TWNK gene

twinkle mtDNA helicase

Normal Function

The *TWNK* gene provides instructions for making two very similar proteins called Twinkle and Twinky. These proteins are found in the mitochondria, which are structures in which a process called oxidative phosphorylation occurs to convert the energy from food into a form that cells can use.

Mitochondria each contain a small amount of DNA, known as mitochondrial DNA (mtDNA), which is essential for the normal function of these structures. The Twinkle protein is involved in the production and maintenance of mtDNA. It functions as a mitochondrial DNA helicase, which means it binds to DNA and temporarily unwinds the two spiral strands (double helix) of the DNA molecule. This unwinding is necessary for copying (replicating) mtDNA. The function of the Twinky protein is unknown.

Health Conditions Related to Genetic Changes

Ataxia neuropathy spectrum

Mutations in the *TWNK* gene have been found in a small number of people with ataxia neuropathy spectrum. This condition is characterized by problems with coordination and balance (ataxia) and disturbances in nerve function (neuropathy). The conditions previously named mitochondrial recessive ataxia syndrome (MIRAS) and sensory ataxia neuropathy dysarthria and ophthalmoplegia (SANDO) are now included in ataxia neuropathy spectrum.

Mutations in the *TWNK* gene disrupt the function of Twinkle and lead to large deletions of mtDNA in the muscle tissue of affected individuals. However, it is unclear how mutations in the *TWNK* gene cause the signs and symptoms of ataxia neuropathy spectrum.

Infantile-onset spinocerebellar ataxia

At least six mutations in the *TWNK* gene have been found to cause infantile-onset spinocerebellar ataxia (IOSCA). The most common mutation replaces the protein building block (amino acid) tyrosine with the amino acid cysteine at position 508 in the Twinkle protein, written as Tyr508Cys or Y508C. Most affected individuals have two

copies of this gene mutation in each cell. At least two additional mutations have been reported that are unique to particular families. In these cases, affected individuals have one copy of the family-specific mutation and one copy of the Tyr508Cys mutation in each cell.

The *TWNK* gene mutations that cause IOSCA interfere with the function of the Twinkle protein and result in reduced quantities of mtDNA (mtDNA depletion). Impaired mitochondrial function, especially in the nervous system (which requires a large amount of energy), leads to neurological dysfunction and other problems associated with IOSCA.

Perrault syndrome

At least four *TWNK* gene mutations have been identified in families with Perrault syndrome, a condition characterized by hearing loss in affected males and females and abnormalities of the ovaries in affected females. The mutations involved in this condition change single amino acids in the Twinkle protein. Researchers predict that these mutations impair the helicase activity of the protein. However, it is unclear exactly how *TWNK* gene mutations lead to hearing problems and ovarian abnormalities in affected individuals.

Progressive external ophthalmoplegia

At least 40 *TWNK* gene mutations have been identified in people with an eye condition called progressive external ophthalmoplegia. This disorder weakens the muscles that control eye movement and causes the eyelids to droop (ptosis). Researchers speculate that the mutated Twinkle protein has impaired helicase activity, which stalls the DNA replication process. Although the mechanism is unclear, replication stalling seems to result in large deletions of genetic material from mtDNA in muscle tissue. Researchers have not determined how deletions of mtDNA lead to the specific signs and symptoms of progressive external ophthalmoplegia, although the features of the condition may be related to impaired oxidative phosphorylation. It has been suggested that eye muscles are commonly affected by mitochondrial defects because they are especially dependent on oxidative phosphorylation for energy.

Other disorders

In a few families, *TWNK* gene mutations lead to mtDNA depletion syndrome, hepatocerebral form. People with this condition experience weak muscle tone (hypotonia), a decrease in liver function, developmental delay, seizures, and loss of sensation and weakness in the limbs (peripheral neuropathy).

Other Names for This Gene

- C10orf2
- chromosome 10 open reading frame 2
- PEO1

- PEO1_HUMAN
- progressive external ophthalmoplegia 1 protein
- T7 gp4-like protein with intramitochondrial nucleoid localization
- T7-like mitochondrial DNA helicase
- twinkle

Additional Information & Resources

Tests Listed in the Genetic Testing Registry

- Tests of TWNK (https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=56652[geneid])

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28%28C10orf2%5BTIAB%5D%29+OR+%28chromosome+10+open+reading+frame+2%5BTIAB%5D%29%29+OR+%28%28PEO%5BTIAB%5D%29+OR+%28PEO1%5BTIAB%5D%29+OR+%28IOSCA%5BTIAB%5D%29+OR+%28SANDO%5BTIAB%5D%29+OR+%28twinkle%5BTIAB%5D%29%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+720+days%22%5Bdp%5D)

Catalog of Genes and Diseases from OMIM

- MITOCHONDRIAL DNA DEPLETION SYNDROME 3 (HEPATOCEREBRAL TYPE); MTDPS3 (https://omim.org/entry/251880)
- TWINKLE mtDNA HELICASE; TWNK (https://omim.org/entry/606075)

Gene and Variant Databases

- NCBI Gene (https://www.ncbi.nlm.nih.gov/gene/56652)
- ClinVar (https://www.ncbi.nlm.nih.gov/clinvar?term=TWNK[gene])

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Genomic Location

The *TWNK* gene is found on chromosome 10 (https://medlineplus.gov/genetics/chromosome/10/).

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