X-linked intellectual disability, Siderius type

Description

X-linked intellectual disability, Siderius type is a condition characterized by mild to moderate intellectual disability that affects only males. Affected boys often have delayed development of motor skills such as walking, and their speech may be delayed.

Individuals with X-linked intellectual disability, Siderius type frequently also have an opening in the lip (cleft lip) with an opening in the roof of the mouth (cleft palate). A cleft can occur on one or both sides of the upper lip.

Some boys and men with this condition have distinctive facial features, including a long face, a sloping forehead, a broad nasal bridge, a prominent bone in the lower forehead (supraorbital ridge), and outside corners of the eyes that point upward (upslanting palpebral fissures). Affected individuals may also have low-set ears and large hands.

Frequency

While X-linked intellectual disability of all types and causes is relatively common, with a prevalence of 1 in 600 to 1,000 males, the prevalence of the Siderius type is unknown. Only a few affected families have been described in the scientific literature.

Causes

X-linked intellectual disability, Siderius type is caused by mutations in the *PHF8* gene. This gene provides instructions for making a protein that is found in the nucleus of cells, particularly in brain cells before and just after birth. The PHF8 protein attaches (binds) to complexes called chromatin to regulate the activity (expression) of other genes. Chromatin is the network of DNA and protein that packages DNA into chromosomes. Binding with the PHF8 protein is part of the process that changes the structure of chromatin (chromatin remodeling) to alter how tightly regions of DNA are packaged. Chromatin remodeling is one way gene expression is regulated; when DNA is tightly packed, gene expression is often lower than when DNA is loosely packed.

Most *PHF8* gene mutations lead to an abnormally short protein that gets transported out of the cell's nucleus. Outside of the nucleus, the PHF8 protein cannot interact with chromatin to regulate gene expression. While the exact disease mechanism is unknown, it is likely that a lack of PHF8 protein in the nucleus of brain cells before birth prevents chromatin remodeling, altering the normal expression of genes involved in intellectual

function and formation of structures along the midline of the skull. This altered gene expression leads to intellectual disability, cleft lip and palate, and the other features of X-linked intellectual disability, Siderius type.

Learn more about the gene associated with X-linked intellectual disability, Siderius type

- PHF8

Inheritance

This condition is inherited in an X-linked recessive pattern. The gene associated with this condition is located on the X chromosome, which is one of the two sex chromosomes. In males (who have only one X chromosome), one altered copy of the gene in each cell is sufficient to cause the condition. In females (who have two X chromosomes), a mutation would have to occur in both copies of the gene to cause the disorder. Because it is unlikely that females will have two altered copies of this gene, males are affected by X-linked recessive disorders much more frequently than females. A characteristic of X-linked inheritance is that fathers cannot pass X-linked traits to their sons.

Other Names for This Condition

- MRXSSD
- Siderius X-linked mental retardation syndrome
- Siderius-Hamel syndrome
- Syndromic X-linked mental retardation, Siderius type
- X-linked mental retardation Hamel type
- X-linked mental retardation Siderius type

Additional Information & Resources

Genetic Testing Information

- Genetic Testing Registry: Syndromic X-linked intellectual disability Siderius type (https://www.ncbi.nlm.nih.gov/gtr/conditions/C1846055/)

Genetic and Rare Diseases Information Center

- X-linked intellectual disability, Siderius type (https://rarediseases.info.nih.gov/diseases/9704/index)

Patient Support and Advocacy Resources

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

Catalog of Genes and Diseases from OMIM

- INTELLECTUAL DEVELOPMENTAL DISORDER, X-LINKED, SYNDROMIC, SIDERIUS TYPE; MRXSSD (https://omim.org/entry/300263)

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28%28mental+retardation%5BTIAB%5D%29+AND+%28PHF8%5BTI%5D%29+OR+%28Siderius%5BTIAB%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D)

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