Mucolipidosis Type IV

Subjects: Genetics & Heredity
Contributor: Rita Xu

Mucolipidosis type IV is an inherited disorder characterized by delayed development and vision impairment that worsens over time. The severe form of the disorder is called typical mucolipidosis type IV, and the mild form is called atypical mucolipidosis type IV.

Keywords: genetic conditions

1. Introduction

Approximately 95 percent of individuals with this condition have the severe form. People with typical mucolipidosis type IV have delayed development of mental and motor skills (psychomotor delay). Motor skills include sitting, standing, walking, grasping objects, and writing. Psychomotor delay is moderate to severe and usually becomes apparent during the first year of life. Affected individuals have intellectual disability, limited or absent speech, difficulty chewing and swallowing, weak muscle tone (hypotonia) that gradually turns into abnormal muscle stiffness (spasticity), and problems controlling hand movements. Most people with typical mucolipidosis type IV are unable to walk independently. In about 15 percent of affected individuals, the psychomotor problems worsen over time.

Vision may be normal at birth in people with typical mucolipidosis type IV, but it becomes increasingly impaired during the first decade of life. Individuals with this condition develop clouding of the clear covering of the eye (cornea) and progressive breakdown of the light-sensitive layer at the back of the eye (retina). By their early teens, affected individuals have severe vision loss or blindness.

People with typical mucolipidosis type IV also have impaired production of stomach acid (achlorhydria). Achlorhydria does not cause any symptoms in these individuals, but it does result in unusually high levels of gastrin in the blood. Gastrin is a hormone that regulates the production of stomach acid. Individuals with mucolipidosis type IV may not have enough iron in their blood, which can lead to a shortage of red blood cells (anemia). People with the severe form of this disorder usually survive to adulthood; however, they may have a shortened lifespan.

About 5 percent of affected individuals have atypical mucolipidosis type IV. These individuals usually have mild psychomotor delay and may develop the ability to walk. People with atypical mucolipidosis type IV tend to have milder eye abnormalities than those with the severe form of the disorder. Achlorhydria also may be present in mildly affected individuals.

2. Frequency

Mucolipidosis type IV is estimated to occur in 1 in 40,000 people. About 70 percent of affected individuals have Ashkenazi Jewish ancestry.

3. Causes

Mutations in the *MCOLN1* gene cause mucolipidosis type IV. This gene provides instructions for making a protein called mucolipin-1. This protein is located in the membranes of lysosomes and endosomes, compartments within the cell that digest and recycle materials. While its function is not completely understood, mucolipin-1 plays a role in the transport (trafficking) of fats (lipids) and proteins between lysosomes and endosomes. Mucolipin-1 appears to be important for the development and maintenance of the brain and retina. In addition, this protein is likely critical for normal functioning of the cells in the stomach that produce digestive acids.

Most mutations in the *MCOLN1* gene result in the production of a nonfunctional protein or prevent any protein from being produced. A lack of functional mucolipin-1 impairs transport of lipids and proteins, causing these substances to build up inside lysosomes. Conditions that cause molecules to accumulate inside the lysosomes, including mucolipidosis type IV,

are called lysosomal storage disorders. Two mutations in the *MCOLN1* gene account for almost all cases of mucolipidosis type IV in people with Ashkenazi Jewish ancestry. It remains unclear how mutations in this gene lead to the signs and symptoms of mucolipidosis type IV.

3.1. The Gene Associated with Mucolipidosis Type IV

- MCOLN1

4. 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.

5. Other Names for This Condition

- ganglioside sialidase deficiency
- ML4
- MLIV
- sialolipidosis

References

1. Altarescu G, Sun M, Moore DF, Smith JA, Wiggs EA, Solomon BI, Patronas NJ,Frei KP, Gupta S, Kaneski CR, Quarrell OW, Slaugenhaupt SA, Goldin E, Schiffmann R. The neurogenetics of mucolipidosis type IV. Neurology. 2002 Aug13;59(3):306-13.
2. Dong XP, Cheng X, Mills E, Delling M, Wang F, Kurz T, Xu H. The type IVmucolipidosis-associated protein TRPML1 is an endolysosomal iron release channel.Nature. 2008 Oct 16;455(7215):992-6. doi: 10.1038/nature07311.
3. Miedel MT, Rbaibi Y, Guerriero CJ, Colletti G, Weixel KM, Weisz OA, KiselyovK. Membrane traffic and turnover in TRP-ML1-deficient cells: a revised model for mucolipidosis type IV pathogenesis. J Exp Med. 2008 Jun 9;205(6):1477-90. doi:10.1084/jem.20072194.
4. Puertollano R, Kiselyov K. TRPMLs: in sickness and in health. Am J PhysiolRenal Physiol. 2009 Jun;296(6):F1245-54. doi: 10.1152/ajprenal.90522.2008.
5. Ruivo R, Anne C, Sagné C, Gasnier B. Molecular and cellular basis of lysosomaltransmembrane protein dysfunction. Biochim Biophys Acta. 2009 Apr;1793(4):636-49.doi: 10.1016/j.bbamcr.2008.12.008.
6. Schiffmann R, Grishchuk Y, Goldin E. Mucolipidosis IV. 2005 Jan 28 [updated2015 Jul 30]. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, Amemiya A, editors. GeneReviews® [Internet]. Seattle (WA): University ofWashington, Seattle; 1993-2020. Available fromhttp://www.ncbi.nlm.nih.gov/books/NBK1214/
7. Venugopal B, Mesires NT, Kennedy JC, Curcio-Morelli C, Laplante JM, Dice JF,Slaugenhaupt SA. Chaperone-mediated autophagy is defective in mucolipidosis type IV. J Cell Physiol. 2009 May;219(2):344-53. doi: 10.1002/jcp.21676.
8. Vergarajauregui S, Connelly PS, Daniels MP, Puertollano R. Autophagicdysfunction in mucolipidosis type IV patients. Hum Mol Genet. 2008 Sep1;17(17):2723-37. doi: 10.1093/hmg/ddn174.
9. Vergarajauregui S, Oberdick R, Kiselyov K, Puertollano R. Mucolipin 1 channel activity is regulated by protein kinase A-mediated phosphorylation. Biochem J.2008 Mar 1;410(2):417-25.
10. Vergarajauregui S, Puertollano R. Mucolipidosis type IV: the importance offunctional lysosomes for efficient autophagy. Autophagy. 2008 Aug;4(6):832-4.
11. Wakabayashi K, Gustafson AM, Sidransky E, Goldin E. Mucolipidosis type IV: an update. Mol Genet Metab. 2011 Nov;104(3):206-13. doi:10.1016/j.ymgme.2011.06.006.