GENEReviews

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Glucose Transporter Type 1 Deficiency Syndrome

[*GLUT1-DS, Glucose Transporter Protein Syndrome, Glut-1 Deficiency Syndrome*]

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Summary

Disease characteristics. Glucose transporter type 1 deficiency syndrome (Glut1-DS) is characterized by infantile seizures refractory to anticonvulsants, followed by deceleration of head growth, delays in mental and motor development, spasticity, ataxia, dysarthria, opsoclonus, and other paroxysmal neurologic phenomena, often occurring prior to meals. Affected infants appear normal at birth following an uneventful pregnancy and delivery. Birth weight and Apgar scores are normal. Seizures usually begin between age one and four months. Apneic episodes and abnormal episodic eye movements simulating opsoclonus may precede the onset of seizures by several months. Five seizure types occur: generalized tonic or clonic, myoclonic, atypical absence, atonic, and unclassified. The frequency of seizures varies among affected individuals. Varying degrees of cognitive impairment, ranging from learning disabilities to severe mental retardation, are characteristic.

Diagnosis/testing. The diagnosis of Glut1-DS is established in neurologically impaired individuals with 1) reduced cerebrospinal fluid (CSF) glucose concentration (hypoglychorrhachia) that seldom, if ever, exceeds 40 mg/dL and 2) low ratio of CSF glucose concentration to blood glucose concentration (consistently ~0.33±0.01; normal ratio: 0.65 ±0.01). *SLC2A1* is the only gene known to be associated with Glut1-DS. Molecular genetic testing is available on a clinical basis.

Management. *Treatment of manifestations:* The ketogenic diet is highly effective in controlling the seizures and is well tolerated in most; however, varying deficits involving cognition and social adaptive behavior remain. *Prevention of primary manifestations:* Anecdotal observations suggest that early initiation of the ketogenic diet may result in better seizure control and improved neurobehavioral development. *Agents to avoid:* barbiturates (e.g., phenobarbital, the most commonly used antiepileptic drug in infants); methylxanthines (e.g., caffeine). *Testing of relatives at risk:* If the disease-causing mutation has been identified in an affected family member, molecular genetic testing of at-risk newborns and symptomatic infants

permits early diagnosis and treatment. *Other:* Antiepileptic drugs (AEDs) are generally ineffective.

Genetic counseling. Glut1-DS is inherited in an autosomal dominant manner. Few individuals diagnosed with Glut1-DS have an affected parent. When one parent is affected by the disease, the degree of impairment may be mild or even subclinical. A proband with Glut1-DS often has the disorder as the result of a *de novo* gene mutation. Offspring of an individual with Glut1-DS have a 50% chance of inheriting the mutation and being clinically affected. Prenatal testing is available for pregnancies at risk if the disease-causing mutation has been identified in an affected family member.

Diagnosis

Clinical Diagnosis

Glucose transporter type 1 deficiency syndrome (Glut1-DS) usually presents in early infancy with seizures refractory to anticonvulsants, followed by deceleration of head growth, delays in mental and motor development, spasticity, ataxia, dysarthria, opsoclonus, and other paroxysmal neurologic phenomena, often occurring prior to meals [De Vivo et al 1991, De Vivo et al 1995, Klepper et al 1999c].

Testing

Glucose concentration

- **Cerebrospinal fluid (CSF).** The single most important laboratory observation in Glut1-DS is hypoglycorrhachia (reduced CSF glucose concentration); the absolute CSF glucose concentration seldom exceeds 40 mg/dL.
- **Ratio of CSF glucose concentration to blood glucose concentration.** CSF glucose concentration is measured following a four-hour fast. Blood glucose concentration is measured shortly before lumbar puncture. Under these conditions, the ratio is consistently about 0.33±0.01 (normal ratio: 0.65±0.01) [De Vivo et al 1995].

CSF lactate concentration. This value is low-normal or low, often below 1.3 mmol/L [Wang et al 2005].

Erythrocyte glucose transporter activity. Decreased 3-0-methyl-D-glucose uptake in erythrocytes also supports the diagnosis of Glut1-DS. Individuals with Glut1-DS have a reduction of approximately 50% in glucose uptake relative to normal controls [Klepper et al 1999b]. Testing is available on a clinical basis.

Positron emission tomography (PET). Cerebral fluoro-deoxy-glucose PET reveals a global decrease in glucose uptake with relative preservation of basal ganglia metabolism. This disparity in metabolism appears in early infancy and persists into adulthood regardless of disease severity or therapy [Pascual et al 2002]. PET is an additional tool that can aid in the diagnosis of Glut1-DS; however, its sensitivity and specificity in this disorder are not yet known.

Molecular Genetic Testing

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

Molecular Genetic Testing—Gene. *SLC2A1* is the only gene currently known to be associated with Glut1-DS.

Clinical uses

- Confirmatory diagnostic testing
- Prenatal diagnosis

Clinical testing

- **Sequence analysis.** Sequence analysis detected mutations in 59/76 (80%) of affected individuals tested [Wang et al 2005].
- **Deletion/duplication analysis.** Four individuals with whole gene deletions have been reported to date [Seidner et al 1998, Wang et al 2000, Vermeer et al 2007].

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Glucose Transporter Type 1 Deficiency Syndrome

Test Method	Mutations Detected	Mutation Detection Frequency [1]	Test Availability
Sequence analysis [2]	*SLC2A1* sequence variants	80%	Clinical Testing
Deletion/duplication analysis	Whole gene deletions	Unknown	

1. Proportion of affected individuals with a mutation(s) as classified by gene/locus, phenotype, population group, genetic mechanism, and/or test method

2. Including the promotor and exons of *SLC2A1* [Wang et al 2005]

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

Testing Strategy

1. Following a four-hour fast, measure glucose concentration in the CSF and calculate the ratio of CSF glucose concentration to blood glucose concentration obtained just before the lumbar puncture.
2. Perform erythrocyte glucose transport assay (when feasible).
3. Perform molecular genetic testing of *SLC2A1*.

Genetically Related (Allelic) Disorders

Heterozygous mutations in *SLC2A1* have been identified in six families and two simplex cases with paroxysmal exercise-induced dyskinesia and epilepsy. These familial cases differ clinically from those with classic glucose transporter type 1 deficiency in that they demonstrate exercise-induced dyskinesias, normal interictal neurologic examination (most individuals), normal head circumference, and later onset of seizures [Suls et al 2008, Weber et al 2008, Zorzi et al 2008].

Clinical Description

Natural History

Infants with glucose transporter type 1 deficiency syndrome (Glut1-DS) appear normal at birth following an uneventful pregnancy and delivery. Birth weight and Apgar scores are normal. Affected children then experience infantile-onset epileptic encephalopathy associated with delayed neurologic development, deceleration of head growth and resulting microcephaly, ataxia, and spasticity [De Vivo et al 2002a, De Vivo et al 2002b].

Seizures, usually occurring between age one and four months, are the first clinical indication of brain dysfunction. Apneic episodes and abnormal episodic eye movements simulating opsoclonus may precede the onset of seizures by several months. The infantile seizures are clinically fragmented (i.e., non-generalized), as is typical at this age.

The electroencephalogram (EEG) demonstrates multifocal spike discharges. With further brain maturation, the seizures become more synchronized and present clinically as generalized events associated with an atypical 3- to 4-Hz spike and wave discharge.

Five seizure types occur: generalized tonic or clonic, myoclonic, atypical absence, atonic, and unclassified. The frequency of seizures varies among individuals: some experience daily events; others have only occasional seizures separated by days, weeks, or months; two individuals never had a clinical seizure [von Moers et al 2002, Leary et al 2003].

Other paroxysmal events including intermittent ataxia, mental confusion, lethargy or somnolence, hemiparesis, abnormalities of movement or posture such as dystonia, total body paralysis, sleep disturbances, and recurrent headaches have also been described [Overweg-Plandsoen et al 2003]. It is unclear whether these events represent epileptic or non-epileptic phenomena. These neurologic symptoms generally fluctuate and may be influenced by factors such as fasting or fatigue.

Varying degrees of speech and language impairment are observed in all affected individuals. Dysarthria is common and associates with dysfluency (i.e., excessively interrupted speech). Both receptive and expressive language abilities are affected, with expressive language skills disproportionately affected.

Varying degrees of cognitive impairment, ranging from learning disabilities to severe mental retardation, are characteristic.

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.

Pathogenesis. 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 member 1), the protein product of *SLC2A1*, is the fundamental vehicle by which glucose enters the brain. The cerebral metabolic rate for glucose is low during fetal development and at birth. The rate increases linearly after birth, peaks around age three years, remains high for the remainder of the first decade of life, and gradually declines 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 and the newborn period is low, whereas the risk is increased later in infancy and early childhood.

Genotype-Phenotype Correlations

In general, the spectrum of disease ranges from mild (associated with missense mutations) to severe (associated with null mutations that either delete one entire allele or code for a nonfunctional transporter); however, these observations are preliminary, as a relatively small number of individuals with Glut1-DS have been studied.

Of particular severity is the disease caused in a single individual by compound heterozygosity for two mutations (p.Arg126Leu/p.Lys256Val) [Wang et al 2000].

It is presumed that homozygosity for a mutant allele leads to embryonic lethality.

Penetrance

Penetrance is complete.

Anticipation

For unknown reasons, familial cases may manifest more severe disease in subsequent generations.

Prevalence

The prevalence of Glut1-DS is unknown because the disease was described only recently.

Affected individuals in virtually all areas of the world have been identified.

Differential Diagnosis

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

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

- Other causes of neuroglycopenia, such as those causing intermittent subclinical 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
- 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 manifested 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 in an individual diagnosed with glucose transporter type 1 deficiency syndrome (Glut1-DS):

- General physical examination
- Neurologic examination
- Lumbar puncture (glucose, lactate)
- EEG
- Brain imaging
- Neuropsychological assessment

Treatment of Manifestations

Ketogenic diet. Because ketone bodies are easily transported across tissue membranes, they are readily available for uptake and metabolism by brain cells. The ketogenic diet was introduced as a treatment for Glut1-DS in 1991 [De Vivo et al 1991]. In the diet, most carbohydrates are replaced by lipids and proteins in varying ratios. Experience over the past decade indicates that the ketogenic diet is highly effective in controlling the seizures and is well tolerated in most cases; however, despite control of seizures, affected individuals continue to have varying neurobehavioral deficits involving cognition and social adaptive behavior [Klepper et al 2002]. Seizures sometimes recur even with the diet [Klepper et al 2005].

Alpha-lipoic acid (thioctic acid) also has 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 [De Vivo et al 1996]. 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

Anecdotal observations suggest that early initiation of a ketogenic diet may result in better seizure control and improved neurobehavioral development by ameliorating cerebral glucose starvation while the brain develops and brain glucose consumption is highest.

Agents/Circumstances to Avoid

Barbiturates are known to inhibit transport of glucose. Generally, individuals with infantile-onset seizures are treated with phenobarbital, the most commonly used antiepileptic drug in this age group. On occasion, parents report that phenobarbital does not improve seizure control, and that it seems to worsen their child's clinical state. In vitro evidence suggests that barbiturates aggravate the Glut1 transport defect in erythrocytes of individuals with Glut1-DS [Klepper et al 1999a].

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

Testing of Relatives at Risk

It is appropriate to offer molecular genetic testing to at-risk newborns and symptomatic infants if the disease-causing mutation has been identified in an affected family member so that morbidity can be reduced by early diagnosis and treatment.

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

Therapies Under Investigation

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

Other

Antiepileptic drugs (AEDs) are generally ineffective or afford only limited improvement.

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

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

Genetic Counseling

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

Mode of Inheritance

Glucose transporter type 1 deficiency syndrome (Glut1-DS) is inherited in an autosomal dominant manner [Brockmann et al 1999, Brockmann et al 2001, Ho et al 2001a, Klepper et al 2001, Wang et al 2001a].

Risk to Family Members

Parents of a proband

- Few individuals diagnosed with Glut1-DS have an affected parent.
- When one parent is affected by the disease, the degree of impairment may be mild or even subclinical.
- A proband with Glut1-DS often has the disorder as the result of a *de novo* gene mutation.
- 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 and molecular genetic testing of both parents if the mutation 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 parents.
- If a parent is affected or has a disease-causing mutation, the risk is 50%.
- When the parents are clinically unaffected, the risk to the sibs of a proband appears to be low.
- If the disease-causing mutation cannot be detected in the DNA extracted from leukocytes of either parent, the risk to sibs is low but greater than that of the general population. Although no instances of germline mosaicism have been reported, it remains a possibility, especially because somatic mosaicism has been reported [Wang et al 2001b].

Offspring of a proband. Each child of an individual with Glut1-DS has a 50% chance of inheriting the mutation 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, his or her family members are at risk.

Related Genetic Counseling Issues

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

Family planning. The optimal time for determination of genetic risk and discussion of the availability of prenatal testing is before pregnancy.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100%. For laboratories offering DNA banking, see Testing.

Prenatal Testing

Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at approximately 15-18 weeks' gestation or chorionic villus sampling (CVS) at approximately ten to 12 weeks' gestation. The disease-causing allele of an affected family member must be identified before prenatal testing can be performed.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

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

Molecular Genetics

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

Table A. Molecular Genetics of Glucose Transporter Type 1 Deficiency Syndrome

Gene Symbol	Chromosomal Locus	Protein Name
SLC2A1	1p34.2	Solute carrier family 2, facilitated glucose transporter member 1

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

Table B. OMIM Entries for Glucose Transporter Type 1 Deficiency Syndrome

138140	SOLUTE CARRIER FAMILY 2 (FACILITATED GLUCOSE TRANSPORTER), MEMBER 1; SLC2A1
606777	GLUCOSE TRANSPORT DEFECT, BLOOD-BRAIN BARRIER

Table C. Genomic Databases for Glucose Transporter Type 1 Deficiency Syndrome

Gene Symbol	Entrez Gene	HGMD
SLC2A1	6513 (MIM No. 138140)	SLC2A1

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

Note: HGMD requires registration.

Normal allelic variants. 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 the SLC2A1 gene have been identified: the first is located between 3.3 and 2.7 kb upstream from the transcription initiation site, while the second is located within the second intron, between 16.7 kb and 18.0 kb downstream from the transcription initiation site [Murakami et al 1992]. No allelic variants have been identified.

Pathologic allelic variants. Summarized in Table 2 (pdf)

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 [Mueckler et al 1985]. Glut1 is expressed predominantly at the blood-brain barrier facilitating transport of glucose across the luminal and abluminal endothelial membranes of the cerebral microvessel. Glut1 also facilitates 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 [Agus et al 1997, Klepper et al 1998].

Abnormal gene product. Abnormal GLUT1 protein results from frameshift mutations that predict a truncated protein or missense mutations, or, in the most severe cases, absent protein production from a deleted allele [Seidner et al 1998, Wang et al 2000]. The range of loss of function with missense mutations and deletions varies from minimal kinetic anomalies to absent plasma membrane transporter from the mutant allele. In all cases, the normal allele contributes approximately 50% of functional Glut1 protein to the plasma membrane [Wang et al 2005].

Resources

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

American Epilepsy Society
342 North Main Street
West Hartford CT 06117-2507
Phone: 860-586-7505
Fax: 860-586-7550
Email: info@aesnet.org
www.aesnet.org

Colleen Giblin Foundation
690 Kinderkamack Road Suite 104
Oradell NJ 07645
Phone: 201-262-2463
www.colleengiblinfound.org

Epilepsy Foundation
8301 Professional Place
East Landover, MD 20785-2238
Phone: 800-EFA-1000 (800-332-1000); 301-459-3700
Fax: 301-577-4941
Email: webmaster@efa.org
www.efa.org

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

Published Statements and Policies Regarding Genetic Testing

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

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Suggested Reading

De Vivo DC, Wang D, Pascual JM (2007) Disorders of glucose transport. In: Rosenberg R, Prusiner S, DiMauro S, Barchi R, Nestler E (eds) The Molecular and Genetic Basis of Neurologic and Psychiatric Disease. Lippincott Williams & Wilkins, Philadelphia, pp 653-62

Chapter Notes

Revision History

- 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 to live Web site
- 4 April 2005 (jp) Revision: sequence analysis clinically available
- 16 July 2004 (me) Comprehensive update posted to live Web site
- 9 August 2002 (jp) Author revisions
- 30 July 2002 (me) Review posted to live Web site
- 21 February 2002 (jp) Original submission