratory insufficiency rare • No cases of cardiac involvement reported.

Welander distal myopathy
ORPHA 603 - OMIM 604454
• Autosomal dominant disease mainly found in Sweden • Caused by mutations in the ***TIA1* gene** (located on chromosome 2) which codes for the TIA1 protein, an RNA-binding protein involved in splicing regulation and translational repression which is a key component of stress granules • Late onset (after the age of 40) with weakness in the extensor muscles of the thumb and index finger spreading to the other fingers, leading to clumsiness in performing fine motor skills with the fingers (buttoning, tying knots, holding a needle, typing on a keyboard, etc.) and subsequent difficulty extending the fingers • Slowly progressive • Muscle weakness limited to below the

Autosomal dominant distal myopathies
- Welander distal myopathy (*TIA1*)
- Tibial muscular dystrophy (titin)
- Laing distal myopathy (myosin, *MYH7*)
- Myofibrillar myopathies:
  - Myofibrillar myopathy-1 (*DES*)
  - Myofibrillar myopathy-3 (*MYOT*)
  - Myofibrillar myopathy-4 (*LDB3*)
  - Myofibrillar myopathy-5 (*FLNC*)

elbows in nearly half of cases • Later distal weakness in the lower limbs (muscles of the anterior compartment of the lower legs) leading to steppage gait with a tendency to stumble and suffer from twisted ankles • Decreased tendon reflexes (Achilles) • Cold hands and feet caused by vasomotor dysfunction • Prevalence: 10/100,000 in Scandinavia.

Tibial muscular dystrophy (Udd myopathy)

ORPHA 609 - OMIM 600334

• Autosomal dominant disease • Caused by mutations in the ***TTN* gene** (located on chromosome 2) which codes for titin, a giant sarcomere protein which maintains myosin filaments and contributes to muscle elasticity • Currently only found in a few families in France • Late onset (after the age of 40, usually between 45 and 55 years old) • Weakness (asymmetric initially) in the dorsiflexor muscles (tibialis anterior muscle) with steppage gait • Foot drop 10 or 20 years after onset • Mild thigh muscle weakness in 10% of cases • Cardiac involvement rare • Normal or mildly increased CK levels • Generally slowly progressive and mildly debilitating • Muscle weakness and atrophy usually confined to the lower legs • Loss of ambulation rare • Homozygous mutation in the *TTN* gene causes a more severe limb-girdle muscular dystrophy (LGMD2J).

Laing distal myopathy

ORPHA 59135 - OMIM 160500

• Autosomal dominant disease • Extremely rare, only found in four families worldwide to date (Australia, Germany and Austria) • Caused by mutations in the ***MYH7* gene** (located on chromosome 14) which codes for beta myosin heavy chain • Onset in infancy or childhood with selective anterior tibial wasting and weakness: weakness in the toe extensors ("hanging" big toe is a characteristic sign) and ankle dorsiflexors leading to walking difficulties (tendency to stumble) • Achilles tendon contractures • Normal or mildly elevated CK levels • Slow progression from the feet to the head, and from the distal parts of the limbs to the proximal parts • Weakness spreading to the finger (in particular the little finger) and wrist extensor muscles during the third decade • Cramps • Proximal weakness after the age of 40 (neck, hip and shoulder flexors), as well as abdominal muscle weakness • Cardiomyopathy possible • Very mildly debilitating, even at an advanced age • Hand tremor possible in some patients.

Late-onset distal myopathy, Markesbery-Griggs type

ORPHA 98912 - OMIM 609452

• Autosomal dominant disease • Caused by mutations in the ***LDB3* gene** (located on chromosome 10) which codes for the ZASP protein, a Z-disc protein that plays an important role in maintaining the structural integrity of skeletal muscle Z-discs • Classed as a myofibrillar myopathy.

Williams distal myopathy

ORPHA 63273 - OMIM 614065

• Autosomal dominant disease • Caused by mutations in the ***FLNC* gene** (located on chromosome 7) which codes for filamin C, an actin-binding protein • *FLNC* gene mutations can also cause myofibrillar myopathy-5.

Distal myopathy with myotilin defect

• Autosomal dominant disease • Caused by mutations in the ***MYOT* gene** (located on chromosome 5) which codes for myotilin, a Z-disc protein which stabilises and anchors thin filaments to Z-discs • Classed as a myofibrillar myopathy.

α-B crystallin-mutated distal myopathy

ORPHA 98910 - OMIM 608810

• Autosomal dominant disease • Caused by mutations in the ***CRYAB* gene** (located

on chromosome 11) which codes for α-B crystallin, a chaperone necessary for the stabilisation of desmin • Also classed as a myofibrillar myopathy.

KLHL9-related early-onset distal myopathy

ORPHA 399081

• Autosomal dominant disease • Caused by mutations in the ***KLHL9* gene** (located on chromosome 9) which codes for Kelch-like homologue 9, a protein involved in the assembly of the cytoskeleton • Early onset • Slowly progressive weakness and atrophy of the tibialis anterior muscles, followed by the intrinsic hand muscles • Loss of sensation in a stocking-glove distribution • Steppage gait • Contractures during the first to second decade • Late mild proximal muscle involvement • Ability to walk retained • Cases from a large German family published.

Distal myopathy, Tateyama type

ORPHA 488650 - OMIM 614321

• Autosomal dominant disease • Caused by mutations in the ***CAV3* gene** (located on chromosome 3) which codes for the sarcolemma protein caveolin 3 • Adult onset • Distal muscle weakness and atrophy particularly affecting the small muscles of the hands as well as the small muscles of the feet • Pes cavus • Calf hypertrophy • Inconstant presence of percussion-induced rapid contraction.

Inclusion body myopathy with Paget disease of bone and frontotemporal dementia

ORPHA 52430 - OMIM 167320

• Autosomal dominant disease • Caused by mutations in the ***VCP* gene** (located on chromosome 9) which codes for valosin-containing protein, a protein involved in the ubiquitin-proteasome degradation system • Onset around the fifth decade • Initial distal weakness progressing to scapuloperoneal weakness • Patients and/or families may have associated Paget disease (40% of cases) and/or early-onset frontotemporal dementia (30% of cases).

X-linked adult-onset distal myopathy-7

OMIM 301075

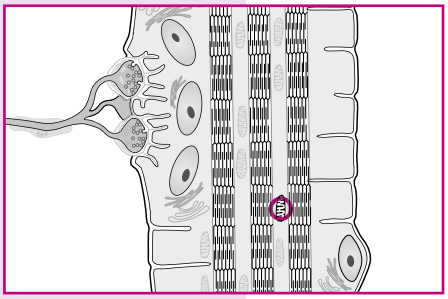
• X-linked recessive • Caused by mutations in the SMPX gene (located on chromosome 22) which codes for a small muscle protein that protects the sarcolemma from mechanical stress • Adult onset • Muscle weakness more distal than proximal • Slowly progressive with no loss of ambulation • 10 cases published.

Management and treatment

• Genetic counselling • Physiotherapy to maintain as much joint flexibility as possible • Orthoses, in particular foot drop supports • Assistive technology (walking stick, scooter, or electric wheelchair if necessary) may be required to ensure the highest level of independence possible.

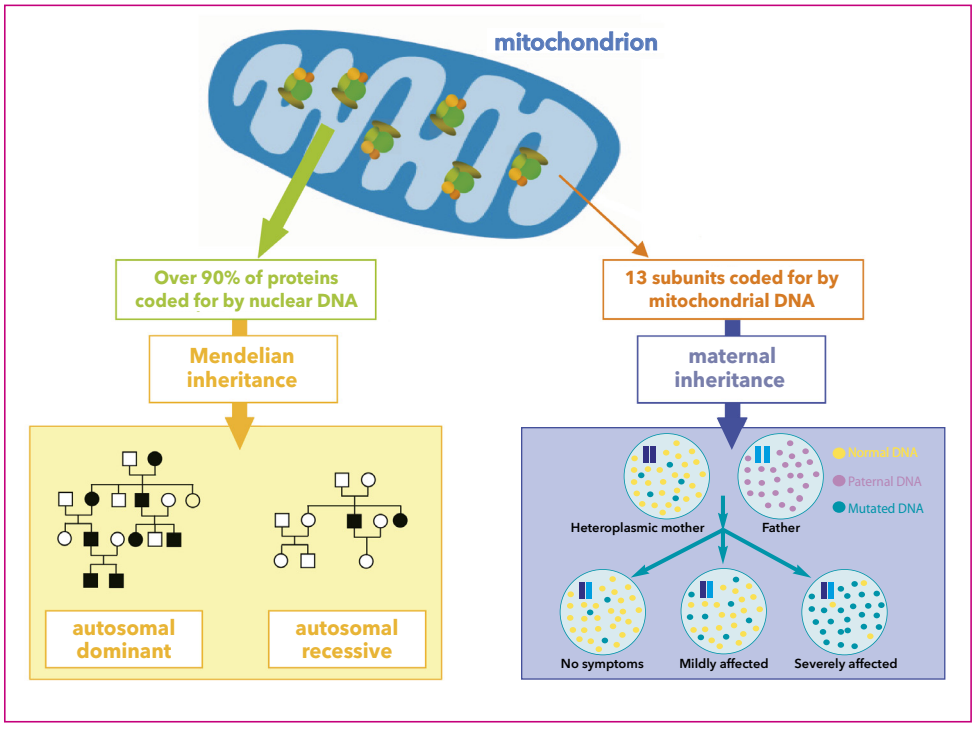
MITOCHONDRIAL MYOPATHIES

ORPHA 254854



Rare genetic diseases caused by mitochondrial respiratory chain dysfunction. Frequently misdiagnosed, therefore, it is important to know how to recognise the main diseases in this category.

• Mitochondria are the "powerhouses" of cells, with each cell containing several hundred, or even several thousand of them • Any cell or organ in the body can be affected • Tissue that requires a lot of energy (such as skeletal muscle, cardiac muscle and the central nervous system) is usually the first and most severely affected by any defects in the respiratory chain • Mitochondrial myopathies are usually passed down via Mendelian inheritance (genes located in the nucleus, i.e. nuclear DNA) - either autosomal recessive or autosomal dominant depending on the case • However, certain forms can be passed down via maternal inheritance (genes located in the mitochondria, i.e. mitochondrial DNA - the mitochondria being inherited from the mother only) • Many clinical forms depending on the area of the body most affected



• Myopathy beginning in early childhood or adulthood • Progressive clinical course without fluctuations: ophthalmoplegia, pigmentary retinopathy, sensorineural hearing loss, heart block, neuropathy, cerebellar ataxia • Clinical manifestations of the same mutation within the same family vary greatly (variation in the degree of heteroplasmy (mtDNA) and variable expressivity of certain mutations) • The same clinical entity may be linked to different mutations • Genetic counselling extremely challenging in cases that involve a mtDNA mutation • Clinical course varies depending on the severity of the disease.

• **MELAS syndrome** (ORPHA 550 – OMIM 540000), which stands for mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes, is caused by the m.3243A>G mutation in the mitochondrial DNA (mtDNA) **gene *MT-TL1*** in 80% of cases • Onset usually between the ages of two and 40 years old • Epilepsy, cognitive impairment, exercise intolerance, migraines, episodic vomiting, hearing loss, peripheral neuropathy and short stature possible • Early psychomotor development generally normal • Prevalence of the m.3243A>G mutation: 0.95 - 236/100,000.

Different clinical forms of mitochondrial myopathy linked to the m.3243A>G mutation in the *MT-TL1* gene

- MELAS syndrome is the most severe clinical form and affects approximately 15% of symptomatic patients;
- MIDD (maternally inherited diabetes and deafness) is the mildest form and accounts for 30% of cases with maternally-inherited diabetes and/or deafness;
- intermediate forms which affect a combination of different bodily systems and functions (neurological, muscular, cardiac, ophthalmological, gastrointestinal, renal);
- asymptomatic forms are common.

• **MERRF** (ORPHA 551 – OMIM 545000), which stands for myoclonic epilepsy with ragged-red fibres, is characterised by myopathy, progressive myoclonic epilepsy, ataxia and hearing loss.

• **Kearns-Sayre syndrome** (ORPHA 480 – OMIM 530000) is characterised by impaired eye movement, balance problems, retinopathy and cardiac conduction defects requiring implantation of a pacemaker.

• **In children:** muscle involvement (hypotonia, lactic acidosis) • Symptoms involving the brain, liver, kidneys or heart • Severe clinical course possible: balance problems, seizures, paralysis • Difficulty eating and swallowing.

• **In adults:** muscle pain and exercise intolerance common • Progressive external ophthalmoplegia and ptosis with or without limbs muscle involvement • Usually slowly progressive.

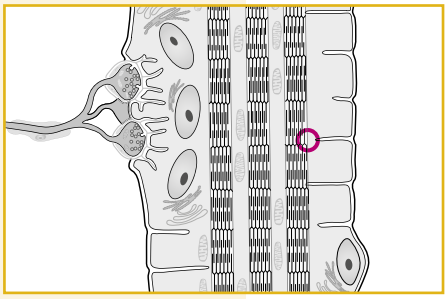
Management and treatment

• If a diagnosis is made early enough, treatment with coenzyme Q10 or certain vitamins can be started, however, the results are inconsistent • Monitoring and treatment of symptoms depending on the condition • Adapted physiotherapy • Wearing special glasses that hold up the eyelids • Equipment • Assistive technology to mitigate functional disabilities • Strength and aerobic exercise training • Planning rest periods.

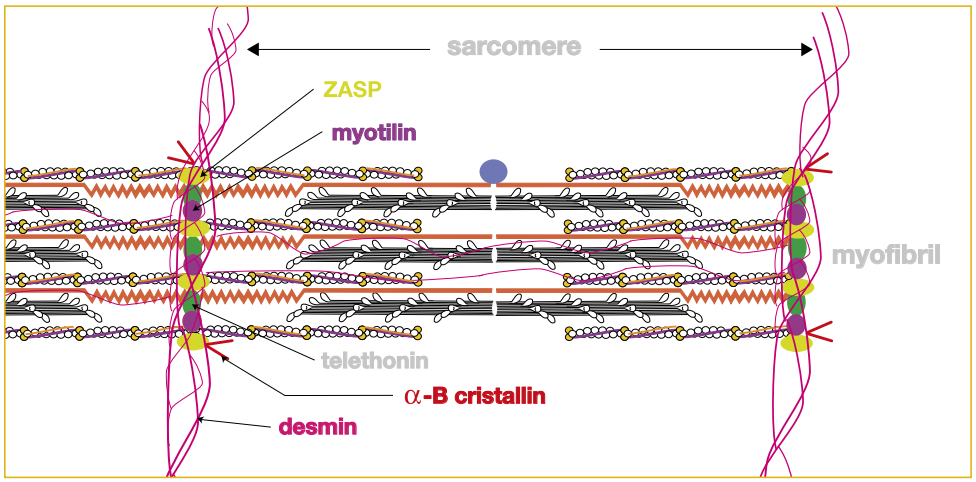
• For more information, please consult the Protocole National de Diagnostic et de Soins for mitochondrial diseases linked to the m.3243A>G mutation in the MT-TL1 gene (27 December 2021): https://www.has-sante.fr/jcms/p_3289848/fr/maladies-mitochondriales-apparentees-au-melas [document in French]

MYOFIBRILLAR MYOPATHIES

ORPHA 593



Heterogeneous group of rare, autosomal dominant or autosomal recessive genetic diseases. Characterised by disorganised myofibrils (which enable muscle cells to contract) and an abnormal intracellular accumulation of proteins.



• The term "myofibrillar myopathy" is a histological concept that encompasses several myopathies that are characterised by a structural change in the myofibrils associated with an abnormal accumulation of proteins brought about by their degradation • A dozen causative genes have been identified to date • Myofibrils, which are made up of myofilaments, are involved in muscle contraction; they are connected to the plasma membrane by intermediate filaments which allow the muscle cell to have a certain degree of elasticity without breaking • These intermediate filaments are made up of protein complexes which play a fundamental role in cellular resistance and contribute to cellular integrity • Desmin is a major intermediate filament • Other filaments, such as vimentin, nestin or synemin, can also be expressed in certain muscles • Onset usually during late adolescence or adulthood • Proximal (shoulders and thighs) or distal (hands and feet) muscle weakness • Cardiac involvement common (which may be one of the first manifestations) with or without skeletal, respiratory and/or pharyngeal muscle involvement • Associated peripheral neuropathy possible.

Myofibrillar myopathy-1 (MFM1)

ORPHA 98909 - OMIM 601419

• Autosomal dominant or recessive • Caused by mutations in the ***DES* gene** (located on chromosome 2) which codes for desmin, a protein that is part of a network of intermediate filaments that protects the structural and functional integrity of myofibrils during mechanical stress • Mutations in the *DES* gene cause a structural change that can lead to the disorganisation and aggregation of these filaments • Desmin filaments can also become disorganised even when there are no mutations in the *DES* gene due to interactions with other mutated proteins such as alpha-B crystallin or plectin • Clinical signs vary depending on the type and location of the mutation • Onset usually in young adulthood • Progressive proximal and distal skeletal muscle weakness • Often associated with cardiomyopathy with respiratory

insufficiency • Early diagnosis is important due to the frequency and severity of cardiac involvement.

Myofibrillar myopathy-2 (MFM2)

ORPHA 98910 - OMIM 608810

• Autosomal dominant • Caused by mutations in the ***CRYAB* gene** (located on chromosome 11) which codes for the alpha-B-crystallin protein, a chaperone required for the stabilisation of desmin • Adult onset • Initial distal muscle weakness with subsequent proximal and axial muscle weakness • Respiratory insufficiency • Cardiomyopathy • Early cataracts • Slowly progressive • Large phenotypic variability both within and between families.

Myofibrillar myopathy-3 (MFM3)

ORPHA 98911 - OMIM 609200

• Autosomal dominant • Caused by mutations in the ***MYOT* gene** (located on chromosome 5) which codes for myotilin, a Z-disc protein which stabilises and anchors thin filaments to Z-discs • Causes 10% of all myofibrillar myopathies • Adult onset • Distal muscle weakness and atrophy • Achilles tendon contractures • Muscle pain • Slowly progressive.

Myofibrillar myopathy-4 (MFM4)

ORPHA 98912 - OMIM 609452

• Autosomal dominant • Caused by mutations in the ***LDB3* gene** (located on chromosome 10) which codes for the ZASP protein, a cytoskeletal protein that plays an important role in maintaining the structural integrity of skeletal muscle Z-discs • Allelic disorder: autosomal dominant late-onset distal myopathy, Markesbery-Griggs type described in a few families in Finland, France and Spain • Onset after the age of 40 • Progressive distal and/or proximal muscle weakness (varies from patient to patient) • Increased CK levels • Less than 50 cases published in France, Germany, the United States and the United Kingdom.

Myofibrillar myopathy-5 (MFM5)

ORPHA 171445 - OMIM 609524

• Autosomal dominant • Caused by mutations in the ***FLNC* gene** (located on chromosome 7) which codes for filamin C, a cytoskeletal protein • Onset after the age of 35 • Slowly progressive proximal muscle weakness mainly affecting the lower limbs • Difficulty climbing stairs • Waddling gait • Scapular winging • Increased CK levels • Respiratory insufficiency • Possible cardiac involvement.

Myofibrillar myopathy-6 (MFM6)

ORPHA 199340 - OMIM 612954

• Autosomal dominant • Caused by mutations in the ***BAG3* gene** (located on chromosome 10) which codes for an antiapoptotic protein • De novo mutations common • Onset during childhood or adolescence • Generalised muscle weakness and atrophy • Significantly increased CK levels • Cardiomyopathy • Respiratory insufficiency • Scoliosis • Contractures • Loss of ambulation • Severe and rapid progression.

Myofibrillar myopathy-7 (MFM7)

ORPHA 496686 - OMIM 617114

• Autosomal recessive • Caused by mutations in the ***KY* gene** (located on chromosome 3) which codes for a protein in the sarcolemma of skeletal muscle • Early childhood onset • Muscle weakness starting in the lower limbs • Difficulty walking • Muscle atrophy • Facial weakness • Kyphosis, mild scoliosis and rigid spine • Achilles tendon and elbow contractures • Increased CK levels • Four cases published.

Myofibrillar myopathy-8 (MFM8)

OMIM 617258

• Autosomal recessive • Caused by mutations in the ***PYROXD1* gene** (located on chromosome 12) • Childhood onset • Difficulty walking, running and climbing stairs • Proximal muscle weakness and atrophy • Facial weakness • High-arched palate • Foot deformities (pes cavus or pes planus) • Increased CK levels • Slowly progressive.

Myofibrillar myopathy-9 with early respiratory failure (MFM9)

ORPHA 178464 - OMIM 603689

• Autosomal dominant • Caused by mutations in the ***TTN* gene** (located on chromosome 2) • Adult onset • Muscle weakness mainly affecting the lower limbs • Early respiratory failure • Diaphragmatic weakness.

Myofibrillar myopathy-10 (MFM10)

OMIM 619040

• Autosomal recessive • Caused by mutations in the ***SVIL* gene** (located on chromosome 10) which codes for supervillin, a protein that connects cytoskeleton actin to the cell membrane • Onset during childhood or adolescence • Muscle pain and cramping • Muscle fatigue • Kyphosis • Contractures of the knee, elbow and finger joints • Mildly increased CK levels • Inconstant mild cardiac involvement • Slowly progressive • Cases from two unrelated consanguineous families published.

Myofibrillar myopathy-11 (MFM11)

OMIM 619178

• Autosomal recessive • Caused by mutations in the ***UNC45B* gene** (located on chromosome 17) which codes for a myosin-specific chaperone involved in myosin assembly in skeletal and cardiac muscle fibres • Onset at birth or during childhood • Hypotonia • Mildly delayed motor development • Proximal muscle weakness • Calf hypertrophy • Normal CK levels • Slowly progressive • 11 cases published.

Infantile-onset myofibrillar myopathy-12 with cardiomyopathy (MFM12)

OMIM 619424

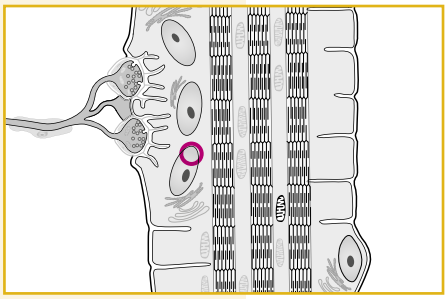
• Autosomal recessive • Caused by mutations in the ***MYL2* gene** (located on chromosome 12) which codes for myosin light chain-2, a protein which regulates myosin ATPase activity • Onset during the first weeks of life • Generalised muscle weakness • Cardiomyopathy • Increased CK levels • Rapidly progressive • Death within the first year of life.

Management and treatment

• Genetic counselling • Adapted physiotherapy • Monitoring of cardiac function • Pacemaker implantation • Monitoring of respiratory function • Mitigation of motor disabilities using assistive technology (foot drop support, walking stick, electric wheelchair, computer, etc.) to ensure the highest level of independence possible.

Oculopharyngodistal **MYOPATHY** (OPDM)

ORPHA 98897



Autosomal dominant genetic disease caused by an expansion of 50 to 200-300 CGG trinucleotide repeats in four distinct genes. Approximately 300 cases recorded around the world, mainly in Asia but also in Europe and the United States.

• Four forms with overlapping clinical and histological features:
- OPDM1 (OMIM 164310), linked to the ***LRP12* gene** (located on chromosome 8) which codes for low density lipoprotein receptor-related protein 12, a protein that is involved in signal transduction and/or endocytosis;
- OPDM2 (OMIM 618940) linked to the ***GIPC1* gene** (located on chromosome 19) which codes for a protein that regulates cell surface receptor expression;
- OPDM3 (OMIM 619473) linked to the ***NOTCH2NLC* gene** (located on chromosome 1) which codes for a Notch signalling protein that plays a role in cortical neurogenesis;
- OPDM4 (OMIM 619790) linked to the ***RILPL1* gene** (located on chromosome 12) which codes for a neuroprotective protein.

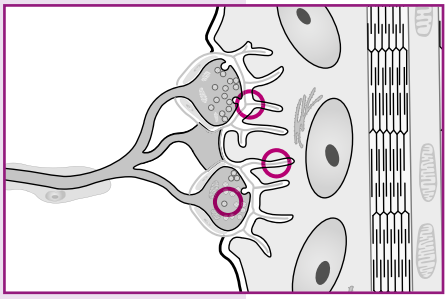
• Clinical onset in adulthood (second or third decade) • Ptosis • Ophthalmoplegia • Dysphagia • Dysarthria • Facial, pharyngeal and distal limb muscle weakness • Mildly increased CK levels • Respiratory insufficiency • Increased risk of cardiovascular disorders • Slowly progressive with gradual worsening of muscle weakness.

Management and treatment

• Genetic counselling • Special diet • Rehabilitation, speech therapy • Gastrostomy or jejunostomy to administer nutrition in the event of severe swallowing difficulties • Monitoring of respiratory function • Regular cardiac monitoring • Wearing special glasses that hold up the eyelids, or even ptosis surgery • Mitigation of impairments (walking stick, foot drop supports, electric wheelchair, etc.) to ensure the highest level of independence possible.

Congenital **MYASTHENIC SYNDROMES** (CMSs)

ORPHA 590



Genetic diseases caused by abnormal neuromuscular junction proteins and characterised by a congenital defect in the transmission of signals at the neuromuscular junction. Prevalence in Europe: 0.30/100,000.

• Onset usually at birth or during the first two years of life • Hypotonia • Suckling and swallowing difficulties, weak cry • Fluctuating limb-girdle muscle weakness (worsening at the end of the day or upon exertion, varies from one day to the next) • Muscle fatigue triggered by repeated or sustained physical activity • Eye problems (unilateral or bilateral ptosis which is usually asymmetric, extraocular muscle weakness, diplopia) and bulbar symptoms (choking, nasal voice, jaw fatigue when chewing) • Antenatal form possible (except for with *CHRNE* and *COLQ* mutations) caused by mutations with almost total loss of function: foetal akinesia and arthrogryposis • Later forms: adolescence/young adulthood, suggestive of proximal myopathy • Positive response to pyridostigmine in 65% of CMSs • No myasthenia gravis-specific antibodies (anti-AChR and anti-MuSK) • Sporadic case with no family history • Family history possible, usually autosomal recessive • Clinical course varies depending on the form: intermittent progression, progressive, not very progressive or may even improve over time • Recovery possible with appropriate treatment • There are three main types of CMSs which are grouped into categories based on the part of the neuromuscular junction affected: presynaptic (the nerve cell), synaptic (the space between the nerve cell and muscle cell) and postsynaptic (the muscle cell).

Presynaptic congenital myasthenic syndromes

ORPHA 98914

• Presynaptic CMSs make up 6% of all CMSs.

Congenital myasthenic syndrome-6 (CMS6 or congenital myasthenic syndrome with episodic apnoea, formally familial infantile myasthenia)

ORPHA 98914 – OMIM 254210

• Autosomal recessive • Caused by a mutation in the ***CHAT* gene** (located on chromosome 10) which codes for choline acetyltransferase (ChAT) • Causes around 5% of all CMSs • Defect in the production of acetylcholine, a neurotransmitter involved in muscle contraction • Onset: neonatal period or early childhood • Very sudden and brief (a few minutes) episodes of apnoea triggered by fever, fatigue or exercise: large failing movements and struggle with asphyxiation, cyanosis and occasional loss of consciousness • Not to be confused with a seizure • Risk of sudden death or cerebral hypoxia caused by asphyxiation if treated too late • Hypotonia • Ptosis • Bulbar symptoms • Mild or even no myasthenic symptoms at all between episodes • Generally improves with age • Development of muscle weakness possible which can gradually lead to being wheelchair-bound • Cholinesterase inhibitors (Prostigmin®, Mestinon®, Mytelase®) • Amifampridine (Firdapse®) as second-line treatment.

Congenital myasthenic syndrome-20 (CMS20)
ORPHA 98914 - OMIM 617143
• Autosomal recessive • Caused by a mutation in the ***SLC5A7* gene** (located on chromosome 2) which codes for the choline transporter SLC5A7 • Onset at birth • Severe hypotonia • Sudden and brief apnoeic episodes, improved with cholinesterase inhibitors • Suckling and swallowing difficulties • Ptosis • Muscle weakness in the lower limbs • Delay in learning to walk • Cognitive impairment resulting from anoxia caused by episodes of apnoea common • Acetylcholinesterase inhibitors or salbutamol/ephedrine.

Congenital myasthenic syndrome-21 (CMS21)
ORPHA 98914 - OMIM 617239
• Autosomal recessive • Caused by a mutation in the ***SLC18A3* gene** (located on chromosome 10) which codes for the vesicular acetylcholine transporter SLC18A3 • Onset in infancy • Sudden and brief apnoeic episodes, improved with cholinesterase inhibitors • Hypotonia • Weakness in all four limbs • Fatigability • Cognitive impairment resulting from anoxia caused by episodes of apnoea common • Cholinesterase inhibitors (Prostigmin®, Mestinon®, Mytelase®).

Congenital myasthenic syndrome-23 (CMS23)
ORPHA 98914 - OMIM 618197
• Autosomal recessive • Caused by a mutation in the ***SLC25A1* gene** (located on chromosome 22) which codes for the mitochondrial tricarboxylate transporter • Onset in infancy • Hypotonia • Ptosis • Ophthalmoparesis • High-arched palate • Proximal weakness in all four limbs • Fatigability • Associated epilepsy possible • Not or only mildly progressive • Cholinesterase inhibitors (Prostigmin®, Mestinon®, Mytelase®) • Amifampridine (Firdapse®) as second-line treatment.

Presynaptic CMSs affecting the exocytosis of synaptic vesicles
• Extremely rare • Only affect a few families, or even just one.

ORPHA 98914 - OMIM 616224
• Autosomal recessive • Caused by mutations in the ***PREPL* gene** (located on chromosome 2) which codes for a serine peptidase • Onset at birth • Hypotonia • Predominantly proximal muscle weakness • Muscle weakness may improve with age • Cholinesterase inhibitors (Prostigmin®, Mestinon®, Mytelase®) • Amifampridine (Firdapse®) as second-line treatment.

ORPHA 98914 - OMIM 616330
• Autosomal dominant • Caused by a mutation in the ***SNAP25* gene** (located on chromosome 20) which codes for a protein that allows synaptic vesicles to bind to the presynaptic membrane • Delayed psychomotor development • Ataxia • Frequently associated with cognitive impairment • Amifampridine (Firdapse®).

ORPHA 98914 - OMIM 616040
• Autosomal dominant or recessive (more severe phenotype) • Caused by mutations in the ***SYT2* gene** (located on chromosome 1) which codes for synaptotagmin 2, a membrane protein of synaptic vesicles which plays a role in their exocytosis • Early childhood onset • Distal muscle weakness, more so in the lower limbs • Slowly progressive • Amifampridine (Firdapse®).

ORPHA 98914 - OMIM 618323
• Autosomal recessive • Caused by a mutation in the ***VAMP1* gene** (located on chromosome 12) which codes for synaptobrevin-1, a small membrane protein involved in the exocytosis of synaptic vesicles at the presynaptic nerve terminal • Onset at birth • Hypotonia and generalised weakness • Delayed motor development • Unable to walk without support • Ophthalmoparesis • Swallowing difficulties • Joint contractures • Scoliosis.

CMS genes

Over 30 genes are currently known to cause (when mutated) congenital myasthenic syndromes.

- The most frequently involved (one third of all cases) is the ***CHRNE* gene** which codes for the epsilon subunit of the acetylcholine receptor. CHRNE-related CMSs are usually postsynaptic CMSs with an acetylcholine receptor deficiency.
- Three other genes that cause CMSs are the ***DOK7*** (10-15% of cases), ***COLQ*** (11-13% of cases) and RAPSN (11-15% of cases) **genes**.
- Eight other genes have been found to cause CMSs at a lower, but still significant, rate. These are the ***CHRNA1*** (missense mutations which cause autosomal dominant slow-channel congenital myasthenic syndrome), ***CHAT*** (in particular CMSs with episodic apnoea in newborns), ***GFPT1, SLC5A7, MUSK, AGRN, COL13A1*** and ***GMPPB* genes**.
- Other genes have been found to be involved in certain families.

Protocole National de Diagnostic et de Soins for congenital myasthenic syndromes, Centre de Référence Nord/Est/Ile de France, Hôpital Armand Trousseau (APHP) [North/East/Île de France Specialist Centre, Armand Trousseau Hospital (APHP)], March 2021.

ORPHA 98914
• Caused by a mutation in the ***UNC13A* gene** (located on chromosome 19) which codes for a presynaptic protein that is essential in synaptic vesicle priming • Frequently associated with cognitive impairment and/or epilepsy • Amifampridine (Firdapse®).

Presynaptic CMSs affecting axonal transport
ORPHA 98914 - OMIM 618198
• Autosomal recessive • Caused by a mutation in the ***MYO9A* gene** (located on chromosome 15) which codes for an "unconventional" myosin protein involved in axonal transport • Onset in early infancy • Distal and proximal hypotonia • Ptosis • ophthalmoplegia • Suckling and swallowing difficulties • Episodic apnoea • Respiratory insufficiency • Delayed motor development • Frequently associated with cognitive impairment resulting from anoxia caused by episodes of apnoea • Cholinesterase inhibitors (Prostigmin®, Mestinon®, Mytelase®) or amifampridine (Firdapse®).

Synaptic congenital myasthenic syndromes
ORPHA 98915

Congenital myasthenic syndrome-5 (CMS5)
ORPHA 98915 - OMIM 603034
• Autosomal recessive • Caused by a mutation in the ***COLQ* gene** (located on chromosome 3) which codes for ColQ, a protein that anchors acetylcholinesterase (AChE) to the basement membrane of the synaptic cleft • Acetylcholinesterase is an enzyme whose function is to break down the acetylcholine released into the synaptic cleft • In the absence of this protein, the lack of acetylcholine breakdown excessively prolongs the interaction between acetylcholine and its receptors (gain of function) • Makes up approximately 10% of all CMS cases • Onset at birth or during childhood • Slow pupillary light reflex (specific but inconsistent) • Proximal weakness (limb-girdle muscles) • Ophthalmoplegia in one third of cases • Respiratory and/or bulbar involvement in approximately one third of cases • Severity variable (usually severe) • Milder forms beginning in adolescence • Unresponsive to anticholinesterases • Salbutamol (Ventolin®) or ephedrine.

Congenital myasthenic syndrome-8 (CMS8)
ORPHA 590 - OMIM 615120
• Autosomal recessive • Caused by a mutation in the ***AGRN* gene** (located on chromosome 1) which codes for agrin, a component of some basal laminae which is involved in the aggregation of acetylcholine receptors • Early onset with lower limb muscle weakness and atrophy • Later forms: ptosis, ophthalmoplegia • Mild facial and bulbar weakness • "Dropped head" and distal weakness possible
• Salbutamol (Ventolin®) or ephedrine.

Agrine/LRP4/MuSK/Dok7 : a complex essential to the development and maintenance of the neuromuscular junction

Agrin, released by the motor neuron into the synaptic cleft, binds to LRP4 and activates (through phosphorylation) MuSK which is situated in the postsynaptic membrane. Dok-7, a postsynaptic molecule, is the second activator of MuSK. Present in muscle from the first few weeks of foetal development, MuSK plays a fundamental role in the differentiation and function of the neuromuscular junction.

Postsynaptic congenital myasthenic syndromes

ORPHA 98913

• The most common type of CMS • Caused by mutations which reduce the number of acetylcholine receptors (AChRs) (genes that code for the subunits of the AChR or rapsyn) or those which affect their kinetic properties, i.e. lengthening or shortening the opening time of the channel (genes that code for the subunits of the AChR).

Escobar syndrome

ORPHA 98913 - OMIM 265000

• The γ subunit of the AChR is expressed from the beginning of foetal development until the 32nd week • After the 32nd week, it is replaced by the epsilon subunit to form the adult AChR • Antenatal onset • Reduced foetal movements • Arthrogryposis multiplex congenita requiring numerous corrective procedures • Myasthenic fatigability which can be improved with salbutamol.

Congenital myasthenic syndromes associated with acetylcholine receptor deficiency

ORPHA 98913 – OMIM 608931 / 616314 / 616323

• Autosomal recessive • Caused by mutations in the ***CHRNE* gene** (located on chromosome 17 - CMS4C) which codes for the ε subunit of the acetylcholine receptor (AChR), responsible for 33% of all CMSs • Mutations in the ***CHRNB1*** (located on chromosome 17 - CMS2C), ***CHRND*** (located on chromosome 2 - CMS3C), and ***CHRNA1*** (located on chromosome 2 - CMS1B) **genes,** which code for the β, δ, and α subunits of the AChR respectively, are less common • Onset at birth is most common, or during childhood • Typical myasthenic syndrome with ocular, facial and bulbar muscle weakness • Cholinesterase inhibitors (Prostigmin®, Mestinon®, Mytelase®) • Amifampridine (Firdapse®) as second-line treatment.

Congenital myasthenic syndrome-11 (CMS11)

ORPHA 98913 - OMIM 616326

• Autosomal recessive • Caused by mutations in the ***RAPSN* gene** (located on chromosome 11), which codes for rapsyn, a protein essential in the clustering of acetylcholine receptors at the endplate • Makes up 15% of all CMS cases • Neonatal, or even antenatal form with arthrogryposis (severe respiratory insufficiency, severe ocular, facial and bulbar muscle weakness and symptoms) • Course usually favourable during childhood and adolescence • Mild, later forms with onset during childhood, adolescence or even adulthood • Acute bulbar involvement possible, particularly against a background of infection, with acute respiratory failure • Cholinesterase inhibitors (Prostigmin®, Mestinon®, Mytelase®) • Amifampridine (Firdapse®) as second-line treatment.

Slow-channel congenital myasthenic syndrome

ORPHA 98913 – OMIM 601462 / 616313 / 616321 / 605809

• Autosomal dominant • Mainly caused by mutations in the ***CHRNA1* gene** (located on chromosome 2) which codes for the α subunit of the AChR, or by mutations in regions of the ***CHRNB1, CHRND*** or ***CHRNE* genes** (located on chromosomes 17, 2 and 17 respectively) which code for parts of the β, δ and ε subunits which form the pore region of the AChR • 5 to 10% of CMSs • Prolonged opening of the AChR • Early onset with severe impairment • Onset around the age of 20 with mild impairment • Muscle weakness and atrophy mainly affecting the finger extensor muscles and neck muscles • No response to cholinesterase inhibitors, or even worsening of symptoms • Effectiveness of fluoxetine and quinidine sulphate therapies variable.

Fast-channel congenital myasthenic syndrome

ORPHA 98913 – OMIM 608930 / 616322 / 616324

• Autosomal recessive • Rarer than slow-channel congenital myasthenic syndrome • Shortening of the AChR opening time • Caused by about ten mutations affec-

Contraindicated drugs

Drugs to avoid

- Aminoglycosides, colistin, polymyxin B, telithromycin, injectable cyclins, macrolides, fluoroquinolones
- Quinine, quinidine (except in slow-channel congenital myasthenic syndrome mutations), hydroxychloroquine, procainamide
- Beta blockers (even eye drops)
- Phenytoin, trimethadione
- Dantrolene
- D-penicillamine
- Magnesium

Drugs to be used with caution

- Neuromuscular blocking agents: rapidly degrading non-depolarising drugs, such as atracurium, can be used with close monitoring
- Benzodiazepines, carbamazepine
- Antipsychotics (phenothiazine)
- Lithium

• Intravenous iodinated contrast media used in imaging can induce acute decompensation of the disease and are not recommended for use during a flare-up.

• The use of nicotine patches to help quit smoking can aggravate myasthenia gravis.

Protocole National de Diagnostic et de Soins for congenital myasthenic syndromes, Centre de Référence Nord/Est/Ile de France, Hôpital Armand Trousseau (APHP) [North/East/Île de France Specialist Centre, Armand Trousseau Hospital (APHP)], March 2021.

ting the α, δ and ε subunits • Onset at birth, or even antenatal onset with reduced foetal movements and arthrogryposis • Ocular, facial and bulbar muscle weakness • Respiratory insufficiency with episodic apnoea • Cholinesterase inhibitors (Prostigmin®, Mestinon®, Mytelase®) • Amifampridine (Firdapse®) as second-line treatment.

Congenital myasthenic syndrome-10 (CMS10)
ORPHA 98913 – OMIM 254300
• Autosomal recessive • Caused by a mutation in the ***DOK7* gene** (located on chromosome 4) which codes for Dok-7, a cytoplasmic protein involved in the maturation of neuromuscular synapses • The cause in 15% of CMSs • Onset at birth in one third of cases: hypotonia, feeding difficulties, respiratory difficulties • Onset in early and middle childhood (two thirds of cases) • Onset can also occur in adolescence or even young adulthood • Limb-girdle muscle weakness/fatigability, difficulty walking • Finger extensor weakness (75% of cases) • Ophthalmoplegia (30% of cases) • Facial weakness • Swallowing difficulties (60% of cases) • Respiratory muscle weakness common • Progressive scoliosis • Fluctuations with flare-ups affecting the limbs, swallowing and breathing which can last several months or even several years • Usually a progressive and severe form with loss of ambulation and/or respiratory insufficiency requiring ventilation • Salbutamol (Ventolin®) or ephedrine.

Congenital myasthenic syndrome-9 (CMS9)
ORPHA 98913 - OMIM 616325
• Autosomal recessive • Caused by a mutation in the ***MUSK* gene** (located on chromosome 9) which codes for MuSK, a muscle-specific tyrosine kinase receptor that plays an important role in the development and stability of the muscle membrane • Onset at birth • Bulbar weakness which can be severe (vocal cord paralysis causing stridor, or even the need for intubation) • Respiratory failure • Ptosis • Ophthalmoplegia • Childhood or adult onset possible: limb girdle weakness and possible acute bulbar symptoms (vocal cord paralysis) • Salbutamol (Ventolin®) or ephedrine.

Congenital myasthenic syndrome-17 (CMS17)
ORPHA 98913 - OMIM 616304
• Autosomal recessive • Caused by a mutation in the ***LRP4* gene** (located on chromosome 11) which codes for LRP4, a low-density lipoprotein receptor that plays a critical role in the development and stability of the neuromuscular junction • Onset at birth • Respiratory and feeding difficulties • Mild ptosis • Ophthalmoparesis • Predominantly proximal muscle weakness • Difficulty walking • Salbutamol (Ventolin®) or ephedrine.

Congenital myasthenic syndrome due to a TOR1AIP1 mutation
ORPHA 98913
• Autosomal recessive • Caused by a frameshift mutation in the ***TOR1AIP1* gene** (located on chromosome 1) which codes for LAP1, a nuclear envelope protein associated with lamins • Onset in the first decade • Fatigue • Difficulty walking and running • Mild, predominantly proximal muscle weakness and atrophy • Cholinesterase inhibitors (Prostigmin®, Mestinon®, Mytelase®).

Congenital myasthenic syndromes with glycosylation defect

ORPHA 353327
• Caused by recessive mutations in genes which code for enzymes involved in N-linked glycosylation • Pre- and postsynaptic CMSs • Exclusively affect the limb-girdle muscles.

Congenital myasthenic syndrome-12 (CMS12)
ORPHA 353327 - OMIM 610542
• Autosomal recessive • Caused by a mutation in the ***GFPT1* gene** (located on chromosome 2) which codes for glutamine:fructose-6-phosphate amidotransferase, which plays a role in the production of glucosamine 6-phosphate for the synthesis of glycoproteins, glycolipids and proteoglycans • 2 to 4% of all CMSs • Early limb-girdle muscle weakness • Minimal bulbar involvement • Tubular aggregates commonly found in muscle biopsies • Cholinesterase inhibitors (Prostigmin®, Mestinon®, Mytelase®) • Amifampridine (Firdapse®) as second-line treatment.

Congenital myasthenic syndrome-13 (CMS13)
ORPHA 353327 - OMIM 614750
• Autosomal recessive • Caused by a mutation in the ***DPAGT1* gene** (located on chromosome 11) which codes for dolichyl-phosphate N-acetylglucosaminephosphotransferase 1, an enzyme involved in the synthesis of glycoproteins • Frequently associated with cognitive impairment • Tubular aggregates commonly found in muscle biopsies • Cholinesterase inhibitors (Prostigmin®, Mestinon®, Mytelase®) • Amifampridine (Firdapse®) as second-line treatment.

Congenital myasthenic syndrome due to GMPPB mutations
ORPHA 353327
• Autosomal recessive • Caused by mutations in the ***GMPPB* gene** (located on chromosome 3) which codes for the β subunit of GDP-mannose pyrophosphorylase • Late onset • Muscle pain common • Overlapping phenotype with a limb-girdle muscular dystrophy • Frequently associated with mild cognitive impairment • Cholinesterase inhibitors (Prostigmin®, Mestinon®, Mytelase®) • Amifampridine (Firdapse®) as second-line treatment.

Congenital myasthenic syndrome-14 (CMS14)
ORPHA 353327 - OMIM 616228
• Autosomal recessive • Caused by mutations in the ***ALG2* gene** (located on chromosome 9) which codes for α-1,3/1,6-mannosyltransferase which is involved in the asparagine-linked glycosylation pathway • Childhood onset • Hypotonia • Delayed postural development • Proximal muscle weakness • Tubular aggregates commonly found in muscle biopsies • Occasionally unable to walk • Possible bulbar symptoms • Great clinical variability, even within the same family • Cholinesterase inhibitors (Prostigmin®, Mestinon®, Mytelase®) • Amifampridine (Firdapse®) as second-line treatment.

Congenital myasthenic syndrome-15 (CMS15)
ORPHA 353327 - OMIM 616227
• Autosomal recessive • Caused by mutations in the ***ALG14* gene** (located on chromosome 1) which codes for the UDP-N-acetylglucosaminyltransferase subunit which is involved in the asparagine-linked glycosylation pathway • Early severe form characterised by CNS impairment and epilepsy • Later form characterised by mild muscle weakness • Associated epilepsy possible • Cholinesterase inhibitors (Prostigmin®, Mestinon®, Mytelase®) • Amifampridine (Firdapse®) as second-line treatment.

Other congenital myasthenic syndromes

Congenital myasthenic syndrome-19 (CMS19)
OMIM 616720
• Autosomal recessive • Caused by a mutation in the ***COL13A1* gene** (located on chromosome 10) which codes for a nonfibrillar transmembrane collagen which plays a role in the development of the neuromuscular junction • Associated with dysmorphic spinal and facial features • Amifampridine (Firdapse®).

Congenital myasthenic syndrome due to plectin deficiency

• Autosomal recessive • Caused by a mutation in the ***PLEC1* gene** (located on chromosome 8) which codes for plectin, a cytoskeleton-anchoring membrane protein • Associated with epidermolysis bullosa simplex • Cholinesterase inhibitors (Prostigmin®, Mestinon®, Mytelase®) • Amifampridine (Firdapse®) as second-line treatment.

Congenital myasthenic syndrome due to a LAMB2 mutation

ORPHA 98915

• Autosomal recessive • Caused by a mutation in the ***LAMB2* gene** (located on chromosome 3) which codes for the laminin β-2 chain • Associated with a severe kidney disease (Pierson syndrome) • Salbutamol (Ventolin®) or ephedrine.

Congenital myasthenic syndrome-16 (CMS16)

ORPHA 98913 - OMIM 614198

• Autosomal recessive • Caused by a mutation in the ***SCN4A* gene** (located on chromosome 17) which codes for the α subunit of the muscle sodium channel, a membrane ion channel • Rare cause of CMS • Cholinesterase inhibitors (Prostigmin®, Mestinon®, Mytelase®) • Amifampridine (Firdapse®) as second-line treatment.

Management and treatment

• Medication depending on the gene involved • Genetic counselling • Adapted and personalised physiotherapy • Respiratory support in severe forms, particularly in children.

• For more information, please consult the Protocole National de Diagnostic et de Soins (25 March 2021): https://www.has-sante.fr/jcms/p_3244112/fr/syndromes-myastheniques-congenitaux [document in French]

FILNEMUS

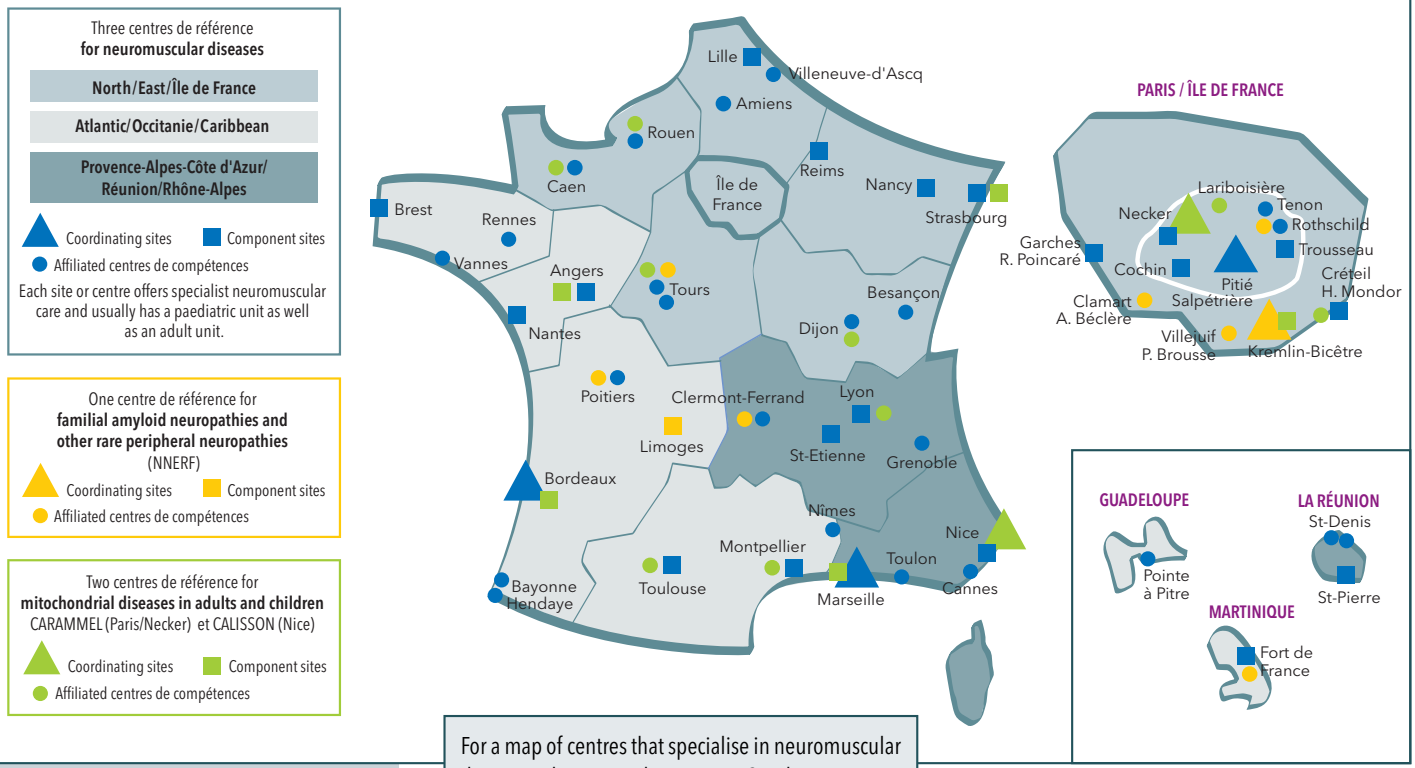
FILNEMUS is one of the 23 Filières de Santé Maladies Rares [French rare diseases healthcare networks] that were selected by the French Ministry of Health as part of the second French National Plan for Rare Diseases 2011-2016. The conditions covered by FILNEMUS include muscle diseases (myopathies), neuromuscular junction diseases, rare peripheral nerve diseases and infantile-onset spinal muscular atrophies. Today, France is home to between 40,000 and 50,000 people living with neuromuscular diseases.

FILNEMUS brings together centres de référence [specialist centres] and centres de compétences [centres of excellence] in neuromuscular diseases as well as diagnostic laboratories, those involved in multidisciplinary care, researchers working on neuromuscular diseases, patient associations, those in the health and social care sector and learned societies interested in neuromuscular diseases.

Its goals are to improve the diagnosis and treatment of patients with neuromuscular diseases and to facilitate interactions between those in the various different roles that support and treat patients.

The FILNEMUS website (www.filnemus.fr) is an information and communication tool for professionals involved in the Filière, but also for patients with neuromuscular diseases and their families.

Geographical distribution of FILNEMUS centres de référence and centres de compétences



For a map of centres that specialise in neuromuscular diseases, please visit the FILNEMUS website:

https://www.filnemus.fr/carte-interactive

https://www.filnemus.fr/la-filiere-de-sante-filnemus/presentation

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FOR MORE INFO

www.afm-telethon.fr
AFM-Téléthon's website.

www.myobase.org
Database of documents on neuromuscular diseases and motor disabilities run by AFM-Téléthon's documentation department.

Les Avancées de la Recherche:
documents produced by AFM-Téléthon on a specific disease or group of diseases which can be found at https://www.afm-telethon.fr/en/news/resources/progress-research

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