CACNA1C Timothy syndrome

https://www.ncbi.nlm.nih.gov/books/NBK1403/

SummaryClinical 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 syndactylyQT prolongation (QTc >480 ms) and arrhythmias in the absence of other syndromic featuresShort QT syndrome (QTc <350 ms) or Brugada syndrome with short QT intervalThese 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.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.

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Timothy syndrome with or without syndactyly

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preimplantation genetic testing for a pregnancy at increased risk for a CACNA1C-related disorder are possible.

GeneReview ScopeWith 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).

DiagnosisSuggestive FindingsA 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 cardiomyopathyUnilateral or bilateral cutaneous syndactyly variably involving fingers two (index), three (middle), four (ring), and five (little) and bilateral cutaneous syndactyly of toes two and threeNeurologic findings including autism, seizures, intellectual disability, hypotoniaFacial anomalies including depressed nasal bridge, low-set ears, thin vermilion of the upper lip, round face, and abnormal tooth developmentST segment elevation in right precordial leads (V1-V2) diagnostic for Brugada syndrome (type 1 EKG) associated with a short QT intervalShort QT interval (QTc <350 ms) and risk of sudden deathFamily 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 DiagnosisThe 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 1Single-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 2Comprehensive

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Clinical CharacteristicsClinical DescriptionThe 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]; andShort 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); andShort 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 VariantView in own windowVariant TypeFeatureFrequencyNearly allCommonInfrequent

Gain-of-

function

pathogenic

variants

CardiacQTc 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

CardiacShort QT syndrome●Brugada syndrome●Sudden death●AV =

atrioventricularAge 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 ManifestationsCardiac 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 basisTachyarrhythmia / 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 ManifestationsCutaneous 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 earsDepressed nasal bridgePremaxillary underdevelopmentBaldness at birth and for the first two years of life, followed by thin scalp hairSmall, 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

SpanAmong 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 CorrelationsThe 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.PenetranceThe 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.NomenclatureThe 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].PrevalenceTimothy 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].

Clinical DescriptionThe 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]; andShort 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); andShort 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 VariantView in

own windowVariant TypeFeatureFrequencyNearly allCommonInfrequent

Gain-of-

function

pathogenic

variants

CardiacQTc 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

CardiacShort QT syndrome●Brugada syndrome●Sudden death●AV = atrioventricularAge 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 ManifestationsCardiac 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 basisTachyarrhythmia / 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 ManifestationsCutaneous 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.

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Low-set earsDepressed nasal bridgePremaxillary underdevelopmentBaldness at birth and for the first two years of life, followed by thin scalp hairSmall, 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].

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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 SpanAmong 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.

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

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PrevalenceTimothy 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) DisordersNo phenotypes other than those discussed in this GeneReview are known to be associated with a heterozygous germline pathogenic variant in CACNA1C.

Differential DiagnosisLong 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 FindingsView in own windowGene(s)DisorderMOIExtracardiac 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, & scoliosisPresents 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 lossClassic 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 inheritanceAcquired 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].

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).

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Long QT Syndrome with Extracardiac Findings

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ManagementNo 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 DiagnosisTo 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 DisorderView in own windowSystem/ConcernEvaluationComment

Cardiac

Eval w/pediatric cardiologist incl EKG & echocardiogram24-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 evalEval for early intervention / special education

Psychiatric/

Behavioral

Neuropsychiatric evalFor 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 testNot required in absence of suggestive symptoms

Genetic counseling

By genetics professionals 1To 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 inheritance1. Medical geneticist, certified genetic counselor, or certified advanced genetic nurseTreatment of ManifestationsStandard 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 DisorderView in own windowManifestation/ConcernTreatmentConsiderations/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 pacingCan be placed in 1st few days of life

Short QT

syndrome

Quinidine normalizes QT interval in majority of personsUnder care of cardiologist

Brugada

syndrome

Consider quinidine or catheter ablation in symptomatic persons

Tachyarrhythmias

ICD as soon as body weight allows in all affected personsTo 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 disability1. 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 IssuesThe 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

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Cardiac

Follow-up evals w/cardiologist incl EKG, Holter, & echocardiogramEvery 6-12 mosEvals of persons w/pacemaker or ICDEvery 12 mos if remote device monitoring is available

Neurologic

Neurologic evalEvery 6-12 mosICD = implantable cardioverter defibrillatorAgents/Circumstances to AvoidThe following should be avoided:All drugs reported to prolong QT interval (See CredibleMeds®.)Drugs and dietary practices that could lead to hypoglycemiaEvaluation of Relatives at RiskIt 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 InvestigationSearch 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.

Evaluations Following Initial DiagnosisTo 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 DisorderView in own windowSystem/ConcernEvaluationComment

Cardiac

Eval w/pediatric cardiologist incl EKG & echocardiogram24-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 evalEval for early intervention / special education

Psychiatric/

Behavioral

Neuropsychiatric evalFor 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 testNot required in absence of suggestive symptoms

Genetic counseling

By genetics professionals 1To 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 inheritance1. Medical geneticist, certified genetic counselor, or certified advanced genetic nurse

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Treatment of ManifestationsStandard 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 DisorderView in own windowManifestation/ConcernTreatmentConsiderations/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 pacingCan be placed in 1st few days of life

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Consider quinidine or catheter ablation in symptomatic persons

Tachyarrhythmias

ICD as soon as body weight allows in all affected personsTo prevent sudden cardiac death

DD/ID

See Developmental Delay / Intellectual Disability Management Issues.

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Evaluation of Relatives at RiskIt 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 InvestigationSearch 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 InheritanceCACNA1C-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 IssuesSee 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 TestingMolecular 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.

Mode of InheritanceCACNA1C-related disorders are autosomal dominant disorders.

Risk to Family Members

Parents of a proband

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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.

Related Genetic Counseling IssuesSee 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.

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Prenatal Testing and Preimplantation Genetic TestingMolecular 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

CanadaEmail: 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 ProgramPhone: 585-276-0016Fax: 585-273-5283Email:

heartajm@heart.rochester.edu

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Molecular GeneticsInformation 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 DatabasesView in own windowGeneChromosome LocusProteinLocus-Specific DatabasesHGMDClinVar

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) View in own window

114205CALCIUM CHANNEL, VOLTAGE-DEPENDENT, L TYPE, ALPHA-1C SUBUNIT; CACNA1C

601005TIMOTHY SYNDROME; TS

611875BRUGADA SYNDROME 3; BRGDA3

618447LONG QT SYNDROME 8; LQT8Molecular PathogenesisExcitable 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 CaV1.2 channel inactivation, leading to maintained depolarizing Ca2+ [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 VariantsView in own windowReferenceSequencesDNA NucleotideChangePredictedProtein ChangeComment [Reference]

NM_001167625.2

NP_001161097.1

c.1216G>Ap.Gly406Arg(exon 8)Timothy syndrome phenotype w/o syndactyly [Splawski et al 2005]

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Notable CACNA1C Pathogenic Variants

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Chapter NotesAuthor NotesCarlo Napolitano is a senior investigator currently in Molecular Cardiology at the IRCCS Maugeri Scientific Institutes and the Department of Molecular Medicine at the University of Pavia. He has more than 400 publications with 20,000 citations in the field of the

genetic basis of cardiac arrhythmias, cardiac electrophysiology, and sudden death (orcid.org/0000-0002-7643-4628).AcknowledgmentsWe are grateful to all of the individuals with Timothy syndrome and their families for donated time and samples. We would also like to thank the physicians who identified and are providing care for individuals with Timothy syndrome.Author HistoryRaffaella Bloise, MD (2006-present)Carlo Napolitano, MD, PhD (2006-present)Silvia G Priori, MD, PhD (2006-present)Igor Splawski, PhD; Harvard Medical School (2006-2021)Katherine W Timothy, BS (2006-present)Revision History11 February 2021 (ha) Comprehensive update posted live16 July 2015 (me) Comprehensive update posted live21 April 2011 (me) Comprehensive update posted live20 August 2009 (cd) Revision: prenatal diagnosis available clinically27 January 2009 (cd) Revision: sequence analysis available clinically29 July 2008 (me) Comprehensive update posted live15 February 2006 (me) Review posted live5 July 2005 (is) Original submission

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AcknowledgmentsWe are grateful to all of the individuals with Timothy syndrome and their families for donated time and samples. We would also like to thank the physicians who identified and are providing care for individuals with Timothy syndrome.

Author HistoryRaffaella Bloise, MD (2006-present)Carlo Napolitano, MD, PhD (2006-present)Silvia G Priori, MD, PhD (2006-present)Igor Splawski, PhD; Harvard Medical School (2006-2021)Katherine W Timothy, BS (2006-present)

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