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Glucose Transporter Type 1 Deficiency Syndrome

Synonyms: De Vivo Disease, Glut1 Deficiency Syndrome, Glut1 DS

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Summary

Clinical characteristics

The phenotypic spectrum of glucose transporter type 1 deficiency syndrome (Glut1 DS) is now known to be a continuum that includes the classic phenotype as well as paroxysmal exercise-induced dyskinesia and epilepsy (previously known as dystonia 18 [DYT18]) and paroxysmal choreoathetosis with spasticity (previously known as dystonia 9 [DYT9]), atypical childhood absence epilepsy, myoclonic astatic epilepsy, and paroxysmal non-epileptic findings including intermittent ataxia, choreoathetosis, dystonia, and alternating hemiplegia. The classic phenotype is characterized by infantile-onset seizures, delayed neurologic development, acquired microcephaly, and complex movement disorders. Seizures in classic early-onset Glut1 DS begin before age six months. Several seizure types occur: generalized tonic or clonic, focal, myoclonic, atypical absence, atonic, and unclassified. In some infants, apneic episodes and abnormal episodic eye-head movements similar to opsoclonus may precede the onset of seizures. The frequency, severity, and type of seizures vary among affected individuals and are not related to disease severity. Cognitive impairment, ranging from learning disabilities to severe intellectual disability, is typical. The complex movement disorder, characterized by ataxia, dystonia, and chorea, may occur in any combination and may be continuous, paroxysmal, or continual with fluctuations in severity influenced by environmental factors such as fasting or with infectious stress. Symptoms often improve substantially when a ketogenic diet is started.

Diagnosis/testing

The diagnosis of Glut1 DS is established in a proband with suggestive clinical findings, normal blood glucose concentration, CSF glucose concentration <60 mg/dL, and the identification of a heterozygous pathogenic variant (or rarely, biallelic pathogenic variants) in *SLC2A1* by molecular genetic testing. If no pathogenic variant is identified, 3-O-methyl-D-glucose uptake in erythrocytes can be performed; results between 35% and 74% of controls are diagnostic.

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Management

Treatment of manifestations: The ketogenic diet is highly effective in controlling the seizures and improving gait disturbance and is generally well tolerated. Affected individuals treated effectively at a younger age have a better outcome The ketogenic diet is deficient in L-carnitine necessitating dietary supplementation.

Prevention of primary manifestations: Early diagnosis and treatment with a ketogenic diet is associated with improved neurologic outcome.

Prevention of secondary complications: For those on a ketogenic diet: L-carnitine supplementation; proper hydration and avoidance of carbonic anhydrase inhibitors; avoidance of carbohydrate-containing foods, intravenous fluids, and medications that interrupt the state of ketosis; avoidance of valproic acid because it increases the risk of a Reye-like illness.

Surveillance: Periodic measurement of blood ketone concentration with a target beta-hydroxybutyrate concentration of 3-5 mmol/L.

Agents to avoid: Barbiturates (e.g., phenobarbital, the antiepileptic drug most commonly used in treating infants), methylxanthines (e.g., caffeine), valproic acid.

Evaluation of relatives at risk: If the pathogenic variant has been identified in an affected family member, it is appropriate to test at-risk newborns, infants, and other relatives at risk in order to identify as early as possible those who would benefit from initiation of treatment and preventive measures.

Genetic counseling

Glut1 DS is most commonly inherited in an autosomal dominant (AD) manner. About 90% of individuals with AD Glut1 DS have the disorder as the result of a *de novo* heterozygous pathogenic variant; about 10% have a clinically affected parent. Parents who are heterozygous for the pathogenic variant may have a mild phenotype or be asymptomatic, findings that can suggest mosaicism in the parent. Offspring of an individual with AD Glut1 DS have a 50% chance of inheriting the pathogenic variant and being clinically affected.

Rarely, Glut1 DS is inherited in an autosomal recessive (AR) manner. Heterozygotes (carriers) in families with AR Glut1 DS are asymptomatic.

Once the *SLC2A1* pathogenic variant(s) have been identified in an affected family member, prenatal diagnosis for a pregnancy at increased risk and preimplantation genetic testing for Glut1 DS are possible.

GeneReview Scope

Included Phenotypes

• Classic glucose transporter type 1 deficiency syndrome
• Non-classic glucose transporter type 1 deficiency syndrome
  ◦ Paroxysmal choreoathetosis with spasticity
  ◦ Paroxysmal exercise-induced dyskinesia and epilepsy
  ◦ Atypical childhood absence epilepsy
  ◦ Myoclonic astatic epilepsy

For synonyms and outdated names see Nomenclature.

Diagnosis

Suggestive Findings

Glucose transporter type 1 deficiency syndrome (Glut1 DS) **should be suspected** in individuals with one of the following two phenotypes.

Classic Glut1 DS (~90% of affected individuals)

- Seizures with onset:
  - Typically before age two years (most frequently between ages 1 and 6 months)
  - Less often after age two years
- Delayed neurologic development
- Dysarthria
- Acquired microcephaly
- Complex movement disorders including:
  - Ataxia
  - Dystonia
  - Chorea

Non-classic Glut1 DS (~10% of affected individuals)

- No clinical seizures
- Milder phenotype
- Frequent paroxysmal dyskinesias including:
  - Intermittent ataxia
  - Choreoathetosis
  - Dystonia
  - Alternating hemiplegia

Testing

CSF glucose concentration. The single most important laboratory observation in Glut1 DS is hypoglycorrhachia (reduced cerebrospinal fluid [CSF] glucose concentration). Following a four-hour fast, a blood sample is obtained just before performing the lumbar puncture:

- The blood glucose concentration should be normal, ruling out hypoglycemia as the cause of the hypoglycorrhachia.
- The CSF/blood glucose ratio id usually less than 0.4 (range 0.19-0.59) in persons with Glut1 DS; however, this value is less reliable than the absolute CSF glucose value.
- All affected individuals reported to date have had CSF glucose values below 60 mg/dL (range: 16.2-52 mg/dL); in more than 90% it is below 40 mg/dL and in approximately 10% it is 41-52 mg/dL [De Vivo & Wang 2008, Yang et al 2011, Leen et al 2013].

Establishing the Diagnosis

The diagnosis of Glut1 DS **is established** in a proband with suggestive clinical findings and one or both of the following:

- Normal blood glucose concentration with CSF glucose concentration <60 mg/dL
- Identification of a heterozygous pathogenic variant (or rarely, biallelic pathogenic variants) in *SLC2A1* by molecular genetic testing (see Table 1)

Molecular genetic testing approaches can include **single-gene testing**, use of a **multigene panel**, and **more comprehensive genomic testing**:

- **Single-gene testing.** Sequence analysis of *SLC2A1* is performed first and followed by gene-targeted deletion/duplication analysis if no pathogenic variant is found.
- **A multigene panel** that includes *SLC2A1* and other genes of interest (see Differential Diagnosis) may be considered. 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*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition at the most reasonable cost while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (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 an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.
- **More comprehensive genomic testing** (when available) including exome sequencing and genome sequencing may be considered. Such testing may provide or suggest a diagnosis not previously considered (e.g., mutation of a different gene or genes that results in a similar clinical presentation).

  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 Glut1 DS

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
SLC2A1	Sequence analysis [3]	84% [4]
	Gene-targeted deletion/duplication analysis [5]	13% [6]
Unknown [7]	NA	

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic 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 small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. 48 (89%) of 54 probands with an *SCL2A1* pathogenic variant [Leen et al 2010]; 60 (81%) of 74 probands with an *SCL2A1* pathogenic variant [Yang et al 2011]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include 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. 6 (11%) of 54 with (multi)exon or whole-gene deletions [Leen et al 2010]; 10 (14%) of 74 with (multi)exon or whole-gene deletions [Yang et al 2011]
7. With the observation of a few individuals with a severe phenotype and laboratory signature of Glut1 DS (low CSF glucose and lactate, normal RBC glucose uptake assay) but without pathogenic variants in *SLC2A1*, mutation of another, as-yet-unidentified gene is suspected [Authors, personal experience].

If molecular genetic testing fails to detect a pathogenic *SLC2A1* variant, consider performing erythrocyte glucose uptake assay (when feasible). An abnormally low assay implies an abnormality in *SLC2A1*.

Erythrocyte 3-O-methyl-D-glucose uptake assay. The uptake assay is a functional measure of glucose transport across the cell membrane. Individuals with Glut1 DS have abnormal values that range from 35% to 74% of controls, with an average reduction of approximately 50% [Yang et al 2011]. As such, it is abnormally low in almost all suspected cases.

- Decreased 3-O-methyl-D-glucose uptake in erythrocytes confirms the diagnosis of *SLC2A1*-related Glut1 DS.
- Molecular genetic testing detects a pathogenic variant in 95% of persons with abnormally low uptake assay.
- Of note, 3% of persons with Glut1 DS have a normal uptake assay, a finding that correlates with the presence of an *SLC2A1* pathogenic missense variant (see Genotype-Phenotype Correlations).

  Note: The 3-O-methyl-D-glucose uptake assay is currently viewed as the diagnostic gold standard for this disease [Yang et al 2011]; however, such testing may not be available on a clinical basis, so it is primarily used if molecular genetic testing fails to detect a pathogenic *SLC2A1* variant.

Clinical Characteristics

Clinical Description

Glucose transporter type 1 deficiency syndrome (Glut1 DS) usually presents as either classic Glut1 DS (~90% of affected individuals) or, more rarely, non-classic Glut1 DS (~10% of affected individuals), which comprises a broad phenotypic spectrum.

- Infants with the **classic phenotype** appear normal at birth following an uneventful pregnancy and delivery. Birth weight and Apgar scores are normal. Affected individuals commonly experience infantile-onset epileptic encephalopathy refractory to anticonvulsants and associated with delayed neurologic development; later deceleration of head growth and acquired microcephaly; and ataxia, dystonia, and spasticity [Klepper et al 1999b, De Vivo et al 2002a, De Vivo et al 2002b, Pons et al 2010, Yang et al 2011].
- The phenotypic spectrum designated as **non-classic Glut1 DS** has expanded over the past few years as more affected individuals have been identified. Paroxysmal non-epileptic manifestations that have been reported include intermittent ataxia, choreoathetosis, dystonia, and alternating hemiplegia. Several disorders including paroxysmal choreoathetosis with spasticity (dystonia 9), paroxysmal exercise-induced dyskinesia and epilepsy (dystonia 18), atypical childhood absence epilepsy, and myoclonic astatic epilepsy are now known to be caused by Glut1 deficiency [Chinnery 2010, Leen et al 2010, Yang et al 2011]. Some findings may show overlap with those seen in classic Glut1 DS.

Seizures. Seizures in classic early-onset Glut1 DS, which usually begin between age one and six months, are often the first clinical indication of brain dysfunction. In some infants, apneic episodes and abnormal episodic eye-head movements similar to opsoclonus may precede the onset of seizures [Pearson et al 2017]. Infantile focal seizures are clinically fragmented (i.e., non-generalized; typical at this age) and may include paroxysmal eye-head movements, cyanotic spells, and complex absence and atonic seizures. The electroencephalogram (EEG) may demonstrate multifocal spike discharges in infancy.

With further brain maturation, the seizures become synchronized and manifest clinically as generalized events associated with 3- to 4-Hz spike and wave discharges. Several seizure types have been described: generalized tonic or clonic, focal, myoclonic, atypical absence, atonic, and unclassified [Leary et al 2003].

The frequency of seizures varies among individuals: some experience daily events; others have only occasional seizures separated by days, weeks, or months. Seizure frequency does not correlate with phenotypic severity.

Some individuals with Glut1 DS never have a clinical seizure [von Moers et al 2002, Leary et al 2003]. About 10%-15% of cases, diagnosed thus far, never have had clinical seizures [Leen et al 2010, Pong et al 2012, Pearson et al 2013].

Speech and language impairment. Varying degrees of speech and language impairment are observed in all affected individuals.

Dysarthria is common and is accompanied by dysfluency (i.e., excessively interrupted speech).

Both receptive and expressive language skills are affected, with expressive language skills being disproportionately affected.

Intellectual disability. Varying degrees of cognitive impairment, ranging from learning disabilities to severe intellectual disability, are observed. Minimally affected individuals have estimated IQ scores in the normal range.

Social adaptive behavior is an exceptional strength. Individuals with Glut1 DS tend to be comfortable in group and school settings and interact well with others. Autistic spectrum disorders appear to be underrepresented in those with Glut1 DS.

Movement disorders. A complex movement disorder is commonly seen and is characterized by ataxia, dystonia, and chorea that may be continuous, paroxysmal, or continual with fluctuations determined by environmental stressors [Leen et al 2010, Pons et al 2010, Pearson et al 2013, Alter et al 2015]. Often, paroxysmal worsening occurs before meals, during fasting, or with infectious stress.

Pons et al [2010] described the frequency of abnormal movements in 57 persons with Glut1 DS. Clinical findings included the following:

- Gait disturbance (89%), the most frequent being ataxia and spasticity together or ataxia alone
- Action limb dystonia (86%)
- Mild chorea (75%)
- Cerebellar action tremor (70%)
- Non-epileptic paroxysmal events (28%)
- Dyspraxia (21%)
- Myoclonus (16%)

The 40 individuals on a ketogenic diet had less severe gait disturbances, but more complex movement disorders than those on a conventional diet [Pons et al 2010], an observation suggesting that the extrapyramidal and cerebellar findings are more apparent in the milder phenotypes.

Paroxysmal movement disorders. Paroxysmal exercise-induced dyskinesia and epilepsy (previously known as dystonia 18 [DYT18] [Suls et al 2008, Weber et al 2008, Zorzi et al 2008, Urbizu et al 2010]) and paroxysmal choreoathetosis with spasticity (previously known as dystonia 9 [DYT9] [Weber et al 2011]) are now recognized to be part of the phenotypic spectrum of Glut1 DS.

- **Paroxysmal exercise-induced dyskinesia and epilepsy** differs clinically from classic Glut1 DS in that most affected individuals appear to have a normal interictal neurologic examination and a normal head circumference, and experience exercise-induced dyskinesias and later-onset seizures [Suls et al 2008, Weber et al 2008, Zorzi et al 2008, Urbizu et al 2010]. The CSF glucose concentrations tend to be higher (41-52 mg/dL) than those in classic Glut1 DS [De Vivo & Wang 2008].
- The two families with **paroxysmal choreoathetosis with spasticity** had paroxysmal, mainly exercise-induced dyskinesia with onset between ages one and 15 years [Weber et al 2011] caused by heterozygous *SLC2A1* pathogenic variants (p.Arg212Cys and p.Arg126Cys). Dyskinesia triggers included prolonged exercise, anxiety, and emotional stress. The dyskinesias decreased in frequency or stopped later in life.

Other associated findings included progressive spastic paraparesis with onset in early adulthood, mild gait ataxia, mild-to-moderate cognitive impairment, and epileptic seizures.

Other paroxysmal events have been reported [Overweg-Plandsoen et al 2003, Pérez-Dueñas et al 2009, Pons et al 2010, Urbizu et al 2010]. It is unclear whether these events represent epileptic or non-epileptic phenomena. These neurologic signs, which generally fluctuate and may be influenced by factors such as fasting or fatigue, include the following:

- Confusion
- Lethargy
- Somnolence
- Recurrent headaches, migraines
- Sleep disturbances
- Hemiparesis
- Total body paralysis
- Intermittent ataxia
- Chorea
- Action limb dystonia
- Cerebellar action tremor
- Writer's cramp
- Dystonic tremor; described as the only finding in a mother and daughter [Roubergue et al 2011]
- Parkinsonism
- Myoclonus
- Dyspraxia
- Nonkinesigenic dyskinesias

Microcephaly. Thirty-two of 58 persons with Glut1 DS had microcephaly ranging from mild (<1 SD below the mean in 14 patients) to moderate (<2 SD below the mean in 10) to severe (<3 SD below the mean in 8).

Additional findings. In addition to the low CSF-to-blood glucose ratio and decreased 3-O-methyl-D-glucose uptake in erythrocytes, the following findings may also be observed in individuals with this disorder:

- **Positron emission tomography (PET).** Cerebral fluoro-deoxy-glucose PET findings are distinctive with diffuse hypometabolism of the cerebral cortex and regional hypometabolism of the cerebellum and thalamus. Basal ganglia metabolism appears relatively preserved. This distinctive PET signature appears in early infancy and persists into adulthood regardless of disease severity or therapy with a ketogenic diet [Pascual et al 2002, Akman et al 2015]. The sensitivity and specificity of PET in the diagnosis of Glut1 DS have not been established.
- **CSF lactate concentration** is low-normal or low, often below 1.3 mmol/L or 11.7 mg/dL (range: 5.4-13.5 mg/dL) [De Vivo et al 1991, Wang et al 2005, Yang et al 2011, Leen et al 2013].

Pathophysiology

The disease manifestations can be explained in terms of current understanding of glucose transport in the brain: glucose is the principal fuel source for brain metabolism; the glucose transporter, Glut1 (solute carrier family 2, facilitated glucose transporter 1), the protein product of *SLC2A1*, is the fundamental vehicle that facilitates glucose entry into the brain. The cerebral metabolic rate for glucose (which is low during fetal development) increases linearly after birth, peaks around age three years, remains high for the remainder of the first decade of life, and declines gradually during the second decade of life to the rate of glucose utilization seen in early adulthood. It thus appears that the risk for clinical manifestations during fetal development is low and then rises throughout infancy and early childhood.

Human and animal data suggest that the margin of safety for glucose transport across the blood-brain barrier to meet the needs of brain metabolism and cerebral function is narrow. A milder clinical phenotype with intermittent symptoms (epilepsy, dyskinesias, and ataxia) may be predicted with 25%-35% reduction in Glut1 transporter function [Rotstein et al 2010]; a more severe phenotype results from greater reductions (perhaps 40%-75%) [Yang et al 2011].

The erythrocyte glucose uptake assay is a functional surrogate measure of residual Glut1 transporter function. Individuals displaying the classic phenotype have on average a 50% uptake assay, resulting from pathogenic loss-of-function variants that result in 50% reduction in Glut1 activity. Absence of Glut1 transporter expression is embryonic lethal [Wang et al 2006].

Genotype-Phenotype Correlations

A correlation between the specific type of *SLC2A1* pathogenic variant and the clinical severity has been noted [Leen et al 2010, Yang et al 2011]. A clinical scoring system developed to classify phenotypic severity for mitochondrial diseases and Glut1 DS [Kaufmann et al 2004] has been used to correlate phenotype with other markers including genotype [Levy et al 2010, Rotstein et al 2010, Yang et al 2011].

Fifty-three affected individuals were stratified clinically according to the Columbia Neurological Score (CNS) into four groups [Yang et al 2011]:

- Minimal (CNS 70-76)
- Mild (CNS 60-69)
- Moderate (CNS 50-59)
- Severe (CNS 40-49)

Comparison of the type of *SLC2A1* heterozygous pathogenic variants among the four groups revealed the following:

- Missense variants occurred predominantly in the mild and moderate clinical categories.
- Splice site and nonsense variants and insertions, deletions, and exon deletions occurred almost exclusively in the moderate and severe clinical categories.
- Complete gene deletions clustered in the severe clinical category.

A significant inverse correlation ($R^2 = 0.94$) was observed between the median values of the erythrocyte 3-O-methyl-D-glucose uptake and the clinical severity as determined by the Columbia Neurological Score. Thus, the erythrocyte glucose uptake is an indication of the functional effect of the pathogenic variant.

Many pathogenic variants have been identified [Wang et al 2005, Pascual et al 2008, Wang et al 2008, Leen et al 2010, Yang et al 2011]; several mutation hot spots and gene regions have been detected:

- Three individuals (each from a different family) have a mild clinical phenotype (as determined by the CNS) and a heterozygous p.Arg333Trp pathogenic missense variant.
- Twelve individuals have a heterozygous pathogenic missense variant at amino acid residue arginine 126.
  - Five had a mild phenotype: three members of one family with a p.Arg126His pathogenic variant [Brockmann et al 2001] and two members of one family with a p.Arg126Cys pathogenic variant [Ho et al 2001a].
  - Five with either the classic phenotype or the non-epileptic phenotype had a p.Arg126Cys pathogenic variant [Zorzi et al 2008, Leen et al 2010].
  - Two monozygotic twin brothers with **paroxysmal choreoathetosis with spasticity** were heterozygous for the p.Arg126Cys pathogenic variant [Weber et al 2011].

- A significant fraction (5/21) of pathogenic variants is located in a vulnerable region of the Glut 1 protein that involves the fourth transmembrane domain encoded by exon 4, suggesting a critical functional disturbance associated with structural alterations in this region of the protein [Pascual et al 2008].
- One individual had a p.Arg126Leu pathogenic variant in *trans* configuration with a p.Lys256Val pathogenic variant associated with a severe phenotype [Pascual et al 2008]. The father, who was clinically well, had neither missense variant. The asymptomatic mother was heterozygous for the p.Lys256Val pathogenic variant. Mutagenesis studies in *Xenopus* oocytes showed that in an uptake study under zero-trans influx conditions the p.Arg126Leu missense variant is more pathogenic than the p.Lys256Val missense variant. Therefore, the asymptomatic mother may have sufficient residual Glut1 activity to allow her to function normally. (Her glucose uptake assay revealed 83% residual activity; values of >74% residual activity correlate with a clinically normal state.) It is unclear whether synergy between the two pathogenic missense variants caused the severe phenotype in the child, a compound heterozygote [Rotstein et al 2010].
- Three individuals heterozygous for the p.Thr295Met pathogenic variant had:
    - A similar early-onset classic phenotype including monthly seizures beginning in infancy, developmental delay, ataxia, microcephaly, and language deficit;
    - Hypoglycorrhachia and low normal CSF lactate concentrations;
    - Normal erythrocyte zero-trans influx of 3-OMG.

      Mutagenesis studies suggest that p.Thr295Met specifically affects glucose flux by perturbing efflux rather than influx. These findings explain the seemingly paradoxic findings of Glut1 DS with hypoglycorrhachia and "normal" erythrocyte glucose uptake [Wang et al 2008, Fujii et al 2011]. Furthermore, this pathogenic missense variant may be a kinetic variant, functioning normally at 4° C (the temperature of the in vitro glucose uptake assay) and abnormally at body temperature [Cunningham & Naftalin 2013].
- A fourth individual heterozygous for the p.Thr295Met pathogenic variant with a similar mild classic phenotype was reported [Leen et al 2010].

Penetrance

Penetrance in Glut1 DS inherited in an autosomal dominant manner is complete.

An asymptomatic parent harboring the pathogenic variant implies a mosaic state.

Fewer pathogenic variants may be transmitted as an autosomal recessive trait; carriers are asymptomatic [Rotstein et al 2010].

Nomenclature

Paroxysmal exercise-induced dyskinesia and epilepsy (previously known as dystonia 18 [DYT18] or DYT-SLC2A1) [Suls et al 2008, Weber et al 2008, Zorzi et al 2008, Urbizu et al 2010] and paroxysmal choreoathetosis with spasticity (DYT9) [Weber et al 2011] are now recognized to be part of the Glut1 DS phenotypic spectrum.

Prevalence

No firm estimates of incidence and prevalence can be made, as cases have been reported worldwide and are biased by physician awareness of the disorder. Authors estimate the incidence/prevalence in Queensland, Australia, at approximately 1:90,000, which is likely a conservative estimate under the conditions of

ascertainment [Coman et al 2006]. A more recent study from Scandinavia yielded a similar incidence/prevalence of 1:83,000 [Larsen et al 2015].

Genetically Related (Allelic) Disorders

Cryohydrocytosis, a form of dominantly inherited stomatocytosis that leads to hemolytic anemia induced by cold exposure, can be caused by pathogenic variants in *SLC2A1*. Findings include hemolytic anemia, hepatosplenomegaly, cataracts, seizures, intellectual disability, and movement disorder [Flatt et al 2011].

Differential Diagnosis

The differential diagnosis of glucose transporter type 1 deficiency syndrome (Glut1 DS) includes the following:

- Other causes of neuroglycopenia including conditions causing chronic or intermittent hypoglycemia (e.g., familial hyperinsulinism)
- All causes of neonatal seizures and of acquired microcephaly; in particular, early presentations of Rett syndrome, Angelman syndrome, and infantile forms of neuronal ceroid-lipofuscinosis
- Opsoclonus-myoclonus syndrome [Pike 2013, Pearson et al 2017]
- Cryptogenic epileptic encephalopathies with developmental delays
- Familial epilepsies with autosomal dominant transmission
- Episodes of paroxysmal neurologic dysfunction responsive to or preventable by carbohydrate intake, especially when manifesting as alternating hemiparesis, ataxia, cognitive dysfunction, or seizures
- Movement disorders including dystonia (see Dystonia Overview)

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs of an individual diagnosed with glucose transporter type 1 deficiency syndrome (Glut1 DS), the following evaluations are recommended if they have not already been completed:

- EEG (pre-prandial and post-prandial tracings)
- Brain imaging, including FDG-PET in selected individuals
- Neuropsychological assessment
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Ketogenic diet. Diffusion of ketone bodies across the blood-brain barrier is facilitated by the monocarboxylic transporter 1 (MCT1). The ketogenic diet, introduced as a treatment for Glut1 DS in 1991, primarily provides an alternative fuel for brain metabolism. The ketogenic diet creates chronic ketosis by largely replacing carbohydrates and proteins with lipids in varying ratios.

Experience over the past two decades indicates that the ketogenic diet is well tolerated in most cases and is highly effective in controlling the seizures and improving gait disturbance. Of note, seizures may recur even with good dietary compliance [Klepper et al 2005]. Even when seizures are controlled, affected individuals may continue to have neurobehavioral deficits involving cognition and social adaptive behavior [Klepper et al 2002].

In the authors' experience, the neurologic outcome is influenced by the age at which treatment is initiated: affected individuals treated effectively at a younger age have a better outcome [Alter et al 2015].

Note: Because the ketogenic diet is deficient in L-carnitine, a cofactor that is essential for the metabolism of fats, dietary supplementation with 50 mg/kg/day of L-carnitine is recommended [De Vivo et al 1998].

Affected individuals develop a mild compensated metabolic acidosis when ketotic.

Antiepileptic drugs (AEDs) are generally ineffective or afford only limited improvement in the absence of a ketogenic diet. Certain AEDs may be relatively contraindicated as adjunctive treatment in children on the ketogenic diet (see Agents/Circumstances to Avoid).

- Phenobarbital and valproic acid can inhibit Glut1 transport.
- Valproic acid may partially inhibit beta-oxidation of fatty acids.
- Acetazolamide, topiramate, and zonisamide inhibit carbonic anhydrase and may potentiate the metabolic acidosis. These agents can also cause kidney stones.

Alpha-lipoic acid (thioctic acid) has also been shown to facilitate glucose transport in Glut4-dependent cultured skeletal muscle cells. Preliminary in vitro studies with Glut1 transport systems have shown similar results. Thus, alpha-lipoic acid supplements have been recommended, without supportive clinical evidence, as a treatment for Glut1 DS. Response has been modest at best; however, the dose taken by mouth may be insufficient to approximate experimental conditions [Kulikova-Schupak et al 2001].

Prevention of Primary Manifestations

Clinical observations suggest that early diagnosis and treatment with a ketogenic diet is associated with improved neurologic outcome by nourishing the immature brain during this critical period of growth and development [Alter et al 2015].

Prevention of Secondary Complications

For those who are treated with the ketogenic diet:

- L-carnitine supplementation to avoid carnitine deficiency
- Proper hydration and avoidance of carbonic anhydrase inhibitors to minimize likelihood of kidney stones
- Avoidance of carbohydrate-containing foods, intravenous fluids, and medications that will interrupt the state of ketosis. Family care providers often need to serve as the "watchdogs" to intercept these indiscretions.
- Avoidance of valproic acid treatment, which may be dangerous in individuals on a ketogenic diet because it increases the risk of a Reye-like illness. Valproic acid may also inhibit glucose transport.

Surveillance

Blood ketone concentrations should be monitored daily, weekly, or as needed to document the state of ketosis. A blood beta-hydroxybutyrate concentration of 3-5 mmol/L is recommended to insure a proper ketotic state.

Urinary measurement of ketonuria is only qualitative, and may be falsely reassuring as a strongly positive urine test for ketones may correlate with hypoketonemia. Blood measurement of ketone concentration is the preferred method.

Agents/Circumstances to Avoid

Barbiturates. Generally, children with infantile-onset seizures are treated with phenobarbital, the most commonly used antiepileptic drug in this age group. In vitro studies indicate that barbiturates aggravate the Glut1 transport defect in erythrocytes of individuals with Glut1 DS [Klepper et al 1999a]. On occasion, parents have reported that phenobarbital did not improve their child's seizure control or may have worsened their child's clinical condition.

Methylxanthines (e.g., caffeine), which are known to inhibit transport of glucose by Glut1 [Ho et al 2001b], have also been reported to worsen the clinical state of individuals with Glut1 DS [Brockmann et al 2001]. Thus, it is advisable for affected individuals to avoid coffee and other caffeinated beverages.

Valproic acid. The following studies suggest that valproic acid effects in vitro are mixed and the clinical consequences of valproic acid usage in patients with Glut1 DS cannot be predicted.

- Valproic acid inhibited Glut1 transport activity in normal and Glut1-deficient erythrocytes by 20%-30%. In primary astrocytes as well as in normal and Glut1-deficient fibroblasts, sodium valproate inhibited glucose transport by 20%-40%, accompanied by an up to 60% downregulation of GLUT1 mRNA expression [Wong et al 2005].
- A study using cultured astrocytes from the Glut1 DS mouse model showed an upregulation of Glut1 activity at lower valproic acid concentrations presumably from the valproic acid-associated inhibition of histone deacetylase activity [Kim et al 2013].

Evaluation of Relatives at Risk

It is appropriate to evaluate at-risk newborns, infants, and other relatives in order to identify as early as possible those who would benefit from initiation of treatment and preventive measures; early initiation of the ketogenic diet, ideally in infancy, results in better seizure control and improves long-term neurologic outcome. Molecular genetic testing can be used to clarify the genetic status of at-risk relatives if the pathogenic variant in the family is known.

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

Therapies Under Investigation

Triheptanoin is a specially designed synthetic triglyceride compound of three seven-carbon (C7) fatty acids intended to provide affected individuals with the medium-length, odd-chain, fatty acid heptanoate. Triheptanoin is metabolized rapidly in the liver to form a series of energy-containing metabolites, including heptanoate, which is further metabolized to 4-carbon (C4) and 5-carbon (C5) ketone bodies. Ketone bodies cross the blood-brain barrier via the monocarboxylate transporter, bypassing the deficient Glut1 transporter and providing alternative energy sources to the brain. The metabolites also have the ability to resupply intermediates of the tricarboxylic acid (TCA) cycle (i.e., anaplerosis). A pilot study of the effects of ingestion of triheptanoin as a dietary supplement in individuals with Glut1 deficiency was conducted and the preliminary results of this trial showed increased oxygen cerebral metabolic rate (CMRO2), decreased seizures, and improved neuropsychological performance [Pascual et al 2014]. A Phase II randomized double-blind placebo-controlled parallel-group study of the triheptanoin effects in those with Glut1 DS is currently enrolling affected persons who are not fully compliant with the ketogenic diet and continue to have seizures. The primary efficacy objective is reduction in seizure frequency [Mochel 2017].

Gene therapy. Murine *Glut1* was packaged into adeno-associated virus 9 (AAV9) and systemically introduced into a neonatal mouse model of Glut1 deficiency. AAV9-Glut1-treated mice and relevant controls were assessed during adult life. In AAV9-Glut1-treated mice, Glut1 RNA and protein levels rose, CSF glucose levels were restored when the mice were treated early in development (but not later), brain size was normalized, and motor defects corrected [Monani et al 2014, Tang et al 2017]. Glut1 DS caused an arrest in cerebral angiogenesis that could be avoided if gene therapy was performed before the age of two weeks.

These results provide important proof-of-concept data of the therapeutic effects of restoring Glut1 protein function early in the life of patients with Glut1 DS and represent an important step toward finding a disease-modifying treatment for the human disease. These findings also indicate the need for newborn screening to treat individuals with genetically confirmed Glut1 DS presymptomatically in infancy.

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for information on clinical studies for a wide range of diseases and conditions.

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

Glucose transporter type 1 deficiency syndrome (Glut1 DS) is most commonly inherited in an autosomal dominant manner and affected individuals are heterozygous for the pathogenic variant.

Two families have demonstrated autosomal recessive inheritance [Klepper et al 2009, Rotstein et al 2010]; one of the families was consanguineous.

Autosomal Dominant Inheritance – Risk to Family Members

Parents of a proband

- About 10% of individuals diagnosed with Glut1 DS have an affected parent [Wang et al 2005, Yang et al 2011]. The degree of impairment in an affected parent may be mild or nonexistent; somatic mosaicism for the *SLC2A1* pathogenic variant may explain this observation [Wang et al 2001].
- About 90% of individuals with Glut DS represent sporadic cases and have the disorder as the result of a *de novo SCL2A1* pathogenic variant.
- Recommendations for the evaluation of parents of an individual with Glut1 DS and no known family history of Glut1 DS include comparison of erythrocyte glucose uptake with control values and molecular genetic testing of both parents when the *SLC2A1* pathogenic variant in the proband has been identified.

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If a parent of the proband is affected or is known to have an *SLC2A1* pathogenic variant, the risk to sibs is 50%.
- If neither parent is clinically affected, the risk to the sibs of a proband appears to be low, but not zero since a clinically unaffected parent may have germline mosaicism for the pathogenic variant.
- If the *SLC2A1* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the risk to sibs is slightly greater than that of the general population because of the possibility of parental germline mosaicism; somatic and germline mosaicism have been reported [Wang et al 2001].

Offspring of a proband. Each child of an individual with Glut1 DS has a 50% chance of inheriting the *SLC2A1* pathogenic variant and being clinically affected.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent is affected, other family members are also at risk.

Autosomal Recessive Inheritance

Risk to Family Members

Parents of a proband

- The parents of an individual with an autosomal recessive Glut1 DS are obligate heterozygotes (i.e., carriers of one *SLC2A1* pathogenic variant).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. The offspring of an individual with an autosomal recessive form of Glut1 DS are obligate heterozygotes (carriers) for a pathogenic variant in *SLC2A1*.

Carrier (Heterozygote) Detection

Carrier testing for at-risk relatives requires prior identification of both *SLC2A1* 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.

Considerations in families with an apparent *de novo* pathogenic variant. When neither parent of a proband with an autosomal dominant condition has the pathogenic variant identified in the proband or clinical evidence of the disorder, the pathogenic variant is likely *de novo*. However, non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) and undisclosed adoption could also be explored.

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 or at risk.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Once the *SLC2A1* pathogenic variant(s) have been identified in an affected family member, prenatal diagnosis for a pregnancy at increased risk and preimplantation genetic testing for Glut1 DS are possible.

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.

- **Glut1 Deficiency Foundation**
  Email: info@G1DFoundation.org
  g1dfoundation.org
- **American Epilepsy Society**
  aesnet.org

- **Epilepsy Foundation**
  Phone: 800-332-1000; 866-748-8008
  epilepsy.com
- **The Child Brain Foundation**
  Phone: 214-234-0742
  Email: Info@childbrainfoundation.org
  Glucose Transporter Type 1 Deficiency Syndrome
- **Glucose Transporter Type I Deficiency (G1D) Registry**
  UT Southwestern Medical Center
  Email: rare.diseases@utsouthwestern.edu

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. Glucose Transporter Type 1 Deficiency Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
SLC2A1	1p34.2	Solute carrier family 2, facilitated glucose transporter member 1	SLC2A1	SLC2A1

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 Glucose Transporter Type 1 Deficiency Syndrome (View All in OMIM)

138140	SOLUTE CARRIER FAMILY 2 (FACILITATED GLUCOSE TRANSPORTER), MEMBER 1; SLC2A1
601042	DYSTONIA 9; DYT9
606777	GLUT1 DEFICIENCY SYNDROME 1; GLUT1DS1
612126	GLUT1 DEFICIENCY SYNDROME 2; GLUT1DS2

Gene structure. The genomic sequence is approximately 35 kb, with ten exons and nine introns. The promoter region contains sequence elements for transcription factors, including a TATA box and a phorbol ester-responsive element. Two enhancer elements within *SLC2A1* have been identified: the first is located between 3.3 and 2.7 kb upstream from the transcription initiation site; the second is located within the second intron, between 16.7 kb and 18.0 kb downstream from the transcription initiation site. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. Missense, nonsense, frameshift, and splice site variants have been reported.

Exon, multiexon, and whole-gene deletions have been reported [Seidner et al 1998, Wang et al 2000, Vermeer et al 2007, Leen et al 2010, Levy et al 2010, Yang et al 2011].

Table 2. *SLC2A1* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.376C>T	p.Arg126Cys	NM_006516.2 NP_006507.2
c.377G>A	p.Arg126His	
c.377G>T	p.Arg126Leu	
c.766_767delAAinsGT	p.Lys256Val	
c.997C>T	p.Arg333Trp	
c.884C>T	p.Thr295Met	
c.1402C>T	p.Arg468Trp	

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.

Normal gene product. Glut1 (solute carrier family 2, facilitated glucose transporter member 1) is a 492-amino-acid, 45- or 55-kd (depending on the state of glycosylation) integral membrane protein with intracellular amino and carboxyl termini and 12 transmembrane domains, which probably span the plasma membrane as alpha-helices and line a pore through which glucose and other substrates are translocated.

Glut1 is expressed at the blood-brain barrier facilitating transport of glucose across the luminal and abluminal endothelial membranes of the cerebral microvessel and facilitating transport of glucose across the astroglial plasma membrane, thus representing the fundamental vehicle by which glucose enters the brain. Additionally, the transporter recognizes other substrates such as galactose, glycopeptides, water, and dihydroascorbic acid (DHA), some or all of which may also be translocated in significant amounts, although the pathophysiologic role of these processes in Glut1 DS is not known [Klepper et al 1998].

Abnormal gene product. Abnormal Glut1 protein results from frameshift variants that predict a truncated protein, pathogenic missense variants, or, in the most severe cases, absent protein production from a deleted allele [Seidner et al 1998, Wang et al 2000, Levy et al 2010]. Loss-of-function missense variants and deletion effects range from minimal kinetic abnormalities to loss of protein synthesis.

Almost all individuals with the diagnosis of Glut1 DS have shown decreased erythrocyte 3-OMG uptake (zero-trans influx) values that are approximately 50% of control values [Wang et al 2005, Fujii et al 2007, Fujii et al 2011, Yang et al 2011]. Values in affected individuals have ranged from 36% to 74%. In all cases, the normal allele contributes approximately 50% of functional Glut1 protein to the plasma membrane [Wang et al 2005].

Two families with Glut1 DS inherited in an autosomal recessive manner have been described [Klepper et al 2009, Rotstein et al 2010]:

- In one family, a severely affected boy inherited a mutated allele from his asymptomatic heterozygous mother. A *de novo* pathogenic variant occurred in the paternal allele, producing compound heterozygosity.
- In another family, two mildly affected sisters were homozygous for the Arg468Trp pathogenic missense variant, which they inherited from their asymptomatic heterozygous consanguineous parents. 3-OMG RBC uptake studies in the older and younger sisters were 66% and 63%, and in the mother and father were 84% and 83%, compared with an intra-assay control. The pattern of inheritance is determined by the relative pathogenicity of the variant and the associated residual Glut1 activity.

References

Literature Cited

Akman CI, Provenzano F, Wang D, Engelstad K, Hinton V, Yu J, Tikofsky R, Ichese M, De Vivo DC. Topography of brain glucose hypometabolism and epileptic network in glucose transporter 1 deficiency. Epilepsy Res. 2015;110:206–15. PubMed PMID: 25616474.

Alter AS, Engelstad K, Hinton VJ, Montes J, Pearson TS, Akman CI, De Vivo DC. Long-term clinical course of Glut1 deficiency syndrome. J Child Neurol. 2015;30:160–9. PubMed PMID: 24789115.

Brockmann K, Wang D, Korenke CG, von Moers A, Ho YY, Pascual JM, Kuang K, Yang H, Ma L, Kranz-Eble P, Fischbarg J, Hanefeld F, De Vivo DC. Autosomal dominant glut-1 deficiency syndrome and familial epilepsy. Ann Neurol. 2001;50:476–85. PubMed PMID: 11603379.

Chinnery PF. Defining neurogenetic phenotypes (or how to compare needles in haystacks). Brain. 2010;133:649–51. PubMed PMID: 20157007.

Coman DJ, Sinclair KG, Burke CJ, Appleton DB, Pelekanos JT, O'Neil CM, Wallace GB, Bowling FG, Wang D, De Vivo DC, McGill JJ. Seizures, ataxia, developmental delay and the general paediatrician: glucose transporter 1 deficiency syndrome. J Paediatr Child Health. 2006; 2006;42:263–7. PubMed PMID: 16712556.

Cunningham P, Naftalin RJ. Implications of aberrant temperature sensitive glucose transport via the glucose transporter deficiency mutant (GLUT1DS) T295M for the alternate-access and fixed-site transport models. J Membr Biol. 2013;246:495–511. PubMed PMID: 23740044.

De Vivo DC, Bohan TP, Coulter DL, Dreifuss FE, Greenwood RS, Nordli DR Jr, Shields WD, Stafstrom CE, Tein I. L-carnitine supplementation in childhood epilepsy: current perspectives. Epilepsia. 1998;39:1216–25. PubMed PMID: 9821988.

De Vivo DC, Leary L, Wang D (2002a) Glucose transporter 1 deficiency syndrome and other glycolytic defects. J Child Neurol. 17 Suppl 3:3S15-23

De Vivo DC, Trifiletti RR, Jacobson RI, Ronen GM, Behmand RA, Harik SI. Defective glucose transport across the blood-brain barrier as a cause of persistent hypoglycorrhachia, seizures, and developmental delay. N Engl J Med. 1991;325:703–9. PubMed PMID: 1714544.

De Vivo DC, Wang D. Glut1 Deficiency: CSF Glucose. How low is too low? Revue Neurologique. 2008;164:877–80. PubMed PMID: 18990414.

De Vivo DC, Wang D, Pascual JM, Ho YY. Glucose transporter protein syndromes. Int Rev Neurobiol. 2002b;51:259–88. PubMed PMID: 12420362.

Flatt JF, Guizouarn H, Burton NM, Borgese F, Tomlinson RJ, Forsyth RJ, Baldwin SA, Levinson BE, Quittet P, Aguilar-Martinez P, Delaunay J, Stewart GW, Bruce LJ. Stomatin-deficient cryohydrocytosis results from mutations in SLC2A1: a novel form of GLUT1 deficiency syndrome. Blood. 2011;118:5267–77. PubMed PMID: 21791420.

Fujii T, Ho YY, Wang D, De Vivo DC, Miyajima T, Wong HY, Tsang PT, Shirasaka Y, Kudo T, Ito M. Three Japanese patients with glucose transporter type 1 deficiency syndrome. Brain Dev. 2007;29:92–7. PubMed PMID: 16949238.

Fujii T, Morimoto M, Yoshioka H, Ho YY, Law PP, Wang D, De Vivo DC. T295M-associated Glut1 deficiency syndrome with normal erythrocyte 3-OMG uptake. Brain Dev. 2011;33:316–20. PubMed PMID: 20630673.

Ho YY, Wang D, Hinton V, Yang H, Vasilescu A, Engelstad K, Jhung S, Hanson KK, Wolf JA, De Vivo DC. Glut-1 deficiency syndrome: autosomal dominant transmission of the R126C missense mutation. Ann Neurol. 2001a;50:S125.

Ho YY, Yang H, Klepper J, Fischbarg J, Wang D, De Vivo DC. Glucose transporter type 1 deficiency syndrome (Glut1DS): methylxanthines potentiate GLUT1 haploinsufficiency in vitro. Pediatr Res. 2001b;50:254–60. PubMed PMID: 11477212.

Kaufmann P, Shungu DC, Sano MC, Jhung S, Engelstad K, Mitsis E, Mao X, Shanske S, Hirano M, DiMauro S, De Vivo DC. Cerebral lactic acidosis correlates with neurological impairment in MELAS. Neurology. 2004;62:1297–302. PubMed PMID: 15111665.

Kim SK, Yang H, Pascual JM, De Vivo DC. Valproic acid enhances glucose transport in the cultured brain astrocytes of glucose transporter 1 heterozygous mice. J Child Neurol. 2013;28:70–6. PubMed PMID: 22532550.

Klepper J, Fischbarg J, Vera JC, Wang D, De Vivo DC. GLUT1-deficiency: barbiturates potentiate haploinsufficiency in vitro. Pediatr Res. 1999a;46:677–83. PubMed PMID: 10590023.

Klepper J, Garcia-Alvarez M, O'Driscoll KR, Parides MK, Wang D, Ho YY, De Vivo DC. Erythrocyte 3-O-methyl-D-glucose uptake assay for diagnosis of glucose-transporter-protein syndrome. J Clin Lab Anal. 1999b;13:116–21. PubMed PMID: 10323476.

Klepper J, Leiendecker B, Bredahl R, Athanassopoulos S, Heinen F, Gertsen E, Florcken A, Metz A, Voit T. Introduction of a ketogenic diet in young infants. J Inherit Metab Dis. 2002;25:449–60. PubMed PMID: 12555938.

Klepper J, Scheffer H, Elsaid MF, Kamsteeg EJ, Leferink M, Ben-Omran T. Autosomal recessive inheritance of GLUT1 deficiency syndrome. Neuropediatrics. 2009;40:207–10. PubMed PMID: 20221955.

Klepper J, Scheffer H, Leiendecker B, Gertsen E, Binder S, Leferink M, Hertzberg C, Näke A, Voit T, Willemsen MA. Seizure control and acceptance of the ketogenic diet in GLUT1 deficiency syndrome: a 2- to 5-year follow-up of 15 children enrolled prospectively. Neuropediatrics. 2005;36:302–8. PubMed PMID: 16217704.

Klepper J, Vera JC, De Vivo DC. Deficient transport of dehydroascorbic acid in the glucose transporter protein syndrome. Ann Neurol. 1998;44:286–7. PubMed PMID: 9708557.

Kulikova-Schupak R, Ho YY, Kranz-Eble P, Yang H, Wang D, De Vivo DC. Stimulation of GLUT-1 gene transcription by thioctic acid and its potential therapeutic value in Glut-1 deficiency syndrome (GLUT1-DS). J Inherit Metab Dis. 2001;24:S106.

Larsen J, Johannesen KM, Ek J, Tang S, Marini C, Blichfeldt S, Kibaek M, von Spiczak S, Weckhuysen S, Frangu M, Neubauer BA, Uldall P, Striano P, Zara F, Kleiss R, Simpson M, Muhle H, Nikanorova M, Jepsen B, Tommerup N, Stephani U, Guerrini R, Duno M, Hjalgrim H, Pal D, Helbig I, Møller RS, et al. The role of SLC2A1 mutations in myoclonic astatic epilepsy and absence epilepsy, and the estimated frequency of GLUT1 deficiency syndrome. Epilepsia. 2015;56:e203–8. PubMed PMID: 26537434.

Leary LD, Wang D, Nordli DR Jr, Engelstad K, De Vivo DC. Seizure characterization and electroencephalographic features in Glut-1 deficiency syndrome. Epilepsia. 2003;44:701–7. PubMed PMID: 12752470.

Leen WG, Klepper J, Verbeek MM, Leferink M, Hofste T, van Engelen BG, Wevers RA, Arthur T, Bahi-Buisson N, Ballhausen D, Bekhof J, van Bogaert P, Carrilho I, Chabrol B, Champion MP, Coldwell J, Clayton P, Donner E, Evangeliou A, Ebinger F, Farrell K, Forsyth RJ, de Goede CG, Gross S, Grunewald S, Holthausen H, Jayawant S, Lachlan K, Laugel V, Leppig K, Lim MJ, Mancini G, Marina AD, Martorell L, McMenamin J, Meuwissen ME, Mundy H, Nilsson NO, Panzer A, Poll-The BT, Rauscher C, Rouselle CM, Sandvig I, Scheffner T, Sheridan E, Simpson N, Sykora P, Tomlinson R, Trounce J, Webb D, Weschke B, Scheffer H, Willemsen MA. Glucose transporter-1 deficiency syndrome: the expanding clinical and genetic spectrum of a treatable disorder. Brain. 2010;133:655–70. PubMed PMID: 20129935.

Leen WG, Wevers RA, Kamsteeg EJ, Scheffer H, Verbeek MM, Willemsen MA. Cerebrospinal fluid analysis in the workup of GLUT1 deficiency syndrome: a systematic review. JAMA Neurol. 2013;70:1440–4. PubMed PMID: 23999624.

Levy B, Wang D, Ullner PM, Engelstad K, Yang H, Nahum O, Chung WK, De Vivo DC. Uncovering microdeletions in patients with severe Glut-1 deficiency syndrome using SNP oligonucleotide microarray analysis. Mol Genet Metab. 2010;100:129–35. PubMed PMID: 20382060.

Mochel F. Triheptanoin for the treatment of brain energy deficit: a 14-year experience. J Neurosci Res. 2017;95:2236–43. PubMed PMID: 28688166.

Monani UR, Tang M, Yang H, Li H, Engelstad K, Shetler K, Gao G, De Vivo DC. Gene therapy for Glut1 deficiency syndrome. Ann Neurol. 2014;76 Suppl 18:S176.

Overweg-Plandsoen WC, Groener JE, Wang D, Onkenhout W, Brouwer OF, Bakker HD, De Vivo DC. GLUT-1 deficiency without epilepsy--an exceptional case. J Inherit Metab Dis. 2003;26:559–63. PubMed PMID: 14605501.

Pascual JM, Liu P, Mao D, Kelly DI, Hernandez A, Sheng M, Good LB, Ma Q, Marin-Valencia I, Zhang X, Park JY, Hynan LS, Stavinoha P, Roe CR, Lu H. Triheptanoin for glucose transporter type I deficiency (G1D): modulation of human ictogenesis, cerebral metabolic rate, and cognitive indices by a food supplement. JAMA Neurol. 2014;71:1255–65. PubMed PMID: 25110966.

Pascual JM, Van Heertum RL, Wang D, Engelstad K, De Vivo DC. Imaging the metabolic footprint of Glut1 deficiency on the brain. Ann Neurol. 2002;52:458–64. PubMed PMID: 12325075.

Pascual JM, Wang D, Yang R, Shi L, Yang H, De Vivo DC. Structural signatures and membrane helix 4 in GLUT1: inferences from human blood-brain glucose transport mutants. J Biol Chem. 2008;283:16732–42. PubMed PMID: 18387950.

Pearson TS, Akman C, Hinton VJ, Engelstad K, De Vivo DC. Phenotypic spectrum of glucose transporter type 1 deficiency syndrome (Glut1 DS). Curr Neurol Neurosci Rep. 2013;13:342. PubMed PMID: 23443458.

Pearson TS, Pons R, Engelstad K, Kane SA, Goldberg ME, De Vivo DC. Paroxysmal eye-head movements in Glut1 deficiency syndrome. Neurology. 2017;88:1666–73. PubMed PMID: 28341645.

Pérez-Dueñas B, Prior C, Ma Q, Fernández-Alvarez E, Setoain X, Artuch R, Pascual JM. Childhood chorea with cerebral hypotrophy: a treatable GLUT1 energy failure syndrome. Arch Neurol. 2009;66:1410–4. PubMed PMID: 19901175.

Pike M. Opsoclonus-myoclonus syndrome. Handb Clin Neurol. 2013;112:1209–11. PubMed PMID: 23622330.

Pong AW, Geary BR, Engelstad KM, Natarajan A, Yang H, De Vivo DC. Glucose transporter type I deficiency syndrome: epilepsy phenotypes and outcomes. Epilepsia. 2012;53:1503–10. PubMed PMID: 22812641.

Pons R, Collins A, Rotstein M, Engelstad K, De Vivo DC. The spectrum of movement disorders in Glut-1 deficiency. Mov Disord. 2010;25:275–81. PubMed PMID: 20063428.

Rotstein M, Engelstad K, Yang H, Wang D, Levy B, Chung WK, De Vivo DC. Glut1 deficiency: inheritance pattern determined by haploinsufficiency. Ann Neurol. 2010;68:955–8. PubMed PMID: 20687207.

Roubergue A, Apartis E, Mesnage V, Doummar D, Trocello JM, Roze E, Taieb G, De Villemeur TB, Vuillaumier-Barrot S, Vidailhet M, Levy R. Dystonic tremor caused by mutation of the glucose transporter gene GLUT1. J Inherit Metab Dis. 2011;34:483–8. PubMed PMID: 21229316.

Seidner G, Alvarez MG, Yeh JI, O'Driscoll KR, Klepper J, Stump TS, Wang D, Spinner NB, Birnbaum MJ, De Vivo DC. GLUT-1 deficiency syndrome caused by haploinsufficiency of the blood-brain barrier hexose carrier. Nat Genet. 1998;18:188–91. PubMed PMID: 9462754.

Suls A, Dedeken P, Goffin K, Van Esch H, Dupont P, Cassiman D, Kempfle J, Wuttke TV, Weber Y, Lerche H, Afawi Z, Vandenberghe W, Korczyn AD, Berkovic SF, Ekstein D, Kivity S, Ryvlin P, Claes LR, Deprez L, Maljevic S, Vargas A, Van Dyck T, Goossens D, Del-Favero J, Van Laere K, De Jonghe P, Van Paesschen W. Paroxysmal exercise-induced dyskinesia and epilepsy is due to mutations in SLC2A1, encoding the glucose transporter GLUT1. Brain. 2008;131:1831–44. PubMed PMID: 18577546.

Tang M, Gao G, Rueda CB, Yu H, Thibodeaux DN, Awano T, Engelstad KM, Sanchez-Quintero MJ, Yang H, Li F, Li H, Su Q, Shetler KE, Jones L, Seo R, McConathy J, Hillman EM, Noebels JL, De Vivo DC, Monani UR (2017) Brain microvasculature defects and Glut1 deficiency syndrome averted by early repletion of the glucose transporter-1 protein. Nat Commun. 20;8:14152 .

Urbizu A, Cuenca-León E, Raspall-Chaure M, Gratacòs M, Conill J, Redecillas S, Roig-Quilis M, Macaya A. Paroxysmal exercise-induced dyskinesia, writer's cramp, migraine with aura and absence epilepsy in twin brothers with a novel SLC2A1 missense mutation. J Neurol Sci. 2010;295:110–3. PubMed PMID: 20621801.

Vermeer S, Koolen DA, Visser G, Brackel HJ, van der Burgt I, de Leeuw N, Willemsen MA, Sistermans EA, Pfundt R, de Vries BB. A novel microdeletion in 1(p34.2p34.3), involving the SLC2A1 (GLUT1) gene, and severe delayed development. Dev Med Child Neurol. 2007;49:380–4. PubMed PMID: 17489814.

von Moers A, Brockmann K, Wang D, Korenke CG, Huppke P, De Vivo DC, Hanefeld F. EEG features of glut-1 deficiency syndrome. Epilepsia. 2002;43:941–5. PubMed PMID: 12181017.

Wang D, Ho Y-Y, Pascual JM, Hinton V, Yang H, Anolik M, Kranz-Eble P, Jhung S, Engelstadt K, De Vivo DC. GLUT1 deficiency syndrome: R333W genotype and paternal mosaicism. Ann Neurol. 2001;50:S124.

Wang D, Kranz-Eble P, De Vivo DC. Mutational analysis of GLUT1 (SLC2A1) in Glut-1 deficiency syndrome. Hum Mutat. 2000;16:224–31. PubMed PMID: 10980529.

Wang D, Pascual JM, Yang H, Engelstad K, Jhung S, Sun RP, De Vivo DC. Glut-1 deficiency syndrome: clinical, genetic, and therapeutic aspects. Ann Neurol. 2005;57:111–8. PubMed PMID: 15622525.

Wang D, Pascual JM, Yang H, Engelstad K, Mao X, Cheng J, Yoo J, Noebels JL, De Vivo DC. A mouse model for Glut-1 haploinsufficiency. Hum Mol Genet. 2006;15:1169–79. PubMed PMID: 16497725.

Wang D, Yang H, Shi L, Ma L, Fujii T, Engelstad K, Pascual JM, De Vivo DC. Functional studies of the T295M mutation Causing Glut1 Deficiency:Glucose efflux preferentially affected by T295M. Pediatr Res. 2008;64:538–43. PubMed PMID: 18614966.

Weber YG, Kamm C, Suls A, Kempfle J, Kotschet K, Schüle R, Wuttke TV, Maljevic S, Liebrich J, Gasser T, Ludolph AC, Van Paesschen W, Schöls L, De Jonghe P, Auburger G, Lerche H. Paroxysmal choreoathetosis/spasticity (DYT9) is caused by a GLUT1 defect. Neurology. 2011;77:959–64. PubMed PMID: 21832227.

Weber YG, Storch A, Wuttke TV, Brockmann K, Kempfle J, Maljevic S, Margari L, Kamm C, Schneider SA, Huber SM, Pekrun A, Roebling R, Seebohm G, Koka S, Lang C, Kraft E, Blazevic D, Salvo-Vargas A, Fauler M, Mottaghy FM, Münchau A, Edwards MJ, Presicci A, Margari F, Gasser T, Lang F, Bhatia KP, Lehmann-Horn F, Lerche H. GLUT1 mutations are a cause of paroxysmal exertion-induced dyskinesias and induce hemolytic anemia by a cation leak. J Clin Invest. 2008;118:2157–68. PubMed PMID: 18451999.

Wong HY, Chu TS, Lai JC, Fung PK, Fok TF, Fuji T, Ho YY. Sodium valproate inhibits glucose transport and exacerbates Glut1-deficiency in vitro. J Cell Biochem. 2005;96:775–85. PubMed PMID: 16149077.

Yang H, Wang D, Engelstad K, Bagay L, Wei Y, Rotstein M, Aggarwal V, Levy B, Ma L, Chung WK, De Vivo DC. Glut1 deficiency syndrome and erythrocyte glucose uptake assay. Ann Neurol. 2011;70:996–1005. PubMed PMID: 22190371.

Zorzi G, Castellotti B, Zibordi F, Gellera C, Nardocci N. Paroxysmal movement disorders in GLUT1 deficiency syndrome. Neurology. 2008;71:146–8. PubMed PMID: 18606970.

Chapter Notes

Revision History

- 1 March 2018 (ha) Comprehensive update posted live
- 22 January 2015 (me) Comprehensive update posted live
- 9 August 2012 (me) Comprehensive update posted live

- 7 July 2009 (me) Comprehensive update posted live
- 9 September 2008 (cd) Revision: mutations in SLC2A1 identified in some families/individuals with paroxysmal exercise-induced dyskinesia and epilepsy; edits to Genetically Related Disorders
- 4 April 2007 (jp) Revision: deletion/duplication analysis clinically available
- 6 December 2006 (me) Comprehensive update posted live
- 4 April 2005 (jp) Revision: sequence analysis clinically available
- 16 July 2004 (me) Comprehensive update posted live
- 9 August 2002 (jp) Author revisions
- 30 July 2002 (me) Review posted live
- 21 February 2002 (jp) Original submission

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