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Biotin-Thiamine-Responsive Basal Ganglia Disease

Synonyms: Biotin-Responsive Basal Ganglia Disease (BBGD), BTBGD, Thiamine Metabolism Dysfunction Syndrome-2, Thiamine Transporter-2 Deficiency

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Summary

Clinical characteristics

Biotin-thiamine-responsive basal ganglia disease (BTBGD) may present in childhood, early infancy, or adulthood.

- The classic presentation of BTBGD occurs in childhood (age 3-10 years) and is characterized by recurrent subacute encephalopathy manifest as confusion, seizures, ataxia, dystonia, supranuclear facial palsy, external ophthalmoplegia, and/or dysphagia which, if left untreated, can eventually lead to coma and even death. Dystonia and cogwheel rigidity are nearly always present; hyperreflexia, ankle clonus, and Babinski responses are common. Hemiparesis or quadriparesis may be seen. Episodes are often triggered by febrile illness or mild trauma or stress. Simple partial or generalized seizures are easily controlled with anti-seizure medication.
- An early-infantile Leigh-like syndrome / atypical infantile spasms presentation occurs in the first three months of life with poor feeding, vomiting, acute encephalopathy, and severe lactic acidosis.
- An adult-onset Wernicke-like encephalopathy presentation is characterized by acute onset of status epilepticus, ataxia, nystagmus, diplopia, and ophthalmoplegia in the second decade of life.

Prompt administration of biotin and thiamine early in the disease course results in partial or complete improvement within days in the childhood and adult presentations, but most with the infantile presentation have had poor outcome even after supplementation with biotin and thiamine.

Diagnosis/testing

The diagnosis of BTBGD is established in a proband with biallelic pathogenic variants in *SLC19A3* identified by molecular genetic testing.

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Management

Treatment of manifestations: Biotin (5-10 mg/kg/day) and thiamine (up to 40 mg/kg/day with a maximum of 1500 mg daily) are given orally as early in the disease course as possible and are continued lifelong. Symptoms typically resolve within days. Acute encephalopathic episodes may require care in an ICU to manage seizures and increased intracranial pressure; during acute decompensations thiamine may be increased to double the regular dose and be given intravenously. Anti-seizure medication is used to control seizures. Treatment of dystonia is symptomatic and includes administration of trihexyphenidyl or L-dopa. Rehabilitation, physiotherapy, occupational therapy, and speech therapy as needed and adaptation of educational programs to meet individual needs. Education of the family regarding the importance of lifelong adherence to medical therapy.

Prevention of primary manifestations: Prompt administration of biotin and thiamine early in the disease course.

Surveillance: Clinical review of neurologic status every six months; annual assessment of developmental progress and educational needs; social support and care coordination each visit.

Agents/circumstances to avoid: Infections, stress, profuse exercise, and trauma.

Evaluation of relatives at risk: It is appropriate to clarify the genetic status of apparently asymptomatic older and younger at-risk relatives (e.g., sibs) of an affected individual in order to identify as early as possible those who would benefit from prompt initiation of treatment with biotin and thiamine and preventive measures (avoidance of stress and trauma).

Pregnancy management: Affected women should continue thiamine and biotin during pregnancy.

Genetic counseling

BTBGD is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Carrier testing for at-risk family members and prenatal testing and preimplantation genetic testing for pregnancies at increased risk are possible if the *SLC19A3* pathogenic variants in the family have been identified.

Diagnosis

Suggestive Findings

Biotin-thiamine-responsive basal ganglia disease (BTBGD) **should be suspected** in individuals with the following:

- Acute/subacute encephalopathy with seizures, extrapyramidal manifestations (dystonia, cogwheel rigidity, dysarthria, dysphagia), and pyramidal tract signs (quadriparesis, hyperreflexia) typically in a child age three to ten years and usually preceded by febrile illness or some other stress. Cerebellar signs, supranuclear facial nerve palsy, external ophthalmoplegia, and ataxia are variably present.
- Brain MRI showing the following:
  - Swelling and bilateral and symmetric increased T_2-weighted signal intensity in the caudate nucleus, putamen, thalamus, infra- and supratentorial brain cortex, and brain stem [Ozand et al 1998]
  - Vasogenic edema during acute crises as demonstrated by diffusion-weighted imaging / apparent diffusion coefficient MRI

- Chronic changes including atrophy and necrosis of caudate and putamen with diffuse cerebral cortical and (to a lesser extent) cerebellar atrophy [Yamada et al 2010]
- Spinal cord involvement (seen in 1 affected individual) [Alfadhel et al 2013]

- Normal laboratory investigations, including tandem mass spectrometry of blood; urine gas chromatography-mass spectrometry (GC-MS); serum concentrations of lactic acid,* ammonia, biotin, and thiamine; serum biotinidase enzyme activity; urine amino acids; plasma amino acids; liver enzymes; coagulation profile; lipid profile; and cerebrospinal fluid (CSF) cell count, protein, glucose, and cultures.

  * In the early-onset form, high lactate levels in the blood and CSF; high alanine, leucine, and isoleucine in the plasma; and elevated excretion of α-ketoglutarate in the urinary organic acid assays can be observed.

- Family history consistent with autosomal recessive inheritance. Note: (1) Presumably affected (but undiagnosed) sibs may have had unexplained coma or encephalopathy. (2) Consanguinity has been reported in a large number of families [Alfadhel et al 2013, Tabarki et al 2013].

Establishing the Diagnosis

The diagnosis of BTBGD **is established** in a proband with biallelic pathogenic (or likely pathogenic) variants in *SLC19A3* 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 variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) Identification of biallelic *SLC19A3* variants of uncertain significance (or of one known *SLC19A3* pathogenic variant and one *SLC19A3* variant of uncertain significance) does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, exome array, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of biotin-thiamine-responsive basal ganglia disease is broad, individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of biotin-thiamine-responsive basal ganglia disease has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of BTBGD, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**.

- **Single-gene testing.** Sequence analysis of *SLC19A3* is performed first 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. If only one pathogenic variant or no pathogenic variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.

- **A multigene panel** that includes *SLC19A3* and other genes of interest (see Differential Diagnosis) is most likely 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 laboratory-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 this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

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

Option 2

When the diagnosis of BTBGD is not considered because an individual has atypical phenotypic features, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

If exome sequencing is not diagnostic, **exome array** (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis.

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 BTBGD

Gene [1]	Method	Proportion of Pathogenic Variants [2] Identified by Method
SLC19A3	Sequence analysis [3]	~95% [4]
	Gene-targeted deletion/duplication analysis [5]	~5% [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. 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.
6. A 45-kb deletion including the promoter region but no coding exons of *SLC19A3* has been reported [Flønes et al 2016].

Clinical Characteristics

Clinical Description

To date, 135 individuals have been identified with a pathogenic variant in *SLC19A3* [Alfadhel et al 2019]. The following description of the phenotypic features associated with biotin-thiamine-responsive basal ganglia disease (BTBGD) is based on this report. While the classic presentation of BTBGD occurs in childhood, early infantile-onset and adult-onset presentations are reported as well.

Table 2. Features of BTBGD

Feature	% of Persons w/Feature
Encephalopathy	50

Table 2. continued from previous page.

Feature	% of Persons w/Feature
Dystonia	45
Spasticity	40
Seizures	37
Dysphagia	35
Ataxia	30
Dysarthria	15
Ophthalmoplegia	15
Opisthotonus	10

Classic BTBGD usually presents in children of preschool or early school age (i.e., ages 3-10 years). In one report onset was at age one month [Pérez-Dueñas et al 2013] and in another at age 20 years [Debs et al 2010].

Classic BTBGD is most commonly characterized by recurrent acute/subacute onset of encephalopathy manifest as confusion, generalized seizures, ataxia, dystonia, supranuclear facial palsy, external ophthalmoplegia, and dysphagia, eventually leading to coma and even death. This encephalopathy may be associated with a variable degree of raised intracranial pressure. Dystonia and cogwheel rigidity are nearly always present. Hyperreflexia, ankle clonus, and Babinski responses are common. Hemiparesis or quadriparesis may be seen. Episodes are often triggered by febrile illness, mild trauma, or stress.

Seizures are mainly simple partial or generalized seizures and are easily controlled with anti-seizure medication. Infantile spasms also occur [Yamada et al 2010].

Administration of biotin and thiamine early in the disease course results in complete clinical improvement within days (see Management). Lifelong treatment is required. Treatment initiated later in the disease course or lack of treatment may result in death or chronic neurologic sequelae including dystonia, quadriparesis, epilepsy, or mild intellectual disability.

The early-infantile Leigh-like syndrome / atypical infantile spasms presentation is characterized by the occurrence in the first three months of life of poor feeding, vomiting, acute encephalopathy, and severe lactic acidosis. Four individuals with atypical infantile spasms have been described [Yamada et al 2010]. Most individuals in this group have had poor outcome or even death (even after supplementation with biotin and thiamine).

Adult Wernicke-like encephalopathy is characterized by acute onset of status epilepticus, ataxia, nystagmus, diplopia, and ophthalmoplegia in the second decade of life [Kono et al 2009]. Affected individuals show dramatic response to high dose of thiamine.

Prevalence

The disorder is pan ethnic; however, it is most prevalent in Saudi Arabia. The carrier frequency of a pathogenic variant in *SLC19A3* is 1:500 in Saudi newborns [Alfadhel et al 2019].

Genotype-Phenotype Correlations

SLC19A3 genotype-phenotype correlations are poorly defined; however:

- Biallelic predicted loss-of-function variants are more likely to present early and develop into the severe Leigh-like phenotype.

- Compound heterozygosity for one missense variant and one predicted loss-of-function variant has been associated with the classic childhood form of BTBGD.
- The founder Saudi variant, c.1264A>G (p.Thr422Ala), is associated with the classic childhood form.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *SLC19A3*.

Differential Diagnosis

Acute biotin-thiamine-responsive basal ganglia disease (BTBGD). See Table 3.

Table 3. Genes of Interest in the Differential Diagnosis of Acute Biotin-Thiamine-Responsive Basal Ganglia Disease (BTBGD)

Gene(s)	Disorder	MOI
BCKDHA *BCKDHB* *DBT* *IVD* *MCEE* *MMAA* *MMAB* *MMADHC* *MMUT* *PCCA* *PCCB* [1]	Organic acid disorders (e.g., IVA, MMA, MSUD, PA) [2]	AR
See footnote 3.	Mitochondrial disorders (incl Leigh syndrome) [4]	AR AD Mat
HTT	Juvenile Huntington disease	AD
ATP7B	Wilson disease	AR
TH	Tyrosine hydroxylase deficient dopa-responsive dystonia (See Tyrosine Hydroxylase Deficiency.)	AR
GCH1	GTP cyclohydrolase 1-deficient dopa-responsive dystonia	AD
SLC5A6	Infantile-onset biotin-responsive neurodegeneration [5]	AR
SPR	Sepiapterin reductase deficiency	AR

AD = autosomal dominant; AR = autosomal recessive; BTBGD = biotin-thiamine-responsive basal ganglia disease; IVA = isovaleric acidemia; Mat = maternal; MMA = methylmalonic acidemia; MOI = mode of inheritance; MSUD = maple syrup urine disease; PA = propionic acidemia

1. More than 65 organic acids are known [Ramsay et al 2018]; listed genes represent those associated with the selected organic acidemias in the **Disorder** column.

2. Major clinical features are developmental delay, seizures, lethargy, coma, hypotonia, vomiting, failure to thrive, hepatomegaly, respiratory distress, cardiac dysfunction, hypoglycemia, and acidosis.

3. Mitochondrial diseases are a clinically heterogeneous group of disorders that arise as a result of dysfunction of the mitochondrial respiratory chain. They can be caused by mutation of genes encoded by either nuclear DNA or mitochondrial DNA (mtDNA). More than 1,000 genes associated with mitochondrial function have been identified [Calvo et al 2006].

4. See also Nuclear Gene-Encoded Leigh Syndrome Overview.

5. Byrne et al [2019]

Note: Dopa-responsive dystonia and Wilson disease are important to consider because they are treatable.

Acquired disorders in the differential diagnosis

- Wernicke encephalopathy
- Toxic encephalopathy
- Infectious encephalopathy
- Inflammatory disease (including CNS vasculitis)
- Acute disseminated encephalomyelitis (ADEM)

Chronic BTBGD. In its chronic stage BTBGD shares clinical features with several conditions including Wilson disease, juvenile Huntington disease, and DYT1 early-onset isolated dystonia; however, BTBGD can be differentiated by its acute to subacute presentation.

See Thiamine-responsive dysfunction syndrome: OMIM Phenotypic Series to view genes associated with this phenotype in OMIM.

Management

Evaluations Following Initial Diagnosis

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

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with BTBGD

System/Concern	Evaluation	Comment
Neurologic	Pediatric neurologist	Baseline exam & eval for seizures
Dystonia & developmental delay	Rehabilitation medicine	Evaluate status & need for therapies.
	Physiotherapist	
	Occupational therapist	
	Speech therapist	
	Psychologist	Assess IQ.
Other	Consultation w/clinical geneticist &/or genetic counselor	

Treatment of Manifestations

Table 5. Treatment of Manifestations in Individuals with BTBGD

Manifestation/ Concern	Treatment	Considerations/Other
Acute encephalopathy	ICU care incl treatment of seizures & ↑ intracranial pressure	Empiric treatment w/antimicrobial/antiviral agents recommended until infectious causes of acute/subacute encephalopathy are ruled out
Neurologic disorder	Both biotin & thiamine oral therapy: • Biotin: 5-10 mg/kg/day • Thiamine: ≤40 mg/kg/day; max of 1500 mg/day	• Note: Some persons respond only to thiamine. • Lifelong treatment w/biotin & thiamine required • During acute decompensation thiamine may be ↑ to 2x regular dose & given intravenously.
	Fever control	Fever exacerbates the disease.
Seizures	Anti-seizure medication to control seizures	Avoid sodium valproate.
Dystonia	Symptomatic treatment incl trihexyphenidyl or L-dopa	

Table 5. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
Developmental delays	Rehab, PT, OT, speech therapy, & educational programs adapted to individual needs	
Social	Education of family re importance of lifelong adherence to medical therapy	

OT = occupational therapy; PT = physical therapy

Prevention of Primary Manifestations

Appropriate measures include the following:

- Prompt administration of biotin and thiamine early in the disease course (See Treatment of Manifestations.)
- Avoidance of triggers/stressors including trauma and optional surgery

Surveillance

Table 6. Recommended Surveillance for Individuals with BTBGD

System/Concern	Evaluation	Frequency
Nervous system	Clinical review of neurologic status	2x/yr
Development/ Education	Monitor developmental progress & educational needs	Annually
Miscellaneous/ Other	Assess family need for social work support (e.g., home nursing, other local resources) & care coordination.	At each visit

Agents/Circumstances to Avoid

Infections, stress, profuse exercise, and trauma should be avoided as they can precipitate acute attacks.

Use of sodium valproate for epilepsy should be avoided.

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of apparently asymptomatic older and younger at-risk relatives (e.g., sibs) of an affected individual in order to identify as early as possible those who would benefit from prompt initiation of treatment with biotin and thiamine and preventive measures (avoidance of stress and trauma).

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

Pregnancy Management

Affected women should continue biotin and thiamine therapy during pregnancy. No information regarding risk to the fetus of an affected mother is available.

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.

Other

Routine administration of immunizations is recommended (without any specific precautions).

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

Biotin-thiamine-responsive basal ganglia disease (BTBGD) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected individual are obligate heterozygotes (i.e., presumed to be carriers of one *SLC19A3* pathogenic variant based on family history).
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for an *SLC19A3* pathogenic variant and allow reliable recurrence risk assessment. (*De novo* variants are known to occur at a low but appreciable rate in autosomal recessive disorders [Jónsson et al 2017].)
- 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 *SLC19A3* 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.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. an affected individual's reproductive partner also has BTBGD or is a carrier, offspring will be obligate heterozygotes (carriers) for a pathogenic variant in *SLC19A*.

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

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *SLC19A3* 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, clarification of carrier status, 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 *SLC19A3* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for BTBGD are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While use of prenatal testing is 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**
  Biotin-thiamine-responsive basal ganglia disease

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. Biotin-Thiamine-Responsive Basal Ganglia Disease : Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
SLC19A3	2q36.3	Thiamine transporter 2	SLC19A3 database	SLC19A3	SLC19A3

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 Biotin-Thiamine-Responsive Basal Ganglia Disease (View All in OMIM)

606152	SOLUTE CARRIER FAMILY 19 (THIAMINE TRANSPORTER), MEMBER 3; SLC19A3
607483	BASAL GANGLIA DISEASE, BIOTIN-THIAMINE RESPONSIVE; BTBGD

Molecular Pathogenesis

SLC19A3 encodes thiamine transporter 2 (hTHTR2). A second gene, *SLC19A2*, encodes the thiamine transporter 1 (hTHTR1). Thiamine enters the cytosol by either hTHTR1 or hTHTR2 and is converted into thiamine pyrophosphate (TPP, the active form) by thiamine pyrophosphokinase 1 (TPK1).

TPP is:

- An essential cofactor for transketolase in the cytoplasm;
- Transported into mitochondria, where it binds to pyruvate dehydrogenase and stimulates conversion of pyruvate to acetyl-CoA;
- A cofactor for α-ketoglutarate and branched-chain α-ketoacid dehydrogenase, entering the tricarboxylic acid cycle for energy production and biosynthesis.

Mechanism of disease causation. Biotin-thiamine-responsive basal ganglia disease (BTBGD) results from loss of hTHTR2 function.

Table 7. Notable *SLC19A3* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_025243.3 NP_079519.1	c.1264A>G	p.Thr422Ala	Founder variant in Saudi population [Alfadhel et al 2013]

Variants listed in the table have been provided by the authors. *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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- 16 April 2020 (ha) Comprehensive update posted live
- 21 November 2013 (me) Review posted live
- 28 May 2013 (aah) Original submission

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