



**JERRY LEWIS**  
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## Facts about Charcot-Marie-Tooth Disease

### What is Charcot-Marie-Tooth Disease?

*Charcot-Marie-Tooth disease (CMT)* is a neurological disorder, named after the three physicians who first described it in 1886 — Jean-Martin Charcot and Pierre Marie of France, and Howard Henry Tooth of the United Kingdom.

Unlike some neurological disorders, CMT isn't life-threatening, and it almost never affects the brain. It causes damage to the *peripheral nerves* — tracts of nerve cell fibres that connect the brain and spinal cord to muscles and sensory organs.

Peripheral nerves control movement by relaying impulses from the spinal cord to muscles. They convey sensation by carrying feelings like pain and temperature from the hands and feet to the spinal cord. They also help control balance, by carrying information about the position of the body in space. They transmit information about the feet and hands to the spinal cord and then the brain, so that the brain knows where to place the feet when walking and where the hands should be placed to reach for something.

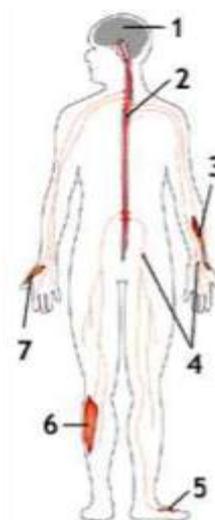
Nerve damage, or *neuropathy*, causes muscle weakness and wasting, and some loss of sensation, in the extremities of the body: the feet, the lower legs, the hands and the forearms.

Although CMT can look very similar to *acquired neuropathy* — a type of nerve damage it caused by overexposure to certain chemicals, or disorders of the immune system — isn't caused by anything a person does, and it isn't contagious. It's hereditary, meaning that it can be passed down through a family from one generation to the next. (See "Does It Run in the Family?")

Because of these features, CMT is sometimes called *hereditary and motor sensory neuropathy (HMSN)*. Some doctors also use the old-fashioned name *peroneal muscular atrophy*, which refers to wasting of the peroneal muscle in the lower leg.

There are even more names for CMT because the disease exists in many different forms, each unique in its severity, age of onset, progression and exact symptoms. For example, *Dejerine-Sottas disease (DS)* is a severe form of CMT that manifests during infancy or early childhood.

Although there's no cure for CMT, there are treatments that can be used to effectively manage its symptoms. Those treatments, described here along with a general overview of CMT, have allowed many people with the disease to lead active, productive lives.



*CMT causes degeneration of the peripheral nerves, leading to muscle weakness in the body's extremities.*

1. Brain
2. Spinal cord
3. Arm muscle
4. Peripheral nerves
5. Foot muscle
6. Leg (peroneus) muscle
7. Hand muscle



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## What causes CMT?

CMT is caused by defects in genes, which are segments of DNA contained in the *chromosomes* of the body's cells. Genes are recipes for making the proteins that serve essential functions in our bodies. Each form of CMT is linked to a specific gene, and all of those genes make proteins found within the peripheral nerves.

Peripheral nerves provide an essential relay between your brain and the rest of your body. When you decide to move your leg, your brain sends an electrical signal to muscle controlling nerve cells in your spinal cord, which then use the peripheral nerves to pass the signal on to your leg muscles.

And if you hurt your leg, you feel it because pain-sensitive nerve cells there have sent an electrical signal through your peripheral nerves to your brain.

The peripheral nerves are made up of fibres, or *axons*, that extend from sensory nerve cells and muscle-controlling nerve cells, and carry electrical signals to and from spinal cord.

In order for you to move and react with precision and speed, axons have to transmit their signals within a fraction of a second. This is a real challenge for axons that have to stretch over long distances, like the ones connected to muscles in your fingers and toes.

To give axons a performance boost, each one is surrounded by a coating called *myelin*. Similar to the way plastic coating is used to insulate electrical wiring, myelin insulates the electrical signals in axons. It also provides essential nourishment to the axons.

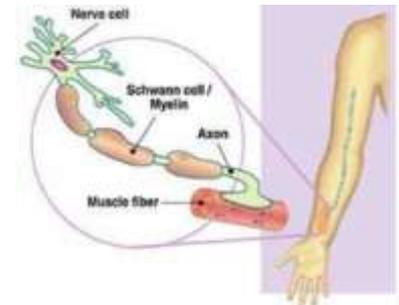
Some 20 genes have been implicated in CMT, each one linked to a specific type (and in many cases, more than in axons, and others make proteins needed in myelin. one type) of the disease. (See "What Are the Different Types of CMT?") Some of those genes make proteins needed

Defective myelin genes can cause a breakdown of myelin (called *demyelination*) while defective axon gene can cause an impairment of axon function (*axonopathy*).

In either case, the end result is the same: Defects in the axon or the myelin cause progressive damage to the axons.

The longest axons in the body are especially sensitive to damage, which explains why CMT mostly causes motor and sensory problems in the body's extremities.

Nerves other than those that go to and from the extremities can be affected at the severe end of the CMT spectrum. If the nerves that go to and from the diaphragm or intercostal (between the ribs) muscles are affected, respiratory impairment can result.



*Peripheral nerves control movement by relaying impulses from the spinal cord (not shown) to our (shown in the foreground) muscles.*

*A single peripheral nerve is composed of many nerve cell branches - or axons - that extend from the spinal cord and connect to muscle fibres. Each axon is surrounded by myelin made from the wrappings of Schwann cells.*



## What happens to someone with CMT, and how is it treated?

Partly because there are different types of CMT, the exact symptoms vary greatly from person to person. This section provides a general picture of CMT, and the next section describes different types of the disease.

### *Muscle weakness*

In general, people with CMT experience slowly progressive weakness and wasting in the *distal muscles*, which control the extremities. These muscles control foot and hand movements. More *proximal* muscles, those closer to the trunk, such as the leg and arm muscles, are rarely affected.

Usually, weakness begins in the feet and ankles, and manifests itself as *foot drop* — difficulty lifting the foot at the ankle, so that the toes point downward during walking. Foot drop causes frequent tripping, and with increasing weakness and attempts at compensation, the affected person develops an abnormal gait.

Many people with CMT make their first visits to a neurologist after they notice frequent trips and falls, ankle sprains, or ankle fractures, caused by foot drop.

When these problems occur, some people find they can overcome them just by wearing boots or high-top shoes to support the ankles.

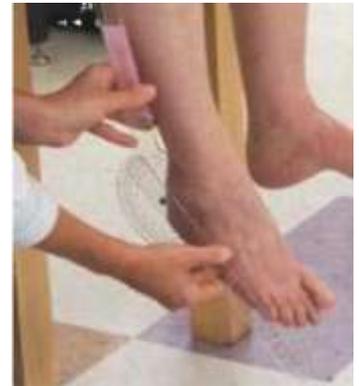
Others might require leg braces, such as an *ankle-foot orthosis (AFO)*, a removable cast that fits snugly around the foot and ankle. Once made of clunky metal struts that required special shoes, AFOs are now made of lightweight plastic that's custom-molded to fit the wearer's legs, and can be worn underneath pants and tennis shoes.

For people with more proximal weakness, very uncommon for CMT, there is the *knee-ankle-foot orthosis (KAFO)*, which extends up the leg, just above the knee. They usually can be worn under trousers. Some orthoses allow movement of the ankle or knee, while others prevent movement to add more support.

Most people with CMT won't need a wheelchair or motorised scooter, but an older person with advanced CMT or someone with a severe type might require one of these to get around, especially when traversing long distances. Like AFOs, wheelchairs aren't what they used to be. There are wheelchairs that can be used on almost any terrain — from shopping mall to hiking trail — many of them powered by the flip of a switch.

Late in the course of CMT, many people experience weakness in the hands and forearms, and have difficulty with gripping and fine finger movements, such as turning doorknobs, and buttoning and zipping clothes. Often, these problems can be overcome with *occupational therapy*, which helps people accomplish the "job" of daily living through the use of assistive devices.

For example, an occupational therapist might recommend that you put special rubber grips on your home's doors, or buy clothes that fasten with Velcro or snaps. Your neuromuscular clinic can refer you to an occupational therapist.



*A doctor examines a patient with foot drop.*





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Weakness of the respiratory muscles is rare in people with CMT, but when it occurs it can be life-threatening. If you regularly experience shortness of breath, you should have your breathing checked by a specialist, who might recommend occasional or nighttime use of a device that delivers air under pressure into the lungs.

Although it's usually too slight to cause disability or discomfort, some people with CMT experience *tremor* (involuntary shaking). CMT with obvious tremor is sometimes called *Roussy-Levy syndrome*.

### **Contractures and Bone Deformities**

Many people with CMT eventually develop contractures (stiffened joints) that result in deformities of the feet and hands. The contractures occur because as some muscles around a joint weaken, others remain strong, contracting and positions.

For example, as muscles that lift the foot at the ankle become weak, muscles that lower and curl the foot downward contract and tighten, causing the most common type of foot deformity — a shortened foot with a high arch (*pes cavus*). As the contracture gets worse, the toes can become locked in a flexed position.

A small fraction of people with CMT develop "flat feet" (*pes planus*), presumably because of a different pattern of muscle weakness.

During walking, these deformities can cause unusual friction against the toes, heel and ball of the foot, leading to painful abrasions, blisters and calluses. If left untreated, the contractures and secondary abrasions tend to worsen over time, making it increasingly difficult to walk.

As CMT progresses, contractures in the hand can lock the fingers in a flexed position and in rare cases, severe proximal weakness can lead to scoliosis (side-to-side curvature of the spine) or *kyphosis* (front-to-back spine curvature).

A small fraction of people with severe CMT also experience hip displacement at an early age.

One of the most effective ways to keep muscles from tightening up and forming contractures is to begin a regular program of *physical therapy*, which usually consists of low-impact exercises and stretching.

Foot contractures can also be delayed by using AFOs, which force the feet into a normal position and decrease stress on the ankles. Similarly, splints can be used to prevent unintended flexing of the toes and fingers.

If these methods fail and severe contractures occur, surgery can be used to loosen up tight muscles and tendons, or to correct bone deformities. Surgery is often necessary for advanced scoliosis.

### **Sensory Loss and Associated Symptoms**

Because CMT causes damage to sensory axons, most people with CMT have a decreased sensitivity to heat, touch and pain in the feet and lower legs.



*Foot contractures resulting in high-arched feet often occur in CMT.*



*Hand contractures can occur late in the course of CMT.*



Although people with CMT often complain that their feet get cold (caused as much by a loss of insulating muscle as by damage to sensory axons), most of these sensory losses are undetectable except by a neurological exam — but it's important to recognise that they occur.

Combined with the regular abrasions caused by foot deformities, the lack of pain sensitivity makes people with CMT at risk for developing *ulcerations* — wounds that have gone unnoticed and become severely infected. If you have CMT, and especially if you have any foot deformities, you should check your feet regularly for injuries.

Paradoxically, some people with CMT experience more pain — a combination of painful muscle cramps and *neuropathic pain*. This pain isn't caused by an external trigger, but by defective signals in sensory axons. Both types of pain can usually be alleviated with medication.

In many people with CMT, sensory loss is associated with dry skin and hair loss in the affected area.

In rare cases, sensory loss can include gradual hearing impairment and sometimes deafness. Watching out for these potential problems will enable you to seek appropriate treatment if necessary.

### **Drug Warning**

The use of certain prescription drugs or excess alcohol can lead to acquired neuropathy, and thus might exacerbate CMT. Case studies have shown that the chemotherapy drug vincristine can cause rapid deterioration in people with CMT.

When taking a prescription drug for the first time, it's a good idea to consult your doctor about its possible effects on CMT. Or, enter the specific name of the drug into an Internet search engine, along with the words "prescribing information," to receive a full explanation of what the drug does and what its side effects may be.

You're unlikely to see anything specific about CMT. However, if the medication's side effect description mentions words like *neuropathy*, *paresthesias*, *neuropathic pain* or *peripheral nerve damage*, you may want to consult your physician about its use in CMT and possible alternatives.

Lists of contraindicated (forbidden) drugs for people with CMT are often composed mostly of medications used to treat serious conditions, such as cancer. In these cases, there may be no alternative to taking the drug, with the awareness that CMT symptoms may worsen.



## What are the different types of CMT?

The many different types of CMT are distinguished by age of onset, inheritance pattern, severity, and whether they're linked to defects in axon or myelin.

While those distinctions are useful, it's important to realise that, because of the vast number of genetic defects that can lead to CMT, some people fall on the borders between different types of CMT, and many have specific "subtypes" not detailed here.

(For more information about the genetics and inheritance of CMT, see "Does It Run in the Family?")

<b>CMT1 and CMT2</b>	
Onset	usually in childhood or adolescence
Inheritance	type 1, autosomal dominant; type 2, autosomal dominant or recessive
Features	These are the two most common forms of CMT. (In fact, a subtype of CMT1 called CMT1A, caused by a defect in the PMP22 gene on chromosome 17, accounts for around 60 percent of all CMT cases.) CMT1 is caused by demyelination and CMT2 is caused by axonopathy, but both produce the classic symptoms described above. CMT2 is sometimes associated with a treatable condition called restless legs syndrome, an irresistible urge to move the legs while sitting or lying down.
<b>CMTX</b>	
Onset	childhood or adolescence
Inheritance	X-linked
Features	CMTX has symptoms similar to those of CMT1 and CMT2. Because of its linkage to the X chromosome, it often affects males more severely than females.
<b>CMT4</b>	
Onset	infancy, childhood or adolescence
Inheritance	autosomal recessive
Features	CMT4, a demyelinating form of CMT, causes weakness, usually mostly distal, but sometimes involving proximal muscles. Sensory dysfunction can also occur. When CMT4 begins in infancy, it's characterised by low muscle tone. Young children with CMT4 generally have delayed motor (movement-related) development.



<b>Dejerine-Sottas Disease</b>	
Onset	early childhood (generally before 3 years)
Inheritance	autosomal dominant or recessive
Features	<p>DS is sometimes classed as a subgroup of CMT4 and is also sometimes called HMSN3. It's a severe neuropathy, with generalised weakness sometimes progressing to severe disability, loss of sensation, curvature of the spine and sometimes mild hearing loss.</p> <p>Several of the genes that, when flawed, cause Dejerine-Sottas disease, are the same genes that, when flawed in a different way, lead to various forms of CMT.</p>
<b>Congenital Hypomyelinating Neuropathy (CHN)</b>	
Onset	congenital (at or near birth)
Inheritance	autosomal recessive, spontaneous
Features	<p>Unlike other types of CMT, CHN is associated with reduced myelin formation (hypomyelination) from birth rather than a breakdown of existing myelin. Both genetically and clinically, it's similar to DS, but usually has an earlier onset and a non-progressive or slowly progressive course.</p> <p>Many children with CHN grow up and experience gradual improvements in strength.</p>
<b>Hereditary Neuropathy with Liability to Pressure Palsies (HNPP)</b>	
Onset	usually adolescence
Inheritance	autosomal dominant
Features	<p>HNPP is caused by a defect in the same gene as CMT1A (PMP22 gene), however it's caused by a different type of defect in this gene, and results in a different condition.</p> <p>Most people with HNPP have recurring attacks of <i>palsy</i> (paralysis) or <i>parasthesia</i> (tingling) that are localised to a single limb and clear up after several weeks. Often, these attacks are brought on by a compression injury to the affected limb, but sometimes there's no obvious trigger. In other people, HNPP is progressive and resembles CMT.</p>



## How is CMT diagnosed?

A combination of lower leg weakness and foot deformities is a red flag for CMT, but isn't sufficient for diagnosis. When a patient has those symptoms, a well-trained neurologist will usually start with a physical exam to look for further signs of distal weakness and sensory loss.

As a test for leg weakness, the neurologist might ask the patient to walk on his heels, or to move part of his leg against an opposing force.

To look for sensory loss, the neurologist will usually test the patient's *deep tendon* reflexes (like the knee-jerk reflex), which are reduced or absent in most people with CMT.

During this initial evaluation, the neurologist will also ask about the patient's family history. A family history of CMT-like symptoms, combined with signs of nerve damage from the individual's physical exam, strongly point to CMT or another hereditary neuropathy.

Lack of a family history doesn't rule out CMT, but might prompt the neurologist to ask about diabetes, overexposure to certain drugs and other potential causes of neuropathy.

The neurologist may perform a nerve *conduction velocity test (NCV)*, which measures the strength and speed of electrical signals transmitted through nerves.

It's done by placing surface electrodes, similar to those used for electrocardiograms, on the skin at various points over a nerve. One electrode delivers a mild shock that stimulates an electrical response in the nerve, and the others record this response as it travels through the nerve. (If necessary, a topical anesthetic or sedative is used to ease discomfort caused by the shocks.)

Delayed responses are a sign of demyelination and small responses are a sign of axonopathy. Thus, NCV is often used to distinguish between CMT1 and CMT2.

Other procedures sometimes used to diagnose CMT include *electromyography (EMG)*, which measures the electrical signals in muscles, and less commonly, *nerve biopsy*, which involves the removal and examination of a small piece of nerve.

Next, if the diagnosis is still consistent with CMT, the neurologist may arrange for *genetic testing*. These tests, done by drawing a blood sample, are designed to detect the most common genetic defects known to cause CMT. Many, but certainly not all, of the genetic mutations underlying CMT can be detected with a DNA blood test.

A positive genetic test result can provide a definite diagnosis and useful information for family planning. But once again, a negative result doesn't rule out CMT.



Doctors have many tests for diagnosing CMT.



## Does it run in the family?

CMT can run in a family, even when there is no obvious family history of it. In part, this is because CMT can be inherited in three different ways that aren't always easy to trace through a family tree: *X-linked*, *autosomal dominant* and *autosomal recessive*.

*X-linked* means that the genetic defect (*or mutation*) is located on the X chromosome. In females, who have two X chromosomes, a normal copy of the gene on one chromosome can often compensate (at least partially) for the defective copy. Therefore, X-linked diseases usually affect males more severely than females, because males only have one X chromosome. X-linked diseases (like CMTX) cannot be passed from father to son.

*Autosomal* means the mutation occurs on a chromosome other than the X or Y. Therefore, autosomal diseases affect males and females equally. *Autosomal recessive* means that two copies of a defective gene are required for the full-blown disease. One copy is inherited from each parent, neither of whom would normally have the disease. *Autosomal dominant* means one copy of a defective gene is enough to cause disease. In that case, a person who inherits the defective gene from a parent will have the disease, as will the parent.

When CMT is passed on in an autosomal dominant pattern, it can be easy to recognise in the family tree. In contrast, X-linked or autosomal recessive types of CMT might seem to occur "out of the blue." But in reality, the mother or both parents might be *carriers* who silently harbour a genetic mutation. Many parents have no idea they're carriers of a disease until they have a child with the disease.

CMT also can occur when a new mutation occurs during the child's conception. These are called *spontaneous mutations*, and after they occur, they can be passed on to the next generation.

Your risk of inheriting or passing on CMT depends largely on what type of CMT you have (see "What Are the Different Types of CMT?"). A good way to find out more about this risk is to talk to your doctor or genetic counselor.

Also, see our pamphlet "Genetics and Neuromuscular Diseases" or visit the website of the Centre for Genetics Education ([www.genetics.com.au](http://www.genetics.com.au))



## Search for treatment and cures

In 1991, the *genetic causes* of CMT were completely unknown. But scientists have now identified more than 10 CMT-linked genes and found evidence for several others. This accomplishment has led to *genetic testing* for many types of CMT, which has greatly improved diagnosis.

Of equal importance, the ongoing hunt for CMT genes has given insights into treatments that might be used to stop or reverse the disorder. Scientists are beginning to investigate *how and why* specific genetic mutations lead to different types of CMT. In the future, this knowledge could enable physicians to more accurately predict the course of CMT in individual patients.

In addition to genetic advances, scientists have made significant progress in understanding the biology of axons and Schwann cells — the cells that make myelin in the peripheral nerves. The formation and maintenance of myelin seems to require a finely tuned interaction between axons and Schwann cells, and within axons, there's an intricate railroad-like system for transporting nutrients from one end to the other. Some scientists hope to treat CMT by finding ways to improve axon-Schwann cell interaction or axonal transport.

Other scientists are investigating gene therapy for CMT. One group is developing a method to supply damaged nerves with genes that encode *neurotrophic factors*, naturally occurring proteins that stimulate nerve cell growth. This approach could perhaps be used to treat all types of CMT, regardless of the underlying defect.

Another group has treated a small group of people with CMT1A with neurotrophin 3, a neurotrophic factor, and found it improved sensory function.

Other lab studies involve blocking the hormone progesterone, and giving high doses of ascorbic acid (vitamin C).

Still other scientists hope to treat CMT with *stem cells* — primitive cells capable of generating specific cell types in the body. In recent laboratory experiments, scientists have found efficient ways to turn stem cells into nerve cells and myelin-producing cells, which might one day be used to repair the damaged nerves in people with CMT.