Glut-1 Deficiency Syndrome: Clinical, Genetic, and Therapeutic Aspects

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Impaired glucose transport across the blood-brain barrier results in Glut-1 deficiency syndrome (Glut-1 DS, OMIM 606777), characterized by infantile seizures, developmental delay, acquired microcephaly, spasticity, ataxia, and hypoglycorrhachia. We studied 16 new Glut-1 deficiency syndrome patients focusing on clinical and laboratory features, molecular genetics, genotype–phenotype correlation, and treatment. These patients were classified phenotypically into three groups. The mean cerebrospinal fluid glucose concentration was 33.1 ± 4.9mg/dl equal to 37% of the simultaneous blood glucose concentration. The mean cerebrospinal fluid lactate concentration was 1.0 ± 0.3mM, which was less than the normal mean value of 1.63mM. The mean V_{max} for the 3-*O*-methyl-D-glucose uptake into erythrocytes was 996 fmol/10^6 red blood cells per second, significantly less (54 ± 11%; *t* test, $p < 0.05$) than the mean control value of 1,847. The mean Km value for the patient group (1.4 ± 0.5mM) was similar to the control group (1.7 ± 0.5mM; *t* test, $p > 0.05$). We identified 16 rearrangements, including seven missense, one nonsense, one insertion, and seven deletion mutations. Fourteen were novel mutations. There were no obvious correlations between phenotype, genotype, or biochemical measures. The ketogenic diet produced good seizure control.

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In 1985, Mueckler and colleagues[1] deduced the amino acid sequence of the first glucose transport protein (Glut-1) from human HepG2 hepatoma cells by analysis of a complementary DNA clone. Additional proteins have been identified that are responsible for the facilitated diffusion of hexoses across tissue barriers.[2] These proteins belong to a large superfamily of transport facilitators, designated SLC2A according to the HUGO Gene Nomenclature Committee,[3–5] consisting of 12 *SLC2A* genes, numbered 1 through 12, encoding 12 Glut proteins. A 13th member of this family is the myoinositol transporter, HMIT1. Glut-1 is the major glucose transporter expressed on vascular endothelial cells comprising the blood–brain barrier and is responsible for glucose entry into the brain.[6] The gene consists of 10 exons and 9 introns, which were localized to the short arm of chromosome 1(1p34.2) (UCSC Human Genome Project Working Draft, April 2002 assembly [hg11]; further information is available online at: http://genome.cse.ucsc.edu).

In 1991, De Vivo and colleagues[7] reported two patients with a novel clinical syndrome characterized by an infantile-onset epileptic encephalopathy associated with delayed neurological development, deceleration of head growth, acquired microcephaly, incoordination, and spasticity. A defect in glucose transport across the blood–brain barrier was proposed based on the finding of low cerebrospinal fluid (CSF) glucose and lactate values in the absence of hypoglycemia. Seven years later, these speculations were substantiated. The first patient had a large-scale deletion involving one allele of the *GLUT-1* gene causing hemizygosity, and the second patient had a heterozygous nonsense mutation (Y449X).[8] The novel disease was termed *Glut-1 deficiency syndrome* (Glut-1 DS) (OMIM #606777 and *138140; more information is available online at: http://www.genereviews.org). Since 1991, approximately 100 Glut-1 DS patients have been identified in the United States and elsewhere in the world,[9] including three familial cases that established Glut-1 DS as an autosomal dominant trait.[10–12] Paternal mosaicism has been shown in an additional Glut-1 DS family.[13] The most severe phenotype, associated with compound heterozygosity in trans, was described in another child.[14] Nonclassic phenotypes also have been identified. For example, one patient had mental retardation and intermittent ataxia without any clinical seizures[15] and one patient had a movement disorder characterized by choreoathetosis and dystonia.[16] In reality, most patients have abnormal movements ranging from motor

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Table 1. Summary of Glut-1DS Clinical Features

Patient No.	Age (yr)	Sex	Seizures	Seizure Onset (age in weeks)	Hypotonia/ Spasticity	Ataxia	Language Deficit	Microcephaly	Ketogenic Diet: Age When Started (mo)
1	6	M	2	8	0	0	1	2	41
2	9	M	2	72	3	2	2	0	N/A
3	0.5	M	1	8	0	0	0	0	3.5
4	8	M	3	8	3	2	3	2	78
5	12	M	1	52	1	1	1	1	96
6	7	M	1	24	1	1	3	0	14
7	9	M	2	12	3	3	3	2	98
8	12	M	0	N/A	1	2	2	0	108
9	1	M	2	12	1	0	0	0	N/A
10	9	F	0	N/A	1	1	1	3	69
11	7	F	1	36	2	2	2	2	68
12	13	M	2	5	2	2	2	0	132
13	9	F	3	6	2	2	2	0	7
14	2	M	0	N/A	3	2	3	1	104
15	8	F	2	12	3	3	2	0	53
16	6	M	2	12	3	2	2	3	37

Seizure: 0 = no clinical seizure; 1 = 1 seizure/mo; 2 = weekly or monthly seizures; 3 = daily or several seizures/week. Hypotonia/spasticity: 0 = normal; 1 = hyperreflexia (3+); 2 = hyperreflexia (4+), clonus, spasticity, Babinski signs; 3 = 2 plus difficulty/inability to walk. Ataxia: 0 = normal; 1 = incoordination, no difficulty walking; 2 = incoordination, difficulty walking; 3 = incoordination, unable to walk. Language deficit: 0 = no deficit; 1 = speaks in sentences; decreased vocabulary; 2 = speaks in simple phrases; 3 = speaks in simple words, or no language. Microcephaly: 0 = no deficit; 1 = within 1 standard deviation of the mean; 2 = between 1 and 2 standard deviations of the mean; 3 = greater than 2 standard deviation of the mean. Ketogenic diet: age when started (mo).
N/A = not started on ketogenic diet.

restlessness to dystonia (D.C.D., personal observations).

In this article, we report our findings in 16 recently diagnosed Glut-1DS patients, focusing on clinical and laboratory features, kinetics of erythrocyte 3-*O*-methyl-D-glucose uptake study, molecular genetics, genotype–phenotype correlation, and treatment efforts.

Patients and Methods

The investigatory studies of blood and skin fibroblasts were exempted from full review and approved by the Columbia University Institutional Review Board. Informed consent was obtained from the parents and patients who participated in this study.

Erythrocyte 3-O-methyl-D-glucose Uptake Studies

Investigations of uptake of 3-*O*-methyl-D-glucose into red blood cells were performed as described elsewhere.[17]

Mutational Analysis of GLUT-1 *Gene*

White blood cells were used to extract genomic DNA from patients and their parents. Mutational analysis of *GLUT-1* was performed as described previously.[18] The mutation identified was further confirmed by sequencing of another independent polymerase chain reaction product.

Results

Clinical Features

Three clinical phenotypes have emerged as more patients are described.[19] The main clinical features are described in Table 1. The first phenotype (classic) is a developmental encephalopathy with seizures, which is shared by 13 (81%) patients in this study.[19] The prenatal and perinatal histories, birth weights, head circumference, and Apgar scores were normal. The earliest paroxysmal events included cyanotic spells, atonic drop attacks, and episodic chaotic eye movements. In nine patients, seizures began between age 3 weeks and 4 months. The infantile seizures were clinically fragmented and the electroencephalographic (EEG) correlate was that of multifocal spike-wave discharges. Seizures became more synchronized with brain maturation and presented clinically as generalized events associated with classic 2.5- to 4-Hz spike-wave discharges electrically.[20] We described five seizure types previously, including generalized tonic or clonic, myoclonic, atypical absence, atonic, and unclassified.[19,20] Seizure frequency varied among patients. Some patients (such as Patients 4 and 13) had daily seizures, whereas others (such as Patients 3, 5, 6, and 11) had only occasional seizures separated by days, weeks, or months. The clinical seizures did not respond to or worsened with antiepileptic drugs, such as phenobarbital, and responded rapidly to a ketogenic diet. Fourteen (88%) patients in this study group remain on a ketogenic diet; their ages when started on the diet ranged from 3.5 to 132 months (see Table 1).

These patients also experienced other paroxysmal events, and it is unclear whether these events are epileptic or nonepileptic nosologically.[19] Paroxysmal events include ataxia, confusion, lethargy or somno-

lence, alternating hemiparesis, abnormalities of movement or posture including myoclonus and dystonia, total body paralysis, sleep disturbances, and recurrent headaches. The frequency of the neurological symptoms fluctuated unpredictably and was influenced by environmental factors such as fasting or fatigue. Other symptoms included speech and language impairment, dysarthria, and receptive and expressive language deficits. Cognitive impairment ranged from learning disabilities to severe mental retardation. Social adaptive behavior was a consistent strength in these children. They were remarkably comfortable in the group setting and interacted comfortably with their peer group and with adults. Acquired microcephaly (head circumference less than 3rd percentile for age) occurred in 50% of patients, but deceleration of head growth was more common. Neurological signs implicated the pyramidal, extrapyramidal, and cerebellar systems predominantly, producing varying degrees of spasticity, dystonia, and ataxia. The limb tone generally was increased, tendon reflexes were brisk, and Babinski signs were present. The gait abnormality was best described as a spastic ataxia. No consistent abnormalities of ocular fundi, cranial, nerves or sensation were described, and results of the general physical examination were normal.

The second phenotype has been identified recently.[15] It is characterized by mental retardation, dysarthric speech, and intermittent ataxia without any clinical seizures. The motor symptoms in this patient responded to the ketogenic diet. This patient has not had any seizures or other paroxysmal symptoms. Patients 10 and 14 also belong to this phenotype, with motor and mental delays, microcephaly, ataxia, and dystonia.

The third phenotype has been characterized by choreoathetosis and dystonia.[16] This patient (Patient 8) had a movement disorder characterized by paroxysmal episodes of blinking and abnormal head and eye movements. These episodes initially occurred every few days and gradually decreased in frequency until ceasing at age 3 years. This patient had moderate dysarthria, hypotonia, and developmental delay, but he had no seizures. The movement disorder responded to a ketogenic diet.

These nonclassic phenotypes, which represent about 15 to 20% of the Glut-1 DS patient population, indicate the importance of Glut-1 DS diagnostic studies in children with unexplained neurological symptoms including mental retardation and movement disorders.[19]

Brain Imaging

Cranial computed tomography, magnetic resonance imaging, or both were performed in 12 patients. Results of brain magnetic resonance and computed tomography imaging were either normal or showed minor, nonspecific abnormalities with slight brain hypotrophy.

Electroencephalography

The EEG abnormalities included generalized spike- or polyspike-wave discharges, mild diffuse slowing, focal epileptiform discharges, and focal slowing. In infancy, the EEG abnormality was focal with temporal and posterior spike discharges. Later in childhood, the EEG pattern was generalized with spike-wave epileptiform discharges. The EEG abnormalities in these 16 patients were consistent with the abnormalities previously described.[20]

Biochemical Results

Patients' glucose and lactate values in blood and CSF and the V_{max} and K_m of the 3-*O*-methyl-D-glucose uptake into erythrocytes are summarized in Table 2. The CSF glucose concentration in these 16 patients ranged from 23 to 40mg/dl (mean value, 33.1 ± 4.9) and represented approximately 37% of the simultaneous blood glucose concentration. The CSF lactate concentration ranged from 0.5 to 1.4mM (mean value, 1.0 ± 0.3), which was less than the normal mean value of 1.63mM. The mean V_{max} for the 3-*O*-methyl-D-glucose uptake into erythrocytes was 996fmol/sec/10^{-6} red blood cells (range, 400–2,500), with a normal control value of 1,847fmol/sec/10^{-6} red blood cells (range, 909–3,333). The patients' values were significantly decreased to about half of the control values (54 ± 11%; t test, $p < 0.05$). The mean K_m value (1.4 ± 0.5mM) in the patient group was not significantly different from the control values (1.7 ± 0.5mM; t test, $p > 0.05$).

Mutational Analysis of GLUT-1 *Gene*

All patients were screened for *GLUT-1* mutations by direct sequencing of polymerase chain reaction product amplified from exons, intron–exon boundaries, and promoter region. We identified 16 mutations, including 7 missense, 1 nonsense, 1 insertion, and 7 deletion mutations. Of these 16 mutations, 14 were novel. All parents were wild type. We could not exclude mosaicism in the parents, because the sensitivity of direct sequencing is insufficient to detect the mutant DNA if less than 10% of the total DNA.[21]

Patient 1 had an A to G transition at nucleotide 280, resulting in Asn 34Ser. Asn34 is the first amino acid in the largest extracellular loop connecting transmembrane domains (TMDs) 1 and 2. It is conserved among GLUT subfamily class I (GLUT-1 to -4) and class II (GLUT-5, -7, -9 and -11) members.[2] The Asn34Ser mutation substitutes a nonpolar for an uncharged polar amino acid, possibly disturbing the protein conformation and affecting protein stability and transport kinetics. We recently reported another mis-

Table 2. Summary of Data from Lumbar Puncture and 3-OMG Uptake into Erythrocytes

Patient No.	CSF Glucose (mg/dl)	Blood Glucose (mg/dl)	CSF/Blood Glucose Ratio	CSF Lactate (mM)	Blood lactate (mM)	Glucose Uptake (%)	Patient V_{max} (fmol/sec/ 10^6 RBC	Control V_{max} (fmol/sec/10^6 RBC)[a]	Patient K_m (mM)	Control K_m (mM)*
1	33	N/A	N/A	N/A	N/A	55	909	1,667	1.9	2.0
2	38	98	0.39	N/A	N/A	57	1,429	2,500	1.0	1.8
3	30	86	0.35	N/A	N/A	75	833	1,111	1.6	1.2
4	36	88	0.41	N/A	N/A	44	1613	3,704	1.2	2.4
5	38	94	0.40	1.0	N/A	75	2,500	3,333	2.3	2.0
6	36	74	0.49	1.0	0.8	43	714	1,667	1.9	2.0
7	30	81	0.37	1.1	1.5	48	435	909	0.7	1.1
8	35	87	0.40	1.2	N/A	57	1,429	2,500	1.0	1.8
9	23	96	0.24	0.6	1.5	67	667	1,000	1.6	1.5
10	40	99	0.40	N/A	1.0	49	676	1,370	1.5	1.4
11	37	83	0.40	1.0	N/A	47	588	1,250	2.2	1.9
12	38	95	0.40	0.9	N/A	49	2,439	5,000	1.8	2.5
13	26	84	0.31	0.5	0.6	44	400	909	1.0	1.8
14	27	86	0.31	0.7	N/A	63	625	1,000	0.9	1.0
15	31	70	0.44	1.3	N/A	61	556	909	0.8	0.9
16	35	N/A	N/A	1.4	N/A	44	400	909	1.0	1.8
Average	33.1	87.7	0.37	1.0	1.2	54	996	1,847	1.4	1.7
SD	4.9	8.5	0.06	0.3	0.4	11	663	1,189	0.5	0.5

[a]Parents are used as the controls in the 3-OMG uptake assay.

CSF = cerebrospinal fluid; RBC = red blood cell; N/A = not applicable; SD = standard deviation.

sense mutation (N34I) in this location.[15] Patient 2 had a G to A transition at nucleotide 556, resulting in Arg126His, which was confirmed in previous *Xenopus* oocyte studies as a pathogenic mutation.[12] Patient 3 had a G to A transition at nucleotide 567, causing Gly130Ser. Gly130 is a nonpolar amino acid located in the fourth TMD. The substitution of an uncharged polar Ser could affect the conformation of Glut-1, because TMD 4 is predicted to be one of the five TMDs comprising the glucose channel.[22] Patient 4 had a C to T transition at nucleotide 636, which resulted in the substitution of a basic Arg153 for an uncharged polar Cys. The Arg153 is located in the conserved loop region between TMDs 3 and 4. Patient 5 had a C to T transition at nucleotide 1032 resulting in the substitution of an uncharged polar Thr295 for a nonpolar Met. Thr295 is located in the extracellular loop between TMDs 7 and 8. Patient 6 had a C to T transition at nucleotide 1176, causing Arg333Trp, a confirmed pathogenic mutation.[13] Patient 7 had a C to T transition at nucleotide 1386 resulting in a premature stop codon at AA379. Patient 8 had an ATCG insertion between nucleotides 1562 and 1563, resulting in a premature stop codon at AA476. Patient 9 had a 5-nucleotide TTGAG insertion between nucleotides 516 and 517, followed by a 15-nucleotide CGAAACT-GGGCAAGT deletion. This caused a premature stop codon at AA118. Patients 10 and 11 had a three-nucleotide CTC deletion, resulting in the deletion of Leu169. Patient 12 had a C deletion at nucleotide 969, causing a frameshift and premature stop codon at AA338. Patient 13 had a C deletion at nucleotide 969, followed by a C to T substitution at nucleotide 971, which also caused a premature stop codon at AA338. Patient 14 had a two-nucleotide TG deletion at nucleotides 1159 and 1160. This deletion created a frameshift and premature stop codon at AA378. Patient 16 had a five-nucleotide GTTGC deletion between nucleotides 1395 and 1399, resulting in a frameshift and premature stop codon at AA451. Patient 15 had a C deletion at nucleotide 1377, resulting in a premature stop codon at AA506.

All the mutations and polymorphisms are summarized in the Figure and in Tables 3 and 4.

Discussion

Molecular Genetics of Glut-1 Deficiency Syndrome

In the 16 patients who participated in this study, we identified 16 mutations, including 7 missense, 1 nonsense, 1 insertion, and 7 deletion mutations; 14 of these were novel mutations, expanding further the spectrum of mutations in the *GLUT-1* gene that cause Glut-1 DS[8,10–12,18,23,24] (see the Figure). The R126 and R333W missense mutations were confirmed previously to be pathogenic by mutagenesis studies in the *Xenopus* oocyte system.[12,13] Transport by the mutant T295C protein in Cys-less Glut-1 was not reduced in the *Xenopus* oocyte system compared with the wild-type system.[25] Joost and colleagues[2] reported a significant decrease of transport activity with T295A, butnot with T295S or T295G. Exofacial 2-*N*-(4-(1-azi-2,2,2-trifluoroethyl)benzoyl)-1,3-bis(D-mannose-4-yloxy)-2-propylamine (ATB-BMPA) binding affinity for T295S,

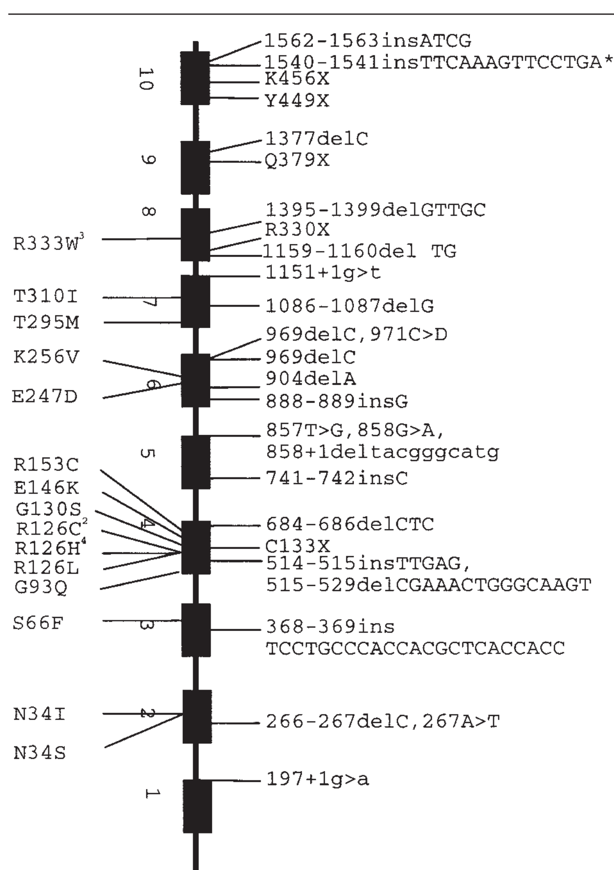

Fig. Summary of the mutations identified in the GLUT-1 *gene causing Glut-1 deficiency syndrome.* Filled boxes *represent the 10 exons and the* lines *represent the introns. Missense mutations are listed on the left side of the gene structure; the other mutations including nonsense, insertion, deletion, and splice-site mutations are listed on the right side. The three patients with hemizygosity are not represented. The superscript numbers represent the number of patients sharing the same mutation.* Asterisk *denotes mutations identified by others.*[10,24]

T295A, and T295G and Cytochalasin B binding affinity for T295G were normal, whereas Cytochalasin B binding affinity for T295A and T295S were significantly decreased. These findings suggest the hydroxyl group in the side chain of Thr295 is important for substrate recognition and subsequent conformational change that permits the passage of substrate.

We also identified a nonsense mutation (Q379X; Patient 7) and six frameshift mutations (see Table 3), which resulted in premature stop codons at amino acid positions 379, 476, 118, 338, 378, 451, and 506. These premature stop codons could cause degradation of messenger RNA or protein, as has been previously shown.[8,26,27] Assuming the truncated proteins are incorporated into the plasma membrane, there would be no residual transport activity based on previous studies that showed loss of activity when the last 37 carboxyl-terminal amino acids of Glut-1 are deleted.[28] The 1377delC mutation resulted in a premature codon at amino acid 506, causing the last 92 amino acids in wild-type Glut-1 to be replaced by 104 different amino acids. This substitution would definitely affect TMDs 11 and 12 in the predicted model of Glut-1.[29,30] A mutant Glut-1 containing 61 instead of 42 wild-type amino acids caused by 1550-1541insTTCAAAGT-TCCTGA has been studied and shown to be pathogenic.[24] Patients 10 and 11 carried a three-nucleotide deletion resulting in the elimination of Leu169. However, the two phenotypes differ, as do the respective polymorphisms (see Table 4). We believe these polymorphisms contribute to the phenotypic difference. We have identified 5 polymorphisms in exons 2, 3 5, 9, and 10, 1 nucleotide deletion in 5′-untranslated terminal region, and a 10-nucleotide insertion in intron 9 in this group of patients (see Table 4). Also, we are currently investigating these polymorphisms to elucidate their possible modifying effects on the expression of the *GLUT-1* gene.

Genotype–Phenotype Correlation of Glut-1 Deficiency Syndrome

There is significant phenotypic variability within this patient population with a wide spectrum of heterozygous mutations, including nonsense, missense, insertion, deletion, and splice site mutations, and with hemizygosity of the *GLUT-1* gene. Correlations between phenotype and genotype remain elusive thus far, but four mutation hotspots (N34, R126, R169, and R333) have been identified in our ongoing studies. We plan to examine these patient clusters carefully to uncover modifying factors that contribute to phenotypic diversity. Patient 1 with the N34S mutation will be compared with a previously reported patient with the N34I mutation.[15] Patient 2 (R126H) will be compared with a previously reported patient with the same missense mutation and with patients who carried different mutations at the same location, R126C[11] and R126L.[14,18] Three unrelated patients share the R333W mutation, and two patients share a deletion mutation, 684-686delCTC.

We propose the following phenotypic spectrum based on the hypothetical residual Glut-1 function in the blood–brain barrier:

1. Minimal phenotype: 75 to 100% residual function of Glut-1 associated with missense mutations that slightly decrease glucose transport activity or with environmental factors such as ethanol,[31,32] caffeine,[33] or medications,[34–37] which inhibit Glut-1 transport activity. We speculate that this clinical phenotype will rarely come to clinical attention, but patients may be at risk for mild transient symptoms when stressed by fever or other environmental factors.

Table 3. Mutations Identified in Glut-1 DS Patients

Mutation	Exon	Nucleotide	Amino Acid	Patient No.
Missense				
N34S	2	280A>G	Asn34→Ser	1
R126H[a]	4	556G>A	Arg126→His	2
G130S	4	567G>A	Gly 130→Ser	3
R153C	4	636C>T	Arg153→Cys	4
T295M	7	1063C>T	Thr295→Met	5
R333W[a]	8	1176C>T	Arg333→Trp	6
Nonsense				
Q379X	9	1368C>T	Gln379→Stop	7
Insertion				
1562–1563insATCG[b]	10	ATCG	FS→Stop476	8
Deletion				
516–517insTTGAG, 517–531del15	4	CTCGAAACTGGGCAAGTC>CTTGAGC	FS→Stop118	9
684–686delCTC (L169del)	4	ATCCTCA>ATCA	Leul69del	10, 11
969delC	6	TTCCGCT>TTCGCT	FS→Stop338	12
969delC, 971C>T	6	TTCCGCT>TTCGTT	FS→Stop338	13
1159–1160delTG	8	TTTGTGGTG>TTTGGTG	FS→Stop378	14
1395–1399delGTTGC	9	GCCGTTGCA>GCCA	FS→Stop451	15
1377delC	9	GTCCACGT>GTCCA	FS→Stop506	16

[a]Mutations reported previously in different patients.[12, 13]
[b]Patient reported previously.[16]

2. Mild phenotype: 50 to 75% residual function of Glut-1 is preserved. Patient 3 may be an example of a heterozygous missense mutation that is mildly pathogenic.
3. Moderate (classic) phenotype: 50% residual function of Glut-1 is preserved. This phenotype most likely predominates and is associated with hemizygosity, nonsense mutations, frameshift mutations, and splice-site mutations, which result in 50% loss of the Glut-1 protein.
4. Severe phenotype: 25 to 50% residual function of Glut-1 is preserved. We have seen one patient with compound heterozygosity in trans.[14] In this case, the mild mutation, shared with the mother, probably encodes a transporter protein with slightly decreased function (? minimal phenotype). The mutation, insufficient to cause the disease as witnessed by the mother's normal phenotype, when combined with the protein product of the mutant allele, produces a severe phenotype.
5. Embryonic lethal: 0 to 25% residual function of Glut-1 is left. This devastating phenotype could be caused by homozygous mutations, resulting in the termination of early development at preembryo or embryo stage because of the lack of glucose supply.[38,39] Glut-1 is the major transporter expressed on the plasma membrane of syncytiotrophoblast and cytotrophoblast.[40]

Phenotypic diversity also may result from the possible action of secondary genes. For example, four patients share the same R126H missense mutation, yet their phenotypes differ. These patients may carry poly-

Table 4. Polymorphisms Identified in the GLUT-1 Gene

Location	AA	Nucleotide	Patients with Genotype (+/+)	Patients with Genotype (+/−)
5′ UTR		−173delA		3, 12, 14
Exon 2	A15A	224T>C	1–3, 5–9, 11, 16	10, 12–14
Exon 4	C133C	578C>T		4, 12–14
Exon 5	P196P	767G>A		4, 12–14
Exon 9	P387P	1340A>T		
Intron 9		1157+30ins ATTTCTCACC	11	1–4, 9, 13–14
Exon 10	D476D	1607T>C	1–5, 7, 9–10, 12–16	

UTR = untranslated region.

morphisms in the wild-type *GLUT-1* allele that may modulate its expression level, or in other transport-related genes that may offer some degree of functional compensation.

Somatic mosaicism also may modify the clinical phenotype. We have one example of this genetic mechanism in which the asymptomatic father is mosaic for the R333W missense mutation and his son is mildly symptomatic.[13] Finally, these phenotypic differences may be caused by the effect of other polymorphic genes not involved in transport, adding another degree of complexity.[41]

Treatment of Glut-1 Deficiency Syndrome

Haploinsufficiency of *GLUT-1* causes Glut-1 DS. Treatment efforts have been based on providing alternative brain fuel sources (ie, ketogenic diet) or increasing Glut-1 activity.[7,9,42] Ketone bodies bypass the Glut-1 defect and enter the brain by a monocarboxylic acid transporter. The ketogenic diet effectively controls the seizures and other paroxysmal activities,[16,20] but it has less effect on the cognitive symptoms. Recently, we have attempted to increase the blood glucose concentrations by using a high-carbohydrate diet regimen with or without a hyperglycemic agent (diazoxide) in patients with the mild phenotype, but the results have been disappointing, and obesity has emerged as a complication (D.C.D., personal observations). Enhancing *GLUT-1* expression or Glut-1 transport activity also has been attempted with little success, although some in vitro studies are encouraging.[42] Avoiding agents that inhibit Glut-1 transport is logical. Patients are advised of the many drugs and substances that share this pharmacological property.[33,34,36] Current treatment is inadequate, and future studies should be directed at mechanisms designed to upregulate *GLUT-1* expression, thereby increasing residual Glut-1 activity to 75 to 100%.

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