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CACNA1C-Related Disorders

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Summary

Clinical characteristics

The first identified *CACNA1C*-related disorder, referred to as Timothy syndrome, consists of the combination of prolonged QT interval, autism, and cardiovascular malformation with syndactyly of the fingers and toes. Infrequent findings also include developmental and speech delay, seizures, and recurrent infections. With increased availability of molecular genetic testing, a wider spectrum of pathogenic variants and clinical findings associated with *CACNA1C*-related disorders has been recognized. Because *CACNA1C* is associated with calcium channel function, all individuals with a pathogenic variant in this gene are at risk for cardiac arrhythmia of a specific type. The clinical manifestations of a *CACNA1C*-related disorder include three phenotypes:

- Timothy syndrome with or without syndactyly
- QT prolongation (QTc >480 ms) and arrhythmias in the absence of other syndromic features
- Short QT syndrome (QTc <350 ms) or Brugada syndrome with short QT interval

These three phenotypes can be separated into two broad categories on the basis of the functional consequences of the pathogenic variants in *CACNA1C*:

- QT prolongation with or without a Timothy syndrome-associated phenotype associated with pathogenic variants inducing a gain of function at the cellular level (i.e., increased calcium current)
- Short QT interval with or without Brugada syndrome EKG pattern associated with pathogenic variants causing loss of function (i.e., reduced calcium current)

Diagnosis/testing

The diagnosis of a *CACNA1C*-related disorder is established in a proband with suggestive findings and a heterozygous pathogenic variant in *CACNA1C* identified by molecular genetic testing.

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Management

Treatment of manifestations: Treatment includes use of beta blockers and/or other antiarrhythmic drugs to maintain QT interval stability to prevent ventricular tachyarrhythmia. In some instances, pacemakers can be placed during the first days of life to control 2:1 atrioventricular block and resultant bradycardia, but an implantable cardioverter defibrillator to prevent sudden cardiac death should be considered in all affected persons. Standard care is recommended for cardiovascular malformations and extracardiac malformations such as syndactyly and hypoglycemia.

Prevention of primary manifestations: Arrhythmias must be prevented with the standard therapy. Because anesthesia is a known trigger for cardiac arrhythmia, close cardiac monitoring is warranted during surgery. Fever can be a trigger for arrhythmias in individuals with *CACNA1C*-related Brugada syndrome and requires aggressive treatment with standard antipyretic drugs.

Surveillance: Cardiac and neurologic evaluations every six to 12 months.

Agents/circumstances to avoid: Drugs reported to prolong QT interval; drugs and dietary practices that could lead to hypoglycemia.

Evaluation of relatives at risk: It is appropriate to clarify the genetic status of the older and younger at-risk relatives of a proband in order to identify as early as possible those who would benefit from a complete cardiac evaluation and institution of measures to prevent cardiac arrhythmias.

Genetic counseling

CACNA1C-related disorders are autosomal dominant disorders. Many individuals diagnosed with a *CACNA1C*-related disorder – particularly those individuals with Timothy syndrome – represent simplex cases (i.e., a single affected family member) and have the disorder as the result of a pathogenic variant that occurred *de novo* in the proband or in a mosaic parent. If a parent of the proband is affected and/or is known to be heterozygous for the pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%. If the proband has a known *CACNA1C* pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is greater than that of the general population because of the possibility of parental germline mosaicism. Once the *CACNA1C* pathogenic variant has been identified in an affected family member, prenatal testing and preimplantation genetic testing for a pregnancy at increased risk for a *CACNA1C*-related disorder are possible.

GeneReview Scope

With the current widespread use of multigene panels and comprehensive genomic testing, it has become apparent that the phenotypic spectrum of heterozygous *CACNA1C* pathogenic variants has broadened to encompass Timothy syndrome as well as other phenotypes. The title of this chapter, "*CACNA1C*-Related Disorders," refers to the entire phenotypic spectrum that can be associated with heterozygous *CACNA1C* pathogenic variants and emphasizes the need to evaluate an individual found to have a *CACNA1C* pathogenic variant for medically actionable manifestations in the entire phenotypic spectrum (regardless of clinical findings that prompted molecular genetic testing).

Diagnosis

Suggestive Findings

A *CACNA1C*-related disorder should be suspected in individuals with any of the following three major clinical findings and family history.

Clinical findings

- A prolonged QT interval on electrocardiogram (EKG) (rate-corrected QT [QTc] interval >480 ms) with or without the following findings:
  - Cardiovascular malformations such as patent ductus arteriosus, patent foramen ovale, ventricular septal defect, tetralogy of Fallot, or hypertrophic cardiomyopathy
  - Unilateral or bilateral cutaneous syndactyly variably involving fingers two (index), three (middle), four (ring), and five (little) and bilateral cutaneous syndactyly of toes two and three
  - Neurologic findings including autism, seizures, intellectual disability, hypotonia
  - Facial anomalies including depressed nasal bridge, low-set ears, thin vermilion of the upper lip, round face, and abnormal tooth development
- ST segment elevation in right precordial leads (V1-V2) diagnostic for Brugada syndrome (type 1 EKG) associated with a short QT interval
- Short QT interval (QTc <350 ms) and risk of sudden death

Family history is consistent with autosomal dominant inheritance (e.g., affected males and females in multiple generations). There may be a history of syncope, aborted cardiac arrest, or sudden death in a child or young adult relative in whom a diagnosis was not recognized. Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of a *CACNA1C*-related disorder is established in a proband with suggestive findings and a heterozygous pathogenic (or likely pathogenic) variant in *CACNA1C* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of a heterozygous *CACNA1C* 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 and multigene panel) and **comprehensive genomic testing** (exome sequencing, 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. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with a phenotype indistinguishable from many other inherited disorders with cardiac or neurologic findings are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

Single-gene testing. Sequence analysis of *CACNA1C* is performed first to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.

A cardiac arrhythmia or epilepsy multigene panel that includes *CACNA1C* and other genes of interest (see Differential Diagnosis) may 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. Note: (1)

The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may 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 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 is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

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 *CACNA1C*-Related Disorders

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
CACNA1C	Sequence analysis [3]	~100% [4]
	Gene-targeted deletion/duplication analysis [5]	Rare [4, 6]

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 small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
5. 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.
6. Deletions have been reported by Rooryck et al [2009], Borlot et al [2017], and Mio et al [2020].

Clinical Characteristics

Clinical Description

The first *CACNA1C*-related disorder was referred to as Timothy syndrome [Splawski et al 2004], a condition with very high mortality with only few individuals who reached reproductive age. Timothy syndrome consisted of the combination of prolonged QT interval, autism, and congenital heart defect with syndactyly of the fingers and toes; all these individuals had the same pathogenic variant, while a similar phenotype but without syndactyly was subsequently identified in association with similar but distinct pathogenic variants (see Genotype-Phenotype Correlations).

With increased availability of molecular genetic testing, a wider spectrum of pathogenic variants and clinical findings associated with *CACNA1C*-related disorders has been recognized. Because *CACNA1C* is associated with calcium channel function, all individuals with a pathogenic variant in this gene are at risk for cardiac arrhythmia of a specific type.

The clinical manifestations of a *CACNA1C*-related disorder include three phenotypes:

- Timothy syndrome with or without syndactyly [Splawski et al 2004, Splawski et al 2005];
- QT prolongation (QTc >480 ms) and arrhythmias in the absence of other syndromic features [Wemhöner et al 2015]; and
- Short QT syndrome (QTc <350 ms) [Raschwitz et al 2020] or Brugada syndrome with short QT interval [Burashnikov et al 2010].

These three phenotypes can be separated into two broad categories on the basis of the functional consequences of the pathogenic variants:

- QT prolongation with or without a Timothy syndrome-associated phenotype associated with pathogenic variants inducing a gain of function at the cellular level (i.e., increased calcium current); and
- Short QT interval with or without Brugada syndrome EKG pattern associated with pathogenic variants causing loss of function (i.e., reduced calcium current).

The clinical phenotype associated with large deletions/duplications is less defined, as few individuals with this phenotype have been reported (see Table 1).

Table 2. *CACNA1C*-Related Disorders: Frequency of Select Features by Type of Pathogenic Variant

Variant Type	Feature		Frequency		
			Nearly all	Common	Infrequent
Gain-of-function pathogenic variants	Cardiac	QTc prolongation	●		
		Bradycardia		●	
		2:1 AV block		●	
		Macroscopic T-wave alternans		●	
		Tachyarrhythmia / sudden death		●	
		Cardiovascular malformations			●
	Cutaneous syndactyly			●	
	Typical craniofacial features			●	
	Developmental delay / Intellectual disability				●
	Speech delay				●
	Autism			●	
	Seizures				●
	Recurrent infections				●
Loss-of-function pathogenic variants	Cardiac	Short QT syndrome	●		
		Brugada syndrome		●	
		Sudden death			●

AV = atrioventricular

Age at diagnosis may vary depending on the associated phenotype.

- In general, the diagnosis of Timothy syndrome is made within the first few days of life based on the markedly prolonged rate-corrected QT (QTc) interval in an infant with bradycardia and 2:1 atrioventricular (AV) block [Reichenbach et al 1992, Marks et al 1995a, Lo-A-Njoe et al 2005]. Rarely, diagnosis may be delayed until age two to four years [Marks et al 1995b, Splawski et al 2005].
- Individuals with QT prolongation only (no other Timothy syndrome features) or individuals with Brugada syndrome or short QT syndrome are generally associated with less severe EKG abnormalities and lower

incidence of events. Therefore, the diagnosis may be established later in life, sometimes as an incidental finding during routine visits or sport pre-participation screening.
- Occasionally, the diagnosis of a *CACNA1C*-related disorder is suspected prenatally because of fetal distress secondary to cardiac findings of bradycardia with a heart rate that is usually 70-80 (normal fetal heart rate is 120-150) or 2:1 AV block. Biventricular hypertrophy and biventricular dysfunction have been observed on a fetal echocardiogram [Splawski et al 2005].

Cardiac Manifestations

Cardiac manifestations vary by type of pathogenic variant present in an individual.

Gain-of-function pathogenic variants

- **Long QT interval.** QTc interval >480 ms on EKG are observed in nearly all with gain-of-function pathogenic variants.
- **Bradycardia.** Lower-than-normal heart rate is frequently observed prenatally or at birth in individuals with markedly increased QT prolongation that causes intermittent 2:1 AV block (see following). In other individuals, sinus bradycardia has been reported in the absence of AV block.
- **Other electrocardiographic manifestations** that are common in individuals with gain-of-function *CACNA1C* pathogenic variants may include:
  - **AV block.** The 2:1 AV block is likely caused by the extremely prolonged ventricular repolarization and refractory periods and not by AV node malfunction.
  - **Macroscopic T-wave alternans.** Positive and negative T waves on a beat-to-beat basis
- **Tachyarrhythmia / sudden death.** Associated with the prolonged QTc interval, ventricular tachyarrhythmias (including ventricular tachycardia and ventricular fibrillation) are reported. Arrhythmias are more often polymorphic ventricular tachycardia and torsade de pointes that may degenerate and leading to cardiac arrest. Syncope may occur due to self-limiting ventricular tachycardia.
- **Cardiovascular malformations** are reported to include patent ductus arteriosus, patent foramen ovale, ventricular septal defect, tetralogy of Fallot, or hypertrophic cardiomyopathy.

Loss-of-function pathogenic variants

- **Short QT syndrome** is associated with a short QT interval with or without Brugada syndrome EKG pattern due to a reduction of the duration of cardiac action potential. The evidence of QTc <350 ms is a hallmark of increased sudden death risk [Mazzanti et al 2017]. No specific trigger for arrhythmic events has been identified. Autism can be present in association with short QT interval [Endres et al 2020].
- **Brugada syndrome** manifests clinically with the typical EKG pattern of ST elevation in V1 and V2 leads. Arrhythmic events and sudden death typically occur at rest or during sleep.

Extracardiac Manifestations

Cutaneous syndactyly may involve fingers two (index), three (middle), four (ring), and five (little), and bilateral cutaneous syndactyly of toes two and three. Syndactyly may be unilateral or bilateral and involve fingers four and five only, fingers three through five, or fingers two through five.

Craniofacial findings

- Low-set ears
- Depressed nasal bridge
- Premaxillary underdevelopment
- Baldness at birth and for the first two years of life, followed by thin scalp hair
- Small, widely spaced teeth and poor dental enamel with severe caries [Splawski et al 2004]

Neuropsychiatric involvement

- Developmental delays observed include language, motor, and generalized cognitive impairment. Children were impaired in all areas of adaptive function, including communication, socialization, and daily living skills.
- Some children did not produce speech sounds (babbling) during infancy; others had significant problems in articulation and receptive and expressive language.
- Autism has been reported in some individuals [Splawski et al 2004].
- Epilepsy, including generalized seizures, staring followed by syncope, severe epileptic encephalopathy during infancy, and late-onset partial epilepsy have been reported [Gillis et al 2012, Hennessey et al 2014, Bozarth et al 2018].

Other findings

- Frequent infections (sinus, ear, respiratory) [Splawski et al 2004]
- Intermittent hypoglycemia [Dufendach et al 2018]
- Joint contractures (reported in a single individual) [Gillis et al 2012]

Life Span

Among the *CACNA1C*-related disorders, the typical Timothy syndrome phenotype has high mortality and most individuals with this phenotype do not reach reproductive age despite appropriate use of implantable cardioverter defibrillator and other therapies for non-cardiac conditions. On the other hand, the nonsyndromic QT prolongation, Brugada syndrome, or short QT syndrome phenotypes may be compatible with normal life span if properly diagnosed and treated.

Genotype-Phenotype Correlations

The classic Timothy syndrome phenotype results from the p.Gly406Arg pathogenic variant in exon 8A, an exon contained in a specific splice variant of *CACNA1C* (see Molecular Genetics).

Timothy syndrome phenotype in the absence of syndactyly (also referred to in the literature as atypical Timothy syndrome) has been associated with the pathogenic variants p.Gly406Arg and p.Gly402Ser occurring in exon 8 of a *CACNA1C* alternate splice form.

All reported *CACNA1C* pathogenic variants associated with QT prolongation (with or without syndromic features) occur in the intracellular portion of the protein.

No specific genotype-phenotype correlation has been found for *CACNA1C* variants associated with Brugada syndrome or short QT syndrome.

Penetrance

The penetrance of pathogenic variants associated with typical Timothy syndrome is 100%. [Splawski et al 2005]. Nonsyndromic forms have lower penetrance that can be estimated in the range of 60%-80% on the basis of published literature [Fukuyama et al 2014, Wemhöner et al 2015].

Penetrance is not known to differ between males and females.

Nomenclature

The term **Timothy syndrome** (also referred to as Timothy syndrome type 1) was named for Katherine Timothy, who followed children with that phenotype for more than 14 years, identifying the non-cardiac manifestations and collecting samples that led to the discovery of the gene in which pathogenic variants are causative.

Atypical Timothy syndrome (formerly referred to as Timothy syndrome type 2) was the term used to describe individuals who had QT interval prolongation without syndactyly.

LQT8. The term LQT8 is used in medical literature to refer to both Timothy syndrome and nonsyndromic *CACNA1C*-related long QT syndrome.

BRGDA3 refers to *CACNA1C*-related Brugada syndrome.

SQT6 refers to *CACNA1C*-related short QT syndrome [Templin et al 2011].

Prevalence

Timothy syndrome is a very rare condition probably because of its very high mortality. Fewer than 100 cases have been described worldwide.

The prevalence of nonsyndromic *CACNA1C*-related disorders (long QT syndrome, Brugada syndrome, and short QT syndrome) is not known. Indirect evidence based on genomic sequencing data and available in vitro expression data suggest a prevalence of around 1:10,000 or lower [Author, personal observation].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with a heterozygous germline pathogenic variant in *CACNA1C*.

Differential Diagnosis

Long QT syndrome (LQTS). Fifteen genes (including *CACNA1C*) are known to be associated with LQTS – of these, *KCNH2* (LQT2), *KCNQ1* (LQT1), and *SCN5A* (LQT3) are the most common. Approximately 20% of families meeting clinical diagnostic criteria for LQTS do not have detectable pathogenic variants in a known gene.

- **Nonsyndromic autosomal dominant LQTS** is characterized by QT interval prolongation and the absence of non-cardiac features. The clinical phenotype of an individual with a *CACNA1C* pathogenic variant but no extracardiac findings (i.e., LQTS type 8) can be indistinguishable from other forms of LQTS. Of note, the macroscopic T-wave alternans EKG pattern seen in those with *CACNA1C*-related disorders may also be observed in individuals with LQTS type 3 (*SCN5A* pathogenic variant).
- See Long QT Syndrome, a review of similar phenotypes that are genetically diverse.
- **LQTS with extracardiac findings.** See Table 3.

Table 3. Long QT Syndrome with Extracardiac Findings

Gene(s)	Disorder	MOI	Extracardiac Findings
KCNJ2	Andersen-Tawil syndrome (LQTS7)	AD	• Episodic flaccid muscle weakness; anomalies incl low-set ears, widely spaced eyes, small mandible, 5th-digit clinodactyly, syndactyly, short stature, & scoliosis • Presents in 1st or 2nd decade w/cardiac symptoms or weakness that occurs spontaneously after prolonged rest or rest following exertion. Mild permanent weakness is common. Mild learning difficulties & a distinct neurocognitive phenotype (i.e., deficits in executive function & abstract reasoning) have been described.
KCNE1 *KCNQ1*	Jervell & Lange-Nielson syndrome	AR	• Congenital profound bilateral sensorineural hearing loss • Classic presentation is a deaf child who experiences syncopal episodes during periods of stress, exercise, or fright. 50% of persons have a cardiac event before age 3 yrs; >50% of untreated children die before age 15 yrs.

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance

Acquired causes of QT prolongation such as electrolyte imbalance (e.g., hypokalemia) or QT-prolonging drugs (e.g., macrolide antibiotics) should be excluded before considering the diagnosis of a *CACNA1C*-related disorder. In such cases the removal of the offending agent should lead to EKG normalization. However, some cases of drug-induced QT prolongation may also have a genetic predisposition (including pathogenic variants in LQTS-related genes).

Brugada syndrome. More than 20 genes are known to be associated with Brugada syndrome – of these, *SCN5A* is the most commonly associated gene, accounting for 15% to 30% of Brugada syndrome. See Brugada Syndrome, a review of similar phenotypes that are genetically diverse.

Syndactyly. Cutaneous syndactyly of the fingers and cutaneous syndactyly of toes two and three can both be seen in numerous disorders. The latter is seen in Bardet-Biedl syndrome and Smith-Lemli-Opitz syndrome, in which it can be a significant clue to diagnosis.

Autism. See OMIM PS209850.

Epilepsy and epileptic encephalopathy have been reported to be associated with pathogenic variants in *CACNA1C*; however, in the absence of a cardiac phenotype the evidence for *CACNA1C* as causative of neurologic-only conditions is currently insufficient [Bozarth et al 2018].

Management

No specific clinical practice guidelines for a *CACNA1C*-related disorder have been published; therefore, the general recommendations for the treatment of the specific disorder – long QT syndrome, Brugada syndrome, short QT syndrome – should apply, independent of the specific genetic cause [Priori et al 2015, Al-Khatib et al 2018].

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with a *CACNA1C*-related disorder, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with a *CACNA1C*-Related Disorder

System/Concern	Evaluation	Comment
Cardiac	• Eval w/pediatric cardiologist incl EKG & echocardiogram • 24-hour Holter monitoring is relevant for initial clinical assessment of persons w/ Brugada syndrome.	Contrast echo, cardiac MR, & ventriculography could be indicated if standard transthoracic echocardiogram is unable to conclusively exclude congenital defects.
Syndactyly	Orthopedics consultation	
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech/ language eval • Eval for early intervention / special education
Psychiatric/ Behavioral	Neuropsychiatric eval	For persons age >12 mos: screening for behavior concerns incl traits suggestive of ASD
Neurologic	Neurologic eval	• Consider EEG if seizures are a concern. • Consider MR if encephalopathy is suspected.
Hypoglycemia	Oral glucose tolerance test	Not required in absence of suggestive symptoms

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of a *CACNA1C*-related disorder to facilitate medical & personal decision making
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support.	

ASD = autism spectrum disorder; MOI = mode of inheritance
1. Medical geneticist, certified genetic counselor, or certified advanced genetic nurse

Treatment of Manifestations

Standard care is recommended for cardiovascular malformations, surgical release of syndactyly, and hypoglycemia.

Note: All medical procedures requiring anesthesia should be performed with caution (see Prevention of Primary Manifestations).

Table 5. Treatment of Manifestations in Individuals with a *CACNA1C*-Related Disorder

Manifestation/ Concern	Treatment	Considerations/Other
Prolonged QT interval	• Beta blockers (nadolol preferred) • Mexiletine can be considered to shorten QT (response is variable & every person must be carefully monitored).	Under care of cardiologist
Bradycardia w/2:1 AV block	Pacemaker placement/temporary pacing	Can be placed in 1st few days of life
Short QT syndrome	Quinidine normalizes QT interval in majority of persons	Under care of cardiologist
Brugada syndrome	Consider quinidine or catheter ablation in symptomatic persons	
Tachyarrhythmias	ICD as soon as body weight allows in all affected persons	To prevent sudden cardiac death
DD/ID	See Developmental Delay / Intellectual Disability Management Issues.	
Epilepsy	Standardized treatment w/ASM by experienced neurologist	• Many ASMs may be effective; none has been demonstrated effective specifically for this disorder. • Education of parents/caregivers [1]

ASM = anti-seizure medication; AV = atrioventricular; DD = developmental delay; ICD = implantable cardioverter defibrillator; ID = intellectual disability
1. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.
  - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
  - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
  - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Motor Dysfunction

Gross motor dysfunction

- Physical therapy is recommended to maximize mobility and to reduce the risk for later-onset orthopedic complications (e.g., contractures, scoliosis, hip dislocation).
- Consider use of durable medical equipment and positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).
- For muscle tone abnormalities including hypertonia or dystonia, consider involving appropriate specialists to aid in management of baclofen, tizanidine, Botox®, anti-parkinsonian medications, or orthopedic procedures.

Fine motor dysfunction. Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as feeding, grooming, dressing, and writing.

Oral motor dysfunction should be assessed at each visit and clinical feeding evaluations and/or radiographic swallowing studies should be obtained for choking/gagging during feeds, poor weight gain, frequent respiratory illnesses, or feeding refusal that is not otherwise explained. Assuming that the child is safe to eat by mouth, feeding therapy (typically from an occupational or speech therapist) is recommended to help improve coordination or sensory-related feeding issues. Feeds can be thickened or chilled for safety. When feeding dysfunction is severe, an NG-tube or G-tube may be necessary.

Communication issues. Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals who have expressive language difficulties. An AAC evaluation can be completed by a speech-language pathologist who has expertise in the area. The evaluation will consider cognitive abilities and sensory impairments to determine the most appropriate form of communication. AAC devices can range from low-tech, such as picture exchange communication, to high-tech, such as voice-generating devices. Contrary to popular belief, AAC devices do not hinder verbal development of speech, but rather support optimal speech and language development.

Social/Behavioral Concerns

Children may qualify for and benefit from interventions used in treatment of autism spectrum disorder, including applied behavior analysis (ABA). ABA therapy is targeted to the individual child's behavioral, social, and adaptive strengths and weaknesses and typically performed one on one with a board-certified behavior analyst.

Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavior management strategies or providing prescription medications, such as medication used to treat attention-deficit/hyperactivity disorder, when necessary.

Concerns about serious aggressive or destructive behavior can be addressed by a pediatric psychiatrist.

Prevention of Primary Manifestations

Arrhythmias must be prevented with the standard therapy described in Treatment of Manifestations.

Anesthesia is a known trigger for cardiac arrhythmia in individuals with a *CACNA1C*-related disorder. Therefore, any surgical intervention must be performed under close cardiac monitoring. Because clinical experience with *CACNA1C*-related disorders is scarce, all compounds used for general anesthesia should be regarded as potentially dangerous.

Fever can be a trigger for arrhythmias in individuals with *CACNA1C*-related Brugada syndrome (as in Brugada syndrome in general) and requires aggressive treatment with standard antipyretic drugs.

Surveillance

Table 6. Recommended Surveillance for Individuals with a *CACNA1C*-Related Disorder

System/Concern	Evaluation	Frequency
Cardiac	Follow-up evals w/cardiologist incl EKG, Holter, & echocardiogram	Every 6-12 mos
	Evals of persons w/pacemaker or ICD	Every 12 mos if remote device monitoring is available
Neurologic	Neurologic eval	Every 6-12 mos

ICD = implantable cardioverter defibrillator

Agents/Circumstances to Avoid

The following should be avoided:

- All drugs reported to prolong QT interval (See CredibleMeds®.)
- Drugs and dietary practices that could lead to hypoglycemia

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of the older and younger at-risk relatives of a proband in order to identify as early as possible those who would benefit from a complete cardiac evaluation and institution of measures to prevent cardiac arrhythmias.

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 access to 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

CACNA1C-related disorders are autosomal dominant disorders.

Risk to Family Members

Parents of a proband

- Many individuals diagnosed with a *CACNA1C*-related disorder – particularly those individuals with Timothy syndrome – represent simplex cases (i.e., a single affected family member) and have the disorder as the result of a *de novo* pathogenic variant.
- Some individuals diagnosed with a *CACNA1C*-related disorder have an affected parent.
- Molecular genetic testing is recommended for the parents of the proband to confirm their genetic status and to allow reliable recurrence risk counseling.
- If the pathogenic variant identified in the proband is not identified in either parent, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant. Note: A pathogenic variant is reported as "*de novo*" if: (1) the pathogenic variant found in the proband is not detected in parental DNA; and (2) parental identity testing has confirmed biological maternity and paternity. If parental identity testing is not performed, the variant is reported as "assumed *de novo*" [Richards et al 2015].
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Parental mosaicism for a *CACNA1C* pathogenic variant has been reported [Splawski et al 2004]. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.

- The family history of some individuals diagnosed with a *CACNA1C*-related disorder may appear to be negative because of failure to recognize the disorder in family members, reduced penetrance, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has demonstrated that neither parent is heterozygous for the pathogenic variant identified in the proband.

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

- If a parent of the proband is affected and/or is known to have the pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%.
- Penetrance in sibs who inherit a familial *CACNA1C* pathogenic variant ranges from 100% (for sibs of a proband with Timothy syndrome) to approximately 60%-80% (for sibs of a proband with a nonsyndromic *CACNA1C*-related cardiac arrhythmia).
- If the proband has a known *CACNA1C* pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is greater than that of the general population because of the possibility of parental germline mosaicism. Parental mosaicism has been reported [Splawski et al 2004].
- If the parents are clinically unaffected but have not been tested for the pathogenic variant, recurrence risk in sibs is estimated to be 50% because a heterozygous parent may be clinically unaffected due to reduced penetrance of long QT syndrome-related EKG changes and symptoms.

Offspring of a proband. Each child of an individual with a *CACNA1C*-related disorder has a 50% chance of inheriting the *CACNA1C* pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the *CACNA1C* pathogenic variant, the parent's family members may be at risk.

Specific risk issues. With the reduced penetrance of symptoms in individuals with a *CACNA1*-related disorder, careful EKG evaluation including exercise EKG is often necessary to identify affected family members accurately. The absence of a family history of sudden death is common and does not negate the diagnosis or preclude the possibility of sudden death in relatives.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

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 adults who are affected or at risk.

Prenatal Testing and Preimplantation Genetic Testing

Molecular genetic testing. Once the *CACNA1C* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing for a pregnancy at increased risk for a *CACNA1C*-related disorder are possible.

Fetal echocardiography. Monitoring of cardiac rate and function during pregnancy is appropriate.

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.

- **National Library of Medicine Genetics Home Reference**
  Timothy syndrome
- **American Heart Association**
  Phone: 800-242-8721
  www.americanheart.org
- **Canadian SADS Foundation**
  Canada
  Email: info@sads.ca
  www.sads.ca
- **Sudden Arrhythmia Death Syndromes (SADS) Foundation**
  Phone: 801-948-0654
  www.sads.org
- **International Long QT Syndrome Registry**
  Heart Research Follow-Up Program
  Phone: 585-276-0016
  Fax: 585-273-5283
  Email: heartajm@heart.rochester.edu

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. CACNA1C-Related Disorders: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
CACNA1C	12p13.33	Voltage-dependent L-type calcium channel subunit alpha-1C	CACNA1C database CACNA1C @ ZAC-GGM	CACNA1C	CACNA1C

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 CACNA1C-Related Disorders (View All in OMIM)

114205	CALCIUM CHANNEL, VOLTAGE-DEPENDENT, L TYPE, ALPHA-1C SUBUNIT; CACNA1C
601005	TIMOTHY SYNDROME; TS
611875	BRUGADA SYNDROME 3; BRGDA3
618447	LONG QT SYNDROME 8; LQT8

Molecular Pathogenesis

Excitable cells contain voltage-dependent calcium channels. These channels (also called CaV1.2) are involved in the control of the duration of the electrical activation (action potential duration), which is the counterpart of QT interval in the myocardium. Furthermore, in cardiac cells the calcium entry triggers the release of more calcium from the sarcoplasmic reticulum, leadin to the contraction of muscle fibers. The role of calcium current in the CNS is less well defined.

Most gain-of-function pathogenic variants impair $Ca_V1.2$ channel inactivation, leading to maintained depolarizing Ca^{2+} [Napolitano & Antzelevitch 2011]. Other pathogenic variants increase the current density [Napolitano & Antzelevitch 2011]. There is relatively little outward current during the plateau phase due to high membrane impedance, so even modest changes in inward calcium current lead to significant QT interval prolongation. This prolongation in turn leads to increased risk of spontaneous, abnormal secondary depolarizations (so-called after-depolarizations), arrhythmia, and sudden death.

Loss-of-function pathogenic variants have an opposite mechanism, with reduced current density [Napolitano & Antzelevitch 2011] that shortens the duration of electrical activation in myocardial cells. Therefore, a shortening of QT interval is the direct consequence of this kind of change. Less clear, due to the lack of experimental models, is the pathogenesis of ST segment elevation leading to a Brugada syndrome phenotype.

CACNA1C has a complex genomic structure that undergoes extensive alternative splicing, producing at least 36 different transcripts. Alternative splicing is regulated by a number of different factors, including a tissue-specific regulation [Napolitano & Antzelevitch 2011]. This may explain the variability of the clinical phenotypes associated with pathogenic variants occurring in alternatively spliced exons or in different regions of the protein.

The gene is also involved in the embryologic development of several organs: CNS [Panagiotakos et al 2019], bones [Ramachandran et al 2013, Atsuta et al 2019], and glucose metabolism [Pan et al 2016].

Mechanism of disease causation. *CACNA1C*-related disorders can occur via a gain-of-function mechanism and, in this case, clinically manifest with QT prolongation with or without Timothy syndrome phenotypes.

Loss-of-function pathogenic variants cause Brugada syndrome and short QT syndrome.

***CACNA1C*-specific laboratory technical considerations.** Due to the possibility of alternative splicing, sequencing of the entire genomic region of *CACNA1C* is required for a thorough molecular analysis.

Table 7. Notable *CACNA1C* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_001167625.2 NP_001161097.1	c.1216G>A	p.Gly406Arg (exon 8)	Timothy syndrome phenotype w/o syndactyly [Splawski et al 2005]

Table 7. continued from previous page.

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_000719.7 NP_000710.5	c.1216G>A	p.Gly406Arg (exon 8A)	Classic Timothy syndrome phenotype [Splawski et al 2004]
	c.1204G>A	p.Gly402Ser	Timothy syndrome phenotype w/o syndactyly [Splawski et al 2005]
	c.3497T>C	p.Ile1166Thr	Nonsyndromic severe QT prolongation [Wemhöner et al 2015]
	c.4418C>G	p.Ala1473Gly	Severe Timothy syndrome phenotype [Gillis et al 2012]
	c.3343G>A	p.Glu1115Lys	Brugada syndrome [Burashnikov et al 2010]

Variants listed in the table have been provided by the authors. *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.

Chapter Notes

Author Notes

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- 27 January 2009 (cd) Revision: sequence analysis available clinically
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