Hereditary folate malabsorption

Hereditary folate malabsorption is a disorder that interferes with the body's ability to absorb certain B vitamins (called folates) from food. Folates are important for many cell functions, including the production of DNA and its chemical cousin, RNA.

Infants with hereditary folate malabsorption are born with normal amounts of folates in their body because they obtain these vitamins from their mother's blood before birth. They generally begin to show signs and symptoms of the disorder within the first few months of life because their ability to absorb folates from food is impaired.

Infants with hereditary folate malabsorption experience feeding difficulties, diarrhea, and failure to gain weight and grow at the expected rate (failure to thrive). Affected individuals usually develop a blood disorder called megaloblastic anemia. Megaloblastic anemia occurs when a person has a low number of red blood cells (anemia), and the remaining red blood cells are larger than normal (megaloblastic). The symptoms of this blood disorder may include decreased appetite, lack of energy, headaches, pale skin, and tingling or numbness in the hands and feet. People with hereditary folate malabsorption may also have a deficiency of white blood cells (leukopenia), leading to increased susceptibility to infections. In addition, they may have a reduction in the amount of platelets (thrombocytopenia), which can result in easy bruising and abnormal bleeding.

Some infants with hereditary folate malabsorption exhibit neurological problems such as developmental delay and seizures. Over time, untreated individuals may develop intellectual disability and difficulty coordinating movements (ataxia).

Frequency

The prevalence of hereditary folate malabsorption is unknown. Approximately 15 affected families have been reported worldwide. Researchers believe that some infants with this disorder may not get diagnosed or treated, particularly in areas where advanced medical care is not available.

Causes

The *SLC46A1* gene provides instructions for making a protein called the proton-coupled folate transporter (PCFT). PCFT is important for normal functioning of intestinal epithelial cells, which are cells that line the walls of the intestine. These cells have fingerlike projections called microvilli that absorb nutrients from food as it passes through the intestine. Based on their appearance, groups of these microvilli are known collectively as the brush border. PCFT is involved in the process of using energy to move folates across the brush border membrane, a mechanism called active transport.

It is also involved in the transport of folates between the brain and the fluid that surrounds it (cerebrospinal fluid).

Mutations in the *SLC46A1* gene result in a PCFT protein that has little or no activity. In some cases the mutated protein is not transported to the cell membrane, and so it is unable to perform its function. A lack of functional PCFT impairs the body's ability to absorb folates from food, resulting in the signs and symptoms of hereditary folate malabsorption.

Inheritance Pattern

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

- congenital defect of folate absorption
- Congenital folate malabsorption
- Folic acid transport defect

Diagnosis & Management

Genetic Testing Information

- What is genetic testing?
  /primer/testing/genetictesting
- Genetic Testing Registry: Congenital defect of folate absorption
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C0342705/

Other Diagnosis and Management Resources

- GeneReview: Hereditary Folate Malabsorption
  https://www.ncbi.nlm.nih.gov/books/NBK1673
- MedlinePlus Encyclopedia: Folate
  https://medlineplus.gov/ency/article/002408.htm
- MedlinePlus Encyclopedia: Folate Deficiency
  https://medlineplus.gov/ency/article/000354.htm
- MedlinePlus Encyclopedia: Folate-Deficiency Anemia
  https://medlineplus.gov/ency/article/000551.htm
- MedlinePlus Encyclopedia: Malabsorption
  https://medlineplus.gov/ency/article/000299.htm

Additional Information & Resources

Health Information from MedlinePlus

- Encyclopedia: Folate
  https://medlineplus.gov/ency/article/002408.htm
- Encyclopedia: Folate Deficiency
  https://medlineplus.gov/ency/article/000354.htm
- Encyclopedia: Folate-Deficiency Anemia
  https://medlineplus.gov/ency/article/000551.htm
- Encyclopedia: Malabsorption
  https://medlineplus.gov/ency/article/000299.htm
- Encyclopedia: Megaloblastic Anemia (image)
  https://medlineplus.gov/ency/imagepages/1214.htm
- Health Topic: Anemia
  https://medlineplus.gov/anemia.html
- Health Topic: Folic Acid
  https://medlineplus.gov/folicacid.html
- Health Topic: Malabsorption Syndromes
  https://medlineplus.gov/malabsorptionsyndromes.html

Genetic and Rare Diseases Information Center

- Hereditary folate malabsorption
  https://rarediseases.info.nih.gov/diseases/12983/hereditary-folate-malabsorption

Educational Resources

- Merck Manual Professional Version: Malabsorption syndromes
  https://www.merckmanuals.com/professional/gastrointestinal-disorders/malabsorption-syndromes/overview-of-malabsorption
- Orphanet: Hereditary folate malabsorption
  https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=90045

Patient Support and Advocacy Resources

- Metabolic Support UK
  https://www.metabolicsupportuk.org/
- National Organization for Rare Disorders (NORD): Megaloblastic Anemia
  https://rarediseases.org/rare-diseases/anemia-megaloblastic/

Clinical Information from GeneReviews

- Hereditary Folate Malabsorption
  https://www.ncbi.nlm.nih.gov/books/NBK1673

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28hereditary+folate+malabsorption%5BTIAB%5D%29+OR+%28congenital+folate+malabsorption%5BTIAB%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+3600+days%22%5Bdp%5D

Catalog of Genes and Diseases from OMIM

- FOLATE MALABSORPTION, HEREDITARY
  http://omim.org/entry/229050

Sources for This Summary

- Andrews NC. When is a heme transporter not a heme transporter? When it's a folate transporter. Cell Metab. 2007 Jan;5(1):5-6.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/17189201
- Kronn D, Goldman ID. Hereditary Folate Malabsorption. 2008 Jun 17 [updated 2017 Apr 27]. In: Pagon RA, Adam MP, Ardinger HH, Wallace SE, Amemiya A, Bean LJH, Bird TD, Ledbetter N, Mefford HC, Smith RJH, Stephens K, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2017. Available from http://www.ncbi.nlm.nih.gov/books/NBK1673/
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/20301716
- Lasry I, Berman B, Straussberg R, Sofer Y, Bessler H, Sharkia M, Glaser F, Jansen G, Drori S, Assaraf YG. A novel loss-of-function mutation in the proton-coupled folate transporter from a patient with hereditary folate malabsorption reveals that Arg 113 is crucial for function. Blood. 2008 Sep 1; 112(5):2055-61. doi: 10.1182/blood-2008-04-150276. Epub 2008 Jun 17.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/18559978
- Min SH, Oh SY, Karp GI, Poncz M, Zhao R, Goldman ID. The clinical course and genetic defect in the PCFT gene in a 27-year-old woman with hereditary folate malabsorption. J Pediatr. 2008 Sep; 153(3):435-7. doi: 10.1016/j.jpeds.2008.04.009.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/18718264
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3835188/
- Qiu A, Jansen M, Sakaris A, Min SH, Chattopadhyay S, Tsai E, Sandoval C, Zhao R, Akabas MH, Goldman ID. Identification of an intestinal folate transporter and the molecular basis for hereditary folate malabsorption. Cell. 2006 Dec 1;127(5):917-28.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/17129779
- Wolf G. Identification of proton-coupled high-affinity human intestinal folate transporter mutated in human hereditary familial folate malabsorption. Nutr Rev. 2007 Dec;65(12 Pt 1):554-7. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/18236695

- Zhao R, Matherly LH, Goldman ID. Membrane transporters and folate homeostasis: intestinal absorption and transport into systemic compartments and tissues. Expert Rev Mol Med. 2009 Jan 28;11:e4. doi: 10.1017/S1462399409000969. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/19173758
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3770294/
- Zhao R, Min SH, Qiu A, Sakaris A, Goldberg GL, Sandoval C, Malatack JJ, Rosenblatt DS, Goldman ID. The spectrum of mutations in the PCFT gene, coding for an intestinal folate transporter, that are the basis for hereditary folate malabsorption. Blood. 2007 Aug 15;110(4): 1147-52. Epub 2007 Apr 19.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/17446347
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1939898/

Reprinted from Genetics Home Reference:
https://ghr.nlm.nih.gov/condition/hereditary-folate-malabsorption

Reviewed: May 2009
Published: August 17, 2020

Lister Hill National Center for Biomedical Communications
U.S. National Library of Medicine
National Institutes of Health
Department of Health & Human Services