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FOLR1-Related Cerebral Folate Transport Deficiency

Synonyms: Folate Receptor-Alpha Deficiency, FOLR1 Deficiency, FOLRα Deficiency, FRα Deficiency

I David Goldman, MD[1]

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Summary

Clinical characteristics

FOLR1-related cerebral folate transport deficiency (*FOLR1*-CFTD), resulting from loss of function of the folate receptor alpha (FOLR1) protein, causes cerebral folate deficiency in the absence of systemic folate deficiency. Individuals with untreated *FOLR1*-CFTD have very low cerebrospinal fluid (CSF) levels and progressive neurologic deterioration with developmental delays and progressive cognitive impairment, behavioral issues, seizures, and movement disorders that may progress to immobility. Despite these incapacitating neurologic findings, untreated individuals can live well into adulthood.

Treatment with 5-formyltetrahydrofolate (5-formylTHF; also known as folinic acid or leucovorin) can result in substantial improvement in neurologic findings when started at a young age. Treatment of asymptomatic or mildly symptomatic younger sibs at the time of diagnosis of their older sibs can either prevent the neurologic signs of this disorder or result in marked or complete regression of the neurologic findings.

Diagnosis/testing

The diagnosis of *FOLR1*-CFTD is established in a proband with biallelic *FOLR1* pathogenic variants identified by molecular genetic testing.

Management

Targeted therapy: Treatment with 5-formylTHF can bring CSF folate levels into the normal range for the age of the individual. While oral administration is often sufficient, intramuscular administration may be necessary. Monitoring CSF folate levels is essential to ensure that the dose of 5-formylTHF is sufficient, particularly when the clinical response is inadequate or there is uncertainty about adherence.

Supportive care: Neurologic manifestations of untreated *FOLR1*-CFTD are treated per standard practice.

Author Affiliation: 1 Departments of Medicine and Molecular Pharmacology, Albert Einstein College of Medicine, Bronx, New York; Email: i.david.goldman@einsteinmed.edu.

Surveillance: For those being treated with 5-formylTHF, the following is recommended for monitoring CSF folate levels, taking into consideration the complexity of lumbar puncture, particularly in infants and children: baseline CSF folate level obtained at the time of diagnosis; once treatment has begun, repeat CSF folate levels obtained to confirm that an adequate therapeutic dose and optimal clinical outcome has been achieved; repeat CSF folate levels if there are changes in the individual's clinical status (e.g., developmental delays or regression, new-onset neurologic findings, seizures) or if there are concerns regarding adherence; optimally and if feasible, yearly CSF folate levels until age five years.

Agents/circumstances to avoid: Folic acid is not used to treat *FOLR1*-CFTD because folic acid binds tightly to FOLR1, possibly interfering with FOLR1 function, which is a concern when treating individuals who have residual FOLR1 activity.

Evaluation of relatives at risk: Clarification of the genetic status of all sibs of a proband is recommended to identify as early as possible those sibs who would benefit from prompt initiation of treatment with 5-formylTHF. Newborns at risk should be evaluated for the familial *FOLR1* pathogenic variants if molecular genetic testing was not performed prenatally.

Genetic counseling

FOLR1-CFTD is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for an *FOLR1* 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 being unaffected and not a carrier. If both pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives, prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing for *FOLR1*-CFTD are possible.

Diagnosis

Suggestive Findings

FOLR1-related cerebral folate transport deficiency (*FOLR1*-CFTD) **should be considered in a proband** with the following clinical, laboratory, and imaging findings and family history.

Clinical findings. Although frank signs of *FOLR1*-CFTD have generally been reported to occur after age one year, the recognition of subtle signs as early as possible in an infant / young child can facilitate early diagnosis and treatment, thereby substantially improving outcome.

- **Subtle early signs evident during the first year of life**
  - Developmental delays, particularly in cognition, speech, and gait
- **Signs that typically develop after age one year**
  - Developmental delays in motor, cognitive, speech, and language
  - Movement disorders, including ocular (nystagmus, strabismus), hypotonia, abnormalities of gait, ataxia, tremors, and myoclonic jerks
  - Seizures, typically myoclonic or tonic. Can be severe with status epilepticus. Initial seizures may be associated with fever.
  - Behavior issues that can include autistic spectrum disorder

Supportive laboratory findings

- Very low concentration of cerebral spinal fluid (CSF) 5-methyltetrahydrofolate (5-methylTHF) (typically ≤10 nmol/L [Pope et al 2019]

- Normal plasma and red blood cell folate levels, indicating the absence of folate deficiency due to inadequate dietary intake or impaired intestinal absorption

Imaging findings. Brain MRI shows nonspecific hyperintensity changes in the white matter indicative of diffuse hypomyelination and atrophy in the cerebral and cerebellar regions. Brain calcifications have been reported [Mafi et al 2020, Gowda et al 2021].

Family history is consistent with autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of *FOLR1*-CFTD **is established** in a proband with suggestive findings and biallelic pathogenic (or likely pathogenic) variants in *FOLR1* identified by 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 variant" in this *GeneReview* is understood to include likely pathogenic variants. (2) Identification of biallelic *FOLR1* variants of uncertain significance (or of one known *FOLR1* pathogenic variant and one *FOLR1* variant of uncertain significance) does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing). Gene-targeted testing requires that the clinician determine which gene(s) are likely involved (see Option 1), whereas comprehensive genomic testing does not (see Option 2).

Note: Single-gene testing (sequence analysis of *FOLR1*, followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended.

Option 1

A neurodevelopment disorders, neurometabolic, or seizure multigene panel that includes *FOLR1* and other genes of interest (see Differential Diagnosis) may be considered to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

Comprehensive genomic testing. Exome sequencing is most commonly used; genome sequencing is also possible. Note: Unlike exome sequencing, genome sequencing can identify variants outside of the coding region. Although the majority of *FOLR1* pathogenic variants reported to date (e.g., missense, nonsense) are within the coding region, an intronic pathogenic variant has been detected in *FOLR1* [Gowda et al 2021].

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in *FOLR1*-Related Cerebral Folate Transport Deficiency

Gene [1]	Method	Proportion of Pathogenic Variants [2] Identified by Method
FOLR1	Sequence analysis [3]	~99% [4]
	Gene-targeted deletion/duplication analysis [5]	~1% (rare) [4, 6]

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. Pope et al [2019] and data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
5. 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. While exome and genome sequencing may be able to detect deletions/duplications using breakpoint detection or read depth, sensitivity can be lower using these methods than using gene-targeted deletion/duplication analysis.
6. One intronic variant outside of the exon and the consensus splice junction typically identified by standard sequencing has been reported [Gowda et al 2021].

Clinical Characteristics

Clinical Description

FOLR1-related cerebral folate transport deficiency (*FOLR1*-CFTD) results from loss of function of the folate receptor alpha (FOLR1) protein. This impairs folate transport into the cerebrospinal fluid (CSF), which results in neural folate deficiency in the absence of systemic folate deficiency. This rare autosomal recessive disorder was first described by Steinfeld et al [2009]. To date, a total of 35 individuals from 21 families have been reported [Cario et al 2009, Steinfeld et al 2009, Pérez-Dueñas et al 2010, Dill et al 2011, Grapp et al 2012, Ohba et al 2013, Al-Baradie & Chaudhary 2014, Toelle et al 2014, Ferreira et al 2015, Delmelle et al 2016, Kobayashi et al 2017, Tabassum et al 2019, Mafi et al 2020, Zhang et al 2020, Brunetti et al 2021, Gowda et al 2021, Papadopoulou et al 2021, Almahmoud et al 2023, Kanmaz et al 2023]. These reports were comprehensively reviewed by Pope et al [2019] and recently updated by Potic et al [2023]. The following descriptions are based on these reports.

Individuals with untreated *FOLR1*-CFTD have progressive neurologic deterioration with developmental delays and progressive cognitive impairment, behavioral issues, seizures, and movement disorders that can progress to severe immobility. In contrast, children treated from a young age with 5-formyltetrahydrofolate (5-formylTHF; also known as folinic acid or leucovorin) can have substantial improvement. In particular, treatment of asymptomatic or mildly symptomatic younger individuals from the time when their sibs are diagnosed with *FOLR1*-CFTD can result in the prevention or complete regression of the signs of this disorder.

Untreated Individuals

Reports describe the consequences of untreated *FOLR1*-CFTD in older individuals – some in their teens or into their 30s – when the profound neurologic damage is well established and essentially irreversible (see Table 2).

Table 2. *FOLR1*-Related Cerebral Folate Transport Deficiency: Frequency of Select Features in Untreated Individuals

Signs	% of Persons w/Feature	Comment
Developmental delay / intellectual disability	Universal finding	Subtle changes may occur in the 1st year of life
Cognitive impairment	≥90%	

Table 2. continued from previous page.

Signs	% of Persons w/Feature	Comment
Behavior issues	≥90%	
Movement disorders	≥90%	
Seizures	≥90%	
Speech impairment	≥65%	Also language impairment; likely underreported
Changes of hypomyelination on MRI	≥90%	

The early clinical signs in untreated children with *FOLR1*-CFTD are subtle. Initially, there are developmental delays, particularly in cognition, speech, and gait. Early onset of unilateral strabismus [Brunetti et al 2021] or nystagmus [Steinfeld et al 2009] has been reported.

In a child who has not been treated with 5-formylTHF, neurologic findings worsen over time, resulting in developmental regression and onset of ataxia, tremors, and hypotonia. Subsequently, untreated children have severe cognitive decline, become increasingly immobile, and develop seizures that are difficult to treat with conventional anti-seizure medications. In addition to these findings, "drop" attacks provoked by specific movements (e.g., washing face or hands) have been reported [Al-Baradie & Chaudhary 2014, Toelle et al 2014].

Despite these incapacitating severe neurologic findings, untreated individuals can live well into adulthood.

Following initiation of treatment with 5-formylTHF (see Management, Targeted Therapy), neurologic findings can improve to varying degrees. However, responses to 5-formylTHF can be subjective, anecdotal, and inconsistently documented. When neurologic findings are long-standing, seizures may decrease in frequency but rarely cease completely. The clinical course of 23 individuals with this disorder was reviewed in Pope et al [2019] and recently updated to encompass 33 individuals in Potic et al [2023]. Two additional affected sibs were subsequently reported in Almahmoud et al [2023].

Treated Individuals

Although limited, data are available regarding younger sibs who were diagnosed with *FOLR1*-CFTD when signs of the disorder were minimal or had not yet developed. In these individuals, early treatment with 5-formylTHF substantially improved, completely reversed, or prevented all clinical manifestations of *FOLR1*-CFTD [Cario et al 2009, Steinfeld et al 2009, Pope et al 2019, Potic et al 2023].

Genotype-Phenotype Correlations

No genotype-phenotype correlations are known.

Although there is a spectrum of clinical presentations and severity associated with *FOLR1*-CFTD, only two reports provided data on the functional consequences of five *FOLR1* pathogenic variants evaluated in expressed proteins [Steinfeld et al 2009, Grapp et al 2012]. Hence, comprehensive data that permit correlation among genotype, transport function, and clinical phenotype are not available.

Nomenclature

Cerebral folate deficiency is a generic term describing a condition in which there is a reduction in the concentration of folate in the CSF with otherwise normal folate homeostasis. The term "*FOLR1*-related cerebral folate transport deficiency" refers specifically to cerebral folate deficiency without systemic folate deficiency caused by loss of function of FOLR1. Isolated deficiency of CSF folate can be associated with a variety of disorders, some inherited, some acquired.

Prevalence

FOLR1-CFTD has been detected in individuals worldwide [Pope et al 2019, Potic et al 2023]. *FOLR1*-CFTD is rare, with only 35 individuals from 21 families with a confirmed diagnosis reported to date (see Clinical Description). Most of these individuals are born to consanguineous parents.

It is likely that the prevalence is greater than currently appreciated given the nonspecific signs and symptoms of untreated *FOLR1*-CFTD and the prevalence of *FOLR1*-CFTD in consanguineous families from populations with limited access to molecular genetic testing.

To date only five families have been reported in which affected individuals were compound heterozygous for *FOLR1* pathogenic variants. While the majority of *FOLR1* pathogenic variants have been "private," the following have been reported in more than one individual:

- Five Finnish individuals were reported with the same c.506G>A (p.Cys169Tyr) pathogenic variant; four were homozygous and the fifth was compound heterozygous, with the second pathogenic variant being c.665A>G (p.Asn222Ser) [Grapp et al 2012], which was also reported in an individual from Saudi Arabia [Tabassum et al 2019]. An individual from Belgium was reported to be homozygous for the latter variant as well [Kanmaz et al 2023].
- Two individuals from different cities in Germany were reported with the same compound heterozygous pathogenic variants, c.525C>A (p.Cys175Ter) and c.352C>T (p.Gln118Ter) [Cario et al 2009, Steinfeld et al 2009].
- Individuals from Turkey [Dill et al 2011] and Ghana [Toelle et al 2014] were reported to be homozygous for the same pathogenic variant, c.610C>T (p.Arg204Ter).

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *FOLR1*.

Differential Diagnosis

FOLR1-related cerebral folate transport deficiency (*FOLR1*-CFTD) is one of several causes of folate deficiency restricted to the central nervous system characterized by very low levels of cerebrospinal fluid (CSF) folate in the absence of clinically significant systemic folate deficiency. The differential diagnosis encompasses inherited disorders that impair either folate transport across the blood-choroid plexus-CSF barrier or folate metabolism in the brain, as well as cerebral folate deficiency associated with antibodies to the folate receptor alpha (FOLR1) protein.

Recent reviews that include a comprehensive description of the differential diagnosis of cerebral folate deficiency are Pope et al [2019] and Ramaekers & Quadros [2022].

Disorders due to inactivation of folate transporters at the choroid plexus. Two inherited disorders are due to defects that directly affect transporters that mediate the translocation of folates across the blood-choroid plexus-CSF barrier [Qiu et al 2006, Steinfeld et al 2009, Grapp et al 2013, Zhao et al 2017]. These include:

- Loss of function of the proton-coupled folate transporter (PCFT) protein (encoded by *SLC46A1*), in which there are defects in both intestinal folate absorption (with systemic folate deficiency) and folate transport into the CSF resulting in hereditary folate malabsorption (see Table 3);
- Loss of function of FOLR1 (encoded by *FOLR1*), which results in cerebral folate deficiency without systemic folate deficiency and is the cause of *FOLR1*-CFTD (the topic of this *GeneReview*).

Disorders that impair blood-CSF transport at the choroid plexus secondary to mitochondrial dysfunction, presumably due to alterations in energy metabolism. These disorders include Kearns-Sayre syndrome (a mitochondrial DNA [mtDNA] deletion syndrome), complex I-V deficiencies (nuclear DNA disorders of the mitochondrial respiratory chain; see Primary Mitochondrial Disorders Overview), and Alpers-Huttenlocher syndrome (a mtDNA depletion syndrome; see *POLG*-Related Disorders). In these disorders, which have characteristic neurologic signs and symptoms, CSF folate levels are variably reduced but may be normal [Pope et al 2019, Ramaekers & Quadros 2022].

Hereditary disorders of folate metabolism. A variety of hereditary disorders of folate metabolism without systemic folate deficiency can result in developmental delay / intellectual disability, seizures, and other neurologic signs accompanied by cerebral and cerebellar hypomyelination and atrophy (see Table 3).

FOLR1 auto-antibodies interfere with FOLR1 function and should be considered in infants with developmental delay / intellectual disability, progressive irritability, sleep disturbances, psychomotor retardation, and ataxia. Auto-antibodies can also accompany other disorders that affect choroid plexus function. CSF folate levels are variably, and usually only modestly, reduced [Ramaekers & Quadros 2022].

Table 3. Hereditary Disorders in the Differential Diagnosis of *FOLR1*-Related Cerebral Folate Transport Deficiency

Gene(s)	Disorder	MOI	CSF Folate	Key Feature(s)	Comment
DHFR	Dihydrofolate reductase deficiency (OMIM 613839)	AR	<10 nmol/L	Onset w/in a few months after birth w/DD, usually macrocytic anemia, pancytopenia, & neurodegeneration of varying intensity [1]	• No response to folic acid • Corrects w/5-formylTHF • Can occur w/isolated macrocytosis w/o anemia [1, 2]
MTHFR	Methylenetetrahydrofolate reductase deficiency (OMIM 236250)	AR	<10 nmol/L	Neurocognitive & motor impairment, DD w/seizures; clinical phenotype correlates w/extent of residual enzyme activity	• Defect in remethylation of homocysteine to methionine • Plasma folate is low but not accompanied by anemia. [3] • Treated w/betaine
MTHFS	5,10-methenyltetrahydrofolate synthetase deficiency (OMIM 618367)	AR	Low to normal	Neurodevelopmental disorder w/microcephaly & seizures	• Defect in 5-formylTHF metabolism [4] • Treated w/5-methylTHF
SLC46A1 [5]	Hereditary folate malabsorption	AR	<10 nmol/L	Folate deficiency resulting in anemia, pancytopenia, & immune deficiency w/DD leading to neurocognitive & motor impairment & seizures	Modest doses of parenteral folate will correct anemia & other systemic manifestations, but if that is inadequate to correct CSF folate levels, neural manifestations will progress & become irreversible.

5-formylTHF = 5-formyltetrahydrofolate; 5-methylTHF = 5-methyltetrahydrofolate; AR = autosomal recessive; CSF = cerebral spinal fluid; DD = developmental delay; MOI = mode of inheritance

1. Banka et al [2011]
2. Cario et al [2011]
3. Huemer et al [2016]
4. Rodan et al [2018]
5. *SLC46A1* encodes the proton-coupled folate transporter (PCFT) protein.

Management

There are no established clinical practice guidelines for *FOLR1*-related cerebral folate transport deficiency (*FOLR1*-CFTD).

Evaluations Following Initial Diagnosis

To establish the extent of the disorder and needs in an individual diagnosed with previously untreated *FOLR1*-CFTD, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. *FOLR1*-Related Cerebral Folate Transport Deficiency: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Neurologic	Neurologic eval	• Eval of seizures: type, frequency • Assessment of gait • Assessment for hypotonia, tremor, strabismus, nystagmus
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / special education
Intellectual disability	Age-related cognitive testing	
Behavior issues	By pediatrician or mental health professional	For persons age >12 mos: screening for behavior concerns incl sleep disturbances
Musculoskeletal/ADL	Orthopedics / physical medicine & rehab / PT & OT eval	To incl assessment of: • Gross motor & fine motor skills • Mobility, ADL, & need for adaptive devices • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of *FOLR1*-CFTD 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.	May be helpful for the families of persons w/neurologic impairment resulting from untreated *FOLR1*-CFTD

ADL = activities of daily living; *FOLR1*-CFTD = *FOLR1*-related cerebral folate transport deficiency; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy

1. 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

5-formyltetrahydrofolate (5-formylTHF; also known as folinic acid or leucovorin) therapy. The objective of 5-formylTHF therapy is to bring the cerebrospinal fluid (CSF) folate concentration into the normal range for the age of the affected individual [Verbeek et al 2008], usually achieved with oral administration (see Table 5). Note that monitoring CSF folate levels is essential to ensure that the dose of 5-formylTHF is sufficient, particularly when there is an inadequate clinical response (see Surveillance).

In symptomatic individuals, movement disorders, behavior issues, and developmental delay / intellectual disability may improve with 5-formylTHF treatment depending on the age of the individual and severity of the neurologic deficits. Rarely, seizures may cease completely with 5-formylTHF treatment. Clinical improvement has been reported to be accompanied by improvement in MRI findings [Delmelle et al 2016, Potic et al 2023].

Symptomatic children treated with 5-formylTHF from a young age can have substantial improvement in their neurologic findings. In particular, treatment of asymptomatic or mildly symptomatic younger sibs at the time of diagnosis of their older sibs can either prevent or completely resolve the neurologic signs of *FOLR1*-CFTD.

While there are no established guidelines for the treatment of *FOLR1*-CFTD, there is experience in treatment and outcomes in individuals with specific transport defects at the choroid plexus due to impaired FOLR1 or proton-coupled folate transporter (PCFT) function (see Hereditary Folate Malabsorption, Folate Formulations). The treatment to date for which there is substantial clinical experience is 5-formylTHF; leucovorin and folinic acid are racemic, consisting of equal proportions of the active and inactive isomers. Levoleucovorin is a formulation of 5-formylTHF comprised solely of the active isomer that is the substrate for folate transporters and folate-dependent enzymatic reactions. It is the preferred folate for parenteral administration but is not available for oral administration.

5-methyltetrahydrofolate (5-methylTHF) is the major physiologic folate found in blood. It is available as the active isomer in appropriate oral formulations; it is not available in parenteral formulations. It is administered orally at one half the racemic 5-formylTHF dose; however, there is no reported clinical experience using this folate in the treatment of *FOLR1*-CFTD or hereditary folate malabsorption.

Clinical observations suggest that normal and supranormal CSF folate levels are more readily achieved with *FOLR1*-CFTD than with PCFT deficiency (i.e., hereditary folate malabsorption) [Torres et al 2015, Delmelle et al 2016, Kobayashi et al 2017, Aluri et al 2018, Lubout et al 2020].

Table 5. *FOLR1*-Related Cerebral Folate Transport Deficiency: Targeted Therapy

5-formylTHF Therapy		Comment
Administration	Dose	
Oral	Starting dose 2.5-5 mg/kg/day w/ close monitoring of CSF folate levels, increasing dose as necessary	Oral administration is usually sufficient to bring CSF folate levels into the normal range for age. Monitoring CSF folate is essential to ensure that the dose of 5-formylTHF is sufficient, particularly when the clinical response is inadequate or there is a change in clinical status.
Intramuscular	Up to 40-50 mg/day [1]	This mode of administration & dose should be sufficient for therapeutic eval in persons w/*FOLR1*-CFTD who have an inadequate response to oral administration. (Note: There is substantial experience in intramuscular dosing in hereditary folate malabsorption.)

Table 5. continued from previous page.

5-formylTHF Therapy		Comment
Administration	Dose	
Intravenous	Variable [2]	5-formylTHF has been administered intravenously periodically in some persons when the clinical response to oral 5-formylTHF was poor despite achieving CSF levels in the normal range. There have been anecdotal reports that this may result in some clinical improvement. [2] There is no evidence that intravenous administration of 5-formylTHF is superior to intramuscular administration in *FOLR1*-CFTD.

5-formylTHF = 5-formyltetrahydrofolate; CSF = cerebrospinal fluid; *FOLR1*-CFTD = *FOLR1*-related cerebral folate transport deficiency
1. Torres et al [2015], Aluri et al [2018], Lubout et al [2020]
2. Toelle et al [2014], Delmelle et al [2016], Ferreira et al [2015]

Not recommended. Folic acid is not recommended to treat *FOLR1*-CFTD because this folate binds tightly to FOLR1, possibly interfering with its function [Zhao et al 2017, Akiyama et al 2022]. While this would not necessarily be relevant to *FOLR1* pathogenic variants that result in a complete loss of FOLR1 function, it would be undesirable when there is a low but important residual level of FOLR1 transport activity.

Supportive Care

Supportive care to improve quality of life, maximize function, and reduce complications is recommended. Treatment for the neurologic findings (including multidisciplinary care by specialists) as outlined in Table 6 is per standard practice.

Table 6. *FOLR1*-Related Cerebral Folate Transport Deficiency: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Seizures	• Standardized treatment with ASMs by experienced neurologists • 5-formylTHF is essential & generally decreases frequency of seizures. In some persons, ASMs can be discontinued when optimal 5-formylTHF dose is achieved (see Table 5).	• Many ASMs may be effective; none has been demonstrated effective specifically for this disorder. • CSF folate levels must be monitored closely to ensure that age-relevant physiologic levels are achieved w/5-formylTHF treatment & that there is reliable ongoing adherence. • Education of parents/caregivers [1]
Movement disorders	Assistance of specialists in physical medicine & rehab &/or PT is advised.	Monitor the CSF folate level as necessary to ensure that therapeutic CSF folate levels are sustained, & an optimal therapeutic outcome has been achieved. [1]
Behavior issues	Assistance of psychosocial support is advisable.	
Developmental delay / Intellectual disability	See Developmental Delay / Intellectual Disability Management Issues.	
Family/Community	• Ensure appropriate social work involvement to connect families w/local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	Consider involvement in adaptive sports or Special Olympics.

5-formylTHF = 5-formyltetrahydrofolate; ASM = anti-seizure medication; CSF = cerebrospinal fluid; OT = occupational therapy; PT = physical therapy
1. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.
  - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
  - Vision consultants should be a part of the child's IEP team to support access to academic material.
  - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
  - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Motor Dysfunction

Gross motor dysfunction

- Physical therapy is recommended to maximize mobility and to reduce the risk for later-onset orthopedic complications (e.g., contractures, scoliosis, hip dislocation).
- Consider use of durable medical equipment and positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).

- For muscle tone abnormalities including hypertonia or dystonia, consider involving appropriate specialists to aid in management of baclofen, tizanidine, Botox®, anti-parkinsonian medications, or orthopedic procedures.

Fine motor dysfunction. Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as feeding, grooming, dressing, and writing.

Oral motor dysfunction should be assessed at each visit and clinical feeding evaluations and/or radiographic swallowing studies should be obtained for choking/gagging during feeds, poor weight gain, frequent respiratory illnesses, or feeding refusal that is not otherwise explained. Assuming that the child is safe to eat by mouth, feeding therapy (typically from an occupational or speech therapist) is recommended to help improve coordination or sensory-related feeding issues. Feeds can be thickened or chilled for safety. When feeding dysfunction is severe, an NG-tube or G-tube may be necessary.

Communication issues. Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals who have expressive language difficulties. An AAC evaluation can be completed by a speech-language pathologist who has expertise in the area. The evaluation will consider cognitive abilities and sensory impairments to determine the most appropriate form of communication. AAC devices can range from low-tech, such as picture exchange communication, to high-tech, such as voice-generating devices. Contrary to popular belief, AAC devices do not hinder verbal development of speech, but rather support optimal speech and language development.

Neurobehavioral/Psychiatric Concerns

Children may qualify for and benefit from interventions used in treatment of autism spectrum disorder, including applied behavior analysis (ABA). ABA therapy is targeted to the individual child's behavioral, social, and adaptive strengths and weaknesses and typically performed one on one with a board-certified behavior analyst.

Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavior management strategies or providing prescription medications, such as medication used to treat attention-deficit/hyperactivity disorder, when necessary.

Concerns about serious aggressive or destructive behavior can be addressed by a pediatric psychiatrist.

Surveillance

To monitor existing manifestations, the response to 5-formylTHF targeted therapy and supportive care, and the emergence of new manifestations, the evaluations summarized in this section are recommended.

For affected individuals who are being treated with 5-formylTHF, in the absence of published guidelines, the following schedule for monitoring CSF folate levels is recommended:

- A baseline CSF folate level should be obtained at the time of diagnosis.
- Once treatment is begun, repeat CSF folate levels should be obtained after two to three weeks to confirm that an adequate therapeutic dose has been achieved, thereby optimizing the clinical outcome.
- CSF folate levels should be repeated if there are changes in the individual's clinical status (e.g., developmental delays or regression, new-onset neurologic findings, seizures) or if there are concerns regarding adherence.
- Optimally and if feasible, a CSF folate level should be obtained yearly to age five years.

Table 7. *FOLR1*-Related Cerebral Folate Transport Deficiency: Recommended Surveillance

System/Concern	Evaluation	Frequency
Neurologic	• Monitor for new- onset or changes in seizure type & frequency. • Assess for other manifestations such as changes in gait, ataxia, tremor, & other movement disorders.	Per treating neurologist
Developmental delay / Intellectual disability	Monitor developmental progress, cognition, & educational needs.	Every 6 mos to age 5; yearly thereafter
Behavior issues	Psychological assessment	

Agents/Circumstances to Avoid

Folic acid is not used to treat *FOLR1*-CFTD because folic acid binds tightly to FOLR1, possibly interfering with its function (see Hereditary Folate Malabsorption) [Zhao et al 2017, Akiyama et al 2022]. While this would not be relevant when there is a complete loss of FOLR1 function, it would be undesirable when there is low but important residual FOLR1 activity.

Evaluation of Relatives at Risk

Clarification of the genetic status of all sibs of a proband is recommended in order to identify as early as possible those who inherited biallelic *FOLR1* pathogenic variants and would benefit from prompt initiation of treatment with 5-formylTHF. Early treatment may prevent or fully reverse the manifestations of *FOLR1*-CFTD, whereas late diagnosis and delayed treatment can result in irreversible neurologic changes. Newborns at risk should be evaluated for the familial *FOLR1* pathogenic variants if molecular genetic testing was not performed prenatally.

Prenatal testing of a fetus at risk. Prenatal testing for the familial *FOLR1* pathogenic variants may be performed via amniocentesis or chorionic villus sampling to allow for institution of 5-formylTHF treatment at birth in infants known to have biallelic *FOLR1* pathogenic variants.

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

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

FOLR1-related cerebral folate transport deficiency (*FOLR1*-CFTD) 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 *FOLR1* pathogenic variant.
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for an *FOLR1* 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, it is possible that 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]. If the proband appears to have homozygous pathogenic variants (i.e., the same two pathogenic variants), additional possibilities to consider include:
  - A single- or multiexon deletion in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity;
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant that resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for an *FOLR1* 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 being unaffected and not a carrier.
- Clarification of the genetic status of all sibs of a proband is recommended in order to identify as early as possible those who inherited biallelic *FOLR1* pathogenic variants and would benefit from prompt initiation of treatment; early treatment with 5-formyltetrahydrofolate (5-formylTHF) may prevent or fully reverse the manifestations of *FOLR1*-CFTD.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. To date, individuals with *FOLR1*-CFTD are not known to reproduce.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an *FOLR1* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *FOLR1* 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

- 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.
- Carrier testing should be considered for the reproductive partners of individuals known to have an *FOLR1* pathogenic variant, particularly if consanguinity is likely. Most individuals with *FOLR1*-CFTD are born to consanguineous parents.

Prenatal Testing and Preimplantation Genetic Testing

Once the *FOLR1* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider 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**
  Cerebral folate transport deficiency
- **Metabolic Support UK**
  United Kingdom
  Phone: 0845 241 2173
  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. FOLR1-Related Cerebral Folate Transport Deficiency: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
FOLR1	11q13.4	Folate receptor alpha	FOLR1 database	FOLR1	FOLR1

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 FOLR1-Related Cerebral Folate Transport Deficiency (View All in OMIM)

136430	FOLATE RECEPTOR, ALPHA; FOLR1
613068	NEURODEGENERATION DUE TO CEREBRAL FOLATE TRANSPORT DEFICIENCY; NCFTD

Molecular Pathogenesis

Folates are essential cofactors for a variety of biological processes such as nucleotide synthesis and repair of DNA, regulation of gene expression, and synthesis of amino acids and neurotransmitters. *FOLR1* encodes folate receptor alpha (FOLR1; also known as FRα), which binds physiologic folates and mediates their transport across the membranes that surround certain cells. Pathogenic variants in *FOLR1* causing cerebral folate transport deficiency can (1) prevent the synthesis of a complete, functional FOLR1 protein, (2) result in a protein that is unstable and rapidly degrades, (3) impair the ability of the protein-folate complex to find its way to and/or be transported across the cell membrane, or (4) decrease the ability of FOLR1 to bind folates, preventing the formation of the necessary transport complex.

The loss of FOLR1 function impairs folate transport across the choroid plexus into the cerebrospinal fluid (CSF) within the cerebral ventricles. This results in folate deficiency in brain tissue nourished by the CSF, where neural stem cells develop into mature brain cells. The brain is also nourished by folates delivered directly from intact blood vessels that are functional in *FOLR1*-CFTD [Grapp et al 2013, Zhao et al 2017, Alam et al 2020a, Alam et al 2020b]. Variability in the effectiveness of this latter route of folate delivery to the brain may explain differences in the severity of clinical manifestations associated with loss of FOLR1 function.

Mechanism of disease causation. Loss of function

***FOLR1*-specific laboratory technical considerations.** Although the one intronic *FOLR1* pathogenic variant identified to date lies close to the splice junction, it may not be detected by standard sequencing methods [Gowda et al 2021].

Table 8. *FOLR1* Pathogenic Variants Referenced in This *GeneReview*

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_016725.3 NP_057937.1	c.352C>T	p.Gln118Ter	Identified in 2 persons from different cities in Germany (in compound heterozygous state w/p.Cys175Ter) [1] (See Prevalence.)
	c.506G>A	p.Cys169Tyr	Reported in 5 Finnish persons, incl 4 homozygotes & 1 heterozygous [2] (See Prevalence.)
	c.525C>A	p.Cys175Ter	Reported in 2 persons from different cities in Germany (in compound heterozygous state w/p.Gln118Ter) [1] (See Prevalence.)
	c.610C>T	p.Arg204Ter	Reported in persons from Turkey [3] & Ghana [4] (See Prevalence.)
	c.665A>G	p.Asn222Ser	Identified in 1 person from Saudi Arabia (in compound heterozygous state w/p.Cys169Tyr) & 1 person from Belgium (in homozygous state) [5] (See Prevalence.)

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.
1. Cario et al [2009], Steinfeld et al [2009]
2. Grapp et al [2012]
3. Dill et al [2011]
4. Toelle et al [2014]
5. Tabassum et al [2019], Kanmaz et al [2023]

Chapter Notes

Author Notes

Dr Goldman has a long-standing research interest in the mechanisms by which folates are absorbed in the intestine and are transported into and out of systemic tissues and the brain. His laboratory discovered the protein-coupled folate transporter (PCFT; encoded by *SLC46A1*) and established that loss of function of this transporter is the molecular basis for hereditary folate malabsorption. Dr Goldman has also studied the mechanism of FOLR1-mediated transport of folates and antifolate drugs. Dr Goldman has a particular interest in clinical disorders that occur with the loss of function of PCFT or FOLR1 as well as characterization of the biochemical and molecular basis for the transport defects.

Experts in *FOLR1*-related cerebral folate transport deficiency and other disorders associated with cerebral folate deficiency include Rafael Artuch (Neuropediatrics and Clinical Biochemistry Departments, Hospital Sant Joan de Deu, Center for Biomedical Research in Rare Diseases, Barcelona, Spain) and Shamima Rahman (Great Ormand Street Hospital for Children, London, United Kingdom).

Dr Goldman is interested in hearing from clinicians treating families with and families affected by *FOLR1*-related cerebral folate transport deficiency, hereditary folate malabsorption, or similar disorders in which there are very low levels of CSF folate (<10 nmol/L). Web page: www.einsteinmed.edu

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