GENEReviews

Funded by the NIH · Developed at GeneTests (www.genetests.org), University of Washington, Seattle

Hereditary Folate Malabsorption

[*Congenital Folate Malabsorption*]

I David Goldman , MD
Departments of Medicine and Molecular Pharmacology
Albert Einstein College of Medicine
Bronx, New York
igoldman@aecom.yu.edu

Sang Hee Min , MD
Departments of Medicine and Molecular Pharmacology
Albert Einstein College of Medicine
Bronx, New York

Claudio Sandoval , MD
Department of Pediatrics
New York Medical College
Valhalla, New York
Claudio_Sandoval@nymc.edu

David Kronn , MD
Department of Pediatrics
New York Medical College
Valhalla, New York
David_Kronn@nymc.edu

Initial Posting: June 17, 2008.

Summary

Disease characteristics. Hereditary folate malabsorption (HFM) is characterized by impaired intestinal folate absorption and impaired folate transport into the CNS. Findings include poor feeding and failure to thrive, anemia often accompanied by leukopenia and/or thrombocytopenia, diarrhea and/or oral mucositis, hypoimmunoglobulinemia, and infection with unusual organisms. Neurologic manifestations include seizures and developmental delay in infants. Ataxia and cognitive impairment may occur in older untreated individuals.

Diagnosis/testing. Diagnosis of HFM is confirmed by impaired absorption of an oral folate load and low cerebrospinal fluid (CSF) folate concentration (even after correction of the serum folate concentration). *SLC46A1*, encoding the proton-coupled folate transporter (PCFT) protein, a member of the superfamily of facilitative carriers, is the only gene known to be associated with HFM. Sequence analysis has identified either homozygous or compound heterozygous mutations in all 11 families tested to date.

Management. *Treatment of manifestations:* for systemic manifestations of folate deficiency, low-dose parenteral (intramuscular) (1.0 to 5.0 mg/day) or high-dose oral (~150-200 mg/day) 5-methyltetrahydrofolate (5-methylTHF) (Metafolin®) or 5-formyltetrahydrofolate (5-formylTHF) (folinic acid or Leucovorin®); neurologic signs can be more difficult to correct. *Prevention of primary manifestations:* Early treatment with 5-methylTHF or 5-formylTHF before symptoms appear can prevent the metabolic consequences of folate deficiency. *Surveillance:* to assess adequacy of treatment, periodic complete blood counts and measurements of the concentrations of serum and CSF folate. *Testing of relatives at risk:* for

sibs of a proband, molecular genetic testing when the family-specific disease-causing mutations are known; otherwise, assessment of intestinal absorption of folate and CSF folate concentration. *Other:* Folic acid should not be used for treatment of HFM; it is not a physiologic folate and binds irreversibly to the folate receptors that transport folates into cells.

Genetic counseling. HFM is inherited in an autosomal recessive manner. Heterozygotes (carriers) are asymptomatic and do not have evidence of folate deficiency. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. In families in which the disease-causing mutations are known, carrier testing for at-risk relatives and prenatal testing for pregnancies at increased risk may be possible through laboratories offering custom genetic testing.

Diagnosis

Clinical Diagnosis

Hereditary folate malabsorption (HFM) is characterized by impaired intestinal folate absorption and impaired folate transport into the CNS [Rosenblatt 2001, Geller et al 2002].

HFM should be considered in infants usually between ages two and five months with the following:

- Anorexia with poor weight gain and failure to thrive
- Anemia, often accompanied by leukopenia and/or thrombocytopenia
- Diarrhea and/or oral mucositis
- Infections with unusual organisms such as pneumonia caused by *Pneumocystis carinii*
- Hypoimmunoglobulinemia
- Neurologic manifestations such as seizures and developmental delays.

  Note: Ataxia and cognitive impairment can be seen in older untreated individuals.
- Family history consistent with autosomal recessive inheritance; in particular, a history of sibling deaths in early infancy as a result of infection, anemia, and/or seizures

Testing

Diagnosis of HFM is confirmed by the following:

- **Impaired absorption of an oral folate load**
  - Baseline serum folate concentrations are below normal (average: ~1.8 ng/mL, often <1.0 ng/mL; NL: 5-15 ng/mL, or as specified by the laboratory)
  - After an oral folate load of 5-10 mg Metafolin® (5-methyltetrahydrofolate [5-methylTHF]) or Leucovorin® (5-formyltetrahydrofolate [5-formylTHF]), serum folate concentrations measured over a minimum of four hours show little or no increase in affected individuals, whereas the serum folate concentration increases to at least 100 ng/mL in controls [Lanzkowsky et al 1969, Santiago-Borrero et al 1973, Poncz et al 1981, Corbeel et al 1985, Urbach et al 1987, Malatack et al 1999, Geller et al 2002].
- **Low cerebrospinal fluid (CSF) folate concentration** (even after correction of the serum folate concentration):

- Baseline CSF folate concentrations range from 0 to 1.5 ng/mL (NL: 2-3 times the normal serum folate concentration or ≥10-45 ng/mL).
- After intramuscular administration of 5 mg of 5-methylTHF or 5-formylTHF, the CSF folate concentration peaks transiently at one to two hours in the normal range and returns to the baseline value within approximately 24 hours. However, even at its peak, the CSF folate concentration remains below the serum folate concentration, a finding consistent with impaired folate transport across the choroid plexus:cerebrospinal fluid barrier [Poncz et al 1981, Corbeel et al 1985, Malatack et al 1999].

The following laboratory findings are consistent with but not diagnostic of HFM:

- Anemia, typically with macrocytic red cell indices (but may be normocytic); macrocytosis and neutrophil hypersegmentation on peripheral smear
- Leukopenia
- Thrombocytopenia, typically mild to moderate but sometimes severe
- Low serum concentrations of IgG, IgM, and IgA [Corbeel et al 1985, Urbach et al 1987, Malatack et al 1999, Geller et al 2002, Zhao et al 2007]
- Low erythrocyte folate concentration (average: ~70 ng/mL; NL: >200 ng/mL)

Bone marrow biopsy confirms the diagnosis of megaloblastic anemia and excludes other causes of anemia. The bone marrow can also show dyserythropoesis.

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Molecular Genetic Testing—Gene. *SLC46A1*, encoding the proton-coupled folate transporter (PCFT) protein, a member of the superfamily of facilitative carriers, is the only gene known to be associated with HFM [Qiu et al 2006, Zhao et al 2007].

Research testing

- **Sequence analysis**. Sequencing of the entire *SLC46A1* coding region and exon-intron junctions detected 11 homozygous or compound heterozygous loss-of-function mutations in 12 individuals from 11 families with a clinical diagnosis of HFM. Eight of the 11 mutations have been reported [Qiu et al 2006, Zhao et al 2007, Min et al 2008]; four additional families with three new mutations have been evaluated in the Goldman laboratory but are not yet published. Two of the individuals who have not yet been reported have compound heterozygous mutations. All mutations identified thus far have been private mutations and none has been *de novo*.

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Hereditary Folate Malabsorption

Gene Symbol	Test Method	Mutations Detected	Mutation Detection Frequency by Test Method	Test Availability
SLC46A1	Sequence analysis	Sequence variants	100% [1]	Research only [2]

1. Represents 12 individuals tested to date [Qiu et al 2006; Zhao et al 2007; Min et al 2008; Goldman, unpublished observations].

2. No laboratories offering clinical molecular genetic testing for this disease are listed in the GeneTests Laboratory Directory. However, clinical confirmation of mutations identified in research laboratories may be available. For laboratories offering such testing, see Testing.

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Testing Strategy

To confirm the diagnosis in a proband

- The diagnosis of HFM is usually based on the findings of macrocytic anemia with low serum folate concentration and failure to correct the anemia with 1.0 to 5.0 mg/day of oral 5-formylTHF or 5-methylTHF.
- With 1.5 to 5 mg/day intramuscular injections of 5-formylTHF or 5-methylTHF the anemia begins to correct within a few days; however, the CSF:serum folate ratio does not normalize.

The diagnosis is confirmed with the demonstration of homozygous or compound heterozygous *SLC46A1* mutations (see Table 1, footnote 2).

Carrier testing for at-risk relatives requires prior identification of the disease-causing mutation(s) in the family.

Note: Carriers are heterozygotes for this autosomal recessive disorder and are not at risk for the disorder (see Table 1, footnote 2).

Genetically Related (Allelic) Disorders

No other phenotypes are associated with mutations in *SLC46A1*.

Clinical Description

Natural History

Hereditary folate malabsorption (HFM) is characterized by (1) impaired intestinal absorption of folates causing systemic folate deficiency and (2) impaired transport of folates across the choroid plexus:CSF barrier resulting in central nervous system (CNS) folate deficiency. Infants with HFM are apparently born with adequate stores of folate but subsequently are unable to absorb folate from breast milk or formula and become folate deficient. Clinical manifestations of folate deficiency occur as early as age two months. The age at which signs of folate deficiency appear depends in part on the infant's folate stores at birth.

Anemia. Folate deficiency results primarily in megaloblastic anemia but may affect all three hematopoietic lineages resulting in pancytopenia. The anemia may be severe and require transfusion, although with rapid diagnosis and folate repletion transfusion should not be necessary. The anemia begins to correct in a few days after parenteral administration of folate (see Treatment of Manifestations).

Immunodeficiency. Leukopenia can be a consequence of untreated severe folate deficiency [Urbach et al 1987, Malatack et al 1999]. Neutrophil dysfunction was observed in one individual [Corbeel et al 1985]; the relationship between this dysfunction and folate deficiency is unclear.

Hypoimmunoglobulinemia not associated with lymphopenia can result in infections with *Pneumocystis carinii* (pneumonia), *C. difficile*, and cytomegalovirus (CMV) in affected infants

and/or their sibs who died undiagnosed and untreated in early infancy [Corbeel et al 1985, Urbach et al 1987, Malatack et al 1999, Geller et al 2002, Sofer et al 2007, Zhao et al 2007].

Neurologic signs. In some individuals with HFM, neurologic signs are part of the initial manifestations or develop later in the disease course. Most common are seizures and developmental delays. Cognitive impairment, ataxia and other movement disorders, and peripheral neuropathy have also been reported in older individuals. It is unclear why some individuals do not have neurologic signs, as all affected individuals have very low CSF folate concentrations [Su 1976,Corbeel et al 1985,Urbach et al 1987,Steinschneider et al 1990,Malatack et al 1999,Geller et al 2002,Sofer et al 2007,Zhao et al 2007].

X-ray, CT, or MRI of the head. In early reports, three individuals with HFM had calcifications in the cortex or basal ganglia [Lanzkowsky et al 1969, Corbeel et al 1985, Jebnoun et al 2001].

Note: Neural calcifications are also a common finding in children treated with methotrexate [McIntosh et al 1977].

Pathophysiology. PCFT is highly expressed at the apical brush-border membrane of the proximal jejunum and duodenum and is required for intestinal folate absorption. PCFT and folate receptor α are expressed in the choroid plexus, and both appear to be required for transport of folates into the CSF [Kamen et al 1991, Qiu et al 2006, Wollack et al 2008]. Although PCFT is also highly expressed in the placenta [Qiu et al 2006], it is apparently not required for fetal folate sufficiency.

Of note, infants with HFM do not have the malformations, such as neural tube defects, that are associated with maternal folate deficiency during pregnancy.

Genotype-Phenotype Correlations

Because of the rarity of HFM, genotype-phenotype correlations have not yet been established.

Prevalence

Fifteen families with HFM have been reported to date; the prevalence is unknown.

To date, *SLC46A1* mutations have been reported in seven families with HFM and observed in four additional families [Goldman, unpublished]. The frequency of this disorder is likely to be much greater than reflected in the clinical reports to date because many infants with HFM may die undiagnosed in early infancy. This may be particularly important in underdeveloped and medically underserved countries, in which consanguinity is common.

The carrier frequency for HFM is unknown.

HFM is pan ethnic.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

The differential diagnosis of hereditary folate malabsorption (HFM) includes the following:

- Vitamin B12 deficiency, as a cause of megaloblastic anemia
- Methyltetrahydrofolate reductase deficiency (homozygous)

- Nutritional folate deficiency as a result of inadequate dietary folate
- Intestinal disease associated with folate malabsorption
- Erythroleukemia
- Methionine synthase deficiency with megaloblastic anemia and developmental delay
- Glutamate formiminotransferase deficiency
- Pharmacologic: the use of phenytoin for the treatment of seizure disorders
- Tyrosinemia type 1. Children presenting with gastrointestinal bleeding should be evaluated for tyrosinemia type 1.
- Mitochondrial disorders

Of particular interest are the potential differences in the pathways to diagnosis that depend on the presenting signs of the disorder. This may delay a definitive diagnosis and the initiation of treatment. For example:

- If the child presents with an infection such as *Pneumocystis carinii* and is found to have hypogammaglobulinemia, the accompanying anemia may be considered secondary and the initial impression may be a primary immune deficiency disorder.
- If the child presents with seizures and/or developmental delays, the initial suspicion may be a primary neurologic disorder with secondary anemia.
- If the child presents with anemia, the initial suspicion may be a dietary deficiency for which oral folate is administered. It may take several weeks before the absence of a hematologic response is recognized. Alternatively, during the initial evaluation, the child may receive intravenous vitamins resulting in correction of the anemia but persistence of the CNS folate deficiency and the appearance of neurologic signs.

Management

Evaluations Following Initial Diagnosis

To establish the extent of neurologic disease in an individual diagnosed with hereditary folate malabsorption (HFM), assessment by a pediatric neurologist is recommended to determine baseline neurologic findings and appropriate monitoring of neurologic response to treatment.

Initial evaluation and follow-up by a metabolic genetic specialist is also recommended.

Treatment of Manifestations

The goal of treatment is to prevent hematologic, immunologic, and neurologic defects and to optimize the intellectual development of children with this disorder. Complete reversal of the systemic consequences of folate deficiency is easily achieved; however, correction of the neurologic consequences is more difficult.

“Folates” refers to a family of B vitamin compounds that are interconvertible in a series of intracellular biochemical reactions. “Reduced folates” include tetrahydrofolate, which is reduced at four positions on the pteridine B-ring and its one-carbon derivatives. Folate can be used effectively by both oral and parenteral routes; however, much higher oral doses than parenteral doses are required to achieve normal CSF folate concentrations in persons with HFM. Based on the current understanding of folate transport and metabolism the following two reduced folates can be used to treat HFM:

- 5-methyltetrahydrofolate (5-methylTHF), the major folate constituent in the blood that is absorbed in the intestine. Because 5-methylTHF is available commercially in a stable form (Metafolin®), it is the preferred folate for the treatment of HFM.
- 5-formyltetrahydrofolate (5-formylTHF), also known as folinic acid and Leucovorin®. 5-formylTHF is a stable form of physiologic folate found in low quantities in human tissues.

Note: Folic acid should not be used for treatment of HFM. Although folic acid is very stable and is the most common pharmacologic source of folate, it is not a physiologic folate and binds irreversibly to folate receptors, which transport folates into cells by an endocytic mechanism [Kamen & Smith 2004]. Thus, folic acid may block folate receptor-mediated transport of 5-methylTHF that appears to be required for folate transport across the choroid plexus.

The dose of reduced folate required to overcome the loss of PCFT-mediated intestinal folate absorption is not clear. Because HFM is rare, controlled studies to establish an optimal dose have not been possible. The folate dose required to obviate the neurologic consequences is much higher than that needed to correct the hematologic defect. The dose should be guided by its effect on peak and trough blood and CSF folate concentrations. The end point is CSF folate trough concentrations as near to normal as possible:

- The oral dose of 5-formylTHF associated with a "good" outcome has been as high as 150-200 mg given once per day [Geller et al 2002]. A reasonable starting oral dose of a reduced folate in an infant could be 50 mg or 10-15 mg/kg given daily as a single dose. The dose should be adjusted to achieve the critical end point: normal nadir CSF folate concentration.
- The parenteral dose of folate is much lower. One individual was treated with 5-formylTHF at 1.5 mg IM per day until age six years, when the frequency was reduced to five times per week. In her teens the frequency was further decreased to three times per week and the dose was increased to 3 mg IM [Poncz et al 1981, Poncz & Cohen 1996]. She is now age 27 years and has completed an advanced academic degree. The decreasing requirement for folate with age is likely related to decreasing folate requirements as the brain matures. The mutations in this individual resulted in the complete absence of the PCFT protein; hence, residual PCFT function is not required for a satisfactory outcome [Min et al 2008].

Prevention of Primary Manifestations

Individuals diagnosed before symptoms appear should be treated as soon as the diagnosis is confirmed to prevent the onset of folate deficiency and the metabolic consequences of the disorder. See Treatment of Manifestations.

Surveillance

The following should be monitored periodically to assess the adequacy of treatment, particularly following initial diagnosis when treatment is being optimized:

- Complete blood count
- Serum and CSF folate concentrations, in particular the trough CSF folate concentration to assure that the dose of folate is sufficient to achieve adequate CSF folate concentrations
- Serum and CSF homocysteine concentrations. High homocysteine concentrations are the most sensitive indicator of folate deficiency.

Note: Measurement of immunoglobulins is not necessary once the hemoglobin level returns to and remains normal.

Testing of Relatives at Risk

If the family-specific disease-causing mutation(s) are known, molecular genetic testing for sibs of a proband is appropriate; if the mutation is unknown, assess intestinal absorption of folate and CSF concentration of folate.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Other

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Hereditary folate malabsorption (HFM) is inherited in an autosomal recessive manner.

Risk to Family Members

This section is written from the perspective that molecular genetic testing for this disorder is available on a research basis only and results should not be used for clinical purposes. This perspective may not apply to families using custom mutation analysis.—ED.

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., carriers of one mutant allele).
- Heterozygotes (carriers) are asymptomatic and do not have evidence of folate deficiency.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3.
- Heterozygotes (carriers) are asymptomatic.

Offspring of a proband. No information on the fertility status of women with HFM who have reached reproductive age is available as yet. Hence, no information about the possible teratogenicity of folate malabsorption and/or its treatment is available. Assuming that women with treated HFM can conceive, their offspring will be obligate heterozygotes (carriers).

Other family members of a proband. Each sib of the proband's parents is at a 50% risk of being a carrier.

Carrier Detection

Testing of at-risk relatives may be available from laboratories offering clinical confirmation of mutations identified in research labs if the mutations have been identified in the family. See Testing.

Heterozygotes do not have hematologic abnormalities or low blood folate concentrations.

Related Genetic Counseling Issues

See Management, Testing of Relatives at Risk for information on testing at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who have been treated or are at risk of being carriers.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which molecular genetic testing is available on a research basis only. See Testing for a list of laboratories offering DNA banking.

Prenatal Testing

No laboratories listed in the GeneTests Laboratory Directory offer molecular genetic testing for prenatal diagnosis of HFM. However, prenatal testing may be available for families in which the disease-causing mutation has been identified. For laboratories offering custom prenatal testing, see Testing.

Prenatal diagnosis of a treatable condition may be controversial if such testing is being considered for the purpose of pregnancy termination rather than early diagnosis. Although most centers would consider this to be the choice of the parents, discussion of these issues is appropriate.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutations have been identified. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Hereditary Folate Malabsorption

Gene Symbol	Chromosomal Locus	Protein Name
SLC46A1	17q11.1	Proton-coupled folate transporter

Data are compiled from the following standard references: gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Hereditary Folate Malabsorption

229050	FOLIC ACID, TRANSPORT DEFECT INVOLVING
611672	SOLUTE CARRIER FAMILY 46 (FOLATE TRANSPORTER), MEMBER 1; SLC46A1

Table C. Genomic Databases for Hereditary Folate Malabsorption

Gene Symbol	Entrez Gene
SLC46A1	113235 (MIM No. 611672)

For a description of the genomic databases listed, click here.

Note: HGMD requires registration.

Molecular Genetic Pathogenesis

Hereditary folate malabsorption (HFM) is caused by loss-of-function mutations in *SLC46A1* (*PCFT)*.

Normal allelic variants. *SLC46A1* is approximately 6.5 kb long (NM_080669.3) and contains five exons. Two mRNA forms of 2.7 kb and 2.1 kb have been detected [Qiu et al 2006].

Pathologic allelic variants. See Table 2. *SLC46A1* mutations are distributed in exons 1-4. No clustering or mutation hot spots have been identified. Point mutations within transmembrane domains resulted in substitution of amino acids with markedly different properties. Of the three deletion mutations in the external loop between the first and second transmembrane domains, one produced a stop codon and two produced a frameshift with early termination.

The mutation c.1082-1G>A caused skipping of exon 3. In cell culture studies, the protein produced was not detectable in the cell membrane, consistent with a trafficking defect [Qiu et al 2006].

Table 2. *SLC46A1* Reported Pathologic Allelic Variants Discussed in This *GeneReview*

DNA Nucleotide Change (Alias [1])	Protein Amino Acid Change	Reference Sequence
c.194delG	p.Gly65AlafsX25	NM_080669.3 NP_542400.2
c.337C>A	p.Arg113Ser	
c.439G>C	p.Gly147Arg	
c.954C>G	p.Ser318Arg	
c.1126C>T	p.Arg376Trp	
c.1274C>G	p.Pro425Arg	
c.1082-1G>A	p.Tyr362_Gly389del [2]	
c.197_198delGCinsAA (c.197GC>AA)	p.Cys66X	

See Quick Reference for an explanation of nomenclature. *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (http://www.hgvs.org).

1. Variant designation that does not conform to current naming conventions

2. In-frame deletion resulting from skipping of exon 3 detected in cDNA from transformed lymphocytes of an individual with HFM [Qiu et al 2006]

Normal gene product. Proton-coupled folate transporter (PCFT) is predicted to have 459 amino acids with a MW of approximately 50 kd. Hydropathy analysis predicted a protein with twelve transmembrane domains [Qiu et al 2006, Nakai et al 2007, Qiu et al 2007]. PCFT has high affinity for folic acid, reduced folates, and antifolates, and has a low pH optimum [Zhao & Goldman 2007].

Abnormal gene product. See Pathologic allelic variants. Some of the mutated proteins did, and some did not, traffic to the cell membrane. In two cases (p.Gly147Arg and p.Pro425Arg) [Zhao et al 2007], mutant forms had approximately 10% residual activity on transfection into cells.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests *for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

Children Living with Inherited Metabolic Diseases (CLIMB)
Climb Building
176 Nantwich Road
Crewe CW2 6BG
United Kingdom
Phone: 0800 652 3181 (toll free)
Email: info.svcs@climb.org.uk
www.climb.org.uk

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

Literature Cited

Corbeel L, Van den Berghe G, Jaeken J, Van Tornout J, Eeckels R. Congenital folate malabsorption. *Eur J Pediatr* 1985;143:284–90. [PubMed: 3987728]

Geller J, Kronn D, Jayabose S, Sandoval C. Hereditary folate malabsorption: family report and review of the literature. *Medicine (Baltimore)* 2002;81:51–68. [PubMed: 11807405]

Jebnoun S, Kacem S, Mokrani CH, Chabchoub A, Khrouf N, Zittoun J. A family study of congenital malabsorption of folate. *J Inherit Metab Dis* 2001;24:749–50. [PubMed: 11804211]

Kamen BA, Smith AK. A review of folate receptor alpha cycling and 5-methyltetrahydrofolate accumulation with an emphasis on cell models in vitro. *Adv Drug Deliv Rev* 2004;56:1085–97. [PubMed: 15094208]

Kamen BA, Smith AK, Anderson RGW. The folate receptor works in tandem with a probenecid-sensitive carrier in MA104 cells in vitro. *J Clin Invest* 1991;87:1442–9. [PubMed: 1849150]

Lanzkowsky P, Erlandson ME, Bezan AI. Isolated defect of folic acid absorption associated with mental retardation and cerebral calcification. *Blood* 1969;34:452–65. [PubMed: 4980683]

Malatack JJ, Moran MM, Moughan B. Isolated congenital malabsorption of folic acid in a male infant: insights into treatment and mechanism of defect. *Pediatrics* 1999;104:1133–7. [PubMed: 10545560]

McIntosh S, Fischer DB, Rothman SG, Rosenfield N, Lobel JS, O'Brien R. Intracranial calcifications in childhood leukemia. An association with systemic chemotherapy. *J Pediatr* 1977;91:909–13. [PubMed: 925819]

Min SH, Oh SY, Karp G, 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. *The Journal of Pediatrics*. 2008 [PubMed: 18718264]

Nakai Y, Inoue K, Abe N, Hatakeyama M, Ohta KY, Otagiri M, Hayashi Y, Yuasa H. Functional characterization of human proton-coupled folate transporter/heme carrier protein 1 heterologously expressed in mammalian cells as a folate transporter. *J Pharmacol Exp Ther* 2007;322:469–76. [PubMed: 17475902]

Poncz M, Cohen A. Long-term treatment of congenital folate malabsorption. *J Pediatr* 1996;129:948. [PubMed: 8969750]

Poncz M, Colman N, Herbert V, Schwartz E, Cohen AR. Therapy of congenital folate malabsorption. *J Pediatr* 1981;98:76–9. [PubMed: 6969796]

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;127:917–28. [PubMed: 17129779]

Qiu A, Min SH, Jansen M, Malhotra U, Tsai E, Cabelof DC, Matherly LH, Zhao R, Akabas MH, Goldman ID. Rodent intestinal folate transporters (SLC46A1): secondary structure, functional properties, and response to dietary folate restriction. *Am J Physiol Cell Physiol* 2007;293:C1669–C1678. [PubMed: 17898134]

Rosenblatt DS (2001) Inherited disorders of folate transport and metabolism. In: Scriver CR, Beaudet AL, Valle D, Sly WS, Childs B, Kinzler KW, Vogestein B (eds.), The metabolic and molecular bases of inherited disease. McGraw-Hill, New York, pp. 3111-3128

Santiago-Borrero PJ, Santini R, Perez-Santiago E, Maldonado N. Congenital isolated defect of folic acid absorption. *J Pediatr* 1973;82:450–5. [PubMed: 4540608]

Sofer Y, Harel L, Sharkia M, Amir J, Schoenfeld T, Straussberg R. Neurological manifestations of folate transport defect: case report and review of the literature. *J Child Neurol* 2007;22:783–6. [PubMed: 17641272]

Steinschneider M, Sherbany A, Pavlakis S, Emerson R, Lovelace R, De Vivo DC. Congenital folate malabsorption: reversible clinical and neurophysiologic abnormalities. *Neurology* 1990;40:1315. [PubMed: 2381546]

Su PC. Letter: Congenital folate deficiency. *N Engl J Med* 1976;294:1128. [PubMed: 176588]

Urbach J, Abrahamov A, Grossowicz N. Congenital isolated folic acid malabsorption. *Arch Dis Child* 1987;62:78–80. [PubMed: 3813642]

Wollack JB, Makori B, Ahlawat S, Koneru R, Picinich SC, Smith A, Goldman ID, Qiu A, Cole PD, Glod J, Kamen B. Characterization of folate uptake by choroid plexus epithelial cells in a rat primary culture model. *J Neurochem* 2008;104:1494–503. [PubMed: 18086128]

Zhao R, Goldman ID. The molecular identity and characterization of a Proton-coupled Folate Transporter--PCFT; biological ramifications and impact on the activity of pemetrexed. *Cancer Metastasis Rev* 2007;26:129–39. [PubMed: 17340171]

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;110:1147–52. [PubMed: 17446347]

Chapter Notes

Revision History

- 17 June 2008 (me) Review posted live
- 4 March 2008 (idg) Initial submission