CACNA1C Timothy syndrome

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Timothy syndrome

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Description

Timothy syndrome is a rare disorder that primarily affects the heart but can affect many other areas of the body. The severity of this condition varies among affected individuals, although it is often life-threatening.Timothy syndrome is characterized by a heart condition called long QT syndrome, which causes the heart (cardiac) muscle to take longer than usual to recharge between beats. This abnormality in the heart's electrical system can cause severe abnormalities of the heart rhythm (arrhythmias), which can lead to sudden death. Some people with Timothy syndrome are also born with structural heart defects (cardiomyopathy) that affect the heart's ability to pump blood effectively.Â As a result of these serious heart problems, some people with Timothy syndrome live only into childhood. In about 80 percent of cases of Timothy syndrome, the cause of death is a severe form of arrhythmia called ventricular tachycardia, in which the lower chambers of the heart (the ventricles) beat abnormally fast, often leading to cardiac arrest (the heart suddenly stops beating) and sudden death.Timothy syndrome is also characterized by webbing or fusion of the skin between some fingers or toes (cutaneous syndactyly). About half of affected people have

distinctive facial features such as a flattened nasal bridge, low-set ears, a small upper jaw, and a thin upper lip. Children with this condition have small, misplaced teeth and frequent cavities (dental caries). Additional signs and symptoms of Timothy syndrome can include baldness at birth, low muscle tone (hypotonia), frequent infections, episodes of low blood glucose (hypoglycemia), and an abnormally low body temperature (hypothermia). The respiratory system and gastrointestinal tract can also be affected.Neuropsychiatric features are also common in individuals with Timothy syndrome. Researchers have found that many children with Timothy syndrome have the characteristic features of autism spectrum disorders. Affected children tend to have impaired communication and socialization skills, as well as delayed development of speech and language. Poor coordination is also frequent in affected individuals. Other nervous system disorders that can occur in Timothy syndrome include attention-deficit/hyperactivity disorder, intellectual disability and recurrent seizures (epilepsy); some affected individuals have photosensitive epilepsy, in which seizures are triggered by flashing lights.

Frequency

Timothy syndrome is a rare condition; fewer than 100 people with this disorder have been reported worldwide.

Causes

Variants (also known as mutations) in the CACNA1C gene cause Timothy syndrome. This gene provides instructions for making a protein that acts as a small hole or pore (a channel) across cell membranes. This channel, known as CaV1.2, transports positively charged calcium atoms (calcium ions) into cardiac cells (cardiomyocytes) and nerve cells (neurons) in the brain. Calcium ions are

important for many cellular functions, including regulating the electrical activity of cells, cell-to-cell communication, the tensing of muscle fibers (muscle contraction), and the regulation of certain genes, particularly those involved in the development of the brain and bones before birth.Variants in the CACNA1C gene that cause Timothy syndrome change the structure of CaV1.2 channels. These gene changes lead to altered channels that stay open much longer than usual, which allows calcium ions to continue flowing into cells abnormally. The resulting overload of calcium ions within cardiac muscle cells changes the way the heart beats and can cause abnormal heart muscle contractions and arrhythmia. It is thought that the altered channels and flow of calcium ions also impair regulation of certain genes, resulting in the facial, dental, and neurological abnormalities in Timothy syndrome.Other variants in the CACNA1C gene can cause isolated features of Timothy syndrome without the other associated health problems of the condition. For example, some people with CACNA1C gene variants may have only long QT syndrome or only neurodevelopmental disorders.

Learn more about the gene associated with Timothy syndrome

CACNA1C

Inheritance

This condition is considered to have an autosomal dominant pattern of inheritance, which means one copy of the altered CACNA1C gene in each cell is sufficient to cause the disorder. Most cases result from new (de novo) variants in the gene. In these cases, there is no history of the disorder in

their family.Â Because of the severity of Timothy syndrome, it is rare for an affected individual to be able to pass on the disease-causing variant. Although rare, some people with Timothy syndrome inherit the altered gene from an unaffected parent who is mosaic for a CACNA1C gene variant. Mosaicism means that the parent has the variant in some cells (including egg or sperm cells), but not in others.

Other Names for This Condition

Long QT syndrome with syndactyly LQT8 TS

Additional Information & Resources

Genetic Testing Information

Genetic Testing Registry: Timothy syndrome

Genetic and Rare Diseases Information Center

Timothy syndrome

Patient Support and Advocacy Resources

National Organization for Rare Disorders (NORD)

Clinical Trials

ClinicalTrials.gov

Catalog of Genes and Diseases from OMIM

TIMOTHY SYNDROME; TS

Scientific Articles on PubMed

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References

Bauer R, Timothy KW, Golden A. Update on the Molecular Genetics of Timothy Syndrome. Front Pediatr. 2021 May 17;9:668546. doi: 10.3389/fped.2021.668546. eCollection 2021. Citation on PubMed

Herold KG, Hussey JW, Dick IE. CACNA1C-Related Channelopathies. Handb Exp Pharmacol. 2023;279:159-181. doi: 10.1007/164_2022_624. Citation on PubMed

Levy RJ, Timothy KW, Underwood JFG, Hall J, Bernstein JA, Pasca SP. A Cross-Sectional Study of the Neuropsychiatric Phenotype of CACNA1C-Related Disorder. Pediatr Neurol. 2023 Jan;138:101-106. doi: 10.1016/j.pediatrneurol.2022.10.013. Epub 2022 Nov 2. Citation on PubMed

Marks ML, Trippel DL, Keating MT. Long QT syndrome associated with syndactyly

identified in females. Am J Cardiol. 1995 Oct 1;76(10):744-5. doi: 10.1016/s0002-9149(99)80216-1. Citation on PubMed

Marks ML, Whisler SL, Clericuzio C, Keating M. A new form of long QT syndrome associated with syndactyly. J Am Coll Cardiol. 1995 Jan;25(1):59-64. doi: 10.1016/0735-1097(94)00318-k. Citation on PubMed

Napolitano C, Timothy KW, Bloise R, Priori SG. CACNA1C-Related Disorders. 2006 Feb 15 [updated 2021 Feb 11]. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Bean LJH, Gripp KW, Amemiya A, editors. GeneReviews(R) [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024. Available from http://www.ncbi.nlm.nih.gov/books/NBK1403/ Citation on PubMed

Splawski I, Timothy KW, Decher N, Kumar P, Sachse FB, Beggs AH, Sanguinetti MC, Keating MT. Severe arrhythmia disorder caused by cardiac L-type calcium channel mutations. Proc Natl Acad Sci U S A. 2005 Jun 7;102(23):8089-96; discussion 8086-8. doi: 10.1073/pnas.0502506102. Epub 2005 Apr 29. Citation on PubMed or Free article on PubMed Central

Splawski I, Timothy KW, Sharpe LM, Decher N, Kumar P, Bloise R, Napolitano C, Schwartz PJ, Joseph RM, Condouris K, Tager-Flusberg H, Priori SG, Sanguinetti MC, Keating MT. Ca(V)1.2 calcium channel dysfunction causes a multisystem disorder including arrhythmia and autism. Cell. 2004 Oct 1;119(1):19-31. doi: 10.1016/j.cell.2004.09.011. Citation on PubMed

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