Timothy Syndrome

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1. Introduction

Timothy syndrome is a rare disorder that primarily affects the heart but can affect many other areas of the body, including the fingers and toes, teeth, nervous system, and immune system. The severity of this condition varies among affected individuals, although it is often life-threatening due to the heart problems.

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. As a result of these serious heart problems, many 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 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, frequent infections, episodes of low blood sugar (hypoglycemia), and an abnormally low body temperature (hypothermia).

Researchers have found that many children with Timothy syndrome have the characteristic features of autism or similar conditions known as autistic spectrum disorders. Affected children tend to have impaired communication and socialization skills, as well as delayed development of speech and language. Other nervous system abnormalities that can occur in Timothy syndrome include intellectual disability and recurrent seizures (epilepsy); some affected individuals have photosensitive epilepsy, in which seizures are triggered by flashing lights.

2. Frequency

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

3. Causes

Mutations in the *CACNA1C* gene are responsible for all reported cases of 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.

Mutations in the *CACNA1C* gene change the structure of CaV1.2 channels. The altered channels 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.

3.1 The gene associated with Timothy syndrome

- CACNA1C

4. 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 mutations in the gene, and occur in people with no history of the disorder in their family. Due to the severity of Timothy syndrome, it is rare for an affected individual to be able to pass on the disease-causing mutation. Although rare, some people with Timothy syndrome inherit the altered gene from an unaffected parent who is mosaic for a *CACNA1C* mutation. Mosaicism means that the parent has the mutation in some cells (including egg or sperm cells), but not in others.

5. Other Names for This Condition

- Long QT syndrome with syndactyly
- LQT8
- TS

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