How common is Timothy syndrome?

Timothy syndrome is very rare. It was first reported in the medical literature in 1995 but it took many years for the gene responsible to be identified. Currently (2020) less than 100 children with TS have been reported in the medical literature. It is expected that many more children will be diagnosed with this condition over the following years as awareness of the syndrome increases.

Why did this happen?

When children are conceived, the genetic material is copied in the egg and sperm that make a new child. The biological copying method is not perfect, and occasionally random rare changes occur in the genetic code of children that are not seen in the DNA of their parents. This happens naturally and is not due to any lifestyle, dietary or environmental factors. No one is to blame when these changes occur, and nobody is at fault.

In most children with Timothy syndrome diagnosed so far, the change in the *CACNA1C* gene occurred by chance in the child (this is known as *de novo*) and was not found in their parents. However, a few parents have been found to carry a pathogenic *CACNA1C* gene variant in a few, but not all, of their cells (this is known as mosaicism) and it means the variant can be passed on to their child(ren).

Can it happen again?

The risk of having another child affected by a rare gene disorder depends on the genetic code of the parents. If the change in the *CACNA1C* gene has been shown to be *de novo*, that means neither parent was found to carry it, the chance of having another child with TS is low (less than 1%). It is possible to have further children with Timothy syndrome if a parent is found to be mosaic for the *CACNA1C* gene variant. A clinical geneticist can give you specific advice for your family.

Can Timothy syndrome be cured?

Timothy syndrome cannot be cured at the present time. However, knowing the diagnosis means that appropriate monitoring and treatment can be put in place.

Management recommendations

Children with Timothy syndrome should be under the care of a multidisciplinary team including a cardiac specialist.

Care for the type of anesthesia should be considered during a surgery. Cardiac and glucose monitoring is highly recommended throughout surgery and recovery periods.

Early intervention with physical and speech therapies, as well as social integration may be beneficial.

Increased magnesium intake may be helpful for bowel movements and also for migraine headaches which can also be problematic.

Inform Network Support

Rare Chromosome Disorder Support Group,
The Stables, Station Road West,
Oxted, Surrey. RH8 9EE. UK.
Tel +44(0)1883 723356
info@rarechromo.org
www.rarechromo.org

Websites, Facebook groups and other links:

Website: https://timothysyndrome.org.uk/
Facebook: Timothy Syndrome and LongQT 8 - support group

Timothy Syndrome Alliance (TSA) is a Registered Charity in England (Number 1185523) dedicated to the support of Timothy Syndrome and all other deleterious *CACNA1C* gene change families through education, shared experience and research.

Join *Unique* for family links, information and support.

Unique is a charity without government funding, existing entirely on donations and grants. If you can, please make a donation via our website at www.rarechromo.org/donate Please help us to help you!

This information guide is not a substitute for personal medical advice. Families should consult a medically qualified clinician in all matters relating to genetic diagnosis, management and health. Information on genetic changes is a very fast-moving field and while the information in this guide is believed to be the best available at the time of publication, some facts may later change. *Unique* does its best to keep abreast of changing information and to review its published guides as needed. This booklet was compiled by Katherine Timothy, the Timothy Syndrome Alliance (TSA) and *Unique* (AP) and reviewed by Katherine Timothy.
Version 1 (AP)

Copyright © Unique 2020

Rare Chromosome Disorder Support Group
Registered in England and Wales
Charity Number 1110661
Company Number 5460413

Understanding Chromosome & Gene Disorders

Timothy syndrome
CACNA1C

rarechromo.org

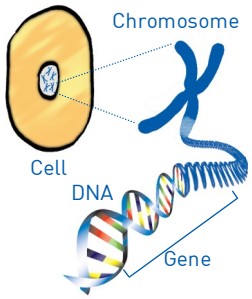
What is Timothy syndrome?

Timothy syndrome is a rare genetic condition that causes a spectrum of complicated health concerns. So far, most children with Timothy syndrome have been found to have an abnormal heart function as well as developmental delays. Children with this syndrome can have additional features including a weak immune system and dysfunction of the endocrine system (glands that secrete hormones).

Timothy syndrome is named after Katherine Timothy who described the syndrome.

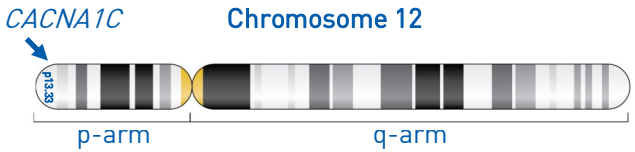
What causes Timothy syndrome?

Timothy syndrome is caused by specific changes (known as pathogenic variants) to a gene called *CACNA1C*. *CACNA1C* is an abbreviation of the gene's full name, 'L-type calcium channel $Ca_V1.2$' which is a description of the gene's function.



Calcium channels are important for movement of calcium into many of our body's different cells which in turn activates numerous important processes.

The *CACNA1C* gene is located at the end of the short 'p' arm of chromosome 12 in a region called 12p13.33.



We have two copies of chromosome 12 in our cells, so we also have two copies of the *CACNA1C* gene.

Timothy syndrome occurs when only one copy of the *CACNA1C* gene is affected, this is known as autosomal dominant since the change occurred on an autosome (this means any of our chromosomes numbered 1-22 and does not include chromosomes X and Y that determine biological sex) and features are apparent when only one copy of the gene is altered (dominant).

Medical concerns

Most children with Timothy syndrome have :

- Abnormal heart (cardiac) function specifically associated with an unusual electrical activity. The heart takes longer to 'recharge' between beats (this is known as a prolonged QT interval) which can lead to an irregular heart beat rate or rhythm (arrhythmias)
- Abnormal heart structure [including PDA (Patent Ductus Arteriosus), TOF (Tetralogy of Fallot), ASD (Atrial Septal Defect), VSD (Ventricular Septal Defect) and others]
- Neuronal developmental delays including physical, social and mental difficulties. These include ASD (autism spectrum disorder), ADD (Attention Deficit Disorder), ADHD Attention Deficit Hyperactivity Disorder), OCD (obsessive compulsive disorder), schizophrenia and others
- Immunodeficiencies (that may result in frequent respiratory, bronchial and laryngeal infections)
- Endocrinological dysfunction (including pancreatic, adrenal and thyroid concerns)
- Affected smooth muscle including gastrointestinal issues (constipation is common)
- Affected skeletal muscle including low muscle tone (hypotonia)
- Facial anomalies, hand and foot syndactyly (when two or more fingers or toes are fused)
- Mild dental, skin, eye and/or hair anomalies

Some children with Timothy syndrome have :

- Significant episodes of low blood sugar levels (hypoglycemia) particularly associated with infections and long periods of time without food. (A nighttime snack before bed is recommended, and fasting for greater than 10 hours is highly discouraged. During illness, regular intake of sugar rich fluids is recommended).
- Seizures (sudden and abnormal electrical activity in the brain)
- An unusually low body temperature (hypothermia)

Development

Physical development

Children with Timothy syndrome show delays in reaching physical milestones such as walking, running and jumping.

Intellectual development and learning

Some Timothy syndrome children have been diagnosed with mild to moderate learning difficulties and have special educational needs.

Speech and language

Significant speech delays are common and receptive speech is generally more advanced than expressive speech.

Behaviour

Social development is generally impaired, most children with Timothy syndrome are shy but a few are overly friendly. A few children have been diagnosed with neurodevelopmental disorders such as autism.

Timothy syndrome types 1-3

Timothy Syndrome is caused by different genetic variants of the *CACNA1C* gene and three different types of TS have been characterized accordingly.

TS1 - often identified at birth if an infant presents with serious cardiac concerns and syndactyly. A genetic test identifies an amino acid change of G406R, in exon 8A of *CACNA1C*.

TS2 - often identified at birth if an infant presents with very serious cardiac concerns, and often hypotonia, but no syndactyly or other physical anomalies. A genetic test identifies an amino acid change of G406R in exon 8 (not 8A).

TS3 - is the atypical form of Timothy syndrome (ATS), often identified at birth if an infant presents with a multisystem health concern that mostly, but not always, includes cardiac and hand anomalies. A genetic test identifies a pathogenic variant of the *CACNA1C* gene different to the TS1 and TS2 causing genetic variants.

Any child suspected of TS should have their *CACNA1C* gene fully sequenced to determine which type of TS they have.