

# Hereditary Peripheral Neuropathy

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## Key Points

### **Genetics**

- Peripheral neuropathy can be an inherited condition. Charcot-Marie-Tooth (CMT) is the most common cause of inherited peripheral neuropathy.
- The majority of CMT is autosomal dominant, but autosomal recessive and X-linked forms also occur.
- Molecular genetic testing for CMT is complicated due to the existence of more than 15 genes associated with this condition.

### **Ethics**

- Physicians do not have a legal obligation to protect the confidentiality of information provided to them by individuals who are not their patients.
- However, when deciding what information to disclose, the basic precept of respect for persons should be followed, and care must be taken to balance the patients' competing needs and interests.

## Learning Objectives

Participants will be able to:

- Describe the clinical characteristics, inheritance patterns, and genetic testing for the most common form of hereditary neuropathy, Charcot-Marie-Tooth;
- Identify possible ethical issues if a physician receives a confidential telephone call from a patient's family member.

## Family History Issues

CMT hereditary neuropathy can be inherited in an autosomal dominant, autosomal recessive, or X-linked manner. See [GeneReview: CMT Overview, Causes](#).

## Red Flags



Symptoms suggestive of peripheral neuropathy, such as tingling, pain, or weakness in the hands or feet, which occur at a young age (first to third decade) or in the absence of a known other cause should suggest the diagnosis of a hereditary peripheral neuropathy.

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## Case 7. Resident Receives a Troubling Phone Call about Peripheral Neuropathy from a Patient's Relative

A resident presents a 42-year-old woman who has come for an annual examination. The resident has performed routine health maintenance, including a pelvic examination with Pap test and a clinician breast examination; a dT booster has been ordered. The patient is a non-smoker, drinks minimal alcohol, and has no known family history of breast, colorectal, or ovarian cancer. Her father has heart disease at age 70 years and she reports no other family history of concern. She notes that she has one brother and he is an alcoholic. Her physical examination is normal.

The resident is troubled because she has received a phone call from the patient's brother prior to the visit, asking her to evaluate the patient for Charcot-Marie-Tooth disease (CMT). The brother states that he is worried about his sister because he has seen her stumble many times and thinks she has the disease, which also affects him and their father. He has tried to talk with his sister about it and she has refused to discuss it. He does not want the resident to mention that he has called. He also asks that the resident inform him of the patient's status so that he can take whatever measures are necessary to ensure that she is protected from complications of her neurological disease.

The resident has reviewed information about CMT disease on the GeneTests Web site. She understands that this disorder causes peripheral neuropathy and is usually inherited in an autosomal dominant manner. Thus, the brother's history (if reliable) would indicate that the patient has a 50% risk of inheriting the condition. In the absence of physical findings, and with conflicting history from the patient and her brother, the resident is unsure

how to proceed.

## Clinical Care Issues

### **Making the diagnosis of Charcot-Marie-Tooth (CMT)**

Establishing the diagnosis of a peripheral neuropathy requires a medical history, physical examination, neurological examination, nerve conduction velocities (NCV), and electromyography (EMG) studies. Establishing the specific cause of a peripheral neuropathy after the diagnosis has been established requires a detailed family history and the use of DNA-based testing when available. See [GeneReview: CMT Overview](#).

In patients with symptoms of CMT, progressive weakness of the distal muscles in the feet and/or hands is usually reported by the patient in the first through third decade, but the age of onset ranges from infancy to the fourth and subsequent decades. NCV and EMG testing are almost always abnormal.

Other non-genetic causes of peripheral neuropathy should be ruled out, such as alcoholism, diabetes, pernicious anemia, and hypothyroidism.

### **Establishing mode of inheritance**

In this case, the patient's brother reported that he and his father are affected with CMT. If this information is correct, we can assume that the likely mode of inheritance is [autosomal dominant](#).

### **If this patient has Charcot-Marie-Tooth, what are the benefits of establishing the diagnosis?**

No treatment is available to reverse or slow the disease process in CMT. Treatment is symptomatic. Important career and employment implications may occur because of the persistent weakness of hands and/or feet. Additionally, certain drugs such as vincristine, taxol, cisplatin, isoniazid, and nitrofurantoin that are known to cause nerve damage should be avoided. One study showed that in 45 women with CMT1, symptoms of CMT worsened during pregnancy [[Rudnik-Schoneborn 1993](#)].

### **Handling the information provided by the phone call from the patient's brother**

First, the physician can try to elicit information from the patient relevant to the question of CMT — for example, whether she has any symptoms suggestive of peripheral neuropathy — without disclosing the phone call. The physician can also ask the patient specifically if she has any history of neurological disorders in her family. Additionally, a screening neurological examination is part of an annual physical examination and can determine the need for additional workup.

If the patient does not reveal to the physician her family history of CMT, and her history and physical examination are normal, the physician must weigh the likelihood and benefit of a potential CMT diagnosis against the potential benefits and harms of disclosing her brother's phone call, as discussed in [Ethical, Legal, Social, and Cultural Issues](#).

## Risk Assessment

**Role of family history and age of onset in assessing risk.** Family history is the most critical factor in assessing risk of Charcot-Marie-Tooth. If the history provided by the patient's brother is correct, CMT is exhibiting autosomal dominant inheritance. Therefore, the patient has a 50% chance of inheriting the mutation causing CMT in her family. Since CMT usually has its onset in the first to third decade of life, an individual at 50% risk who has reached her fifth decade of life and is still asymptomatic is less likely to be affected.

**What other syndromes should be considered?** CMT hereditary peripheral neuropathy needs to be distinguished from other acquired causes of peripheral neuropathy, such as diabetes mellitus and alcoholism, and other genetic neuropathies, such as hereditary ataxias with neuropathy. See [GeneReview: CMT Overview, Differential Diagnosis](#).

## Genetic Counseling and Testing

**Are there molecular genetic testing options?** Molecular genetic testing is typically available. It is helpful to know which subtype of CMT is inherited in this family. There are three types of autosomal dominant Charcot-Marie-Tooth: CMT1, CMT2, and Intermediate CMT, which can often be distinguished clinically. CMT1 is associated with mutations in at least four genes (CMT1A-D), CMT2 is associated with mutations in at least five genes (CMT2A-E), and intermediate CMT is associated with mutations in at least three genes. Molecular genetic testing is presently clinically available for

CMT1A, CMT1B, CMT1D, and CMT2E. See [GeneReview: CMT Overview, Autosomal dominant CMT](#).

**What is the optimal testing strategy for the family?** Testing of asymptomatic adult relatives who are at risk of developing CMT is most informative after molecular genetic testing has identified the specific gene mutation in an individual with an established diagnosis. If the patient is interested in having genetic testing but a mutation has not already been identified in the patient's family, genetic testing should first be pursued in either her father or brother. Since mutations in multiple genes can cause autosomal dominant CMT, a cost-effective strategy for molecular genetic testing for CMT has been developed. See [GeneReview: CMT Overview, Testing Strategies](#). Such testing is typically performed in the context of formal genetic counseling.

If the family's mutation has already been found, genetic testing in the patient would determine the presence or absence of the identified mutation, allowing for a definitive answer regarding whether she inherited the disease-causing mutation. Obtaining her family's genetic test results would require that the patient request this information directly from her brother or father.

## Interventions

**Preventive care.** No treatment is available to reverse or slow the disease process in CMT.

**Other clinical management.** Treatment is symptomatic and patients are often evaluated and managed by a multidisciplinary team that includes neurologists, physiatrists, orthopedic surgeons, and physical and occupational therapists. See [GeneReview: CMT Overview, Management](#).

## Ethical/Legal/Social/Cultural Issues

The patient did not report her father's and brother's diagnosis of CMT. The history from the brother may be unreliable, but CMT would be an unusual diagnosis to provide in a fabricated medical history. The patient may be unaware of this history, she may not know or be "in denial" of her genetic risk of developing this disease, or she may have simply failed to report this information.

The ethical concerns include:

- Respecting family relationships
- Maintaining a good doctor-patient relationship
- Providing the best care recommendations to the patient
- Confidentiality of patient information
- Confidentiality of information not obtained from the patient

**Family relationships.** Physicians are obligated to respect the confidentiality of medical information. In this case, the resident has obtained information with potential consequences for her patient from an outside source. The provider of the information (the patient's brother) has requested that his call not be disclosed; but his call is not protected by medical confidentiality. However, revealing the call could damage the relationship between the brother and sister. The patient might react with anger to the information that her brother called, and her brother might be angry if his call is revealed.

**Doctor-patient relationship.** Disclosing the call could lead to important discussions on CMT, providing an opportunity to assess the patient's knowledge of the disease and her attitude toward her potential risk. Not revealing the discussion could lead to feeling of mistrust if the patient were to discover the brother's call later on. However, if the doctor judged that telling the patient about her brother's phone call would cause more harm than good, the doctor could later justify his or her decision on this basis.

**Patient's best care.** How will this information contribute to the well-being of the patient? Is this information relevant to her care? Disclosure could allow for a better understanding of family diagnosis. If the patient is tested, the results could provide useful predictive information but could also upset her. Testing might alleviate stress or allow her time to make preparations for future care.

Physicians have a duty to disclose information if it will improve the health outcome of the patient. However, since no medical treatment exists that reverses or slows the natural disease process, the physician must consider whether there would be a benefit to pursuing this diagnosis in the patient. Those treatments that do exist for CMT are for symptomatic relief, such as referrals to rehabilitation therapy for environmental adaptations or durable medical equipment. (See [Occupational Therapy Revision Notes: CMT.](#))

**Confidentiality of patient information.** The phone conversation with the patient's brother might allow the resident to gain an understanding of the family relationships and assess the validity of the brother's information. However, it is important that the resident explain to the brother that

information concerning the patient cannot and will not be shared without the patient's consent. Despite the brother's good intentions, he has no right to any of his sister's medical information without her approval. Laws and regulations such as the [HIPAA Privacy Rule](#) protect patient information from being shared or distributed without the patient's consent. The resident must make it clear that she will not relay any information from the patient's visit and that any inquiries concerning the visit must be addressed to his sister.

**Confidentiality of information not obtained from the patient.** In this case, the resident has obtained information with potential consequences for her patient from an outside source. The provider of the information (the patient's brother) has requested that his call not be disclosed; but his call is not protected by medical confidentiality. As a result, whether to disclose the call is a matter of physician discretion. Among the issues the resident should consider are: preserving family relationships, whether knowing about the call will foster or hinder trust from her patient, and whether the source of the information is especially germane to the patient's care. Will it help or hurt the patient's care or the doctor-patient relationship to disclose the call? On the one hand, disclosing the call could provide the basis for a discussion of CMT and family members who are reportedly affected. This discussion could be helpful in assessing the patient's knowledge and attitudes toward her potential risk. It might also provide further insights about the patient's family and how family members view health and disease management. On the other hand, the patient might react with anger to the information that her brother called, and her brother might be angry if his call is revealed. At minimum, the information provided by the brother's call should be evaluated for its contribution to the patient's care and well-being.

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## Resources

- **Charcot-Marie-Tooth Association**  
2700 Chestnut Street  
Chester, PA 19013-4867  
**Phone:** 610-499-9264; 610-499-9265; 1-800-606-CMTA (2682)  
**Fax:** 610-499-9267  
**Email:** CMTAssoc@aol.com
- **Hereditary Neuropathy Foundation**  
PO Box 287103

New York, NY 10128

**Phone:** 917-648-6971

**Email:** info@hnf-cure.org

- **The Neuropathy Association**

60 E 42nd Street

Suite 942

New York City, NY 10165-0999

**Phone:** 212-692-0662

**Email:** info@neuropathy.org

- **National Library of Medicine Genetics Home Reference**

[Charcot-Marie-Tooth disease](#)

- **GeneTests Online Medical Genetics Information Resource**

- **GeneReviews, GeneTests Online Medical Genetics Information Resource**

- **GeneTests Resources for CMT** 

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