

# GLUCOSE TRANSPORTER TYPE 1 DEFICIENCY SYNDROME (G1D)

## Educational Materials

(all materials are available at  
<http://www.childbrainfoundation.org/resources.html>)

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## I. GLUT101: AN INTRODUCTION

### a. What is GLUT1 deficiency syndrome?

GLUT1 deficiency syndrome (G1D) is a genetic condition, i.e., a disease caused by an alteration or mutation <sup>1</sup> in a gene <sup>2</sup> that primarily affects the brain. Most but not all affected <sup>3</sup> individuals develop seizures within the first few months of life. These seizures are very difficult to treat with the common anti-seizure medications. Other individuals suffer from severely abnormal uncontrollable movements that interfere with their daily activities, with or without additional seizures. Babies with G1D are born normally and usually have a normal head size at birth, but overtime may show signs of delayed brain growth and development.

### b. What are some other common symptoms of G1D?

- Developmental delays and learning disabilities
- Stiffness caused by abnormal tensing of the muscles (spasticity)
- Difficulty in coordinating movements (ataxia)
- Speech abnormalities (dysarthria)
- Episodes of confusion
- Lack of energy (lethargy)
- Headaches
- Muscle twitches (myoclonus)
- Involuntary irregular eye movements, particularly in early infancy
- Lifelong epilepsy and seizures of various types

### c. Less common symptoms of G1D include:

Spells of uncontrollable movements while awake (dyskinesia)  
Constant movements at rest and while awake (chorea)  
Episodes of paralysis of either side of the body, left or right (alternating hemiplegia)  
Hemolytic anemia (abnormal breakdown of red blood cells)

<sup>1</sup> Any alteration in a [gene](#) from its natural state; may be disease-causing or a benign, normal variant

<sup>2</sup> The basic unit of heredity, consisting of a segment of [DNA](#) arranged in a linear manner along a [chromosome](#). A [gene](#) codes for a specific protein or segment of protein leading to a particular characteristic or function.

<sup>3</sup> Referring to an individual who manifests symptoms of a particular condition

Like many other genetic conditions, it is important to understand that not all affected individuals experience all of the characteristic symptoms and the severity of each symptom can vary tremendously between individuals.

#### **d. How common is G1D?**

G1D is a rare disorder. Fewer than 300 cases have been reported since the disease was identified in 1991. However, the number of affected individuals may actually be greater because it is believed that not only individuals who suffer from seizures, but also people with other types of neurological disabilities may have undiagnosed G1D. G1D affects males and females of all races and ethnicities equally.

#### **e. How is the diagnosis of G1D made?**

When a diagnosis of G1D is suspected, a lumbar puncture (spinal tap) can be performed by a neurologist (a medical specialist who manages and treats disorders of the brain and spinal cord) or other physician. Low, and otherwise unexplained, glucose (sugar) values which are commonly found in the spinal fluid of affected individuals suggest the diagnosis. Genetic testing<sup>4</sup> can then be done to confirm the diagnosis (see genetic testing). Genetic testing can also be performed in individuals with specific symptoms highly suggestive of G1D without performing a lumbar puncture. The first line of genetic testing involves direct DNA analysis<sup>5</sup>.

#### **f. What causes G1D?**

G1D is caused by a defect in the SLC2A1 gene, the only gene currently known to be associated with G1D. The SLC2A1 gene makes a protein called the glucose transporter protein type 1 (GLUT1). This protein is responsible for transporting glucose (a simple sugar) from the blood into the cells for energy. Glucose transporter protein type 1 is involved in moving glucose across the blood-brain barrier, the wall that separates tiny blood vessels (capillaries) from the surrounding brain tissue. In normal conditions, glucose is the brain's main energy source. Alterations or mutations<sup>6</sup> in the SLC2A1 gene can reduce or eliminate the function of the glucose transporter protein type 1 resulting in the signs and symptoms of G1D.

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<sup>4</sup> Testing designed to confirm or exclude a known or suspected genetic disorder in a symptomatic individual or, prenatally, in a fetus at risk for a certain genetic condition

<sup>5</sup> The use of any test method, such as [sequence analysis](#), [mutation scanning](#), or [mutation](#) analysis to detect a [mutation](#) in a [gene](#)

<sup>6</sup> Any alteration in a [gene](#) from its natural state; may be disease-causing or a benign, normal variant

### g. Is G1D inherited?

G1D can be inherited as an autosomal dominant <sup>7</sup> genetic condition meaning that only one nonworking copy of the gene in each cell is enough to cause the disorder.

Most cases of this disorder, however, result from new spontaneous mutations in the gene that began with the affected individual at the time of conception. In these instances, there is typically no familial <sup>8</sup> history of the disorder. In some cases, an affected individual may inherit the nonworking copy of the gene or mutation from an affected parent. For affected individuals, there is a 50% chance in each pregnancy to pass the nonworking copy of the gene to a child. Unfortunately, due to the variability of symptoms, it is difficult to predict the severity of the condition in a child of an affected parent.

It is important to understand that having a child born with G1D is no one's fault and that we cannot control the genes we pass on to our children.

## II. TREATMENT OF G1D

### a. Is there a cure or treatment for individuals diagnosed with G1D?

At this time, there is no cure for G1D. Therefore, treatment is directed toward preventing or controlling symptoms. Because anti-seizure medications typically do not work in patients with G1D, the ketogenic diet has been shown to be effective in controlling seizures in most patients with the condition, therefore improving overall cognitive development. Unfortunately, some degree of seizure activity may continue even while on the diet and patients may still continue to show other neurological and developmental symptoms of the disorder.

G1D patients afflicted by movement disorders without seizures also benefit from the ketogenic diet and the effect of the diet on brain metabolism is probably identical to that in patients with epilepsy.

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<sup>7</sup> Describes a trait or disorder in which the [phenotype](#) (the observable physical and/or biochemical characteristics of the expression of a [gene](#)) is expressed in those who have inherited only one copy of a particular [gene mutation \(heterozygotes\)](#); specifically refers to a [gene](#) on one of the 22 pairs of autosomes (non-sex [chromosomes](#))

<sup>8</sup> A [phenotype](#) (the observable physical and/or biochemical characteristics of the expression of a [gene](#)) that occurs in more than one family member; may have genetic or non-genetic etiology.

**b. What is the ketogenic diet and how does it work?**

The ketogenic diet is a high fat, low carbohydrate diet which is usually prescribed by a physician and carefully monitored by a dietician. Ketones are formed when the body uses fat instead of glucose for its source of energy. In patients with G1D and certain other seizure disorders, the ketone bodies pass into the brain and replace the glucose as an energy source helping to eliminate seizures.

**c. Are there side effects from the ketogenic diet?**

Common but easily treatable side effects of the diet include constipation, poor weight gain, and possible kidney stones. It is important to talk to your doctor or clinical nutritionist about how to reduce these possible side effects. Also, because the diet does not provide all the necessary vitamins and minerals of a well balanced diet, a vitamin supplement may be indicated. Blood zinc and selenium levels can drop on the ketogenic diet but this can be prevented with supplementation under professional supervision.

**d. Are there any experimental treatments that may help control seizures in G1D?**

Alpha-lipoic acid (thioctic acid) has been shown to assist glucose transport in test tube cells. Therefore, in some cases, alpha-lipoic acid supplements have been suggested. However, significant gastrointestinal side effects such as intolerance may result.

**e. Are there any medications or supplements to avoid?**

There is no definitive proof that certain medications should be avoided. However, reports indicate that phenobarbital, the most commonly prescribed anti-seizure drug for infants and children, has been shown not to improve seizure control, and in some cases, actually worsens a child's seizures and symptoms.

Methylxanthine (caffeine) found in coffee, tea, chocolate and some cola-flavored and "energy boosting" beverages, has also been reported to block glucose transport in laboratory experiments. Therefore, it is recommended that individuals with G1D avoid caffeinated beverages and foods rich in caffeine.

### III. COMMON QUESTIONS AFTER THE DIAGNOSIS OF G1D

#### a. What happens once a diagnosis of G1D is made?

Once the diagnosis of G1D is confirmed, it is not uncommon for parents to feel both a sense of relief now knowing the actual cause for their child's symptoms as well as a sense of urgency to learn as much as possible about the treatment and management of the disorder. Because there is still so much more to learn about this rare disorder, treating and managing the condition is a life-long learning process for both families and their physicians. Families are therefore encouraged to develop strong collaborative relationships with their physicians. It is encouraging that the number of families and health care professionals interested in the disease is growing rapidly and significant advances and changes in the way we think about G1D may come in the near future.

#### b. How will my child develop?

Although developmental and cognitive delays are common in individuals with G1D, the degree of intellectual and developmental disability can vary greatly from person to person. This has been shown even among multiple affected members of the same family with the same gene mutation. This is most likely due to other genes as well as environmental factors not yet known that can influence and modify the symptoms of G1D. Early childhood intervention programs and targeted therapies can be effective in helping affected individuals reach their full developmental potential. It is encouraging that most individuals with G1D tend to have strong social and interpersonal skills enabling them to better interact with their peers and within their communities. In the case of G1D patients with seizures, and although the data are preliminary, there appears to be a correlation between the age of initiation of therapy to control seizures (ketogenic diet) and overall prognosis.

#### c. Are G1D patients prone to other diseases?

No other disease associations are known at this time.



**d. Are there side effects from the ketogenic diet?**

Common but easily treatable side effects of the diet include constipation, poor weight gain, and possible kidney stones. It is important to talk to your doctor about how to reduce these possible side effects. Also, because the diet does not provide all the necessary vitamins and minerals of a well balanced diet, a vitamin supplement may be indicated.

**e. Does the ketogenic diet need to be maintained for life?**

For unknown reasons, some patients with G1D have been able to successfully discontinue the diet at the onset of puberty. Others have remained on the diet and others resume treatment with seizure and other medications to reduce their symptoms.

**f. Could G1D have been prevented?**

Since most cases of G1D are a result of a new spontaneous mutation<sup>9</sup> that occurs at the time of conception and nothing a parent did or did not do caused this to happen, there is no way to know if a child is at risk of having the disorder. Unless a disease causing mutation<sup>10</sup> has been previously identified in a family at risk to have a child with G1D, there is no prenatal test to determine if a child will be born with G1D. Prenatal ultrasounds and current mandatory newborn screening tests do not detect G1D. If a disease causing mutation is known, prenatal diagnosis<sup>11</sup> (amniocentesis or chorionic villus sampling) and possible preimplantation genetic diagnosis (the combination of in vitro fertilization and genetic testing to identify unaffected embryos) would be available.

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<sup>9</sup> An alteration in a [gene](#) that is present for the first time in one family member as a result of a [mutation](#) in a germ cell (egg or sperm) of one of the parents or in the fertilized egg itself

<sup>10</sup> A [gene](#) alteration that causes or predisposes an individual to a specific disease

<sup>11</sup> Testing performed during pregnancy to determine if a fetus is [affected](#) with a particular disorder. Chorionic villus sampling (CVS), amniocentesis, periumbilical blood sampling (PUBS), ultrasound, and fetoscopy are examples of procedures used either to obtain a sample for testing or to evaluate fetal anatomy.

**g. Will there ever be a cure for G1D?**

More research is needed. At the moment, there is no evidence that the brain will allow the introduction of normal DNA or cells capable of replacing the abnormal brain cells affected by G1D. New developments and advances in gene therapy are expected in the future.

## IV. G1D RESEARCH

**a. What is the state of research on G1D?**

Research is taking place on several fronts:

**b. Research on animal models of G1D**

Laboratory studies focus on understanding how the brain develops and functions in G1D. This type of research is called mechanistic. Rodent and fish models with G1D were created by several researchers around 2003-2006. While these models do not replace the information that can be obtained from patients, they allow for the study of animals across their entire life cycle, while simultaneously providing a source of brain cells for detailed analysis not allowed in human subjects. Mouse models with G1D are used to characterize the basis of epilepsy in the disease by electrophysiological (electrical) recording of brain neurons by patch-clamp, a highly informative technique that measures brain cell communication, and by analyzing brain metabolism using labeled glucose probes (stable isotopes, used in  $^{13}\text{C}$  NMR, or nuclear magnetic resonance). As is always the case with biomedical research, it is expected that laboratory research will result in a more complete understanding of the disease and open new (and probably unexpected) directions for the development of treatments.

**c. Research on G1D patients**

There is reason to believe that not all forms of G1D are yet known because affected patients with nonclassical symptoms of the disease continue to be identified. New mutations in the Glut1 gene are periodically found in many laboratories around the world. It is not yet clear what happens to patients with G1D across the lifespan or how the human brain is altered by the disease. In comparison with other diseases, for which scientists have had access to numerous patients and to matched brain autopsy specimens, G1D remains a rare and understudied disease. In addition to finding new mutations, new genes and new treatments, clinical research

efforts include the performance of high-field brain NMR (nuclear magnetic resonance, a special type of MRI) in patients with G1D and other neurometabolic disorders. The brain contents of several key neurochemicals important for brain cell function and communication can be measured for the first time in select patients with G1D without the use of any substances for research purposes only.

#### **d. Research relevant to genetic brain disorders in general**

There is a very significant amount of work being done worldwide on new methods for the treatment of neurometabolic and neurogenetic disorders in general, one of which is G1D. Some involve the use of stem cells, some use viruses to replace abnormal brain genes, and some focus on the discovery of new drugs that may not cure a disease but could ameliorate common and debilitating symptoms. These initiatives, when successful, can often be translated to other diseases like G1D and vice versa, allowing advances in one particular disease to potentially benefit others.

#### **e. How can I contribute to research?**

The best way to contribute is to become and remain informed about any new advances and to talk and ask questions to health care professionals. Creating or becoming part of a patient advocacy or support group for families with G1D is another important way to help disseminate information, improve patient access to experts and resources, and facilitate and fund research. Lastly, financial contributions at any level help researchers answer specific questions related to potential treatments for G1D.

## **V. MOVEMENT DISORDERS IN G1D**

### **a. What are movement disorders?**

Movement disorders are a group of symptoms that indicate an impaired ability to produce and control body movement. Every body movement, from raising a hand to smiling, involves a complex interaction between the brain and spinal cord, nerves, and muscles. Damage to or malfunction of any of these components may result in a movement disorder. There is reason to believe that G1D movement disorders originate in the brain.

The term 'paroxysmal' is also often used, to indicate the abnormal movements are sudden and unpredictable, with a fairly rapid return to normal.

#### **b. What movement disorders are seen in G1D?**

- **Ataxia** is unsteady or poorly controlled movement due to problems with the control of coordination and balance.
- **Dyskinesia**, which simply means abnormal ('dys') movement ('kinesia'). Tics, spasm, athetosis (slow, writhing motions), chorea (rapid, randomly irregular jerky movements) and dystonia are all different types of dyskinesia.
- **Chorea** is repetitive, brief, jerky, rapid involuntary movements that start in one part of the body and move abruptly, unpredictably, and often continuously to another part.
- In **dystonia** there are sustained or persistent contractions of one or more muscles. This leads to abnormal postures or writhing, twisting movements of part of the body. There are many different types, with various muscles involved. Writer's cramp is an example of focal dystonia (limited to one group of muscles), causing bizarre postures in one arm when writing or typing and disappearing at rest.
- **Myoclonus** refers to quick, lightning-like jerks (contractions) of a muscle or a group of muscles. Myoclonus may involve only one hand, a group of muscles in the upper arm or leg, or a group of facial muscles. Or it may involve many muscles at the same time.

#### **c. Can G1D cause movement disorders and also seizures?**

Yes. Movement disorders may occur in G1D in isolation, in combination with other movement disorders, or in G1D patients who also have seizures and epilepsy.

#### **d. How are G1D movement disorders treated?**

The treatment of movement disorders in general may include several drugs prescribed by a neurologist. There is very limited experience with the use of these drugs in G1D, but there is no known reason to withhold any of these drugs in G1D, particularly if they show efficacy.

However, the ketogenic diet has proven effective for the treatment of G1D-related movement disorders.

## VI. G1D RESOURCES

### a. G1D medical and diagnostic referral laboratory information

General information: Collaboration, Education, and Test Translation (CETT) Program for Rare Genetic Diseases [NIH Office of Rare Diseases Research](#)

G1D genetic diagnosis (CETT program): The Child Brain Foundation: [www.ChildBrainFoundation.org](http://www.ChildBrainFoundation.org)

### b. G1D disease information for patients and caretakers

The Child Brain Foundation: [www.ChildBrainFoundation.org](http://www.ChildBrainFoundation.org)

Genetics Home Reference: <http://ghr.nlm.nih.gov/condition=glut1deficiencysyndrome>

Glut1 Deficiency Foundation: [www.g1dfoundation.org](http://www.g1dfoundation.org)

### c. Voluntary G1D patient registry

The Child Brain Foundation: Coming Soon

### d. Advocacy information




The Child Brain Foundation: [www.ChildBrainFoundation.org](http://www.ChildBrainFoundation.org)

Glut1 Deficiency Foundation: [www.g1dfoundation.org](http://www.g1dfoundation.org)

Office of Rare Diseases Research, NIH: <http://rarediseases.info.nih.gov/>

National Organization for Rare Disorders: <http://www.rarediseases.org/>

**e. Professional information**

- [Gene Reviews](#)  - Periodically updated clinical summary and testing options
- [Gene Tests](#)  - DNA tests ordered by healthcare professionals
- [PubMed](#) - Recent literature, searchable by keyword, author or publication title
- [OMIM](#)  - Genetic disorder catalog

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### About the Collaborators

The Child Brain Foundation:

The Child Brain Foundation is a 501 (c) 3 certified non-for-profit organization, based in Dallas, Texas. It supports research projects to understand and treat pediatric neurological disorders and encourages greater communication between scientists, professionals, families and the general public. For additional information, please visit [www.childbrainfoundation.org](http://www.childbrainfoundation.org).

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About the Sponsor, The National Institute of Health:

The National Institutes of Health (NIH), a part of the U.S. Department of Health and Human Services, is the nation's medical research agency—making important discoveries that improve health and save lives. The Collaboration, Education, and Test Translation (CETT) Program for Rare Genetic Diseases was developed by the NIH Office of Rare Diseases Research. The goals were to promote new test development for rare genetic diseases, to facilitate the translation of genetic tests from research laboratories to clinical practice, to establish collaborations and provide education about each rare genetic diseases, to stimulate related genetic research, to enhance the clinical impact of testing, and to support the collection and storage of genetic test result information in publicly accessible databases to leverage the information into new research and new treatment possibilities

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