

**Charcot-Marie-Tooth Association Disorder**  
**Symptoms and Treatment**  
**Frequently Asked Questions and Answers**

**1) What is Charcot-Marie-Tooth (CMT) Disorder?**

Charcot-Marie-Tooth Disorder (CMT) is the most commonly inherited peripheral neuropathy. It is a progressive disorder that causes the nerve cells leading to the extremities to slowly degenerate. It may cause people to lose normal use of their feet/legs and hands/arms.

**2) Who is most likely to get CMT?**

CMT is estimated to affect one in every 2,500 people—more than 2.6 million worldwide. It can begin at any age, affecting children and adults of either sex. Men and women of all racial and ethnic groups can develop CMT.

**3) What are the symptoms of CMT?**

The first signs may be frequent tripping or clumsiness that often occurs along with an unusual burning sensation in the extremities. As the disorder progresses, symptoms may include weakness in the hands or ankles, high arches, foot drop, hammertoes, muscle loss in the feet/legs and hands/arms, deformities and loss of fine motor skills.

**4) What causes CMT?**

CMT is an inherited disorder and can be passed from generation to generation. Each case is caused by a variation on one of 33 genes known to cause CMT. The most common form, type CMT1A, makes up about 60% of the population of people who develop CMT. The many different forms of CMT are inherited in different ways.

**5) How is CMT inherited?**

There are three ways that CMT may be inherited: an autosomal dominant form; an autosomal recessive form and an X-linked form. In some instances, a spontaneous (new) mutation of a gene can occur for the first time in a family and children with CMT due to a new mutation can pass the disorder on to their children.

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- *Autosomal Dominant Inheritance:* Most cases of CMT are inherited in this fashion. People with this form of inheritance have a genetic mutation on a chromosome other than the X or Y chromosome. An affected person will have one normal gene and one CMT gene and their children will have a 50/50 chance of inheriting CMT. Affected children can pass CMT on to their children; however, children of an affected parent who did not inherit the defective gene cannot pass CMT on to their children.
- *Autosomal Recessive Inheritance:* Only a few forms of CMT are inherited in this manner. In autosomal recessive forms, both parents have to be “carriers” of the defective gene in order to produce an affected child. As carriers, neither of the parents will have symptoms of CMT, but their children will have a 25% chance of developing the disorder and a 50% chance of becoming a carrier. Although this is a rare type of CMT, children who develop it tend to have a more severe form.
- *X-Linked Inheritance:* In this form, the faulty CMT gene is carried on the female sex chromosome. Because women have two “X” chromosomes, a mother with X-linked CMT may be only mildly affected. Her children will have a 50% chance of developing CMT, but male children are likely to be more severely affected than their mother or female siblings. Also, while an affected mother can pass CMT to children of either gender, an affected father can only pass CMT to a female child.

Overall, except for carriers of a recessive CMT gene, unaffected children cannot pass the disorder on to their children since they do not carry the gene.

## 6) **How do you diagnose CMT?**

CMT is usually first noticed when a person develops lower leg weakness or foot deformities, such as foot drop, hammertoes or high arches. This in itself does not diagnose the disorder but provides a reason for a more extensive examination by a neurologist. A physical exam will then be done to check for weakness and loss of sensation in the feet/legs and hands/arms. Since CMT is hereditary, a doctor will also get a detailed history about family members who have CMT or who may have CMT-like symptoms. Electrodiagnostic tests and genetic testing are also used to diagnose the disorder.

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## 7) **How do you treat and manage CMT?**

There is no cure for CMT, but it is possible to treat the symptoms and manage the disease using a variety of methods such as physical and/or occupational therapy; bracing; surgery, and pain management. Because the severity of CMT can vary from patient to patient, an individualized exercise routine should be developed and followed to maintain the best quality of life. In general, patients should start with the least invasive way to manage or correct their problem(s).

- *Physical/Occupational Therapy:*  
After being diagnosed with CMT, a patient should be referred to a physical or occupational therapist who can design an exercise program that fits their personal strengths and flexibility.
- *Bracing:*  
Bracing is a non-invasive form of correcting problems caused by CMT. Often gait abnormalities can be corrected by the use of molded braces (called AFOs—ankle-foot orthoses). These braces control foot drop and ankle instability and often provide a better sense of balance for patients.
- *Surgery:*  
Surgery is yet another option patients have for correcting foot or leg deformities. Common procedures include straightening and pinning the toes, lowering the arch and sometimes fusing the ankle joint to provide stability, but they are performed less frequently now than in the past because of the possibility of arthritis and other complications.
- *Pain Management:*  
Patients with CMT experience different types of pain, and strategies are available to treat them. At times pain might be sharp and sudden or a gnawing, continuous dull ache. Some pain is associated with dysfunctional nerves while other pain is due to weakened or poorly functioning muscles.

## 8) **What is the CMTA Strategy to Accelerate Research™ (STAR)?**

STAR™ represents an extraordinary opportunity to advance science. Unlike other genetic disorders, enormous progress has been made in researching the causes of Charcot-Marie-Tooth (CMT) disorder. To date, 33 specific genes known to cause the disorder have been identified. Now that the genetic mutations can now be replicated in laboratory models and grown as tissue cultures, there is a window of opportunity to develop treatments and cures for this disease in the immediate and foreseeable future. STAR provides specific focus for all CMTA-funded research efforts. The principal investigators for the STAR initiative have been drawn from an international body of the world's most accomplished research physicians and scientists.

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**9) How did STAR evolve?**

CMT1A, the most common form of CMT, is caused by a genetic duplication that results in an overproduction of the PMP22 protein in cells known as Schwann cells. Like the insulation surrounding the wires in an electrical cord, Schwann cells form the myelin sheath that surrounds and insulates the nerve fiber. The overproduction of PMP22 causes deterioration of the myelin sheath, which results in deterioration of the nerve fiber itself. Two separate medications (high-dosage Vitamin C and a progesterone antagonist, onapristone) have been shown to reduce PMP22 overproduction in animal models. It is probable that other medical compounds could lead to effective therapies for CMT. However, compounds currently available in the National Institutes of Health Libraries number in the millions. Using robots and cultured Schwann cells in a process known as “high-throughput screening,” it becomes feasible to study this vast library of compounds and identify possible treatments.

**10) What will STAR initially involve?**

STAR involves three specific research initiatives:

**Project 1: Develop a stabilized cell line that expresses PMP22**

High-throughput screening requires the development of a stable Schwann cell line genetically engineered to express PMP22 and coupled to a fluorescent “reporter” molecule. Thousands of medicines will be combined with the cells in tissue cultures for screening. Medicines that dim the fluorescent glow of the reporter molecule suggest a decrease in the amount of PMP22 being produced and will become candidates for further study.

**Project 2: Create a laboratory model that produces cells closer to human Schwann cells**

There are no lines of human Schwann cells suitable for high-throughput screening. The creation of a new laboratory model will produce a cell line with characteristics that more closely mimic human cells. This new line will improve the test results in Project 1 and laboratory models will be used to further test the candidate medicines as they are identified.

**Project 3: Evaluate the regulation of the human PMP22 gene**

The first two projects rely on Schwann cells produced in laboratory models. This project will examine in detail how the human PMP22 gene is regulated and “turned on,” causing the overexpression of the PMP22 protein.

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**11) How can I support the efforts of the CMTA and the STAR initiative?**

Researchers estimate that it will take \$10 million raised over the next 5 years to support the three projects of the STAR initiative. You can make a tax-deductible donation to the Charcot-Marie-Tooth Association on their website at [www.charcot-marie-tooth.org](http://www.charcot-marie-tooth.org); by calling the CMTA at 1-800-606-CMTA (2682); or by mailing a check to the Charcot-Marie-Tooth Association, 2700 Chestnut Street, Chester, PA 19013.

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