Charcot-Marie-Tooth disease

Charcot-Marie-Tooth disease is a group of progressive disorders that affect the peripheral nerves. Peripheral nerves connect the brain and spinal cord to muscles and to sensory cells that detect sensations such as touch, pain, heat, and sound. Damage to the peripheral nerves can result in loss of sensation and wasting (atrophy) of muscles in the feet, legs, and hands.

Charcot-Marie-Tooth disease usually becomes apparent in adolescence or early adulthood, but onset may occur anytime from early childhood through late adulthood. Symptoms of Charcot-Marie-Tooth disease vary in severity, even among members of the same family. Some people never realize they have the disorder, but most have a moderate amount of physical disability. A small percentage of people experience severe weakness or other problems which, in rare cases, can be life-threatening. In most affected individuals, however, Charcot-Marie-Tooth disease does not affect life expectancy.

Typically, the earliest symptoms of Charcot-Marie-Tooth disease involve balance difficulties, clumsiness, and muscle weakness in the feet. Affected individuals may have foot abnormalities such as high arches (pes cavus), flat feet (pes planus), or curled toes (hammer toes). They often have difficulty flexing the foot or walking on the heel of the foot. These difficulties may cause a higher than normal step (or gait) and increase the risk of ankle injuries and tripping.

As the disease progresses, muscles in the lower legs usually weaken, but leg and foot problems rarely require the use of a wheelchair. Affected individuals may also develop weakness in the hands, causing difficulty with daily activities such as writing, fastening buttons, and turning doorknobs. People with this disorder typically experience a decreased sensitivity to touch, heat, and cold in the feet and lower legs, but occasionally feel aching or burning sensations. In some cases, affected individuals experience gradual hearing loss, deafness, or loss of vision.

There are several types of Charcot-Marie-Tooth disease. Type 1 Charcot-Marie-Tooth disease (CMT1) is characterized by abnormalities in myelin, the fatty substance that covers nerve cells, protecting them and helping to conduct nerve impulses. These abnormalities slow the transmission of nerve impulses. Type 2 Charcot-Marie-Tooth disease (CMT2) is characterized by abnormalities in the fiber, or axon, that extends from a nerve cell body and transmits nerve impulses. These abnormalities reduce the strength of the nerve impulse. Type 4 Charcot-Marie-Tooth disease (CMT4) affects either the axon or myelin and is distinguished from the other types by its pattern of inheritance. In intermediate forms of Charcot-Marie-Tooth disease, the nerve impulses are both slowed and reduced in strength, probably due to abnormalities in both axons and myelin. Type X Charcot-Marie-Tooth disease (CMTX) is caused by mutations in a
gene on the X chromosome, one of the two sex chromosomes. Within the various types of Charcot-Marie-Tooth disease, subtypes (such as CMT1A, CMT1B, CMT2A, CMT4A, and CMTX1) are distinguished by the specific gene that is altered.

Sometimes other, more historical names are used to describe this disorder. For example, Roussy-Levy syndrome is a form of Charcot-Marie-Tooth disease defined by the additional feature of rhythmic shaking (tremors). Dejerine-Sottas syndrome is a term sometimes used to describe a severe, early childhood form of Charcot-Marie-Tooth disease; it is also sometimes called Charcot-Marie-Tooth disease type 3 (CMT3). Depending on the specific gene that is altered, this severe, early onset form of the disorder may also be classified as CMT1 or CMT4. CMTX5 is also known as Rosenberg-Chutorian syndrome. Some researchers believe that this condition is not actually a form of Charcot-Marie-Tooth disease. Instead, they classify it as a separate disorder characterized by peripheral nerve problems, deafness, and vision loss.

**Frequency**

Charcot-Marie-Tooth disease is the most common inherited disorder that involves the peripheral nerves, affecting an estimated 150,000 people in the United States. It occurs in populations worldwide with a prevalence of about 1 in 2,500 individuals.

**Causes**

Charcot-Marie-Tooth disease is caused by mutations in many different genes. These genes provide instructions for making proteins that are involved in the function of peripheral nerves in the feet, legs, and hands. The gene mutations that cause Charcot-Marie-Tooth disease affect the function of the proteins in ways that are not fully understood; however, they likely impair axons, which transmit nerve impulses, or affect the specialized cells that produce myelin. As a result, peripheral nerve cells slowly lose the ability to stimulate the muscles and to transmit sensory signals to the brain.

The list of genes associated with Charcot-Marie-Tooth disease continues to grow as researchers study this disorder. Different mutations within a particular gene may cause signs and symptoms of differing severities or lead to different types of Charcot-Marie-Tooth disease.

CMT1 is caused by mutations in the following genes: *PMP22* (CMT1A and CMT1E), *MPZ* (CMT1B), *LITAF* (CMT1C), *EGR2* (CMT1D), and *NEFL* (CMT1F).

CMT2 can result from alterations in many genes, including *MFN2* and *KIF1B* (CMT2A); *RAB7A* (CMT2B); *LMNA* (CMT2B1); *TRPV4* (CMT2C); *BSCL2* and *GARS* (CMT2D); *NEFL* (CMT2E); *HSPB1* (CMT2F); *MPZ* (CMT2I and CMT2J); *GDAP1* (CMT2K); and *HSPB8* (CMT2L). Certain *DNM2* gene mutations also cause a form of CMT2.

CMT4 is caused by mutations in the following genes: *GDAP1* (CMT4A), *MTMR2* (CMT4B1), *SBF2* (CMT4B2), *SH3TC2* (CMT4C), *NDRG1* (CMT4D), *EGR2* (CMT4E), *PRX* (CMT4F), *FGD4* (CMT4H), and *FIG4* (CMT4J).
Intermediate forms of the disorder can be caused by alterations in genes including *DNM2*, *MPZ*, *YARS*, and *GDAP1*. CMTX is caused by mutations in genes including *GJB1* (CMTX1) and *PRPS1* (CMTX5). Mutations in additional genes, some of which have not been identified, also cause various forms of Charcot-Marie-Tooth disease.

**Inheritance Pattern**

The pattern of inheritance varies with the type of Charcot-Marie-Tooth disease. CMT1, most cases of CMT2, and most intermediate forms are inherited in an autosomal dominant pattern. This pattern of inheritance means that one copy of the altered gene in each cell is sufficient to cause the disorder. In most cases, an affected person has one affected parent.

CMT4, a few CMT2 subtypes, and some intermediate forms are inherited in an autosomal recessive pattern, which means both copies of the gene in each cell have mutations. Most often, the parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but do not show signs and symptoms of the condition.

CMTX is inherited in an X-linked dominant pattern. A condition is considered X-linked if the mutated gene that causes the disorder is located on the X chromosome. The inheritance is dominant if one copy of the altered gene is sufficient to cause the condition. In most cases, affected males, who have the alteration on their only copy of the X chromosome, experience more severe symptoms of the disorder than females, who have two X chromosomes. A characteristic of X-linked inheritance is that fathers cannot pass X-linked traits to their sons. All daughters of affected men will have one altered X chromosome, but they may only have mild symptoms of the disorder.

Some cases of Charcot-Marie-Tooth disease result from a new mutation and occur in people with no history of the disorder in their family.

**Other Names for This Condition**

- Charcot-Marie-Tooth hereditary neuropathy
- Charcot-Marie-Tooth syndrome
- CMT
- hereditary motor and sensory neuropathy
- HMSN
- peroneal muscular atrophy
- PMA
Diagnosis & Management

Genetic Testing Information

• What is genetic testing?
  https://primer/testing/genetictesting

• Genetic Testing Registry: Charcot-Marie-Tooth disease

Research Studies from ClinicalTrials.gov

• ClinicalTrials.gov
  https://clinicaltrials.gov/ct2/results?cond=%22Charcot-Marie-Tooth+disease%22

Other Diagnosis and Management Resources

• GeneReview: Charcot-Marie-Tooth Hereditary Neuropathy Overview
  https://www.ncbi.nlm.nih.gov/books/NBK1358

• GeneReview: Charcot-Marie-Tooth Neuropathy Type 2A
  https://www.ncbi.nlm.nih.gov/books/NBK1511

• GeneReview: Charcot-Marie-Tooth Neuropathy Type 2E/1F
  https://www.ncbi.nlm.nih.gov/books/NBK1187

• GeneReview: Charcot-Marie-Tooth Neuropathy Type 4C
  https://www.ncbi.nlm.nih.gov/books/NBK1340

• GeneReview: Charcot-Marie-Tooth Neuropathy X Type 1
  https://www.ncbi.nlm.nih.gov/books/NBK1374

• GeneReview: Charcot-Marie-Tooth Neuropathy X Type 5
  https://www.ncbi.nlm.nih.gov/books/NBK1876

• GeneReview: DNM2-Related Intermediate Charcot-Marie-Tooth Neuropathy
  https://www.ncbi.nlm.nih.gov/books/NBK45014

• GeneReview: GARS-Associated Axonal Neuropathy
  https://www.ncbi.nlm.nih.gov/books/NBK1242

• GeneReview: GDAP1-Related Hereditary Motor and Sensory Neuropathy
  https://www.ncbi.nlm.nih.gov/books/NBK1539

• GeneReview: TRPV4-Associated Disorders
  https://www.ncbi.nlm.nih.gov/books/NBK201366

• MedlinePlus Encyclopedia: Charcot-Marie-Tooth Disease
  https://medlineplus.gov/ency/article/000727.htm

• MedlinePlus Encyclopedia: Hammer Toe
  https://medlineplus.gov/ency/article/001235.htm

• MedlinePlus Encyclopedia: High Arch
  https://medlineplus.gov/ency/article/001261.htm
Additional Information & Resources

Health Information from MedlinePlus
- Encyclopedia: Charcot-Marie-Tooth Disease
  https://medlineplus.gov/ency/article/000727.htm
- Encyclopedia: Hammer Toe
  https://medlineplus.gov/ency/article/001235.htm
- Encyclopedia: High Arch
  https://medlineplus.gov/ency/article/001261.htm
- Health Topic: Charcot-Marie-Tooth Disease
  https://medlineplus.gov/charcotmarietoothdisease.html
- Health Topic: Peripheral Nerve Disorders
  https://medlineplus.gov/peripheralnervedisorders.html

Genetic and Rare Diseases Information Center
- Charcot-Marie-Tooth disease

Additional NIH Resources
- National Human Genome Research Institute
  https://www.genome.gov/11009201/
- National Institute of Neurological Disorders and Stroke
  https://www.ninds.nih.gov/Disorders/All-Disorders/Charcot-Marie-Tooth-Disease-Information-Page

Educational Resources
- MalaCards: charcot-marie-tooth disease
  http://www.malacards.org.card/charcot_marie_tooth_disease
- Merck Manual Consumer Version
- National Health Service (UK)
  https://www.nhs.uk/conditions/charcot-marie-tooth-disease/
- Orphanet: Autosomal dominant Charcot-Marie-Tooth disease type 2
  https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=64746
- Orphanet: Autosomal dominant Charcot-Marie-Tooth disease type 2C
  https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=99937
- Orphanet: Autosomal dominant Charcot-Marie-Tooth disease type 2D
  https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=99938
• Orphanet: Autosomal dominant Charcot-Marie-Tooth disease type 2E
  https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=99939
• Orphanet: Autosomal dominant Charcot-Marie-Tooth disease type 2F
  https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=99940
• Orphanet: Autosomal dominant Charcot-Marie-Tooth disease type 2I
  https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=99942
• Orphanet: Autosomal dominant Charcot-Marie-Tooth disease type 2L
  https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=99945
• Orphanet: Autosomal dominant Charcot-Marie-Tooth disease type 2N
  https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=228174
• Orphanet: Autosomal recessive Charcot-Marie-Tooth disease with hoarseness
  https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=101097
• Orphanet: Charcot-Marie-Tooth disease type 1
  https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=65753
• Orphanet: Charcot-Marie-Tooth disease type 1A
  https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=101081
• Orphanet: Charcot-Marie-Tooth disease type 1B
  https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=101082
• Orphanet: Charcot-Marie-Tooth disease type 1C
  https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=101083
• Orphanet: Charcot-Marie-Tooth disease type 1D
  https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=101084
• Orphanet: Charcot-Marie-Tooth disease type 1E
  https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=90658
• Orphanet: Charcot-Marie-Tooth disease type 1F
  https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=101085
• Orphanet: Charcot-Marie-Tooth disease type 2B1
  https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=98856
• Orphanet: Charcot-Marie-Tooth disease type 2B2
  https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=101101
• Orphanet: Charcot-Marie-Tooth disease type 2H
  https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=101102
• Orphanet: Charcot-Marie-Tooth disease type 4
  https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=64749
• Orphanet: Charcot-Marie-Tooth disease type 4A
  https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=99948
• Orphanet: Charcot-Marie-Tooth disease type 4B1
  https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=99955
• Orphanet: Charcot-Marie-Tooth disease type 4B2
  https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=99956
• Orphanet: Charcot-Marie-Tooth disease type 4C
  https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=99949
• Orphanet: Charcot-Marie-Tooth disease type 4D
  https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=99950
• Orphanet: Charcot-Marie-Tooth disease type 4E
  https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=99951
• Orphanet: Charcot-Marie-Tooth disease type 4F
  https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=99952
• Orphanet: Charcot-Marie-Tooth disease type 4H
  https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=99954
• Orphanet: Charcot-Marie-Tooth disease type 4J
  https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=139515
• Orphanet: Charcot-Marie-Tooth disease/Hereditary motor and sensory neuropathy
  https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=166
• Orphanet: Dejerine-Sottas syndrome
  https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=64748
• Orphanet: Dejerine-Sottas syndrome
  https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=64748
• Orphanet: X-linked Charcot-Marie-Tooth disease
  https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=64747

Patient Support and Advocacy Resources

• Charcot-Marie-Tooth Association
  http://www.cmtausa.org/index.php
• Hereditary Neuropathy Foundation
  https://www.hnf-cure.org/
• Muscular Dystrophy Association
  https://www.mda.org/disease/charcot-marie-tooth
• National Organization for Rare Disorders (NORD): Charcot-Marie-Tooth Disease
  https://rarediseases.org/rare-diseases/charcot-marie-tooth-disease/
• National Organization for Rare Disorders (NORD): Dejerine Sottas Disease
  https://rarediseases.org/rare-diseases/dejerine-sottas-disease/
• National Organization for Rare Disorders: Rosenberg-Chutorian Syndrome
  https://rarediseases.org/rare-diseases/rosenberg-chutorian-syndrome/

• National Organization for Rare Disorders: Roussy-Levy Syndrome
  https://rarediseases.org/rare-diseases/roussy-levy-syndrome/

Clinical Information from GeneReviews
• Charcot-Marie-Tooth Hereditary Neuropathy Overview
  https://www.ncbi.nlm.nih.gov/books/NBK1358

• Charcot-Marie-Tooth Neuropathy Type 2A
  https://www.ncbi.nlm.nih.gov/books/NBK1511

• Charcot-Marie-Tooth Neuropathy Type 2E/1F
  https://www.ncbi.nlm.nih.gov/books/NBK1187

• Charcot-Marie-Tooth Neuropathy Type 4C
  https://www.ncbi.nlm.nih.gov/books/NBK1340

• Charcot-Marie-Tooth Neuropathy X Type 1
  https://www.ncbi.nlm.nih.gov/books/NBK1374

• Charcot-Marie-Tooth Neuropathy X Type 5
  https://www.ncbi.nlm.nih.gov/books/NBK1876

• DNM2-Related Intermediate Charcot-Marie-Tooth Neuropathy
  https://www.ncbi.nlm.nih.gov/books/NBK45014

• GARS-Associated Axonal Neuropathy
  https://www.ncbi.nlm.nih.gov/books/NBK1242

• GDAP1-Related Hereditary Motor and Sensory Neuropathy
  https://www.ncbi.nlm.nih.gov/books/NBK1539

• TRPV4-Associated Disorders
  https://www.ncbi.nlm.nih.gov/books/NBK201366

Scientific Articles on PubMed
• PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28Charcot-Marie-Tooth+Disease%5BMAJR%5D%29+AND+%28Charcot-Marie-Tooth+disease%5BTI%5D%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+360+days%22%5Bdp%5D
Catalog of Genes and Diseases from OMIM

- CHARCOT-MARIE-TOOTH DISEASE AND DEAFNESS
  http://omim.org/entry/118300

- CHARCOT-MARIE-TOOTH DISEASE, AXONAL, AUTOSOMAL DOMINANT, TYPE 2A2A
  http://omim.org/entry/609260

- CHARCOT-MARIE-TOOTH DISEASE, AXONAL, TYPE 2A1
  http://omim.org/entry/118210

- CHARCOT-MARIE-TOOTH DISEASE, AXONAL, TYPE 2B
  http://omim.org/entry/600882

- CHARCOT-MARIE-TOOTH DISEASE, AXONAL, TYPE 2B1
  http://omim.org/entry/605588

- CHARCOT-MARIE-TOOTH DISEASE, AXONAL, TYPE 2B2
  http://omim.org/entry/605589

- CHARCOT-MARIE-TOOTH DISEASE, AXONAL, TYPE 2D
  http://omim.org/entry/601472

- CHARCOT-MARIE-TOOTH DISEASE, AXONAL, TYPE 2E
  http://omim.org/entry/607684

- CHARCOT-MARIE-TOOTH DISEASE, AXONAL, TYPE 2F
  http://omim.org/entry/606595

- CHARCOT-MARIE-TOOTH DISEASE, AXONAL, TYPE 2I
  http://omim.org/entry/607677

- CHARCOT-MARIE-TOOTH DISEASE, AXONAL, TYPE 2J
  http://omim.org/entry/607736

- CHARCOT-MARIE-TOOTH DISEASE, AXONAL, TYPE 2K
  http://omim.org/entry/607831

- CHARCOT-MARIE-TOOTH DISEASE, AXONAL, TYPE 2L
  http://omim.org/entry/608673

- CHARCOT-MARIE-TOOTH DISEASE, AXONAL, TYPE 2N
  http://omim.org/entry/613287

- CHARCOT-MARIE-TOOTH DISEASE, AXONAL, TYPE 2O
  http://omim.org/entry/614228

- CHARCOT-MARIE-TOOTH DISEASE, AXONAL, TYPE 2P
  http://omim.org/entry/614436

- CHARCOT-MARIE-TOOTH DISEASE, AXONAL, WITH VOCAL CORD PARESIS, AUTOSOMAL RECESSIVE
  http://omim.org/entry/607706
• CHARCOT-MARIE-TOOTH DISEASE, DEMYELINATING, TYPE 1A
  http://omim.org/entry/118220
• CHARCOT-MARIE-TOOTH DISEASE, DEMYELINATING, TYPE 1B
  http://omim.org/entry/118200
• CHARCOT-MARIE-TOOTH DISEASE, DEMYELINATING, TYPE 1C
  http://omim.org/entry/601098
• CHARCOT-MARIE-TOOTH DISEASE, DEMYELINATING, TYPE 1D
  http://omim.org/entry/607678
• CHARCOT-MARIE-TOOTH DISEASE, DEMYELINATING, TYPE 1F
  http://omim.org/entry/607734
• CHARCOT-MARIE-TOOTH DISEASE, DOMINANT INTERMEDIATE B
  http://omim.org/entry/606482
• CHARCOT-MARIE-TOOTH DISEASE, DOMINANT INTERMEDIATE C
  http://omim.org/entry/608323
• CHARCOT-MARIE-TOOTH DISEASE, DOMINANT INTERMEDIATE D
  http://omim.org/entry/607791
• CHARCOT-MARIE-TOOTH DISEASE, DOMINANT INTERMEDIATE E
  http://omim.org/entry/614455
• CHARCOT-MARIE-TOOTH DISEASE, RECESSIVE INTERMEDIATE A
  http://omim.org/entry/608340
• CHARCOT-MARIE-TOOTH DISEASE, TYPE 4A
  http://omim.org/entry/214400
• CHARCOT-MARIE-TOOTH DISEASE, TYPE 4B1
  http://omim.org/entry/601382
• CHARCOT-MARIE-TOOTH DISEASE, TYPE 4B2
  http://omim.org/entry/604563
• CHARCOT-MARIE-TOOTH DISEASE, TYPE 4C
  http://omim.org/entry/601596
• CHARCOT-MARIE-TOOTH DISEASE, TYPE 4D
  http://omim.org/entry/601455
• CHARCOT-MARIE-TOOTH DISEASE, TYPE 4H
  http://omim.org/entry/609311
• CHARCOT-MARIE-TOOTH DISEASE, TYPE 4J
  http://omim.org/entry/611228
• CHARCOT-MARIE-TOOTH DISEASE, X-LINKED DOMINANT, 1
  http://omim.org/entry/302800
• CHARCOT-MARIE-TOOTH DISEASE, X-LINKED RECESSIVE, 5
  http://omim.org/entry/311070

• HEREDITARY MOTOR AND SENSORY NEUROPATHY, TYPE IIC
  http://omim.org/entry/606071

• HYPERTROPHIC NEUROPATHY OF DEJERINE-SOTTAS
  http://omim.org/entry/145900

• NEUROPATHY, CONGENITAL HYPOMYELINATING OR AMYELINATING, AUTOSOMAL RECESSIVE
  http://omim.org/entry/605253

• ROUSSY-LEVY HEREDITARY AREFLEXIC DYSTASIA
  http://omim.org/entry/180800

Sources for This Summary
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/20301532
• OMIM: CHARCOT-MARIE-TOOTH DISEASE, TYPE 4H
  http://omim.org/entry/609311
• OMIM: CHARCOT-MARIE-TOOTH DISEASE, TYPE 4J
  http://omim.org/entry/611228
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/25901280
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4392824/
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/24434692
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/26527893
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4621202/
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/20301731

Reprinted from Genetics Home Reference: