Timothy syndrome

Other Names: Long QT syndrome with syndactyly

*Timothy syndrome is a rare condition involving the heart, nervous system, fingers and toes. It is caused by mutations in the CACNA1C gene that makes a protein called voltage-dependent L-type calcium channel subunit alpha-1C.*

Characteristics of Timothy syndrome

Timothy syndrome is a rare condition that affects multiple organ systems including the heart, nervous system, fingers and toes. Timothy syndrome is characterized by a heart condition called long QT syndrome (see trait profile) -- a heart rhythm disorder that can cause fast, chaotic heart heartbeats that can lead to sudden death. There can be other structural heart defects present at birth. Due to these heart defects, most affected individuals live only into early childhood due to complications from ventricular tachyarrhythmia, where the two lower heart chambers beat abnormally fast.

Nearly all individuals with Timothy syndrome show webbing of the skin between the fingers and toes (syndactyly). Approximately half of affected individuals also have distinctive facial features including a round face, flattened nasal bridge, low-set ears, a small upper jaw; small, misplaced teeth; and multiple cavities. Children may be bald at birth and have thin hair later in childhood, have frequent infections, low blood sugar (hypoglycemia) and abnormally low body temperature (hypothermia).

Many affected individuals have impaired communication and social skills, delayed development of language, and intellectual disabilities. They may also have characteristics of autism spectrum disorder. Some individuals also have seizures.

There are currently two forms of Timothy syndrome. Type 1, often referred to as classic Timothy syndrome, includes the features described above. Type 2, often referred to as atypical type, causes a more severe long QT syndrome resulting in a higher risk for arrhythmia (abnormal heart rhythm) that can lead to sudden death. Individuals with type 2 Timothy syndrome do not have webbing of the fingers or toes.

Diagnosis/Testing

Timothy syndrome is diagnosed by clinical features, as described above, and the presence of one of three currently recognized changes or mutations in the CACNA1C gene. This gene makes the voltage-dependent L-type calcium channel subunit alpha-1C protein. This protein is necessary for normal heart function. Mutations in the CACNA1C gene does not allow the protein to functional normally thus leading to the features seen in Timothy syndrome.

Management/Surveillance

Individuals with Timothy syndrome are typically managed by a team of specialty providers that can include: cardiologists, geneticists, genetic counselors, speech and language specialists, and primary care doctors. Treatment includes beta-blockers (medication that controls the heart rhythm) to maintain QT stability in order to prevent the occurrence of ventricular tachyarrhythmia (fast, abnormal heart rhythm). In some instances, pacemakers are implanted within the first days of life in order to maintain a normal heart rate, and control heart block and bradycardia (slow heart beat).
Surveillance should include frequent monitoring of serum glucose concentration. This surveillance is especially important in patients using beta-blockers because these medications have the ability to mask hypoglycemic symptoms.

Medications that are reported to prolong QT intervals in the heart should be avoided along with drugs and dietary habits that could lead to hypoglycemia.

If an affected individual is undergoing surgery, close cardiac monitoring is extremely important because anesthesia is a known trigger for cardiac arrhythmia.

Mode of inheritance

Timothy syndrome is inherited in an autosomal dominant pattern. This means inheriting one CACNA1C mutation is enough for an individual to be affected and show signs of Timothy syndrome. The mutation can be inherited from an affected parent or it can occur brand new (de novo) in an affected child. In most cases, it occurs as a result of a de novo mutation.

In less common cases, affected individuals inherit the altered gene from an unaffected parent who is mosaic for a mutation in CACNA1C gene. Mosaicism means that the CACNA1C mutation is only present in some of the cells, but not all. Individuals who are mosaic for a genetic condition usually have milder symptoms of the condition.

Risk to family members

The risk to family members depends on whether or not the individual with Timothy syndrome has a parent affected with the condition. If a parent also has Timothy syndrome, the risk of having a child with Timothy syndrome is 50% with each pregnancy. However, since the majority of cases occur de novo, the risk of other siblings being affected is very low. When an affected individual’s parent has mosaicism for the condition, there is a potential risk for future children to also be affected. Genetic counseling and genetic testing is important for the parents in order to determine whether their future children are at risk.

Special considerations

None

Resources

Genetics Home Reference: Timothy Syndrome  

National Organization for Rare Disorders: Timothy Syndrome  

References
