TPP1 gene

tripeptidyl peptidase 1

Normal Function

The *TPP1* gene provides instructions for making an enzyme called tripeptidyl peptidase 1. This enzyme is produced as an inactive enzyme, called a proenzyme, which has an extra segment attached. This segment must be removed, followed by additional processing steps, for the enzyme to become active. The active tripeptidyl peptidase 1 enzyme is found in cell structures called lysosomes, which digest and recycle different types of molecules. Tripeptidyl peptidase 1 acts as a peptidase, which means that it breaks down protein fragments, known as peptides, into their individual building blocks (amino acids). Specifically, tripeptidyl peptidase 1 cuts (cleaves) peptides into groups of three amino acids.

Health Conditions Related to Genetic Changes

CLN2 disease

At least 115 mutations in the *TPP1* gene have been found to cause CLN2 disease. This condition impairs motor and mental development, typically starting in early childhood, causing gradually worsening movement disorders and a decline in intellectual function. In addition, affected children often develop recurrent seizures (epilepsy) and vision impairment. In some cases, signs and symptoms of CLN2 disease do not appear until later in childhood, usually after age 4.

Most of the *TPP1* gene mutations that cause CLN2 disease change single amino acids in tripeptidyl peptidase 1, resulting in a severe decrease in enzyme activity. A reduction in functional enzyme results in the incomplete breakdown of certain peptides. CLN2 disease is characterized by the accumulation of proteins or peptides and other substances in lysosomes. These accumulations occur in cells throughout the body; however, nerve cells seem to be particularly vulnerable to their effects. The accumulations can cause cell damage leading to cell death. The progressive death of nerve cells in the brain and other tissues leads to the signs and symptoms of CLN2 disease.

Individuals who are diagnosed with CLN2 disease later in childhood likely have *TPP1* gene mutations that result in the production of an enzyme with a small amount of normal function. Protein function in these individuals is higher than in those who have

the condition beginning earlier in childhood. As a result, it takes longer for peptides and other substances to accumulate in the lysosomes and damage nerve cells.

Other disorders

Mutations in the *TPP1* gene have also been found to cause spinocerebellar ataxia, autosomal recessive 7 (SCAR7), which is a condition characterized by progressive problems with movement. During childhood, individuals with SCAR7 develop walking difficulties; impaired speech (dysarthria); and eye movement problems, such as involuntary movement of the eyes (nystagmus), rapid eye movements (saccades), and trouble moving the eyes side-to-side (oculomotor apraxia). People with SCAR7 have progressive loss of cells (atrophy) of various parts of the brain, particularly within the cerebellum, which is the area of the brain involved in coordinating movements.

Compared to individuals with CLN2 disease (described above), individuals with SCAR7 likely have a higher level of normally functioning tripeptidyl peptidase 1. As a result, SCAR7 is associated with milder signs and symptoms than CLN2 disease and tends to develop in late childhood or adolescence. When examined, cells from some individuals with SCAR7 showed lysosomal accumulations while cells from other affected individuals did not.

Other Names for This Gene

- cell growth-inhibiting gene 1 protein
- CLN2
- GIG1
- growth-inhibiting protein 1
- LPIC
- lysosomal pepstatin insensitive protease
- TPP-1
- TPP1_HUMAN
- tripeptidyl aminopeptidase
- tripeptidyl peptidase I
- tripeptidyl-peptidase 1
- tripeptidyl-peptidase 1 preproprotein

Additional Information & Resources

Tests Listed in the Genetic Testing Registry

- Tests of TPP1 (https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=1200[geneid])

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28%28TPP1%5BTIAB%5D%29+OR+%28CLN2%5BTIAB%5D%29+NOT+%28telomere%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+1800+days%22%5Bdp%5D)

Catalog of Genes and Diseases from OMIM

- TRIPEPTIDYL PEPTIDASE I; TPP1 (https://omim.org/entry/607998)
- SPINOCEREBELLAR ATAXIA, AUTOSOMAL RECESSIVE 7; SCAR7 (https://omim.org/entry/609270)

Gene and Variant Databases

- NCBI Gene (https://www.ncbi.nlm.nih.gov/gene/1200)
- ClinVar (https://www.ncbi.nlm.nih.gov/clinvar?term=TPP1[gene])

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Genomic Location

The *TPP1* gene is found on chromosome 11 (https://medlineplus.gov/genetics/chromosome/11/).

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