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GJB1 Disorders: Charcot-Marie-Tooth Neuropathy (CMT1X) and Central Nervous System Phenotypes

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Summary

Clinical characteristics

GJB1 disorders are typically characterized by peripheral motor and sensory neuropathy with or without fixed CNS abnormalities and/or acute, self-limited episodes of transient neurologic dysfunction (especially weakness and dysarthria). Peripheral neuropathy typically manifests in affected males between ages five and 25 years. Although both men and women are affected, manifestations tend to be less severe in women, some of whom may remain asymptomatic.

Less commonly, initial manifestations in some affected individuals are stroke-like episodes (acute fulminant episodes of reversible CNS dysfunction).

Diagnosis/testing

The diagnosis of CMT1X is established in a male by identification of a hemizygous *GJB1* pathogenic variant on molecular genetic testing and in a female by identification of a heterozygous *GJB1* pathogenic variant.

Management

Treatment of manifestations: Treatment by a multidisciplinary team includes special shoes and/or ankle/foot orthoses to correct foot drop and to aid walking; surgery as needed for severe *pes cavus*; forearm crutches, canes, wheelchairs as needed for mobility; daily heel cord stretching to prevent Achilles' tendon shortening; exercise as tolerated. Treatment of stroke-like episodes is supportive, as these are self-limited.

Surveillance: Yearly examinations by: a neurologist of motor function and pain; a physical therapist of gross motor skills and activities of daily living (ADL), an occupational therapist of fine motor skills and ADL; a foot care specialist for pressure sores and/or poorly fitting footwear. More frequent self-foot examination by the affected individual.

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Agents/circumstances to avoid: Obesity (makes ambulation more difficult); medications that are toxic or potentially toxic to persons with CMT.

Genetic counseling

CMT1X is inherited in an X-linked manner. Affected males transmit the *GJB1* pathogenic variant to all of their daughters and none of their sons. Women with a *GJB1* pathogenic variant have a 50% chance of transmitting the pathogenic variant to each child. Males who inherit the pathogenic variant will be affected; females who inherit the pathogenic variant will be heterozygotes and may have mild-to-no manifestations or, more often, mild-to-moderate manifestations that may progress. Once the *GJB1* pathogenic variant has been identified in an affected family member, molecular genetic testing of at-risk female relatives to determine their genetic status, prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

GJB1 Charcot-Marie-Tooth neuropathy with or without central nervous system dysfunction (CMT1X) **should be suspected** in an individual with the following clinical findings, electrophysiologic findings, and family history.

Clinical findings

- **Peripheral motor and sensory neuropathy** with or without the following:
  - Occasionally fixed CNS abnormalities
  - Acute, self-limited episodes of transient neurologic dysfunction, especially weakness and dysarthria
- **Stroke-like episodes.** Acute fulminant episodes of reversible CNS dysfunction, usually with peripheral neuropathy or a family history of peripheral neuropathy
- **Familial ataxia** with peripheral neuropathy

Electrophysiologic findings. Nerve conduction velocities (NCVs):

- Forearm NCVs are typically in the "intermediate" range of 30-40 m/sec for males; in females NCVs from 30-60 m/sec are seen [Jerath et al 2016].
- Median nerve conductions are more severely affected than those of the ulnar nerve [Tsai et al 2013].

  Note: NCV can vary from nerve to nerve in a single individual [Gutierrez et al 2000]. NCVs can also vary significantly within and between families.

Family history is consistent with X-linked inheritance (i.e., no male-to-male inheritance). Because females can be as severely affected as males, some family histories will have multi-generation involvement of males and females. If the family is large enough, the fact that no male-to-male transmission is observed may be helpful.

Establishing the Diagnosis

Male proband. The diagnosis of CMT1X **is established** in a male proband with suggestive findings and a hemizygous pathogenic (or likely pathogenic) variant in *GJB1* identified by molecular genetic testing (see Table 1).

Female proband. The diagnosis of CMT1X **is usually established** in a female proband with suggestive findings and a heterozygous pathogenic (or likely pathogenic) variant in *GJB1* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) Identification of a hemizygous or heterozygous *GJB1* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (chromosomal microarray analysis, exome sequencing, exome array, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of CMT1X is broad and overlaps with other forms of CMT, individuals with the findings of peripheral neuropathy described in Suggestive Findings are likely to be diagnosed using gene-targeted testing, often using a multigene panel (see Option 1), whereas those with stroke-like episodes in whom the diagnosis of a CMT1X has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

Single-gene testing is probably most appropriate when X-linked inheritance is possible and the proband has both peripheral nervous system and CNS manifestations typical of CMT1X.

Sequence analysis of *GJB1* detects missense, nonsense, and splice site variants and small intragenic deletions/insertions. If no pathogenic variant is found, gene-targeted deletion/duplication analysis is performed to detect intragenic deletions or duplications.

Note: Disease-causing variants have been reported in the upstream regulatory region, 5'UTR, noncoding exons and splice sites, and 3'UTR (see Molecular Genetics); therefore, sequence analysis should include these regions of *GJB1*.

An inherited neuropathy **multigene panel** that includes *GJB1* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (1) The genes included in multigene panels and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Multigene panels generally include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. For this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1). (5) Variants in upstream regulatory regions, 5' untranslated regions, and putative splice sites as well as 3' UTR variants have been shown to cause CMT1X [Tomaselli et al 2017]. Because these variants are outside of typically sequenced gene regions, they may not be identified in inherited neuropathy panels (see Molecular Genetics).

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

Comprehensive genomic testing does not require the clinician to determine which gene(s) are likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

If exome sequencing is not diagnostic, **exome array** (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in *GJB1* Charcot-Marie-Tooth Neuropathy with or without CNS Dysfunction (CMT1X)

Gene [1]	Method	Proportion of Pathogenic Variants [2] Identified by Method
GJB1	Sequence analysis [3, 4]	>99% [4, 5]
	Gene-targeted deletion/duplication analysis [6]	Rare [7]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Kulshrestha et al [2017], Panosyan et al [2017], Yuan et al [2018], Hsu et al [2019]
5. Note, disease-associated variants in the upstream regulatory region, 5'UTR, non-coding exons, and 3'UTR are frequently associated with disease; therefore, sequence analysis should include these regions [Tomaselli et al 2017]. See Molecular Genetics for additional details.
6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
7. Ainsworth et al [1998], Nakagawa et al [2001], Takashima et al [2003], Gonzaga-Jauregui et al [2010], Capponi et al [2015]

Clinical Characteristics

Clinical Description

Neuropathy. Manifestations typically develop between ages five and 25 years; many males are symptomatic by early adolescence [Dubourg et al 2001, Shy et al 2007]. Earlier onset with delayed walking in infancy as well as later onset in the fourth and subsequent decades can occur. In some individuals, manifestations can be extremely mild and go unrecognized by the individual and/or physician. Clinical manifestations can vary, even within the same family.

Although both men and women are affected, manifestations tend to be less severe in women because of X-chromosome inactivation, as a result of which some women may remain asymptomatic [Siskind et al 2011, Jerath et al 2016].

Signs and symptoms are those of progressive peripheral motor and sensory neuropathy including sensory loss, weakness and atrophy of the distal muscles of the upper and lower extremities, and loss of deep tendon reflexes. The typical affected adult has bilateral foot drop, symmetric atrophy of muscles below the knee (stork leg appearance), *pes cavus*, atrophy of intrinsic hand muscles (especially the thenar muscles of the thumb), and absent tendon reflexes in upper and lower extremities. The dominant hand may be more involved than the non-dominant one [Arthur-Farraj et al 2012]. Proximal muscles usually remain strong.

Mild-to-moderate sensory deficits of position, vibration, and pain/temperature commonly occur in the feet.

Fixed CNS abnormalities can include fixed dysarthria, ataxia, spasticity, hyperreflexia, extensor plantar response, and/or MRI abnormalities in the myelinated tracts of the brain. These have been recently reviewed [Abrams 2019].

Stroke-like episodes are acute self-limited often recurrent episodes of CNS dysfunction. Findings typically include upper motor neuron weakness and dysarthria. Ataxia, respiratory distress, dysphagia, and altered consciousness have also been described. Symptoms last between a few hours and a few weeks. While some episodes appear to occur without provocation [Halbrich et al 2008, Srinivasan et al 2008], most are associated with stressors such as hyperventilation or exertion [Hanemann et al 2003, Taylor et al 2003, Srinivasan et al 2008, Basu et al 2011], re-acclimatization after return from high altitude [Paulson et al 2002, Sagnelli et al 2014], fever [Schelhaas et al 2002, Fusco et al 2010], head trauma [Halbrich et al 2008], or minor infections [Hanemann et al 2003, Anand et al 2010].

MRI changes, seen on both diffusion-weighted and T_2-weighted sequences, preferentially involve subcortical white matter and the splenium of the corpus callosum [Paulson et al 2002, Schelhaas et al 2002, Hanemann et al 2003, Halbrich et al 2008, Srinivasan et al 2008, Anand et al 2010, Fusco et al 2010, Rosser et al 2010, Kim et al 2014]. While diffusion-weighted abnormalities tend to resolve within weeks, T_2-weighted changes may persist longer. Most of these episodes have been reported in males, typically younger than age 21 years [Al-Mateen et al 2014]; females with stroke like episodes have also been described [Hanemann et al 2003, Kim et al 2014]. In rare instances stroke-like episodes may precede peripheral neuropathy [Sagnelli et al 2014].

Other fixed central nervous system involvement, reported on occasion:

- Extensor plantar responses [Marques et al 1999, Hisama et al 2001, Lee et al 2002, Kassubek et al 2005, Karadima et al 2006, Kleopa et al 2006]
- Hyperreflexia and/or spasticity [Hisama et al 2001, Kleopa et al 2006]
- Ataxia with upper motor neuron signs in a large kindred (SCA-X1) [Caramins et al 2013] and ataxia with dysarthria [Siskind et al 2009]
- Vocal cord paresis with dysphonia and dysphagia (reported in 4/8 affected members of a single family) [Chung et al 2005]
- Hearing loss (occasionally reported) [Stojkovic et al 1999, Lee et al 2002, Takashima et al 2003]

Other imaging findings can include:

- MRI evidence of fixed pathology in CNS myelin [Bort et al 1997, Hisama et al 2001, Lee et al 2002, Kassubek et al 2005, Karadima et al 2006, Basri et al 2007, Siskind et al 2009];
- Reduced cerebellar blood flow on SPECT analysis [Kawakami et al 2002].

Other electrophysiologic findings

- Most affected individuals show abnormalities in visual, brain stem auditory, and/or somatosensory evoked responses (reviewed in Abrams & Freidin [2015]).
- Most *GJB1* variants cause subclinical abnormalities of visual evoked responses and brain stem auditory evoked responsess [Nicholson & Corbett 1996, Cao et al 1998, Nicholson et al 1998, Panas et al 1998, Bähr et al 1999, Stojkovic et al 1999, Seeman et al 2001, Huang et al 2005, Murru et al 2006, Srinivasan et al 2008].
- Abnormal motor evoked potentials [Kassubek et al 2005], sensory evoked potentials [Kawakami et al 2002], and transcranial magnetic stimulation evoked central motor conduction [Zambelis et al 2008] have also been reported.

Nerve biopsy. Light microscopy typically reveals axonal loss with evidence of regeneration. Scattered onion bulbs as well as thinly myelinated fibers, resulting from either regeneration and associated remyelination or segmental demyelination and remyelination, are also seen.

Electron microscopy reveals widened collars of adaxonal Schwann cell cytoplasm and separation of axons from their surrounding myelin sheaths [Senderek et al 1998, Senderek et al 1999, Tabaraud et al 1999, Hahn et al 2001, Vital et al 2001].

Nerve biopsies rarely show nerve hypertrophy or generalized onion bulb formation, findings considered to be typical for demyelinating CMT(e.g., CMT type 1A caused by a duplication of a ~1-MB region of chromosome 17 that includes *PMP22*).

Note that the widespread availability of molecular genetic testing has rendered nerve biopsy unnecessary for diagnosis unless genetic testing is unrevealing.

Genotype-Phenotype Correlations

The six variants that have been reported in multiple unrelated individuals with stroke-like episodes and which may confer a higher risk for this phenotype are included in Table 4. Of note, approximately 20 additional variants have been reported in a single individual or family with stroke-like episodes.

From a severity standpoint, most pathogenic variants cause a similar phenotype [Shy et al 2007, Record et al 2023]. Some data suggest that the relatively common c.-17G>A pathogenic variant produces a more severe phenotype than other common pathogenic variants, while missense pathogenic variants in the intracellular domain of *GJB1* cause a less severe phenotype [Record et al 2023].

Nomenclature

The term XL-CMTIn-*GJB1* may be used to describe CMT1X. This term is based on the classification system proposed by Magy et al [2018] in which expression of a particular type of CMT combines three elements: mode of inheritance, neuropathy type (i.e., axonal, demyelinating, or intermediate), and the gene involved.

See CMT Overview for a review of other approaches to CMT classification.

Prevalence

The overall prevalence of hereditary neuropathies is estimated at 30:100,000 population. More than half of these cases are CMT type 1 (15 to 20:100,000).

CMT1X represents at least 10%-20% of those with the CMT neuropathy (see CMT Overview).

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *GJB1*.

Differential Diagnosis

Neuropathy. See CMT Overview.

Stroke-like episodes and peripheral neuropathy. Disorders to consider in the differential diagnosis include the following:

- MELAS (mitochondrial encephalopathy lactic acidosis and stroke) due mitochondrial DNA (mtDNA) variants
- *POLG*-related disorders [Pareyson et al 2013]
- CADASIL [Sicurelli et al 2005]; however, peripheral neuropathy has not been seen in all studies [Kang et al 2009].
- Fabry disease manifesting with ischemic stroke and small fiber neuropathy
- Metabolic encephalopathy or ischemia due to complications of diabetes mellitus, kidney disease, or liver disease
- Neurosarcoidosis [Hodge et al 2007]

- Lupus and other collagen vascular diseases
- Vasculitis

Isolated stroke-like episodes. The vast differential diagnosis includes many genetic and acquired conditions. In particular, the autosomal recessive disorder acute reversible leukoencephalopathy with increased urinary alpha-ketoglutarate (ARLIAK) (OMIM 618384), caused by biallelic pathogenic variants in *SLC13A3*, should be considered, as the phenotype is remarkably similar to that seen in CMT1X [Dewulf et al 2019].

Management

Individuals with *GJB1* Charcot-Marie-Tooth neuropathy with or without central nervous system dysfunction (CMT1X) are often evaluated and managed by a multidisciplinary team that includes neurologists, physiatrists, orthopedic surgeons, physical therapists, and occupational therapists.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with CMT1X , the evaluations summarized in Table 2 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 2. Recommended Evaluations Following Initial Diagnosis in Individuals with CMT1X

System/Concern	Evaluation	Comment
Neurologic	Neurologic eval	• To determine extent of weakness & atrophy, *pes cavus*, gait stability, & sensory loss • To evaluate for pain • To evaluate for less common fixed manifestations (e.g., spasticity, hyperreflexia, ataxia) • To determine if affected person &/or any family member has had episodes of acute transient neurologic dysfunction
Musculoskeletal	Orthopedics / physical medicine & rehab / PT/OT eval	To incl assessment of: • Gross motor & fine motor skills & need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills) • Feet for evidence of *pes cavus*, need for AFOs, specialized shoes • Mobility, activities of daily living, & need for adaptive devices • Need for handicapped parking
Hearing	Audiologic eval	Assessment for hearing loss if concerns
Miscellaneous/ Other	Consultation w/clinical geneticist &/or genetic counselor	To incl genetic counseling

OT = occupational therapy; PT = physical therapy

Treatment of Manifestations

Treatment is symptomatic.

Neuropathy

Special shoes, including those with good ankle support, may be needed.

Ankle/foot orthoses (AFO) are often required to correct foot drop and aid walking. Daily heel cord stretching exercises to prevent Achilles' tendon shortening are desirable.

Orthopedic surgery may be required to correct severe *pes cavus* deformity interfering with ambulation; however, it should be reserved for affected individuals in whom the gait cannot be corrected by use of appropriate orthotic devices.

Forearm crutches or canes may be required for gait stability. Use of a wheelchair may occasionally be required.

Exercise is encouraged within the individual's capability, as many affected individuals remain physically active.

Stroke-Like Episodes

Treatment is supportive, as these are self-limited. See Agents/Circumstances to Avoid for lifestyle recommendations to potentially reduce the risk of these episodes.

Surveillance

Table 3. Recommended Surveillance for Individuals with CMT1X

System/Concern	Evaluation	Frequency
Neurologic	• Screening neurologic exam focused on motor system & cerebellar function • Eval for pain	Annually
Musculoskeletal	• PT (gross motor skills) & ADL • OT (fine motor skills) & ADL	
Foot exam	For pressure sores or poorly fitting footwear	Annually by physician; more often by affected person

ADL = activities of daily living; OT = occupational therapy; PT = physical therapy

Agents/Circumstances to Avoid

Obesity is to be avoided because it makes walking more difficult.

Medications that are toxic or potentially toxic to persons with CMT comprise a spectrum of risk ranging from definite high risk to negligible risk. See the Charcot-Marie-Tooth Association website (pdf) for an up-to-date list.

Affected individuals should be informed of the small possibility of stroke-like episodes, which appears to be higher in younger individuals with a family history or in individuals who have a variant previously associated with such events (see Table 4). The author recommends advising affected individuals that the avoidance of known precipitants such as hyperventilation or exertion [Hanemann et al 2003, Taylor et al 2003, Srinivasan et al 2008, Basu et al 2011], re-acclimatization after return from high altitude [Paulson et al 2002, Sagnelli et al 2014], fever [Schelhaas et al 2002, Fusco et al 2010], head trauma [Halbrich et al 2008], or minor infections [Hanemann et al 2003, Anand et al 2010] **may** reduce the likelihood of such events. However, these recommendations must be balanced with quality-of-life considerations.

Evaluation of Relatives at Risk

Examination of at-risk relatives is recommended since individuals with few manifestations may go unrecognized. Even individuals with few manifestations may benefit from use of orthotics.

It may be appropriate to clarify the genetic status of apparently asymptomatic older and younger at-risk relatives of an affected individual when the apparent risk for stroke-like episodes may be higher (family history or a variant previously associated with such episodes; see Table 4), since avoidance of precipitating factors may be warranted to help reduce the incidence of such events.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

GJB1 Charcot-Marie-Tooth neuropathy with or without central nervous system dysfunction (CMT1X) is inherited in an X-linked manner.

Risk to Family Members

Parents of a male proband

- The father of an affected male will not have the disorder nor will he be hemizygous for the *GJB1* pathogenic variant; therefore, he does not require further evaluation/testing.
- In a family with more than one affected individual, the mother of an affected male is an obligate heterozygote. Note: If a woman has more than one affected child and no other affected relatives and if the *GJB1* pathogenic variant cannot be detected in her leukocyte DNA, she most likely has germline mosaicism. Presumed somatic and germline mosaicism has been reported in CMT1X [Borgulová et al 2013].
- If a male is the only affected family member (i.e., a simplex case), the mother may be a heterozygote or the affected male may have a *de novo GJB1* pathogenic variant (in which case the mother is not a heterozygote). About 5% to 10% of affected males represent apparently simplex cases. While Dubourg et al [2001] estimated that 5% of individuals had a *de novo* pathogenic variant, no *de novo* variants were identified in a more recent study of 40 individuals with CMT1X [Rudnik-Schöneborn et al 2016].

Parents of a female proband

- A female proband may have inherited the *GJB1* pathogenic variant from either her mother or her father, or the pathogenic variant may be *de novo*.
- Detailed evaluation of the parents and review of the extended family history may help distinguish probands with a *de novo GJB1* pathogenic variant from those with an inherited pathogenic variant. Molecular genetic testing of the mother (and possibly the father, or subsequently the father) can determine if the pathogenic variant was inherited.

Sibs of a male proband. The risk to sibs depends on the genetic status of the mother:

- If the mother of the proband has a *GJB1* pathogenic variant, the chance of transmitting it in each pregnancy is 50%. Males who inherit the pathogenic variant will be affected; females who inherit the pathogenic variant will be heterozygotes and may have mild-to-no manifestations or, more often, have mild-to-moderate signs and symptoms that may progress.

- If the proband represents a simplex case and if the *GJB1* pathogenic variant cannot be detected in the leukocyte DNA of the mother, the risk to sibs is slightly greater than that of the general population because of the possibility of maternal germline mosaicism.

Sibs of a female proband. The risk to sibs depends on the genetic status of the parents:

- If the mother of the proband has a *GJB1* pathogenic variant, the chance of transmitting it in each pregnancy is 50%. Males who inherit the pathogenic variant will be affected; females who inherit the pathogenic variant will be heterozygotes and may have mild-to-no manifestations or, more often, have mild-to-moderate signs and symptoms that may progress
- If the father of the proband has a *GJB1* pathogenic variant, he will transmit it to all his daughters and none of his sons.
- If the proband represents a simplex case (i.e., a single occurrence in a family) and if the *GJB1* pathogenic variant cannot be detected in the leukocyte DNA of either parent, the risk to sibs is slightly greater than that of the general population because of the possibility of parental germline mosaicism.

Offspring of a male proband. Affected males transmit the *GJB1* pathogenic variant to all of their daughters and none of their sons.

Offspring of a female proband. Women with a *GJB1* pathogenic variant have a 50% chance of transmitting the pathogenic variant to each child.

Other family members. If a parent of the proband also has a *GJB1* pathogenic variant, the parent's family members may be at risk of having a *GJB1* pathogenic variant.

Note: Molecular genetic testing may be able to identify the family member in whom a *de novo* pathogenic variant arose – information that could help determine genetic risk status of the extended family.

Heterozygote Detection

Molecular genetic testing of at-risk female relatives to determine their genetic status is most informative if the *GJB1* pathogenic variant has been identified in the proband.

Note: (1) Females who are heterozygous for this X-linked disorder may have no clinical findings of peripheral neuropathy (but an abnormal EMG/NCV); or, more often, have mild-to-moderate signs and symptoms that may progress (see Clinical Description). (2) Identification of female heterozygotes requires either (a) prior identification of the *GJB1* pathogenic variant in the family or, (b) if an affected male is not available for testing, molecular genetic testing first by sequence analysis, and if no pathogenic variant is identified, by gene-targeted deletion/duplication analysis.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adult males who are affected (i.e., hemizygous) or females who are known to be heterozygous or who are at increased risk of being heterozygotes.

Prenatal Testing and Preimplantation Genetic Testing

Once the *GJB1* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Association CMT France**
  France
  Phone: 820 077 540; 2 47 27 96 41
  www.cmt-france.org
- **Charcot-Marie-Tooth Association (CMTA)**
  Phone: 800-606-2682
  Email: info@cmtausa.org
  cmtausa.org
- **CMT Research Foundation**
  Phone: 404-806-7180
  Email: info@cmtrf.org
  www.cmtrf.org
- **European Charcot-Marie-Tooth Consortium**
  Department of Molecular Genetics
  University of Antwerp
  Antwerp Antwerpen B-2610
  Belgium
  Fax: 03 2651002
  Email: gisele.smeyers@ua.ac.be
- **Hereditary Neuropathy Foundation**
  Phone: 855-435-7268 (toll-free); 212-722-8396
  Fax: 917-591-2758
  Email: info@hnf-cure.org
  www.hnf-cure.org
- **Medical Home Portal**
  Charcot-Marie-Tooth Disease (Hereditary Motor Sensory Neuropathy)
- **National Library of Medicine Genetics Home Reference**
  Charcot-Marie-Tooth disease
- **NCBI Genes and Disease**
  Charcot-Marie-Tooth syndrome
- **TREAT-NMD**
  Institute of Translational and Clinical Research
  University of Newcastle upon Tyne
  International Centre for Life

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United Kingdom
Phone: 44 (0)191 241 8617
Fax: 44 (0)191 241 8770
Email: info@treat-nmd.eu
Charcot-Marie-Tooth Disease

- **Association Francaise contre les Myopathies (AFM)**
  France
  Phone: +33 01 69 47 28 28
  Email: dmc@afm.genethon.fr
  afm-telethon.fr
- **European Neuromuscular Centre (ENMC)**
  Netherlands
  Phone: 31 35 5480481
  Email: enmc@enmc.org
  enmc.org
- **Muscular Dystrophy Association (MDA) - USA**
  Phone: 833-275-6321
  Email: ResourceCenter@mdausa.org
  mda.org
- **Muscular Dystrophy UK**
  United Kingdom
  Phone: 0800 652 6352
  musculardystrophyuk.org
- **RDCRN Patient Contact Registry: Inherited Neuropathies Consortium**
  Patient Contact Registry

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. GJB1 Disorders: Charcot-Marie-Tooth Neuropathy (CMT1X) and Central Nervous System Phenotypes: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
GJB1	Xq13.1	Gap junction beta-1 protein	GJB1 homepage - Leiden Muscular Dystrophy pages Inherited Neuropathy Variant Browser The Connexin-deafness homepage (GJB1)	GJB1	GJB1

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for GJB1 Disorders: Charcot-Marie-Tooth Neuropathy (CMT1X) and Central Nervous System Phenotypes (View All in OMIM)

302800	CHARCOT-MARIE-TOOTH DISEASE, X-LINKED DOMINANT, 1; CMTX1
304040	GAP JUNCTION PROTEIN, BETA-1; GJB1

GJB1 encodes gap junction beta-1 protein (GJB1; also known as connexin 32 or Cx32), which is expressed in peripheral myelin and specifically located in uncompacted folds of Schwann cell cytoplasm at the nodes of Ranvier and at Schmidt-Lanterman incisures. It is also found in central myelin. GJB1 has two extracellular loops, four transmembrane domains, and three cytoplasmic domains. Gap junctions form direct channels between cells that facilitate transfer of ions and small molecules. Six connexins oligomerize to form hemichannels, or connexons. When properly apposed to each other on cell membranes, two connexins form gap junction channels that permit the diffusion of ions and small molecules [Abrams 2019].

Mechanism of disease causation. The exact mechanism by which *GJB1* pathogenic variants produce disease is unknown. Some variants likely lead to little or no protein production, including deletion of the entire coding sequence for Cx32 [Ainsworth et al 1998, Lin et al 1999, Hahn et al 2000, Nakagawa et al 2001, Takashima et al 2003, Capponi et al 2015], start codon [Brozková et al 2010, Chen et al 2011, Schabhüttl et al 2014, Hong et al 2017] and nonsense variants in the upstream part of the coding sequence [Ionasescu et al 1996a, Panosyan et al 2017]. Pathogenic variants in the upstream regulatory region, 5' untranslated region, splice junctions of non-coding exons, and 3' untranslated region [Ionasescu et al 1996b, Flagiello et al 1998, Houlden et al 2004, Beauvais et al 2006, Li et al 2009, Kabzińska et al 2011, Murphy et al 2011, Tsai et al 2013, Kulshrestha et al 2017, Panosyan et al 2017, Tomaselli et al 2017] are also likely to reduce or eliminate protein expression.

Almost all disease-associated variants are predicted to be loss-of-function variants. Some cause Cx32 to traffic inappropriately, thus leading to a failure to form gap junction plaques [Omori et al 1996, Deschênes et al 1997, Martin et al 2000, Matsuyama et al 2001, Kleopa et al 2002, Yum et al 2002, Abrams et al 2003]. Others form gap junctions but interfere with gap junction function by reducing pore size [Oh et al 1997, Bicego et al 2006], increasing sensitivity to acidification-induced closure [Ressot et al 1998, Abrams et al 2003], or most commonly by stabilizing the closed state of the channel [Oh et al 1997, Ri et al 1999, Abrams et al 2000, Abrams et al 2013]. See recent reviews for further details [Abrams & Freidin 2015, Abrams 2019]. Evidence suggests that in the central nervous system some variants have a toxic gain-of-function consequence [Olympiou et al 2016].

Gap junction-independent mechanisms may also play a role. At least one disease-associated *GJB1* variant shows increased opening of hemichannels that may damage cells through loss of ionic gradients and increased influx of Ca^{++} [Abrams et al 2002]. A number of studies have suggested roles for connexins in regulation of cell growth [Omori & Yamasaki 1998, Moorby & Patel 2001, Qin et al 2002, Freidin et al 2009] and resistance to both apoptotic and necrotic cell death [Abdipranoto et al 2003], independent of formation of functional gap junction channels. One example is the demonstration that Schwann cell proliferation is regulated by Cx32 in a gap junction-independent manner [Freidin et al 2009]. Other non-junctional actions of connexins include binding to other proteins and possibly acting as trafficking or scaffolding proteins [Giepmans 2004, Stout et al 2004].

***GJB1*-specific laboratory technical considerations.** *GJB1* consists of two promotors – P1 and P2 – that are expressed in a tissue-specific manner [Neuhaus et al 1996]. The P1 promotor is upstream of the P2 promotor and each promoter produces a transcript with a unique noncoding exon 1 and the entire coding sequence in a single exon 2. It is thought that only the P2 promoted transcript (NM_000166) is expressed in Schwann cells. Therefore, noncoding variants that fall outside of this transcript and its regulatory regions are highly unlikely to be causal for CMT1X. (Note that in the literature the first [P1 promoted] exon is sometimes referred to as 1A, the second [P2 promoted] exon as 1B, and the third coding exon as exon 2.) As noted and referenced in Establishing the Diagnosis, pathogenic variants have been identified in the upstream regulatory region, 5' untranslated region, splice between exon one and exon two, and 3' untranslated region of NM_000166.

Table 4. Notable *GJB1* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change (Alias [1])	Predicted Protein Change	Comment [Reference]
NM_000166.5	c.-103C>T (-459C>T)	--	Recurrent pathogenic variant in noncoding exon (1B) [Ionasescu et al 1996b, Li et al 2009, Tsai et al 2013, Tomaselli et al 2017]
	c.-17G>A	--	Most common noncoding pathogenic variant in a large international study (4% of total) at splice site [Panosyan et al 2017]; phenotype is more severe than the phenotypes assoc w/a number of single-nucleotide variants [Record et al 2023].
NM_000166.5 NP_000157.1	c.44G>A	p.Arg15Gln	Most common coding pathogenic variant ~7% of total in a large international study [Panosyan et al 2017]
	c.65G>A	p.Arg22Gln	Observed in 2 unrelated cases w/stroke-like episodes [Srinivasan et al 2008, Rosser et al 2010]
	c.223C>T	p.Arg75Trp	Observed in 3 unrelated cases w/stroke-like episodes [Taylor et al 2003; Parissis et al 2017; SS Scherer, personal communication]
	c.283G>A	p.Val95Met	Apparently common pathogenic variant in Korea (6/63 families) [Hong et al 2017]
	c.415G>A	p.Val139Met	2 unrelated cases w/stroke like episodes [Halbrich et al 2008, Al-Mateen et al 2014]
	c.424C>T	p.Arg142Trp	Observed in 3 unrelated cases w/stroke-like episodes [Paulson et al 2002; SS Scherer, personal communication]
	c.425G>A	p.Arg142Gln	Observed in 2 unrelated cases w/stroke-like episodes [Kulkarni et al 2015, Lu et al 2017]
	c.490C>T	p.Arg164Trp	Observed in 2 unrelated cases w/stroke-like episodes [Schelhaas et al 2002, Isoardo et al 2005]; common pathogenic variant in Korea (4/63 families) [Hong et al 2017]
	c.491G>A	p.Arg164Gln	Apparently common pathogenic variant in Korea (5/63 families) [Hong et al 2017]

Variants listed in the table have been provided by the author. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Variant designation that does not conform to current naming conventions

Chapter Notes

Author Notes

Author's laboratory website

Charles K Abrams directs a laboratory at the University of Illinois College of Medicine at Chicago (UIC) studying the role of connexins including connexin 32 in the central and peripheral nervous system. A major area of focus is understanding how pathogenic variants in *GJB1* cause CMT1X. He also directs the CMTA association sponsored inherited peripheral neuropathies clinic at UIC.

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Revision History

- 25 April 2024 (tb) Revision: add new findings from Record et al [2023]
- 20 February 2020 (bp) Comprehensive update posted live
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- 15 April 2005 (me) Comprehensive update posted live
- 10 April 2003 (me) Comprehensive update posted live
- 25 August 2000 (me) Comprehensive update posted live
- 18 June 1998 (pb) Review posted live
- April 1996 (tb) Original submission

References

Published Guidelines / Consensus Statements

Committee on Bioethics, Committee on Genetics, and American College of Medical Genetics and Genomics Social, Ethical, Legal Issues Committee. Ethical and policy issues in genetic testing and screening of children. Available online. 2013. Accessed 1-19-22.

National Society of Genetic Counselors. Position statement on genetic testing of minors for adult-onset conditions. Available online. 2018. Accessed 1-19-22.

Literature Cited

Abdipranoto A, Liu GJ, Werry EL, Bennett MR. Mechanisms of secretion of ATP from cortical astrocytes triggered by uridine triphosphate. Neuroreport. 2003;14:2177-81. PubMed PMID: 14625443.

Abrams CK. Diseases of connexins expressed in myelinating glia. Neurosci Lett. 2019;695:91-9. PubMed PMID: 28545922.

Abrams CK, Bennett MV, Verselis VK, Bargiello TA. Voltage opens unopposed gap junction hemichannels formed by a connexin 32 mutant associated with X-linked Charcot-Marie-Tooth disease. Proc Natl Acad Sci U S A. 2002;99:3980-4. PubMed PMID: 11891346.

Abrams CK, Freidin M. GJB1-associated X-linked Charcot-Marie-Tooth disease, a disorder affecting the central and peripheral nervous systems. Cell Tissue Res. 2015;360:659-73. PubMed PMID: 25370202.

Abrams CK, Freidin M, Bukauskas F, Dobrenis K, Bargiello TA, Verselis VK, Bennett MV, Chen L, Sahenk Z. Pathogenesis of X-linked Charcot-Marie-Tooth disease: differential effects of two mutations in connexin 32. J Neurosci. 2003;23:10548-58. PubMed PMID: 14627639.

Abrams CK, Islam M, Mahmoud R, Kwon T, Bargiello TA, Freidin MM. Functional requirement for a highly conserved charged residue at position 75 in the gap junction protein connexin 32. J Biol Chem. 2013;288:3609-19. PubMed PMID: 23209285.

Abrams CK, Oh S, Ri Y, Bargiello TA. Mutations in connexin 32: the molecular and biophysical bases for the X-linked form of Charcot-Marie-Tooth disease. Brain Res Brain Res Rev. 2000;32:203-14. PubMed PMID: 10751671.

Ainsworth PJ, Bolton CF, Murphy BC, Stuart JA, Hahn AF. Genotype/phenotype correlation in affected individuals of a family with a deletion of the entire coding sequence of the connexin 32 gene. Hum Genet. 1998;103:242-4. PubMed PMID: 9760211.

Al-Mateen M, Craig AK, Chance PF. The central nervous system phenotype of X-linked Charcot-Marie-Tooth disease: a transient disorder of children and young adults. J Child Neurol. 2014;29:342-8. PubMed PMID: 23400245.

Anand G, Maheshwari N, Roberts D, Padeniya A, Hamilton-Ayers M, van der Knaap M, Fratter C, Jayawant S. X-linked hereditary motor sensory neuropathy (type 1) presenting with a stroke-like episode. Dev Med Child Neurol. 2010;52:677-9. PubMed PMID: 20491857.

Arthur-Farraj PJ, Murphy SM, Laura M, Lunn MP, Manji H, Blake J, Ramdharry G, Fox Z, Reilly MM. Hand weakness in Charcot-Marie-Tooth disease 1X. Neuromuscul Disord. 2012;22:622-6. PubMed PMID: 22464564.

Bähr M, Andres F, Timmerman V, Nelis ME, Van Broeckhoven C, Dichgans J. Central visual, acoustic, and motor pathway involvement in a Charcot-Marie-Tooth family with an Asn205Ser mutation in the connexin32 geen. J Neurol Neurosurg Psychiatry. 1999;66:202-6. PubMed PMID: 10071100.

Basri R, Yabe I, Soma H, Matsushima M, Tsuji S, Sasaki H. X-linked Charcot-Marie-Tooth disease (CMTX) in a severely affected female patient with scattered lesions in cerebral white matter. Intern Med. 2007;46:1023-7. PubMed PMID: 17603245.

Basu A, Horvath R, Esisi B, Birchall D, Chinnery PF. Recurrent stroke-like episodes in X-linked Charcot-Marie-Tooth disease. Neurology. 2011;77:1205-6. PubMed PMID: 21900630.

Beauvais K, Furby A, Latour P. Clinical, electrophysiological and molecular genetic studies in a family with X-linked dominant Charcot-Marie-Tooth neuropathy presenting a novel mutation in GJB1 Promoter and a rare polymorphism in LITAF/SIMPLE. Neuromuscul Disord. 2006;16:14-8. PubMed PMID: 16373087.

Bicego M, Morassutto S, Hernandez VH, Morgutti M, Mammano F, D'Andrea P, Bruzzone R. Selective defects in channel permeability associated with Cx32 mutations causing X-linked Charcot-Marie-Tooth disease. Neurobiol Dis. 2006;21:607-17. PubMed PMID: 16442804.

Borgulová I, Mazanec R, Sakmaryová I, Havlová M, Safka Brožková D, Seeman P. Mosaicism for GJB1 mutation causes milder Charcot-Marie-Tooth X1 phenotype in a heterozygous man than in a manifesting heterozygous woman. Neurogenetics. 2013;14:189-95. PubMed PMID: 23912496.

Bort S, Nelis E, Timmerman V, Sevilla T, Cruz-Martinez A, Martinez F, Millan JM, Arpa J, Vilchez JJ, Prieto F, Van Broeckhoven C, Palau F. Mutational analysis of the MPZ, PMP22 and Cx32 genes in patients of Spanish ancestry with Charcot-Marie-Tooth disease and hereditary neuropathy with liability to pressure palsies. Hum Genet. 1997;99:746-54. PubMed PMID: 9187667.

Brozková D, Mazanec R, Haberlová J, Sakmaryová I, Subrt I, Seeman P. Six new gap junction beta 1 gene mutations and their phenotypic expression in Czech patients with Charcot-Marie-Tooth disease. Genetic testing and molecular biomarkers. 2010;14:3-7. PubMed PMID: 20039784.

Cao F, Eckert R, Elfgang C, Nitsche JM, Snyder SA, DF Hu, Willecke K, Nicholson BJ. A quantitative analysis of connexin-specific permeability differences of gap junctions expressed in HeLa transfectants and Xenopus oocytes. J Cell Sci. 1998;111:31-43. PubMed PMID: 9394010.

Capponi S, Geroldi A, Pezzini I, Gulli R, Ciotti P, Ursino G, Lamp M, Reni L, Schenone A, Grandis M, Mandich P, Bellone E. Contribution of copy number variations in CMT1X: a retrospective study. Eur J Neurol. 2015;22:406-9. PubMed PMID: 24724718.

Caramins M, Colebatch JG, Bainbridge MN, Scherer SS, Abrams CK, Hackett EL, Freidin MM, Jhangiani SN, Wang M, Wu Y, Muzny DM, Lindeman R, Gibbs RA. Exome sequencing identification of a GJB1 missense mutation in a kindred with X-linked spinocerebellar ataxia (SCA-X1). Hum Mol Genet. 2013;22:4329-38. PubMed PMID: 23773993.

Chen SD, Li ZX, Guan YT, Zhou XJ, Jiang JM, Hao Y. A novel mutation of gap junction protein beta 1 gene in X-linked Charcot-Marie-Tooth disease. Muscle Nerve. 2011;43:887-92. PubMed PMID: 21607969.

Chung KW, Sunwoo IN, Kim SM, Park KD, Kim WK, Kim TS, Koo H, Cho M, Lee J, Choi BO. Two missense mutations of EGR2 R359W and GJB1 V136A in a Charcot-Marie-Tooth disease family. Neurogenetics. 2005;6:159-63. PubMed PMID: 15947997.

Deschênes SM, Walcott JL, Wexler TL, Scherer SS, Fischbeck KH. Altered trafficking of mutant connexin32. J Neurosci. 1997;17:9077-84. PubMed PMID: 9364054.

Dewulf JP, Wiame E, Dorboz I, Elmaleh-Berges M, Imbard A, Dumitriu D, Rak M, Bourillon A, Helaers R, Malla A, Renaldo F, Boespflug-Tanguy O, Vincent MF, Benoist JF, Wevers RA, Schlessinger A, Van Schaftingen E, Nassogne MC, Schiff M. SLC13A3 variants cause acute reversible leukoencephalopathy and alpha-ketoglutarate accumulation. Ann Neurol. 2019;85:385-95. PubMed PMID: 30635937.

Dubourg O, Tardieu S, Birouk N, Gouider R, Leger JM, Maisonobe T, Brice A, Bouche P, LeGuern E. Clinical, electrophysiological and molecular genetic characteristics of 93 patients with X-linked Charcot-Marie-Tooth disease. Brain. 2001;124:1958-67. PubMed PMID: 11571214.

Flagiello L, Cirigliano V, Strazzullo M, Cappa V, Ciccodicola A, D'Esposito M, Torrente I, Werner R, Di Iorio G, Rinaldi M, Dallapiccola A, Forabosco A, Ventruto V, D'Urso M. Mutation in the nerve-specific 5'non-coding region of Cx32 gene and absence of specific mRNA in a CMTX1 Italian family. Mutations in brief no. 195. Online. Hum Mutat. 1998;12:361. PubMed PMID: 10671058.

Freidin M, Asche S, Bargiello TA, Bennett MV, Abrams CK. Connexin 32 increases the proliferative response of Schwann cells to neuregulin-1 (Nrg1). Proc Natl Acad Sci U S A. 2009;106:3567-72. PubMed PMID: 19218461.

Fusco C, Frattini D, Pisani F, Spaggiari F, Ferlini A, Della Giustina E. Coexistent central and peripheral nervous system involvement in a Charcot-Marie-Tooth syndrome X-linked patient. J Child Neurol. 2010;25:759-63. PubMed PMID: 20382840.

Giepmans BN. Gap junctions and connexin-interacting proteins. Cardiovasc Res. 2004;62:233-45. PubMed PMID: 15094344.

Gonzaga-Jauregui C, Zhang F, Towne CF, Batish SD, Lupski JR. GJB1/Connexin 32 whole gene deletions in patients with X-linked Charcot-Marie-Tooth disease. Neurogenetics. 2010;11:465-70. PubMed PMID: 20532933.

Gutierrez A, England JD, Sumner AJ, Ferer S, Warner LE, Lupski JR, Garcia CA. Unusual electrophysiological findings in X-linked dominant Charcot-Marie-Tooth disease. Muscle Nerve. 2000;23:182-8. PubMed PMID: 10639608.

Hahn AF, Ainsworth PJ, Bolton CF, Bilbao JM, Vallat JM. Pathological findings in the x-linked form of Charcot-Marie-Tooth disease: a morphometric and ultrastructural analysis. Acta Neuropathol (Berl). 2001;101:129-39. PubMed PMID: 11271367.

Hahn AF, Ainsworth PJ, Naus CC, Mao J, Bolton CF. Clinical and pathological observations in men lacking the gap junction protein connexin 32. Muscle Nerve. 2000;9:S39-S48. PubMed PMID: 11135283.

Halbrich M, Barnes J, Bunge M, Joshi C. A V139M mutation also causes the reversible CNS phenotype in CMTX. Can J Neurol Sci. 2008;35:372-4. PubMed PMID: 18714809.

Hanemann CO, Bergmann C, Senderek J, Zerres K, Sperfeld AD. Transient, recurrent, white matter lesions in X-linked Charcot-Marie-Tooth disease with novel connexin 32 mutation. Arch Neurol. 2003;60:605-9. PubMed PMID: 12707076.

Hisama FM, Lee HH, Vashlishan A, Tekumalla P, Russell DS, Auld E, Goldstein JM. Clinical and molecular studies in a family with probable X-linked dominant Charcot-Marie-Tooth disease involving the central nervous system. Arch Neurol. 2001;58:1891-6. PubMed PMID: 11709000.

Hodge MH, Williams RL, Fukui MB. Neurosarcoidosis presenting as acute infarction on diffusion-weighted MR imaging: summary of radiologic findings. AJNR Am J Neuroradiol. 2007;28:84-6. PubMed PMID: 17213430.

Hong YB, Park JM, Yu JS, Yoo DH, Nam DE, Park HJ, Lee JS, Hwang SH, Chung KW, Choi BO. Clinical characterization and genetic analysis of Korean patients with X-linked Charcot-Marie-Tooth disease type 1. J Peripher Nerv Syst. 2017;22:172-81. PubMed PMID: 28448691.

Houlden H, Girard M, Cockerell C, Ingram D, Wood NW, Goossens M, Walker RWH, Reilly MM. Connexin 32 promoter P2 mutations: A mechanism of peripheral nerve dysfunction. Ann Neurol. 2004;56:730-4. PubMed PMID: 15470753.

Hsu YH, Lin KP, Guo YC, Tsai YS, Liao YC, Lee YC. Mutation spectrum of Charcot-Marie-Tooth disease among the Han Chinese in Taiwan. Ann Clin Transl Neurol. 2019;6:1090-101. PubMed PMID: 31211173.

Huang Y, Sirkowski EE, Stickney JT, Scherer SS. Prenylation-defective human connexin32 mutants are normally localized and function equivalently to wild-type connexin32 in myelinating Schwann cells. J Neurosci. 2005;25:7111-20. PubMed PMID: 16079393.

Ionasescu V, Ionasescu R, Searby C. Correlation between connexin 32 gene mutations and clinical phenotype in X-linked dominant Charcot-Marie-Tooth neuropathy. Am J Med Genet. 1996a;63:486-91. PubMed PMID: 8737658.

Ionasescu VV, Searby C, Ionasescu R, Neuhaus IM, Werner R. Mutations of the noncoding region of the connexin32 gene in X-linked dominant Charcot-Marie-Tooth neuropathy. Neurology. 1996b;47:541-4. PubMed PMID: 8757034.

Isoardo G, Di Vito N, Nobile M, Benetton G, Fassio F. X-linked Charcot-Marie-Tooth disease and progressive-relapsing central demyelinating disease. Neurology. 2005;65:1672-3. PubMed PMID: 16301507.

Jerath NU, Gutmann L, Reddy CG, Shy ME. Charcot-marie-tooth disease type 1X in women: Electrodiagnostic findings. Muscle Nerve. 2016;54:728-32. PubMed PMID: 26873881.

Kabzińska D, Kotruchow K, Ryniewicz B, Kochański A. Two pathogenic mutations located within the 5'-regulatory sequence of the GJB1 gene affecting initiation of transcription and translation. Acta Biochim Pol. 2011;58:359-63. PubMed PMID: 21918739.

Kang SY, Oh JH, Kang JH, Choi JC, Lee JS. Nerve conduction studies in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. J Neurol. 2009;256:1724-7. PubMed PMID: 19488673.

Karadima G, Panas M, Floroskufi P, Kalfakis N, Vassilopoulos D. Four novel connexin 32 mutations in X-linked Charcot-Marie-Tooth disease with phenotypic variability. J Neurol. 2006;253:263-4. PubMed PMID: 16096811.

Kassubek J, Bretschneider V, Sperfeld AD. Corticospinal tract MRI hyperintensity in X-linked Charcot-Marie-Tooth Disease. J Clin Neurosci. 2005;12:588-9. PubMed PMID: 16051098.

Kawakami H, Inoue K, Sakakihara I, Nakamura S. Novel mutation in X-linked Charcot-Marie-Tooth disease associated with CNS impairment. Neurology. 2002;59:923-6. PubMed PMID: 12297581.

Kim GH, Kim KM, Suh SI, Ki CS, Eun BL. Charcot-marie-tooth disease masquerading as acute demyelinating encephalomyelitis-like illness. Pediatrics. 2014;134:e270-3. PubMed PMID: 24958582.

Kleopa KA, Yum SW, Scherer SS. Cellular mechanisms of connexin32 mutations associated with CNS manifestations. J Neurosci Res. 2002;68:522-34. PubMed PMID: 12111842.

Kleopa KA, Zamba-Papanicolaou E, Alevra X, Nicolaou P, Georgiou DM, Hadjisavvas A, Kyriakides T, Christodoulou K. Phenotypic and cellular expression of two novel connexin32 mutations causing CMT1X. Neurology. 2006;66:396-402. PubMed PMID: 16476939.

Kulkarni GB, Mailankody P, Isnwara PP, Prasad C, Mustare V. Episodic neurological dysfunction in hereditary peripheral neuropathy. Ann Indian Acad Neurol. 2015;18:111-4. PubMed PMID: 25745327.

Kulshrestha R, Burton-Jones S, Antoniadi T, Rogers M, Jaunmuktane Z, Brandner S, Kiely N, Manuel R, Willis T. Deletion of P2 promoter of GJB1 gene a cause of Charcot-Marie-Tooth disease. Neuromuscul Disord. 2017;27:766-70. PubMed PMID: 28601552.

Lee MJ, Nelson I, Houlden H, Sweeney MG, Hilton-Jones D, Blake J, Wood NW, Reilly MM. Six novel connexin32 (GJB1) mutations in X-linked Charcot-Marie-Tooth disease. J Neurol Neurosurg Psychiatry. 2002;73:304-6. PubMed PMID: 12185164.

Li M, Cheng TS, Ho PW, Chan KH, Mak W, Cheung RT, Ramsden DB, Sham PC, Song Y, Ho SL. -459C>T point mutation in 5' non-coding region of human GJB1 gene is linked to X-linked Charcot-Marie-Tooth neuropathy. Journal of the peripheral nervous system. J Peripher Nerv Syst. 2009;14:14-21. PubMed PMID: 19335535.

Lin C, Numakura C, Ikegami T, Shizuka M, Shoji M, Nicholson G, Hayasaka K. Deletion and nonsense mutations of the connexin 32 gene associated with Charcot-Marie-Tooth disease. Tohoku J Exp Med. 1999;188:239-44. PubMed PMID: 10587015.

Lu Y-Y, Lyu H, Jin S-Q, Zuo Y-H, Liu J, Wang Z-X, Zhang W, Yuan Y. Clinical and genetic features of Chinese X-linked Charcot-Marie-Tooth type 1 disease. Chin Med J (Engl). 2017;130:1049-54. PubMed PMID: 28469099.

Magy L, Mathis S, Le Masson G, Goizet C, Tazir M, Vallat JM. Updating the classification of inherited neuropathies: Results of an international survey. Neurology. 2018;90:e870-6. PubMed PMID: 29429969.

Marques W, Jr., Sweeney JG, Wood NW, Wroe SJ, Marques W. Central nervous system involvement in a novel connexin 32 mutation affecting identical twins. J Neurol Neurosurg Psychiatry. 1999;66:803-4. PubMed PMID: 10400511.

Martin PE, Mambetisaeva ET, Archer DA, George CH, Evans WH. Analysis of gap junction assembly using mutated connexins detected in Charcot-Marie-Tooth X-linked disease. J Neurochem. 2000;74:711-20. PubMed PMID: 10646523.

Matsuyama W, Nakagawa M, Moritoyo T, Takashima H, Umehara F, Hirata K, Suehara M, Osame M. Phenotypes of X-linked Charcot-Marie-Tooth disease and altered trafficking of mutant connexin 32 (GJB1). J Hum Genet. 2001;46:307-13. PubMed PMID: 11393532.

Moorby C, Patel M. Dual functions for connexins: Cx43 regulates growth independently of gap junction formation. Exp Cell Res. 2001;271:238-48. PubMed PMID: 11716536.

Murphy SM, Polke J, Manji H, Blake J, Reiniger L, Sweeney M, Houlden H, Brandner S, Reilly MM. A novel mutation in the nerve-specific 5'UTR of the GJB1 gene causes X-linked Charcot-Marie-Tooth disease. J Peripher Nerv Syst. 2011;16:65-70. PubMed PMID: 21504505.

Murru MR, Vannelli A, Marrosu G, Cocco E, Corongiu D, Tranquilli S, Cherchi MV, Mura M, Barberini L, Mallarini G, Marrosu MG. A novel Cx32 mutation causes X-linked Charcot-Marie-Tooth disease with brainstem involvement and brain magnetic resonance spectroscopy abnormalities. Neurol Sci. 2006;27:18-23. PubMed PMID: 16688595.

Nakagawa M, Takashima H, Umehara F, Arimura K, Miyashita F, Takenouchi N, Matsuyama W, Osame M. Clinical phentoype in X-linked Charcot-Marie-Tooth disease with an entire deletion of the connexin 32 coding sequence. J Neurol Sci. 2001;185:31-7. PubMed PMID: 11266688.

Neuhaus IM, Bone L, Wang S, Ionasescu V, Werner R. The human connexin32 gene is transcribed from two tissue-specific promoters. Biosci Rep. 1996;16:239-48. PubMed PMID: 8842374.

Nicholson G, Corbett A. Slowing of central conduction in X-linked Charcot-Marie-Tooth neuropathy shown by brain stem auditory evoked responses. J Neurol Neurosurg Psychiatry. 1996;61:43-6. PubMed PMID: 8676158.

Nicholson GA, Yeung L, Corbett A. Efficient neurophysiologic selection of X-linked Charcot-Marie-Tooth families: ten novel mutations. Neurology. 1998;51:1412-6. PubMed PMID: 9818870.

Oh S, Ri Y, Bennett MV, Trexler EB, Verselis VK, Bargiello TA. Changes in permeability caused by connexin 32 mutations underlie X- linked Charcot-Marie-Tooth disease. Neuron. 1997;19:927-38. PubMed PMID: 9354338.

Olympiou M, Sargiannidou I, Markoullis K, Karaiskos C, Kagiava A, Kyriakoudi S, Abrams CK, Kleopa KA. Systemic inflammation disrupts oligodendrocyte gap junctions and induces ER stress in a model of CNS manifestations of X-linked Charcot-Marie-Tooth disease. Acta Neuropathol Commun. 2016;4:95. PubMed PMID: 27585976.

Omori Y, Mesnil M, Yamasaki H. Connexin 32 mutations from X-linked Charcot-Marie-Tooth disease patients: functional defects and dominant negative effects. Mol Biol Cell. 1996;7:907-16. PubMed PMID: 8816997.

Omori Y, Yamasaki H. Mutated connexin43 proteins inhibit rat glioma cell growth suppression mediated by wild-type connexin43 in a dominant-negative manner. Int J Cancer. 1998;78:446-53. PubMed PMID: 9797133.

Panas M, Karadimas C, Avramopoulos D, Vassilopoulos D. Central nervous system involvement in four patients with Charcot-Marie-Tooth disease with connexin 32 extracellular mutations. J Neurol Neurosurg Psychiatry. 1998;65:947-8. PubMed PMID: 9854984.

Panosyan FB, Laura M, Rossor AM, Pisciotta C, Piscosquito G, Burns J, Li J, Yum SW, Lewis RA, Day J, Horvath R, Herrmann DN, Shy ME, Pareyson D, Reilly MM, Scherer SS. Cross-sectional analysis of a large cohort with X-linked Charcot-Marie-Tooth disease (CMTX1). Neurology. 2017;89:927-35. PubMed PMID: 28768847.

Pareyson D, Piscosquito G, Moroni I, Salsano E, Zeviani M. Peripheral neuropathy in mitochondrial disorders. Lancet Neurol. 2013;12:1011-24. PubMed PMID: 24050734.

Parissis D, Ioannidis P, Papadopoulos G, Karacostas D. Charcot-Marie-Tooth Disease 1X Simulating Paraparetic Guillain-Barre Syndrome. Neurologist. 2017;22:234-6. PubMed PMID: 29095325.

Paulson HL, Garbern JY, Hoban TF, Krajewski KM, Lewis RA, Fischbeck KH, Grossman RI, Lenkinski R, Kamholz JA, Shy ME. Transient central nervous system white matter abnormality in X-linked Charcot-Marie-Tooth disease. Ann Neurol. 2002;52:429-34. PubMed PMID: 12325071.

Qin H, Shao Q, Curtis H, Galipeau J, Belliveau DJ, Wang T, Alaoui-Jamali MA, Laird DW. Retroviral delivery of connexin genes to human breast tumor cells inhibits in vivo tumor growth by a mechanism that is independent of significant gap junctional intercellular communication. J Biol Chem. 2002;277:29132-8. PubMed PMID: 12042301.

Record CJ, Skorupinska M, Laura M, Rossor AM, Pareyson D, Pisciotta C, Feely SME, Lloyd TE, Horvath R, Sadjadi R, Herrmann DN, Li J, Walk D, Yum SW, Lewis RA, Day J, Burns J, Finkel RS, Saporta MA, Ramchandren S, Weiss MD, Acsadi G, Fridman V, Muntoni F, Poh R, Polke JM, Zuchner S, Shy ME, Scherer SS, Reilly MM; Inherited Neuropathies Consortium—Rare Disease Clinical Research Network. Genetic analysis and natural history of Charcot-Marie-Tooth disease CMTX1 due to GJB1 variants. Brain. 2023;146:4336-49. PubMed PMID: 37284795.

Ressot C, Gomes D, Dautigny A, Pham-Dinh D, Bruzzone R. Connexin32 mutations associated with X-linked Charcot-Marie-Tooth disease show two distinct behaviors: loss of function and altered gating properties. J Neurosci. 1998;18:4063-75. PubMed PMID: 9592087.

Ri Y, Ballesteros JA, Abrams CK, Oh S, Verselis VK, Weinstein H, Bargiello TA. The role of a conserved proline residue in mediating conformational changes associated wtih voltage gating of cx32 gap junctions. Biophys J. 1999;76:2887-98. PubMed PMID: 10354417.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405-24. PubMed PMID: 25741868.

Rosser T, Muir J, Panigrahy A, Baldwin EE, Boles RG. Transient leukoencephalopathy associated with X-linked Charcot-Marie-Tooth disease. 2010;J Child Neurol. 25:1013-6. PubMed PMID: 20472869.

Rudnik-Schöneborn S, Tolle D, Senderek J, Eggermann K, Elbracht M, Kornak U, von der Hagen M, Kirschner J, Leube B, Muller-Felber W, Schara U, von Au K, Wieczorek D, Bussmann C, Zerres K. Diagnostic algorithms in Charcot-Marie-Tooth neuropathies: experiences from a German genetic laboratory on the basis of 1206 index patients. Clin Genet. 2016;89:34-43. PubMed PMID: 25850958.

Sagnelli A, Piscosquito G, Chiapparini L, Ciano C, Salsano E, Saveri P, Milani M, Taroni F, Pareyson D. X-linked Charcot-Marie-Tooth type 1: stroke-like presentation of a novel GJB1 mutation. J Peripher Nerv Syst. 2014;19:183-6. PubMed PMID: 24863494.

Schabhüttl M, Wieland T, Senderek J, Baets J, Timmerman V, De Jonghe P, Reilly MM, Stieglbauer K, Laich E, Windhager R, Erwa W, Trajanoski S, Strom TM, Auer-Grumbach M. Whole-exome sequencing in patients with inherited neuropathies: outcome and challenges. J Neurol. 2014;261:970-82. PubMed PMID: 24627108.

Schelhaas HJ, Van Engelen BG, Gabreels-Festen AA, Hageman G, Vliegen JH, Van Der Knaap MS, Zwarts MJ. Transient cerebral white matter lesions in a patient with connexin 32 missense mutation. Neurology. 2002;59:2007-8. PubMed PMID: 12499506.

Seeman P, Mazanec R, Ctvrteckova M, Smilkova D. Charcot-Marie-Tooth type X: A novel mutation in the Cx32 gene with central conduction slowing. Int J Mol Med. 2001;8:461-8. PubMed PMID: 11562788.

Senderek J, Bergmann C, Quasthoff S, Ramaekers VT, Schroder JM. X-linked dominant Charcot-Marie-Tooth disease: nerve biopsies allow morphological evaluation and detection of connexin32 mutations (Arg15Trp, Arg22Gln). Acta Neuropathol (Berl). 1998;95:443-9. PubMed PMID: 9600589.

Senderek J, Hermanns B, Bergmann C, Boroojerdi B, Bajbouj M, Hungs M, Ramaekers VT, Quasthoff S, Karch D, Schroder JM. X-linked dominant Charcot-Marie-Tooth neuropathy: clinical, electrophysiological, and morphological phenotype in four families with different connexin32 mutations. J Neurol Sci. 1999;167:90-101. PubMed PMID: 10521546.

Shy ME, Siskind C, Swan ER, Krajewski KM, Doherty T, Fuerst DR, Ainsworth PJ, Lewis RA, Scherer SS, Hahn AF. CMT1X phenotypes represent loss of GJB1 gene function. Neurology. 2007;68:849-55. PubMed PMID: 17353473.

Sicurelli F, Dotti MT, De Stefano N, Malandrini A, Mondelli M, Bianchi S, Federico A. Peripheral neuropathy in CADASIL. J Neurol. 2005;252:1206-9. PubMed PMID: 15827866.

Siskind C, Feely SM, Bernes S, Shy ME, Garbern JY. Persistent CNS dysfunction in a boy with CMT1X. J Neurol Sci. 2009;279:109-13. PubMed PMID: 19193385.

Siskind CE, Murphy SM, Ovens R, Polke J, Reilly MM, Shy ME. Phenotype expression in women with CMT1X. J Peripher Nerv Syst. 2011;16:102-7. PubMed PMID: 21692908.

Srinivasan J, Leventer RJ, Kornberg AJ, Dahl HH, Ryan MM. Central nervous system signs in X-linked Charcot-Marie-Tooth disease after hyperventilation. Pediatr Neurol 2008;38:293-5. PubMed PMID: 18358413.

Stojkovic T, Latour P, Vandenberghe A, Hurtevent JF, Vermersch P. Sensorineural deafness in X-linked Charcot-Marie-Tooth disease with connexin 32 mutation (R142Q). (Published erratum in Neurology 1999;52:1952.) Neurology. 1999;52:1010-4. PubMed PMID: 10102421.

Stout C, Goodenough DA, Paul DL. Connexins: functions without junctions. Curr Opin Cell Biol. 2004;16:507-12. PubMed PMID: 15363800.

Tabaraud F, Lagrange E, Sindou P, Vandenberghe A, Levy N, Vallat JM. Demyelinating X-linked Charcot-Marie-Tooth disease: unusual electrophysiological findings. Muscle Nerve. 1999;22:1442-7. PubMed PMID: 10487913.

Takashima H, Nakagawa M, Umehara F, Hirata K, Suehara M, Mayumi H, Yoshishige K, Matsuyama W, Saito M, Jonosono M, Arimura K, Osame M. Gap junction protein beta 1 (GJB1) mutations and central nervous system symptoms in X-linked Charcot-Marie-Tooth disease. Acta Neurol Scand. 2003;107:31-7. PubMed PMID: 12542510.

Taylor RA, Simon EM, Marks HG, Scherer SS. The CNS phenotype of X-linked Charcot-Marie-Tooth disease: more than a peripheral problem. Neurology. 2003;61:1475-8. PubMed PMID: 14663027.

Tomaselli PJ, Rossor AM, Horga A, Jaunmuktane Z, Carr A, Saveri P, Piscosquito G, Pareyson D, Laura M, Blake JC, Poh R, Polke J, Houlden H, Reilly MM. Mutations in noncoding regions of GJB1 are a major cause of X-linked CMT. Neurology. 2017;88:1445-53. PubMed PMID: 28283593.

Tsai PC, Chen CH, Liu AB, Chen YC, Soong BW, Lin KP, Yet SF, Lee YC. Mutational analysis of the 5' non-coding region of GJB1 in a Taiwanese cohort with Charcot-Marie-Tooth neuropathy. J Neurol Sci. 2013;332:51-5. PubMed PMID: 23827825.

Vital A, Ferrer X, Lagueny A, Vandenberghe A, Latour P, Goizet C, Canron MH, Louiset P, Petry KG, Vital C. Histopathological features of X-linked Charcot-Marie-Tooth disease in 8 patients from 6 families with different connexin32 mutations. J Peripher Nerv Syst. 2001;6:79-84. PubMed PMID: 11446387.

Yuan JH, Sakiyama Y, Hashiguchi A, Ando M, Okamoto Y, Yoshimura A, Higuchi Y, Takashima H. Genetic and phenotypic profile of 112 patients with X-linked Charcot-Marie-Tooth disease type 1. Eur J Neurol. 2018;25:1454-61. PubMed PMID: 29998508.

Yum SW, Kleopa KA, Shumas S, Scherer SS. Diverse trafficking abnormalities of connexin32 mutants causing CMTX. Neurobiol Dis. 2002;11:43-52. PubMed PMID: 12460545.

Zambelis T, Panas M, Kokotis P, Karadima G, Kararizou E, Karandreas N. Central motor and sensory pathway involvement in an X-linked Charcot-Marie-Tooth family. Acta Neurol Belg. 2008;108:44-7. PubMed PMID: 18795595.

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