TUBB4A gene

tubulin beta 4A class IVa

Normal Function

The *TUBB4A* gene provides instructions for making a protein called beta-tubulin (β-tubulin). This protein is part of the tubulin family of proteins that form and organize structures called microtubules. Microtubules are rigid, hollow fibers that make up the cell's structural framework (the cytoskeleton). They are composed of β-tubulin and a similar protein called alpha-tubulin (α-tubulin) that is produced from a different gene.

The β-tubulin protein produced from the *TUBB4A* gene is found primarily in the brain, particularly in regions called the basal ganglia (specifically a part called the putamen) and the cerebellum. These regions help control movement. The protein is also found extensively in the brain's white matter, which consists of nerve fibers covered by a fatty substance called myelin that insulates and protects them. During brain development, microtubules help move nerve cells (neurons) to their proper location (neuronal migration). The microtubules also form scaffolding within neurons that provides structure and aids in the transport of substances.

Health Conditions Related to Genetic Changes

TUBB4A-related leukodystrophy

More than 30 mutations in the *TUBB4A* gene cause *TUBB4A*-related leukodystrophy. This disorder is characterized by abnormalities of the white matter, particularly a reduced ability of the nervous system to produce myelin (hypomyelination). *TUBB4A*-related leukodystrophy has a wide range of severity, with a condition called hypomyelination with atrophy of the basal ganglia and cerebellum (H-ABC) at the most severe end of the spectrum and isolated hypomyelination at the mildest end; the features in some affected individuals fall in between these two extremes. In addition to hypomyelination in certain brain regions, including those that help control movements, affected individuals can have breakdown (atrophy) of brain tissue in these regions, movement abnormalities, difficulty swallowing and speaking, and learning problems.

The mutations that cause *TUBB4A*-related leukodystrophy change single protein building blocks (amino acids) in the β-tubulin protein. H-ABC is most commonly caused by a mutation that replaces the amino acid aspartate with the amino acid asparagine at protein position 249 (written as Asp249Asn or D249N). This and other *TUBB4A* gene

mutations are thought to alter the structure of the β-tubulin protein, likely impairing the formation or stability of microtubules.

While it is unclear how these genetic changes lead to the signs and symptoms of *TUBB4A*-related leukodystrophy, researchers suspect that problems with microtubules impair neuronal migration or the transport of important substances within neurons, which may lead to dysfunction and loss of these cells in the brain, particularly in the putamen, cerebellum, and white matter. Abnormalities in these brain regions underlie the movement, speech, and learning problems that can occur in *TUBB4A*-related leukodystrophy. It is unclear what causes the wide range of severity in this disorder.

Other disorders

At least two *TUBB4A* gene mutations have been found to cause another neurological disorder called dystonia 4 (also known as DYT4 dystonia or whispering dysphonia), which is characterized by a weak, whispery voice (dysphonia) that typically begins in adulthood. Affected adults later develop involuntary muscle contractions (dystonia), difficulty walking, and sometimes swallowing problems (dysphagia). Individuals with dystonia 4 do not have hypomyelination or other brain abnormalities like those that occur in people with *TUBB4A*-related leukodystrophy (described above).

The most common *TUBB4A* gene mutation that causes dystonia 4 replaces the amino acid arginine with the amino acid glycine at protein position 2 (written as Arg2Gly or R2G). The mutations that cause this condition are thought to disrupt the structure of the β-tubulin protein and, consequently, the formation or stability of microtubules. However, it is unclear how these genetic changes lead to the signs and symptoms of dystonia 4 or why they do not cause hypomyelination like other *TUBB4A* gene mutations.

Other Names for This Gene

- beta-5
- dystonia 4, torsion (autosomal dominant)
- DYT4
- TUBB4
- tubulin beta-4 chain
- tubulin beta-4A chain isoform 1
- tubulin beta-4A chain isoform 2
- tubulin beta-4A chain isoform 3
- tubulin beta-4A chain isoform 4
- tubulin, beta 4
- tubulin, beta, 5

Additional Information & Resources

Tests Listed in the Genetic Testing Registry

- Tests of TUBB4A (https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=10382[geneid])

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28%28TUBB4A%5BTIAB%5D%29+OR+%28tubulin+beta+4A+class+IVa%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+1800+days%22%5Bdp%5D)

Catalog of Genes and Diseases from OMIM

- TUBULIN, BETA-4A; TUBB4A (https://omim.org/entry/602662)

Gene and Variant Databases

- NCBI Gene (https://www.ncbi.nlm.nih.gov/gene/10382)
- ClinVar (https://www.ncbi.nlm.nih.gov/clinvar?term=TUBB4A[gene])

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Genomic Location

The *TUBB4A* gene is found on chromosome 19 (https://medlineplus.gov/genetics/chromosome/19/).

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