FBXL4-related encephalomyopathic mitochondrial DNA depletion syndrome

Description

FBXL4-related encephalomyopathic mitochondrial DNA (mtDNA) depletion syndrome is a severe condition that begins in infancy and affects multiple body systems. It is primarily associated with brain dysfunction combined with muscle weakness (encephalomyopathy).

Infants with *FBXL4*-related encephalomyopathic mtDNA depletion syndrome have weak muscle tone (hypotonia) and a failure to grow or gain weight at the expected rate (failure to thrive). Children with *FBXL4*-related encephalomyopathic mtDNA depletion syndrome have delayed development of mental and motor skills and severely impaired speech development. Many affected individuals have seizures, movement abnormalities, and an unusually small head size (microcephaly) with a loss of nerve cells in the brain (cerebral atrophy).

All individuals with *FBXL4*-related encephalomyopathic mtDNA depletion syndrome have a buildup of a chemical called lactic acid in the body (lactic acidosis), and about half of individuals have an accumulation of ammonia in the blood. Buildup of these substances can be life-threatening. Many affected individuals also have heart abnormalities, such as congenital heart defects or heart rhythm abnormalities (arrhythmias). In addition, individuals with this condition can have vision problems, hearing loss, liver abnormalities (hepatopathy), and immune deficiency due to a decrease in white blood cells. Many children with *FBXL4*-related encephalomyopathic mtDNA depletion syndrome have distinctive facial features that can include thick eyebrows; outside corners of the eyes that point upward (upslanting palpebral fissures); a broad nasal bridge and tip; and a long, smooth space between the upper lip and nose (philtrum).

Because the encephalomyopathy and other signs and symptoms are so severe, people with *FBXL4*-related encephalomyopathic mtDNA depletion syndrome usually live only into early childhood.

Frequency

FBXL4-related encephalomyopathic mtDNA depletion syndrome is a rare condition; the exact prevalence is unknown. At least 50 affected individuals have been described in

the medical literature.

Causes

As its name suggests, *FBXL4*-related encephalomyopathic mtDNA depletion syndrome is caused by mutations in the *FBXL4* gene. This gene provides instructions for producing a protein that is found within cell structures called mitochondria. Mitochondria are involved in a wide variety of cellular activities, including energy production, chemical signaling, and regulation of cell growth and division (proliferation) and cell death (apoptosis). Mitochondria contain their own DNA, known as mitochondrial DNA (mtDNA), which is essential for the normal function of these structures. The FBXL4 protein is likely involved in the maintenance of mtDNA. Having an adequate amount of mtDNA is essential for normal energy production within cells.

FBXL4 gene mutations that cause *FBXL4*-related encephalomyopathic mtDNA depletion syndrome lead to a loss of FBXL4 protein function. A lack of this protein's activity leads to problems with the maintenance of mtDNA, which can reduce the amount of mtDNA in cells (known as mtDNA depletion). Depletion of mtDNA impairs mitochondrial function in many of the body's cells and tissues. Reduced mitochondrial function eventually leads to cell dysfunction, most noticeably affecting the brain, muscles, and other tissues that have high-energy requirements. This cell dysfunction leads to encephalomyopathy and other features of *FBXL4*-related encephalomyopathic mtDNA depletion syndrome.

Learn more about the gene associated with FBXL4-related encephalomyopathic mitochondrial DNA depletion syndrome

- FBXL4

Inheritance

This condition is inherited in an autosomal recessive pattern, which means both copies of the gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition.

Other Names for This Condition

- FBXL4 deficiency
- FBXL4-related early onset mitochondrial encephalopathy
- Mitochondrial DNA depletion syndrome 13, encephalomyopathic type
- MTDPS13

Additional Information & Resources

Genetic Testing Information

- Genetic Testing Registry: Mitochondrial DNA depletion syndrome 13 (https://www.ncbi.nlm.nih.gov/gtr/conditions/C3809592/)

Genetic and Rare Diseases Information Center

- Mitochondrial DNA depletion syndrome (https://rarediseases.info.nih.gov/diseases/13643/index)
- Mitochondrial DNA depletion syndrome, encephalomyopathic form with variable craniofacial anomalies (https://rarediseases.info.nih.gov/diseases/13298/index)

Patient Support and Advocacy Resources

- National Organization for Rare Disorders (NORD) (https://rarediseases.org/)

Catalog of Genes and Diseases from OMIM

- MITOCHONDRIAL DNA DEPLETION SYNDROME 13 (ENCEPHALOMYOPATHIC TYPE); MTDPS13 (https://omim.org/entry/615471)

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28%28mitochondrial+DNA%29+AND+%28FBXL4%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D)

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