

## Expected life span in Timothy syndrome

The numbers of actual diagnosed Timothy syndrome children in the world are extremely small (currently there are only about 70 known cases, 50 are of the “Classic” variety). About half of Timothy syndrome children still experience an early demise, particularly when they present with overwhelming electrical or structural heart disease at birth. Other significant etiologies of death in these children have been aspiration during feeding, infections (lung, device site, etc.), unexpected hypoglycemia and unexplained hypoxia or cyanosis. With a greater understanding of this rare condition by health care providers and the vigilant care of parents, some children have survived into adulthood; one young lady is now attending college. Hopefully with the continued advancement of knowledge about the condition, improved therapeutic options and diligent attention to the multiple manifestations of Timothy syndrome, we will improve not only the length of survival but also the quality of life in this population.

The original genetic discoveries were made by the collaborative efforts of researchers from the University of Utah, Children’s Hospital Boston and University of Pavia, Italy.



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The Sudden Arrhythmia Death Syndromes (SADS) Foundation is a leader in education, research and advocacy. Our Mission is to save the lives and support the families of children & young adults who are genetically predisposed to sudden death due to heart rhythm abnormalities.

# Timothy Syndrome

## A Guide for Patients and Health Care Providers

By Katherine W. Timothy, January 2017



## A note from the SADS Foundation

We provide this information with the hope that informing physicians, other health care providers, and the public will encourage early and correct diagnosis and proper therapy, resulting in the reduction and ultimately elimination of cardiac arrest and sudden death from Timothy syndrome and other inherited arrhythmias.

## What is Timothy syndrome?

Timothy syndrome (TS) is a rare and serious genetic disorder characterized by a spectrum of complicated health concerns, which includes:

- an abnormally prolonged *repolarization* time of the heart (the process of returning the heart cells to a resting state in preparation for the next heart beat), as measured by a rate corrected QT interval of >480 ms to greater than 700 ms, predisposing an individual to serious cardiac events including cardiac arrest and sudden death.
- potentiality of blood sugar fluctuations resulting in severe life-threatening hypoglycemic events including hypoglycemic seizures
- physical, mental and social developmental delays, and sometimes autistic spectral disorders.
- facial and dental abnormalities are common.

Timothy syndrome is currently known to result from a genetic change in the L-type calcium channel gene, CACNA1C on chromosome 12. There are three identified subgroups of Timothy syndrome, each based upon the location of an individual’s specific genetic change. All groups have a constellation of the before mentioned health concerns, but in addition to these concerns, each group presents with additional subtle differences.

“Classic” Timothy Syndrome is currently understood to be the most common form of the condition and results from a specific spontaneous de novo mutation (G406R) located on **exon 8A**. This mutation has also been identified in a few parents of affected children, however the parent has a milder form; unfortunately, when inherited by a child the spectrum of Timothy syndrome is more severe.

The “Classic” Timothy syndrome, in addition to the concerns listed above, the child has evidence of unilateral or bilateral finger syndactyly and/or syndactyly of the 2nd and 3rd toes. The Classic Timothy syndrome child often has congenital heart defect (ASD, VSD, PDA, PFO, TOF), and is generally born bald. Gastric reflux, frequent pneumonia, and gastrointestinal problems are often noted.



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**W Variant 2, Timothy Syndrome** also results from the same specific mutational change (G406R) but is located on **exon 8**. This variant is not known to present with syndactyly but tends to have more musculoskeletal concerns. Often the Variant 2 Timothy syndrome children are born with congenital heart defects, hip conjunctures, and nemoline rod disorder.

**Variant 3, Timothy Syndrome** is presently a category for all other individual specific mutations identified in the CACNA1C gene which cause health concerns similar to Timothy syndrome as listed above. Some Timothy syndrome children with these specific mutations located throughout the CACNA1C gene can be of a much more severe TS type, depending on the location and cellular function the change affects.

How is Timothy syndrome recognized and diagnosed?

All forms of Timothy syndrome can be suspected in utero when the fetal heart rate is noted to be *slow* (fetal bradycardia) or the fetus is found to be in distress. At birth or with the first feeding the neonate can suddenly develop *hypoxia* (diminished availability of oxygen) and present with *cyanosis* (a bluish discoloration of the skin). Upon evaluation of bradycardia and/or cyanosis the infant is often found to be in 2:1 AV block (AV or atrio-ventricular block refers to a functional block due to an extremely prolonged ventricular repolarization rather than an AV conduction abnormality), and always a markedly prolonged QT interval is observed. Within days of birth the infant often requires a pacemaker in an effort to stabilize the heart rate and reduce the risk for induction of arrhythmias.

All types of Timothy syndrome can be suspected with a rate corrected QT interval (QTc) of >480 ms - 700 ms or greater, congenital heart defects and facial anomalies. When these features are noted in the presence of finger and/or toe syndactyly, a diagnosis of Classic Timothy Syndrome is probable. All infants in whom Timothy syndrome is suspected should be genetically screened for the CACNA1C gene to confirm a the diagnosis.

What is the genetic basis for Timothy syndrome?

All children studied for Timothy syndrome, who presented at birth with syndactyly, were identified as harboring the exact same single *de novo* (new or spontaneous) G406R mutation located on **Exon 8A** of the L-type calcium channel

gene known as CACNA1C. Other suspected children, without syndactyly, were found to either have the same G406R change in **Exon 8** or another individual CACNA1C change sprinkled throughout the gene. CACNA1C gene expression studies have shown that this gene is highly expressed in nearly all organs and tissues of the body; therefore, any change in this gene has the potential to alter fundamental cellular ion channel function. Ion channel closure is altered and dysfunctional cells become overwhelmed by the continuous influx of calcium. This lack of proper ion channel cell closure is the underlying cause for the prominent cardiac feature of prolongation of the QT interval, associated with increased risk of arrhythmias and sudden death. It is also the etiology of dysfunction of the smooth muscles of the gastrointestinal system, lungs, immune system, brain and teeth. Cellular brain dysfunction can include regions which control hormones for organ communications, and other areas associated with social, physical and mental development, sometimes associated with autism and autistic spectral disorders.



Is Timothy syndrome an inherited disorder?

Early genetic researchers discovered “Classic” Timothy syndrome originated from the exact same single spontaneous or new mutation in each child studied; however, they were perplexed when one family was identified which had multiple children affected by the syndrome. Further DNA studies from other tissues (saliva, cheek and sperm cells) were performed on the non-syndromic parents. Mosaicism (cells of one tissue differ in genetic make-up from normal cells) was identified in one of the seemingly normal parent. The parent’s mosaic change was identified in reproductive tissue, which during fertilization was

passed and inherited by multiple children. This explained why the mosaic parent was free of any indication of health concerns related to Timothy syndrome.

When a child is born with any genetic form of Timothy syndrome, the inheritance pattern is considered autosomal (meaning males and females are equally susceptible of inheriting or developing the genetic change), but having the change is a dominant (or dominates the body’s expression of the disorder) characteristic. Theoretically, about one half of the cells would be affected by the disorder while the other half would be completely normal. If a child with Timothy syndrome survives and is capable of reproducing children, each of his/her off-spring would have a 50/50 chance of inheriting the disorder.



What about genetic testing for Timothy syndrome?

Molecular genetic testing of the CACNA1C gene for suspected Timothy syndrome is commercially available and recommended. Most pediatric cardiologists would be familiar with protocols for genetic diagnostic attainment.

Because parental mosaicism might be of concern in families where possible future children would be desired, it is considered prudent for parents to also be specifically screened for identified Timothy syndrome changes as found in their child.

What is the treatment for Timothy syndrome?

Treatment for all forms of Timothy syndrome is complex and is dependent on the severity of the disease in each child. Ventricular arrhythmias (ventricular tachycardia, torsades de pointes and ventricular fibrillation) are present in at least 80%. Treating TS children to improve cardiac survival is of utmost importance. Beta-blockers (Propranolol and Nadolol are considered most effective in treating all types LQTS in children) are generally prescribed. Beta-blockers often further reduce the TS heart rate, thus pacemaker implantation may be needed to control heart rate and ICD implantation is often undertaken in this high risk population. Device site

infections sometimes occur, causing additional concerns for the TS child. In an effort to shorten QT repolarization and restore 1:1 AV conduction other medications (Mexiletine and calcium channel blockers such as Verapamil) have been tried with some success. Left cardiac sympathetic denervation has been undertaken in some as an extra measure of arrhythmia protection.

The congenital heart defects in Timothy syndrome are generally treated with standard procedures. The combination of Beta-blockers, fasting and anesthesia are often known to trigger arrhythmias during in the perioperative period. Because of the cardiac, dental and orthopedic issues in this population, surgery is often necessary. Extreme care must be taken with cardiac monitoring and anesthetic selection. Severe hypoglycemia in this patient population can be an issue when these children are fasting in preparation for surgery. Glucose monitoring and the early use of intravenous glucose is prudent.

| Table of health concerns in Timothy syndrome                    |            |
|-----------------------------------------------------------------|------------|
| Health concern                                                  | % affected |
| Prolonged QT interval .....                                     | 100%       |
| Finger/2-3 toe syndactyly (“Classic” TS only) .....             | 100%       |
| Ventricular arrhythmias .....                                   | 80%        |
| Congenital heart defects, cardiomyopathies .....                | 60%        |
| Facial dysmorphism (flat bridge nose, low set ears, etc.) ..... | 90%        |
| Metabolic (immune response, hypoglycemia) .....                 | 50%        |
| Neuro-psychiatric involvement .....                             | 80%        |

Neuro-psychiatric concerns in Timothy syndrome

Improved survival in Timothy syndrome has allowed for neuro-psychiatric evaluations for physical, mental and social developmental abilities. It is currently recognized that some affected children have delayed motor skill development (walking, running, skipping, jumping, etc.). Significant speech delays are common in most and audiology testing has shown that most of these children have normal or near normal hearing. Social development is generally impaired; shyness often predominates with a common preference for solitary. Mild mental deficiencies have been observed, and a small number have been diagnosed with autism. Early interventions in speech, social integration and physical therapy have proved beneficial.