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Hereditary Folate Malabsorption

Synonym: Congenital Folate Malabsorption

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Summary

Clinical characteristics

Hereditary folate malabsorption (HFM) is characterized by folate deficiency due to impaired intestinal folate absorption and impaired folate transport into the central nervous system. Findings include poor feeding, failure to thrive, and anemia. There can be leukopenia and thrombocytopenia, diarrhea and/or oral mucositis, hypoimmunoglobulinemia, and other immunologic dysfunction resulting in infections, most often *Pneumocystis jirovecii* pneumonia. Neurologic manifestations include developmental delays, cognitive and motor disorders, behavioral disorders, and seizures.

Diagnosis/testing

The diagnosis of HFM is established in a proband with: anemia, impaired absorption of an oral folate load, and very low cerebrospinal fluid (CSF) folate concentration (even after correction of the serum folate concentration); and/or biallelic pathogenic variants in *SLC46A1* identified on molecular genetic testing.

Management

Targeted therapy: Early treatment with intramuscular or high-dose oral 5-formyltetrahydrofolate (5-formylTHF; also known as folinic acid or leucovorin) or, preferably, the active isomer of 5-formylTHF (Isovorin® or Fusilev®) readily corrects the systemic folate deficiency and, if the dose is sufficient, can achieve CSF folate levels that prevent or mitigate the neurologic consequences of HFM. Dosing is aimed at achieving CSF folate trough concentrations as close as possible to the normal range for the age of the affected individual (infants and children have higher CSF folate levels than adults).

Supportive care: Blood transfusion is rarely needed for severe anemia; in affected individuals with selective IgA deficiency, appropriate precautions for blood product transfusion should be taken.

Surveillance: To assess adequacy of treatment, surveillance should include: complete blood counts; measurement of serum and CSF folate concentrations; measurement of CSF homocysteine concentrations; and monitoring of

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neurologic and cognitive function. Serum immunoglobulins are monitored until they return to the normal range and serum folate level and hemogram remain normal and stable.

Agents/circumstances to avoid: If possible, folic acid should not be used for the treatment of HFM because it binds very tightly to the folate receptor. This may impair transport of physiologic folates across the choroid plexus.

Evaluation of relatives at risk: For at-risk sibs, molecular genetic testing when the family-specific pathogenic variants are known; otherwise, assessment of serum and CSF folate levels and, if warranted, intestinal absorption of folate, immediately after birth or as soon as the diagnosis is confirmed in the proband.

Pregnancy management: Affected women should increase their 5-formylTHF intake above the maintenance dose well in advance of attempting to conceive; infants with HFM do not appear to be at increased risk for neural malformations typically associated with maternal folate deficiency during pregnancy, but care must be taken to assure that maternal folate intake is increased and sufficient.

Genetic counseling

HFM is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for an *SLC46A1* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of inheriting neither of the familial *SLC46A1* pathogenic variants. If both pathogenic variants have been identified in the family, carrier testing for at-risk relatives, prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing for HFM are possible.

Diagnosis

Hereditary folate malabsorption (HFM) is characterized by folate deficiency with impaired intestinal folate absorption and impaired folate transport into the central nervous system.

Suggestive Findings

HFM **should be suspected** in infants with the following clinical features, family history, and supportive laboratory and bone marrow examination findings.

Clinical features

- Anorexia with poor weight gain and failure to thrive
- Diarrhea and/or oral mucositis
- Infections with unusual organisms (typically pneumonia caused by *Pneumocystis jirovecii*) associated with hypoimmunoglobulinemia
- Neurologic manifestations including developmental delays, cognitive and behavioral disorders, motor disorders, and, frequently, seizures

Family history is consistent with autosomal recessive inheritance: affected sibs, sib deaths in early infancy as a result of infection, anemia, seizure disorders, parental consanguinity, and/or Puerto Rican ancestry. Absence of a known family history does not preclude the diagnosis.

Supportive laboratory findings

- **Complete blood count**
  - Anemia, typically with macrocytic red cell indices, macrocytosis, and neutrophil hypersegmentation on peripheral smear, associated with low serum folate. Note: Normocytic anemia is possible when there is accompanying poor nutrition and/or iron deficiency.

- In ~30% of individuals, thrombocytopenia and/or pancytopenia
- **Quantitative serum immune globulin levels.** In ~25% of individuals, low concentrations of serum IgG, IgM, and IgA [Kishimoto et al 2014, Erlacher et al 2015, Zhao et al 2017, Tozawa et al 2019]
- **Erythrocyte and serum folate concentrations**
  - Low erythrocyte folate concentration (normal: >200 ng/mL)
  - Very low baseline serum folate concentrations in untreated individuals (typically <1.5 nmol/L). In countries in which grains are folate supplemented, the normal level is 10-45 nmol/L to age 12 years or as specified by the laboratory.
  - After an oral load of 5 mg of folic acid, measurement of serum folate concentration over a minimum of four hours demonstrates little or no increase in affected individuals; in unaffected individuals the serum folate concentration increases to at least 200-3,000 nmol/L [Malatack et al 1999, Geller et al 2002].
- **Cerebrospinal fluid (CSF) folate concentration**
  - Low CSF folate concentration even after correction of the serum folate level:
    - Baseline CSF folate concentration in untreated affected individuals is typically <1.5 nmol/L.
    - Normal CSF folate levels are higher in infancy and through adolescence (see Treatment of Manifestations).
    - Note: In unaffected adults, normal CSF folate levels are 2-3 times the normal serum folate concentration.
  - Following intramuscular administration of 5 mg of 5-formyltetrahydrofolate (5-formylTHF or leucovorin), the CSF folate concentration peaks transiently at one to two hours and returns to the baseline value within approximately 24 hours. However, the CSF folate concentration remains far below the serum folate concentration in individuals with HFM, a finding consistent with impaired folate transport across the blood-choroid plexus-CSF barrier [Torres et al 2015, Aluri et al 2018, Manea et al 2018].

Supportive bone marrow biopsy findings. Megaloblastic erythropoiesis with exclusion of other causes of anemia

Radiographic findings. Frequent intracranial calcifications, particularly involving the basal ganglia, when treatment is delayed or the dose of 5-formylTHF is insufficient to restore adequate CSF folate levels

Establishing the Diagnosis

The diagnosis of HFM **is established** in a proband:

- With anemia, impaired absorption of an oral folate load, and low serum and CSF folate concentrations (the latter even after correction of the serum folate level);
- By the identification of biallelic pathogenic (or likely pathogenic) variants in *SLC46A1* on molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) Identification of biallelic *SLC46A1* variants of uncertain significance (or of one known *SLC46A1* pathogenic variant and one *SLC46A1* variant of uncertain significance) does not establish or rule out the diagnosis.

The recommended approach to molecular genetic testing is **single-gene testing**.

Single-gene testing. Sequence analysis of *SLC46A1* is performed to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. Note: Depending on the sequencing method used, single-

exon, multiexon, or whole-gene deletions/duplications may not be detected. However, to date, large deletions or duplications have not been reported in individuals with HFM.

Note: Targeted analysis for founder variants can be performed first in individuals of Puerto Rican or Japanese ancestry (see Table 6).

Table 1. Molecular Genetic Testing Used in Hereditary Folate Malabsorption

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
SLC46A1	Sequence analysis [3]	100% [4, 5]
	Gene-targeted deletion/duplication analysis [6]	See footnote 7.

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
5. One variant found in several individuals of Japanese ancestry was a single-nucleotide deep intron 3 variant that generated a cryptic splice donor site resulting in a 168-bp insertion [Kishimoto et al 2014, Tozawa et al 2019]. Sequencing methodologies that can detect splice donor and acceptor variants should be considered.
6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
7. To date, large intragenic *SLC46A1* deletions and duplications have not been reported.

Clinical Characteristics

Clinical Description

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 blood-choroid plexus-cerebrospinal fluid (CSF) barrier, resulting in central nervous system folate deficiency. Infants with HFM may be born with adequate stores of folate but subsequently are unable to absorb folate from breast milk or formula and thus rapidly become folate deficient. Low serum and CSF folate concentrations are documented prior to the onset of clinical signs within one month after birth. One infant presented with pancytopenia (macrocytic) and pneumonia at age one month [Tan et al 2017].

Anemia. Folate deficiency results primarily in megaloblastic anemia but often affects all three hematopoietic lineages. The anemia may be severe but with rapid diagnosis and folate repletion; transfusion is rarely necessary. The anemia begins to correct within a few days after intramuscular administration of folate (see Treatment of Manifestations).

Thrombocytopenia. At least 30% of affected individuals present with thrombocytopenia alone or within the context of pancytopenia, but bleeding complications have not been reported. Leukopenia with anemia in the absence of thrombocytopenia is unusual.

Immunodeficiency. Hypoimmunoglobulinemia results in pulmonary infections with *Pneumocystis jirovecii* (pneumonia), cytomegalovirus, and other pathogens. Overall, approximately 25% of reported individuals have documented hypogammaglobulinemia. The incidence is likely to be much higher since many reports of individuals with pneumonia and other infections did not include immunoglobulin levels. The immune deficiency may be associated with T and B cell abnormalities. Infants with HFM may die of infections in early

infancy prior to diagnosis. The immunologic defects are reversed rapidly when systemic folate sufficiency is restored [Kishimoto et al 2014, Erlacher et al 2015, Zhao et al 2017].

Neurologic signs. Subtle developmental delays are often present when the disorder is diagnosed early in infancy (within a few months). As the disease progresses without treatment or with inadequate treatment, neurologic complications develop in the majority of individuals. These can include marked developmental delays, movement disorders, peripheral neuropathy, and behavioral and cognitive impairments. In approximately 40% of individuals, seizures typically begin at age six to 12 months, although they can occur earlier, and can become intractable when treatment is delayed. Rapid diagnosis and treatment can prevent or mitigate the seizures and improve neurologic and developmental status. It is unclear why some individuals do not have neurologic signs, as all affected individuals have very low CSF folate concentrations [Geller et al 2002, Zhao et al 2017, Lubout et al 2020].

Radiograph, CT, or MRI of the head. Intracranial calcifications, particularly involving the basal ganglia, are common [Ahmad et al 2015, Wang et al 2015, Aluri et al 2018, Gowda et al 2021].

Genotype-Phenotype Correlations

Because of the rarity of HFM, genotype-phenotype correlations have not as yet been established. Anecdotally, a benign clinical phenotype was seen in an individual (now age 41 years) with homozygous *SLC46A1* variants resulting in a stop codon and the complete absence of the proton-coupled folate transporter (PCFT) protein, who was treated from early in infancy with low-dose intramuscular 5-formylTHF (see Pregnancy Management).

Prevalence

Fifty-three individuals with HFM (44 with genotypic confirmation) have been reported from 45 families. Another six affected individuals are known to the author [Zhao et al 2017, Aluri et al 2018, Tozawa et al 2019, Gowda et al 2021, Huddar et al 2021]. Prevalence is likely to be much greater than reflected in clinical reports to date, as infants with HFM may die undiagnosed, particularly in populations with a higher rate of consanguinity and limited access to health care.

Three carriers of the common Puerto Rican c.1082-1G>A pathogenic variant were detected in a random screen of 1,582 newborns in selected provinces in Puerto Rico [Mahadeo et al 2011].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *SLC46A1*.

Differential Diagnosis

The differential diagnosis of hereditary folate malabsorption (HFM) includes hereditary disorders (see Table 2), and the following nutritional and pharmacologic conditions:

- Vitamin B_{12} deficiency as a cause of megaloblastic anemia
- Nutritional folate deficiency as a result of inadequate dietary folate
- Intestinal disease associated with folate malabsorption
- The use of phenytoin for the treatment of seizure disorders

Table 2. Hereditary Disorders in the Differential Diagnosis of Hereditary Folate Malabsorption

Gene(s)	Disorder	MOI	Key Feature(s)	Comment
FOLR1	Cerebral folate transport deficiency [1, 2]	AR	Very low CSF folate concentrations but, unlike HFM, normal serum folate & hemogram. Neurologic signs occur much later, usually in 2nd & 3rd yrs of life, although there are earlier exceptions. [1]	The defect is due to loss of function of FOLR1, which, along w/PCFT, is required for folate transport into the CSF.
FTCD	Glutamate formiminotransferase deficiency (OMIM 229100) [3]	AR	A severe form of the disorder is assoc w/megaloblastic anemia, DD, cognitive deficits.	*FTCD* encodes a bifunctional enzyme that channels 1-carbon units from formiminoglutamate (a metabolite of the histidine degradation pathway) to the folate pool.
MTR (*cblG*) *MTRR* (*cblE*)	Homocystinuria-megaloblastic anemia [4] (See Disorders of Intracellular Cobalamin Metabolism.)	AR	Megaloblastic anemia, DD, & cognitive & other neurologic deficits	*MTR* & *MTRR* encode 2 enzymes required for methionine synthesis from homocysteine. Age of appearance of disorder ranges from infancy to adulthood depending on specific pathogenic variant. Serum folate is normal. Affected persons respond to cobalamin.
MTHFD1	Methylenetetrahydrofolate dehydrogenase 1 deficiency (combined immunodeficiency & megaloblastic anemia ± hyperhomocysteinemia) (OMIM 617780)	AR	Early onset, megaloblastic anemia, hemolytic uremic syndrome, microangiopathy w/ retinopathy & SCID-like syndrome	MTHFD1 is a component of a trifunctional enzyme required for provision of one-carbons in biosynthetic processes.
ADA *AK2* *CD247* *CD3D* *CD3E* *CORO1A* *DCLRE1C* *IL2RG* *IL7R* *JAK3* *PRKDC* *PTPRC* *RAG1* *RAG2*	Typical SCID (genetically & clinically heterogeneous group of disorders w/ defective cellular & humoral immune function) (See X-Linked SCID.)	XL [5] AR	Presents in infancy w/recurrent, persistent infections & profound lymphopenia w/ diminished or absent immunoglobulins	Affected persons have frequent infections w/opportunistic organisms (e.g., *Pneumocystis jirovecii*, CMV). There may be secondary anemia & vitamin deficiencies that may confuse this disorder w/HFM.

AR = autosomal recessive; CMV = cytomegalovirus; CSF = cerebrospinal fluid; DD = developmental delay; HFM = hereditary folate malabsorption; MOI = mode of inheritance; SCID = severe combined immunodeficiency; XL = X-linked

1. Grapp et al [2012]
2. Pope et al [2019]
3. Hilton et al [2003]
4. Froese & Gravel [2010]
5. IL2RG-related severe combined immunodeficiency (SCID) is inherited in an X-linked manner. The other listed genes associated with SCID are inherited in an autosomal recessive manner.

Note: A variety of mitochondrial disorders, such as Kearns-Sayre syndrome (see Mitochondrial DNA Deletion Syndromes), result in low CSF folate [Pérez-Dueñas et al 2011, Pope et al 2019]. However, Kearns-Sayre syndrome has defining features that distinguish it from HFM, and the serum folate level in this and other

mitochondrial disorders is normal. There is no evidence that these disorders are caused by a specific defect in a folate transporter. Impaired transport into the CSF may be due to the mitochondrial metabolic defects that impair energy metabolism and, secondarily, choroid plexus transport function in general.

Management

No clinical practice guidelines for hereditary folate malabsorption (HFM) have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in a child diagnosed with HFM, the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3. Hereditary Folate Malabsorption: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Metabolic	• Serum & CSF folate concentrations • CSF homocysteine concentration [1] • Eval by metabolic genetic specialist	
Hematologic	CBC w/peripheral smear	
Immune system	Serum immunoglobulin levels	
Neurologic	• Assessment by pediatric neurologist to determine baseline neurologic status • Assess for mvmt disorders or seizures. • Formal developmental assessment • Formal cognitive testing	
Genetic counseling	By genetics professionals [2]	To inform affected persons & their families re nature, MOI, & implications of HFM to facilitate medical & personal decision making
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.	

CBC = complete blood count; CSF = cerebral spinal fluid; HFM = hereditary folate malabsorption; MOI = mode of inheritance
1. A high CSF homocysteine concentration is the most sensitive indicator of folate deficiency and inadequate CSF folate levels.
2. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Targeted Therapy

In GeneReviews, a targeted therapy is one that addresses the specific underlying mechanism of disease causation (regardless of whether the therapy is significantly efficacious for one or more manifestation of the genetic condition); would otherwise not be considered without knowledge of the underlying genetic cause of the condition; or could lead to a cure. —ED

The goal of treatment is to prevent, reverse, or mitigate hematologic, immunologic, and neurologic deficits and to optimize the cognitive development of children with this disorder. Complete reversal of the systemic consequences of folate deficiency is easily achieved. While correction of the neurologic consequences is more difficult, favorable neurologic outcomes are possible when adequate treatment is initiated promptly after birth

[Zhao et al 2017]. Severe neurologic and cognitive complications, including seizures, are invariably due to delay in diagnosis and implementation of treatment to achieve adequate CSF folate levels.

"Folates" refers to a family of B_9 vitamin compounds that are interconvertible in a series of biochemical reactions within cells. Folate can be effective when administered by oral or intramuscular routes. However, much higher oral than intramuscular doses are required to correct the systemic folate deficiency and very high doses are required to achieve adequate CSF folate levels. The intramuscular route is more effective in achieving age-appropriate CSF folate levels. In either case, achieving CSF folate levels in the normal range for the age of the affected individual is challenging [Torres et al 2015, Zhao et al 2017, Manea et al 2018].

Folate Formulations

Based on the current understanding of folate transport and metabolism, the following reduced folates can be used to treat HFM:

- 5-formyltetrahydrofolate (5-formylTHF), also known as folinic acid or leucovorin, is a racemic, stable form of this folate. Leucovorin is available in oral and intramuscular formulations. There is considerable experience in dosing with this folate form (see Folate Dosing). Only half of the dose of this racemic folate form is biologically active.
- The active, physiologic, isomer of 5-formylTHF is (6S)5-formylTHF (also known as Isovorin® or Fusilev®); it is available for intramuscular administration. The biologic impact of the active isomer is twice that of the racemic mixture when the dose is the same. This is the preferred form of folate if it is available and cost is not a limiting factor. The active isomer should be utilized especially when there is refractory neurologic disease.
- The physiologic folate predominant in blood and tissues, (6S)5-methyltetrahydrofolate or (6S)5-methylTHF, is available commercially as Metafolin® and Deplin®. Neither drug is available for intramuscular administration. Published information on the use of (6S)5-methylTHF for the treatment of HFM is not available, although the dosing should be comparable to that of (6S)5-formylTHF. The formulation of Metafolin® is too low (1,000-µg tablets) to make this agent feasible for the treatment of HFM. Deplin® is available as 15- and 30-mg tablets.

Note: If at all possible, folic acid should be avoided as a treatment of HFM (see Agents/Circumstances to Avoid).

Folate Dosing

Because HFM is rare, controlled studies to establish optimal treatment have not been possible. The oral dose of 5-formylTHF required to overcome the loss of the proton-coupled folate transporter (PCFT)-mediated intestinal folate absorption appears to vary among individuals. The dose required to obviate the neurologic consequences is much higher than that needed to correct the systemic folate deficiency. The dose should be guided by its effect on trough CSF folate concentrations. The endpoint is CSF folate concentrations as close as possible to the normal range for the affected individual's age.

- The reported oral dose of 5-formylTHF associated with a "good" outcome is approximately 150-200 mg daily [Geller et al 2002]. Much higher doses have been used as well [Author, personal communication]. A reasonable starting oral dose of 5-formylTHF in an infant could be 50 mg or 10-15 mg/kg given daily as a single dose, with subsequent dosing dependent on correction of the systemic signs of the disorder and achievement of an adequate CSF folate level.

  Note: Normal CSF folate is ~100 nmol/L for infants to age two years, decreasing to ~75 nmol/L by age five years and to ~65 nmol/L by age 19 years [Verbeek et al 2008].

- The intramuscular dose required to achieve adequate serum and CSF folate levels is much lower than the oral dose. With intramuscular injections of approximately 1 mg/day of 5-formylTHF, the anemia,

immunologic, and gastrointestinal manifestations will fully resolve. However, the endpoint for treatment is based on achieving an adequate CSF folate level to mitigate the neurologic consequences of HFM, which will require much higher folate doses. It would appear that the maximum achievable CSF folate levels are in the range of 40-50 nmol/L [Torres et al 2015, Zhao et al 2017, Aluri et al 2018, Manea et al 2018]. For instance, with a 5-formylTHF oral dose of 28 mg/kg/day versus a parenteral dose of 2 mg/kg/day (both racemic), the CSF folate levels were 16 nmol/L and 43 nmol/L, while the blood levels were ~800 nmol/L and ~2,000 nmol/L, respectively [Aluri et al 2018, Lubout et al 2020].

Supportive Care

Table 4. Hereditary Folate Malabsorption: Supportive Care

Manifestation/Concern	Treatment	Considerations/Other
Folate deficiency	Folate replacement therapy (See Targeted Therapy.)	Infants diagnosed before signs/symptoms appear should be treated immediately to prevent onset of folate deficiency & clinical manifestations.
Anemia/ Thrombocytopenia	Responds rapidly to folate replacement therapy w/hematopoietic response w/in a few days	• On very rare occasions when transfusion is required, administer blood products appropriate to the person's immunologic status (e.g., washed packed red blood cells in those w/IgA deficiency). • Bleeding complications from thrombocytopenia have not been reported.
Immunodeficiency	• Folate replacement therapy will rapidly correct immune deficiencies. • The most common infection, *Pneumocystis jirovecii* pneumonia, is treated w/trimethoprim-sulfamethoxazole.	Because of reports of onset of pneumocystis infection w/ initiation of folate therapy, prophylaxis w/trimethoprim-sulfamethoxazole has been used prior to folate treatment. [1]
Developmental delay / Intellectual disability	Developmental services & educational support as needed	
Seizures	ASM is administered when seizures occur; per neurologist recommendations.	Once seizures are well controlled & adequate CSF folate levels have been achieved, an attempt can be made to taper & discontinue ASM as guided by neurologist.

ASM = anti-seizure medication
1. Malatack et al [1999], Aluri et al [2018]

Surveillance

The following should be monitored periodically to assess the adequacy of treatment, and more frequently following initial diagnosis when treatment is being optimized.

Table 5. Recommended Surveillance for Individuals with Hereditary Folate Malabsorption

System/Concern	Evaluation	Frequency
Metabolic	• Serum folate concentrations • Trough CSF folate concentration [1] • CSF homocysteine concentrations [2]	• **Once remission is achieved:** monitor serum folate levels every 6 mos. • **Once reliable compliance is established:** monitor serum folate levels annually. • **Once folate dose necessary to achieve acceptable & stable CSF folate level is determined:** monitor CSF folate as needed based upon neurologic status (see **Neurologic** in this table) or every 1-2 yrs.

Table 5. continued from previous page.

System/Concern	Evaluation	Frequency
Hematologic	CBC	• **Once remission is achieved:** monitor CBC every 6 mos. • **Once reliable compliance is established:** monitor CBC annually.
Immunologic	Serum immunoglobulin concentrations	Once immunoglobulin levels are corrected, no need to monitor unless there is compliance issue or suggestive infection.
Neurologic	Neurologic & developmental assessment incl cognitive function	• Close follow up w/neurologist most frequently during infancy, then childhood, & into adolescence • Changes in neurologic status may warrant re-evaluating CSF folate level.

CBC = complete blood count; CSF = cerebrospinal fluid
1. Monitoring of the trough CSF folate concentration is critical to assure that the dose of folate is sufficient to achieve CSF folate concentrations as close to normal as possible for the affected individual's age.
2. A high CSF homocysteine concentration is the most sensitive indicator of folate deficiency and low CSF folate levels.

Agents/Circumstances to Avoid

If possible, folic acid should be avoided as a treatment for HFM. Although folic acid is very stable and inexpensive, and is the most common pharmacologic source of folate, it is not a physiologic folate. Folic acid binds very tightly to folate receptors, which transport the physiologic folate, 5-methylTHF, into cells by an endocytic mechanism [Kamen & Smith 2004]. Thus, folic acid may interfere with the interaction between 5-methylTHF and folate receptors required for 5-methylTHF transport across the choroid plexus into the CSF [Grapp et al 2013, Zhao et al 2017]. As indicated above, when the administration of the active (6S) isomer of 5-formylTHF is feasible, it is the preferred form of folate, because unlike the racemic form the entire, versus half, of the dose is effective. Also, the inactive isomer may interfere/compete with transport of the active isomer into cells and its subsequent polyglutamation.

Evaluation of Relatives at Risk

It is appropriate to evaluate newborn sibs and apparently asymptomatic younger sibs of a proband to identify as early as possible those who would benefit from prompt initiation of treatment and preventive measures. Early treatment will prevent or fully reverse the hematologic, immunologic, and gastrointestinal complications of HFM. Achievement of adequate CSF folate levels can prevent or mitigate the neurologic consequences of HFM and optimize the cognitive development of children with this disorder.

Prenatal testing of a fetus at risk. When the *SLC46A1* pathogenic variants in the family are known, prenatal testing of fetuses at risk may be performed via amniocentesis or chorionic villus sampling to allow for institution of 5-formylTHF treatment at birth.

Newborn sibs and apparently asymptomatic younger sibs

- If the pathogenic variants in the family are known, molecular genetic testing of younger at-risk sibs who have not undergone prenatal testing should be performed immediately after birth. Those with biallelic *SLC46A1* pathogenic variants should be treated with 5-formylTHF immediately.
- If the pathogenic variants in the family are not known and genetic testing is not possible, assessment of serum and CSF folate levels and, if warranted, intestinal absorption of folate in at-risk sibs should commence immediately after birth, or as soon as the diagnosis is confirmed in the proband.

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

Pregnancy Management

There is no systematic information on the outcome of pregnancy in women with HFM.

Although PCFT is highly expressed in the placenta [Qiu et al 2006], a woman with *SLC46A1* homozygous nonsense variants that resulted in no PCFT had two normal pregnancies and delivered two healthy infants. The affected woman's intramuscular 5-formylTHF dose was increased when pregnancy was planned [Poncz et al 1981; Poncz & Cohen 1996; Min et al 2008; M Poncz, personal communication].

Women with HFM who wish to become pregnant should increase their dose of 5-formylTHF intake above the maintenance dose well in advance of attempting to conceive. Prenatal vitamins are available containing 5-methylTHF rather than folic acid.

Of note, infants with HFM do not appear to be at an increased risk for malformations (e.g., neural tube defects) typically associated with maternal folate deficiency during pregnancy, assuming that maternal folate intake has been increased well before attempting conception.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe 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.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of 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; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

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

Risk to Family Members

Parents of a proband

- The parents of an affected child are presumed to be heterozygous for an *SLC46A1* pathogenic variant. Note: At least one fertile woman with biallelic pathogenic variants in *SLC46A1* treated with an intramuscular drug soon after birth had no discernable phenotype (see Pregnancy Management).
- If a molecular diagnosis has been established in the proband, molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for an *SLC46A1* pathogenic variant and to allow reliable recurrence risk assessment. If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - One of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017].
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant resulted in homozygosity for the pathogenic variant in the proband.

- Heterozygotes (carriers) are asymptomatic and do not have clinically apparent evidence of folate deficiency. It is unclear at this time whether heterozygotes may have a mild decrease in serum folate and hemoglobin.

Sibs of a proband

- If both parents are known to be heterozygous for an *SLC46A1* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of inheriting neither of the familial *SLC46A1* pathogenic variants.
- Heterozygotes (carriers) are asymptomatic and do not have clinically apparent evidence of folate deficiency. It is unclear at this time whether heterozygotes may have a mild decrease in serum folate and hemoglobin.

Offspring of a proband. Unless an affected individual's reproductive partner also has HFM or is a carrier, offspring will be obligate heterozygotes (carriers) for a pathogenic variant in *SLC46A1*.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an *SLC46A1* pathogenic variant.

Carrier Detection

Carrier testing of at-risk relatives requires prior identification of the *SLC46A*1 pathogenic variants in the family.

Related Genetic Counseling Issues

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

Family planning

- Women with HFM who wish to become pregnant should increase their dose of 5-formylTHF intake above the maintenance dose well in advance of attempting to conceive (see Pregnancy Management).
- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the *SLC46A1* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing for HFM are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **MedlinePlus**
  Hereditary folate malabsorption
- **Metabolic Support UK**
  United Kingdom
  Phone: 0845 241 2173
  www.metabolicsupportuk.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Hereditary Folate Malabsorption: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
SLC46A1	17q11.2	Proton-coupled folate transporter	SLC46A1 database	SLC46A1	SLC46A1

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Hereditary Folate Malabsorption (View All in OMIM)

229050	FOLATE MALABSORPTION, HEREDITARY
611672	SOLUTE CARRIER FAMILY 46 (FOLATE TRANSPORTER), MEMBER 1; SLC46A1

Molecular Pathogenesis

SLC46A1 encodes the proton-coupled folate transporter (PCFT) protein, a member of the superfamily of solute carriers. PCFT is highly expressed at the apical membrane of the proximal jejunum and duodenum and is required for intestinal folate absorption. PCFT and folate receptor alpha are expressed in the choroid plexus, and both appear to be required for transport of folates into the CSF [Qiu et al 2006, Zhao et al 2011, Grapp et al 2012, Grapp et al 2013, Visentin et al 2014, Zhao et al 2017].

Hydropathy analysis by the substituted cysteine accessibility model predicted a protein with twelve transmembrane domains [Qiu et al 2006, Qiu et al 2007, Zhao et al 2010, Duddempudi et al 2013, Date et al 2016], now confirmed by a cryo-electron microscopy structure of mammalian PCFT [Parker et al 2021]. PCFT has high affinity for folic acid, reduced folates, and anti-folates and has a low pH optimum [Qiu et al 2006, Zhao et al 2017].

Single-nucleotide variants within transmembrane domains, causing amino acid substitutions, result in unstable proteins, proteins with markedly impaired function, or complete loss of protein. Some of the mutated proteins trafficked to the cell membrane and some did not. Three mutated isoforms had residual transport activity upon transfection into HeLa cells null for constitutive folate-specific transporters [Mahadeo et al 2010, Zhao et al 2017, Aluri et al 2018]. Pathogenic variants identified in individuals with HFM have informed understanding of the relationship between the structure and function of PCFT. For instance, variant p.Asn411Lys is located in the

external gate that controls entry of folates into the transport channel [Aluri et al 2018]. Variant p.Phe392Val affects a residue of the transport protein required for the opening of the external gate to allow folates into the transport channel [Zhan et al 2020].

Mechanism of disease causation. Loss of transport function

***SLC46A1*-specific laboratory technical considerations**. One reported variant was a deep intron 3 single-nucleotide variant (c.1166-284T>G) that generated a cryptic splice donor site resulting in a 168-bp insertion [Kishimoto et al 2014, Tozawa et al 2019]. A variant found in individuals with HFM of Puerto Rican ancestry occurs at the splice acceptor site of intron 2, resulting in the deletion of exon 3 [Mahadeo et al 2011, Zhao et al 2017]. Sequencing methodologies that can detect such variants should be considered.

Table 6. Notable *SLC46A1* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_080669.6	c.1082-1G>A	--	Reported in 10 apparently unrelated families of Puerto Rican ancestry [Zhao et al 2017]. Additional Puerto Rican families w/this variant are known to the author.
	c.1166-284T>G	--	Possible founder variant in persons of Japanese ancestry [Kishimoto et al 2014, Tozawa et al 2019]
NM_080669.6 NP_542400.2	c.1233C>G	p.Asn411Lys	See Molecular Pathogenesis.
	c.1174T>G	p.Phe392Val	

Variants listed in the table have been provided by the author. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Chapter Notes

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