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.), unexplained hypoxia and unexplained hypoglycemia. 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 increased awareness by health care providers and the vigilant support of parents of affected children, however the parent has a milder form; unfortunately, when inherited by a child the spectrum is more severe.

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.

• potential for blood sugar fluctuations which can result 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.

In “Classic” Timothy syndrome, in addition to these concerns, each group presents with additional subtle differences.

The SADS Foundation has long had a desire to provide more individualized support to Timothy syndromes (TS) families, to increase the targeted education to medical professionals regarding the diagnosis and treatment of TS, and to deliberately encourage research that would benefit the TS community. With this desire in mind, the Timothy Syndromes Alliance (TSA) was established as a specific group within the SADS Foundation to maximize resources and opportunities that will lead to improved family support, medical education and research for Timothy syndromes.

The TSA focuses on the following areas of influence:

• Provide intake services to all new TSA families (to include collection of basic personal and medical information, sending a TS informational packet and Registry questionnaire)
• Provide support and networking to TSA families as needed
• Educate the medical community regarding specific Timothy syndrome type disorders
• Develop materials, website, etc.
• Foster and support research for Timothy syndromes

The TSA may be reached at tsa@sads.org.

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.

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.

A Guide for Patients and Health Care Providers  
By Katherine W. Timothy, September 2017

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Within days of birth the infant often requires a pacemaker. All forms of Timothy syndrome can be suspected with a thorough examination in an effort to stabilize the heart rate and reduce the risk for the infant or the first feeding the neonate can suddenly develop 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. It is also the cause of dysfunction of the gastrointestinal system, the 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 that “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 parents. 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 testing. 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?
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 (Metluxetine 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 prophylaxis. 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 setting. 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 usual care of intravenous glucose is prudent.

Is Timothy syndrome a genetic disorder? Yes, it is. Timothy syndrome is a genetic disorder caused by a mutation in the CACNA1C gene.

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. As 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. It is also the cause of dysfunction of the gastrointestinal system, the 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.

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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 audiologic 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 solitude. 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.