Journal of Inherited Metabolic Disease

WILEY

JIMD SSIEM

REVIEW OPEN ACCESS

Glut1 Deficiency Syndrome: Novel Pathomechanisms, Current Concepts, and Challenges

Joerg Klepper

Department of Pediatrics and Neuropediatrics, Childrens' Hospital Aschaffenburg, Aschaffenburg, Germany

Correspondence: Joerg Klepper (joerg.klepper@klinikum-ab-alz.de)

Received: 7 February 2025 | **Revised:** 2 May 2025 | **Accepted:** 5 May 2025

Communicating Editor: Jirair Krikor Bedoyan

Funding: The author received no specific funding for this work.

Keywords: De Vivo disease | GLUT1 | Glut1 Deficiency Syndrome | Glut1DS | hypoglycorrhachia | ketogenic dietary therapies | SLC2A1 | treatable

ABSTRACT

Glut1 Deficiency Syndrome (Glut1DS) has emerged as a treatable, but complex entity. Increasing data on pathogenic mechanisms, phenotype, genotype, and ketogenic dietary therapies (KDT) are available, as summarized in this review. Many challenges remain: novel symptoms emerge and vary with age. In Glut1DS, KDT in pregnancy and the clinical features in neonates and adults are poorly understood. KDT are ineffective in some patients for reasons yet unknown. Research reaches beyond the concept of brain energy depletion by impaired GLUT1-mediated glucose transfer across the blood–brain barrier. Novel concepts investigate alternative substrates, transport mechanisms, and metabolic interactions of different brain cell types. Future, yet currently unavailable prospects are neonatal screening for Glut1DS, reliable biomarkers, predictors for outcome, and alternative therapies, along with and beyond KDT.

1 | Introduction

In 1991, Darryl De Vivo described the defective glucose transport across the blood–brain barrier (BBB) as a cause of persistent hypoglycorrhachia, seizures, and developmental delay, a condition now recognized as Glut1 Deficiency Syndrome (Glut1DS) [1]. Glucose transport across the BBB is exclusively facilitated by GLUT1. As glucose is the essential fuel for brain energy metabolism, defective transport results in intractable childhood epilepsy, global developmental delay, and movement disorders with constant and paroxysmal elements of ataxia, dyskinesia, and spasticity. Symptoms are age-specific and highly variable. The diagnosis is based on clinical features, low cerebrospinal fluid (CSF) glucose concentrations (hypoglycorrhachia), and pathological *SLC2A1* variants. Ketogenic dietary therapies (KDT) remain the only effective treatment as they mimic the metabolic state of fasting and provide ketones as an alternative fuel to the brain.

Almost 30 years have passed since the initial description and much has been learned and summarized (for review, see [2]). Current recommendations for diagnosis and treatment have been outlined in an international consensus on Glut1DS [3]. This review focuses on pathological mechanisms unraveled to date and current challenges for physicians and researchers. The objective is to highlight the numerous lines of thought on Glut1DS discussed in recent years and to provide new approaches towards this complex entity.

Abbreviations: 3OHB, 3-hydroxy-butyrate; AED, antiepileptic drug; BBB, blood–brain barrier; CSF, cerebrospinal fluid; GLUT1, facilitative glucose transporter type I; Glut1DS, Glut1 Deficiency Syndrome; KDT, Ketogenic dietary therapies.

2 | Pathomechanisms of Glut1DS

2.1 | Genetics

Glut1DS describes a state of haploinsufficiency—a complete loss of Glut1-mediated glucose transport into the brain would not be compatible with life. About 90% of patients carry pathological *SLC2A1* variants encoding the GLUT1 transporter. Transmission is mostly autosomal-dominant de novo, although we and others have described familial autosomal dominant transmission [4, 5] and autosomal-recessive transmission in consanguineous families [6, 7]. Glut1DS can also be part of a larger deletion syndrome on chromosome 1p, deleting *SLC2A1* among other genes [8, 9].

Within *SLC2A1*, multiple variants comprising nonsense, missense, frameshift, and splice site variants have been identified at various positions within the gene (https://www.ncbi.nlm.nih.gov/clinvar/?term=SLC2A1[all. "Hot-spot" residues often affect amino acid motifs conserved within the GLUT family and generate various pathomechanisms (see Figure 1). Next-generation sequencing has significantly increased the number of patients with Glut1DS worldwide. However, often "variants of uncertain significance (VUS)"—stating that there is insufficient information to determine if the variant is disease related—are generated, a general problem shared with many genetic diseases. In this situation, the presence of hypoglycorrhachia determined by a lumbar puncture will complete the diagnosis of Glut1DS in case of genetic uncertainty [3]. Novel genetic tools such as variant reclassification based on genomic databases, reassignment of the pathogenicity of variants over time, standardized guidelines, clinical phenotype–genotype correlations through deep phenotyping and ancestry studies, large-scale databases, and bioinformatics tools will increase the accuracy of molecular genetics [11]. Trio exome analysis, sequencing the patient and parents, can offer additional information, but in an autosomal dominant condition, it will not identify a de novo variant as pathogenic. Recently, a growth assay in HAP1 cells in which *SLC2A1* is required for growth was utilized to quantify the functional impact of single-nucleotide variants in *SLC2A1*. Nonsense variants were reliably distinguished from benign variants in this in vitro functional assay [12]. Extending genetic screening to noncoding regions will identify further patients with hypoglycorrhachia and clinical features of GLUT1 when exome sequencing is negative. Liu et al. showed that three of 55 patients had deep intronic *SLC2A1* variants [13]. Willemsen et al. identified a de novo 5′-UTR variant in *SLC2A1*, generating a novel translation initiation codon, severely compromising *SLC2A1* function [14].

2.2 | Alternative Genes

Alternative genes in Glut1DS have been discussed, but not identified to date—in a genetic analysis of 56 patients suspected of Glut1DS, 23.2% had a variant in 1 of the 13 different genes. In this study, a reduction in *SLC2A1* mRNA was evident in one patient with a pathogenic variant in *SLC9A6* and in three patients for whom no candidate variant was identified [15]. As such, the

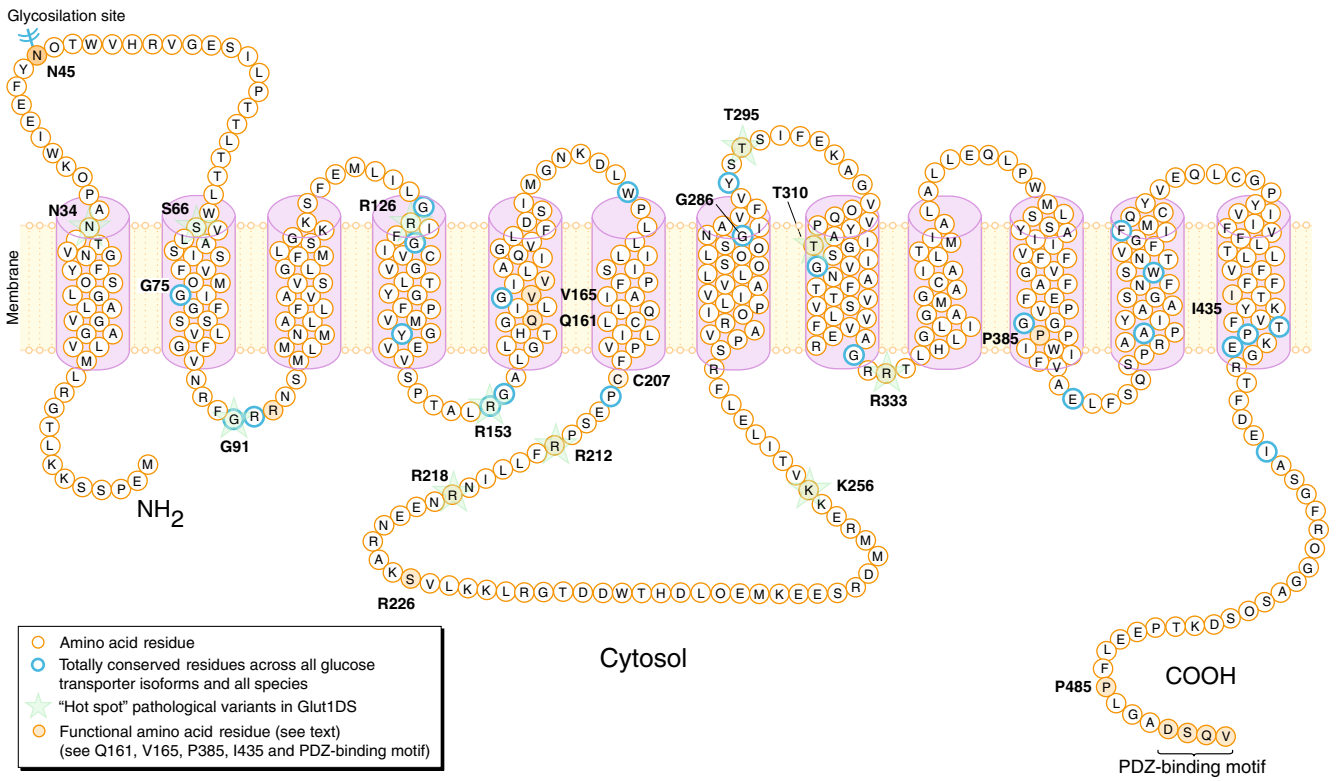

FIGURE 1 | Conformational sideview model for GLUT1 in the membrane as proposed by Mueckler and Makepeace [10]. The 12 transmembrane helices are shown with a large intracellular loop connecting helices 6 and 7. The amino- and carboxy-termini are located in the cytosol. Amino acid residues as discussed in the text are shown in single-letter code.

differential diagnosis of Glut1DS may also include other genetic epileptic encephalopathies:

- Loss-of-function variants in *SLC9A6* (Xq26.3) encoding the endosomal Na^+/H^+ exchange protein 6 (NHE-6) cause Christianson syndrome, a rare genetic disorder that affects the X chromosome and causes intellectual disability, microcephaly, seizures, ataxia, and absent speech [16].
- Recessive mutations in *SLC45A1* encoding a neuronal glucose transporter and involved in neurodevelopmental disability and epilepsy have been described [17].
- PURA syndrome, a neurodevelopmental disorder caused by haploinsufficiency of the purine-rich element binding protein A (PURA), shares clinical features such as intellectual disability and epilepsy with Glut1DS. Recently, the observation of hypoglycorrhachia in a patient with a frameshift deletion in the PURA gene led to the hypothesis that GLUT1 could be downregulated by PURA [18]. However, hypoglycorrhachia was not mentioned in a report of 32 individuals with PURA syndrome, the largest cohort reported to date [19].

2.3 | GLUT1 Structure

The GLUT1 protein has 12 transmembrane spans (TMs 1–12) with intracellular N- and C-termini. Signature motifs in the GLUTs include highly conserved salt-bridging motifs RXGRR and other conserved motifs unique to the GLUT family (for review, see [20]).

In Glut1DS, pathogenic *SLC2A1* variants within these conserved motifs will impair glucose transport. For instance, the carboxy-terminal 30 amino acids are primarily responsible for the differential targeting of the glucose transporter isoforms GLUT1 and GLUT4. *SLC2A1* variants within the carboxy-terminus may affect or even truncate GLUT1 and potentially lock the transporter in an inward-facing form without transport activity [21]. A frame shift mutation expanding the carboxy terminus of the GLUT1 protein resulted in reduced transport velocity and substrate affinity, whereas substrate specificity and GLUT1 expression remained unchanged [22].

The pathogenicity of several *SLC2A1* variants (G91D, R126H, T310I, G75W, S66F, R126C, and T295M) has been confirmed by site-directed mutagenesis and in vitro expression of mutant GLUT1 transporters in the *Xenopus* oocyte system. When modelled into the 3-D structure of the GLUT1 protein, most of them were shown to be located in the immediate vicinity of the transport channel and in a region of high relative mobility [23].

Examples for "hot-spot variants" detected in a number of patients are N34, S66, G91, R126, R153, R212, R218, K256, T295, Y310, and R333 [24, 25]. When the crystal structure of GLUT1 was described in 2014, it allowed the accurate mapping and potential mechanistic interpretation of such variants [26]. Raja et al. investigated the mechanistic insights of the variants N34S, S66F, G76D, G91D, R126H/L, E146K, L156R/N, R218H, L256V, T310I, and R333W. The authors showed that these variants could destabilize native interactions, generate novel interactions, trigger protein misfolding, and enhance protein aggregation [27] (Figure 2a–c).

In vitro studies identified single amino acid residues and motifs of functional importance in GLUT1. In individual patients with Glut1DS, variants may explain pathogenicity and may encourage research.

2.4 | Asparagine 45

N-glycosylation of GLUT1 glucose transporter on N45 plays an important role in maintaining its intracellular targeting and protein stability [28, 29]. Of note, NAsn45 variants in Glut1DS have not been described to date.

2.5 | Glycine75

This residue is essential for the GLUT1 transport function [30]. A heterozygous G75W variant was identified in a 10-year-old girl with Glut1DS. In silico three-dimensional modeling provided a smaller gyration radius for transmembrane segment 2 as the potential pathogenic mechanism in this patient [31].

2.6 | Glycine 91

An autosomal-dominant G91D variant, positioned within an 89 RXGRR 93 motif, was identified within a Glut1DS family [32]. This highly conserved motif is present at equivalent positions within the cytoplasmic loops joining transmembrane segments 2–3 and 8–9 and is required for the catalytic conformational change that occurs in mediated transport [33]. Experimental data confirm that the substitution of the three arginine residues within this motif by glycine resulted in a translocation of the cytoplasmic loop into the exoplasm along with the two flanking transmembrane segments, thus completely abolishing GLUT1-mediated transport in *Xenopus* oocytes [34].

2.7 | Valine 165

Valine 165 lies near the exofacial substrate-binding site or directly in the sugar permeation pathway. V165I generates a side chain, which resides in the middle of transmembrane helix 5 and juts into the aqueous permeation pathway of GLUT1, causing impaired glucose transport [35].

2.8 | Cysteine 207

GLUT1 is palmitoylated at Cysteine 207, and S-palmitoylation is required for maintaining GLUT1 plasma membrane localization [36]. In vitro studies indicate that the single substitution of C207 does not impair glucose transport or GLUT1 tetramerization [37, 38]. However, C207 variants, though yet undescribed, may potentially result in GLUT1 delocalization.

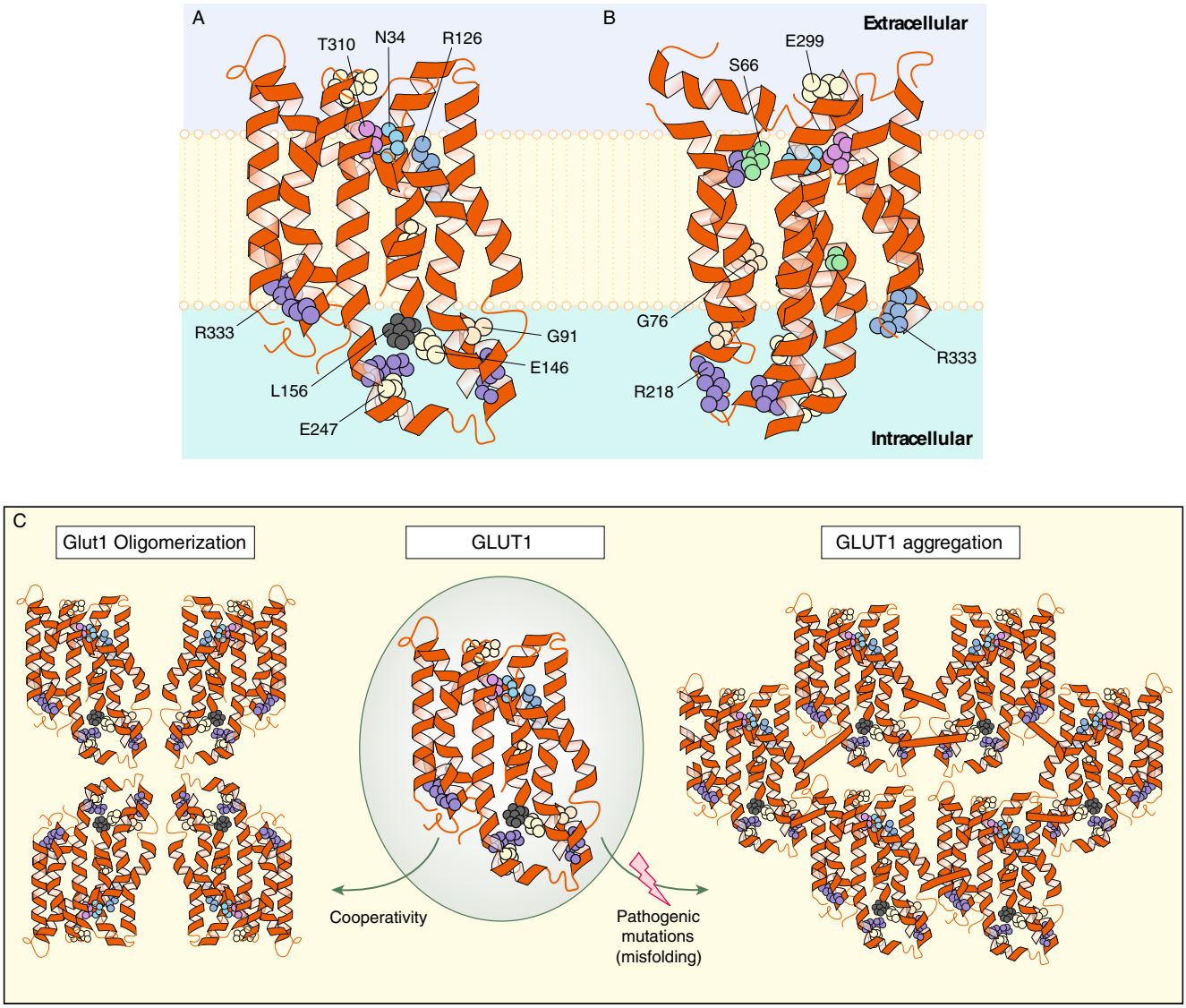

FIGURE 2 | (a, b) Three-dimensional structure of human GLUT1 (PDB ID: 5EQI) in the membrane plane depicting the positions of LOF pathogenic genetic mutations triggering GLUT-DS. The positions of intracellular helices (ICHs) and several natural mutations (N34S, S66F, G76D, G91D, R126H/L, E146K, L156R/N, R218H, K256V, T310I, or R333W) in ball-and-stick model are highlighted. The structure was analyzed in a PyMol computer modeling program (http://www.pymol.org/). For clarity, two side views (a and b) are shown to depict the positions of genetic mutations with regard to the membrane plane (highlighted in light green). (c) A hypothetical model of oligomerization of WT-GLUT1 and aggregation of misfolded mutant GLUT1. In the healthy state, the cooperativity among GLUT1 subunits leads to tetramerization or oligomerization. In Glut1DS, destabilizing pathogenic mutations may elicit unfavorable conformation, misfolding, and aggregation. With permission from Raja and Kinne (2020).

2.9 | Serine 226

Serine 226 was identified as a Protein Kinase C phosphorylation site, required for the regulation of glucose uptake and enhanced cell surface localization of GLUT1. Lee et al. demonstrated that disruption of phosphorylation at this site impairs glucose transport and proposed that this modification is important in the physiological regulation of glucose transport [39].

2.10 | Threonine 310

Threonine 310 is located in the wall of the predicted glucose channel. Missense variants have been confirmed by functional studies as a disease-causing in Glut1DS [40].

2.11 | Asparagine 317

The GLUT1 sugar binding site has been identified at this highly conserved amino acid residue unique to the GLUT family and preserved among species [26].

2.12 | Glycine 286/Isoleucine 435

Glycine 286/Isoleucine 435 give rise to the very rare pathomechanism of stomatin deficiency in Glut1DS. Stomatin is an integral plasma membrane protein closely associated with Glut1 and present at a high abundance in the human RBC plasma membrane [41]. Stomatin-deficient cryohydrocytosis is characterized by the leakage of sodium and potassium from

red blood cells at low temperatures, resulting in pseudohyperkalemia. Two spontaneous de novo mutations in residues G286 and I435 were involved. Glycine 286 is completely conserved across all species and positioned adjacent to the putative glucose transport pathway as part of an exofacial glucose binding site. The G286D variant is thought to reduce the conformational mobility of GLUT1 by the potential formation of a novel salt bridge between D286 and L38 within the N-terminus [42]. Since seven additional cases have been reported, indicating that this pathomechanism might be underdiagnosed within Glut1DS [43–46].

2.13 | Proline 485

Proline 485 variants impair intracellular GLUT1 trafficking. Meyer et al. reported a patient with a P485L *SLC2A1* variant resulting in GLUT1 mislocalization to intracellular compartments and impaired glucose transport. The variant creates a dileucine motif known to mediate clathrin-dependent trafficking. Mutant GLUT1 interacted with adaptor proteins in vitro, and knocking down AP-2 reverted the cellular mislocalization and restored glucose transport [47].

2.14 | PDZ-Binding Motif

Little is known about the hormonal and energy-level control of translocation between subcellular compartments of GLUT1 and associated proteins [33]. Cell surface localization of GLUT1 is a cytokine-controlled process. The last four amino acids within the C-terminal of GLUT1 (asparagine, serine, glutamine, and valine) represent a class I PDZ-binding motif. This PDZ-binding motif in GLUT1 promotes maximal cytokine-stimulated GLUT1 cell surface localization and prevents GLUT1 lysosomal degradation in the absence of growth factor. Disruption of this PDZ-binding sequence decreases surface GLUT1 levels and GLUT1 proteolysis in lysosomes, particularly in growth factor-deprived cells. The PDZ domain protein, GIPC, binds to GLUT1 in part via the GLUT1 C-terminal PDZ binding motif. GIPC deficiency impairs the GIPC/GLUT1 interaction and decreases GLUT1 surface levels and glucose uptake [48].

2.15 | ATP-Binding Sites

ATP allosterically inhibits GLUT1. In situations of reduced glucose availability or high demand, such as high insulin or hypoxia, GLUT1–ATP interaction reversibly increases GLUT1 activity. In chronic conditions of low energy availability, gene and protein expression levels also increase, boosting BBB glucose transport [49]. The GLUT1 nucleotide-binding site is located on the endofacial surface of GLUT1, involving cytoplasmic loop 8–9 and transmembrane helices 8 and 9, and critically affects transporter activity [50–52] (Figure 1). Glucose transport regulation also involves ATP-dependent conformational changes of the GLUT1 C terminus and the C-terminal half of GLUT1 cytoplasmic loops 6–7 [53]. Consequently, *SLC2A1* variants in these functional domains will significantly impair glucose transport.

2.16 | GLUT1 Inhibition

GLUT1 inhibition has been described for tea [54–56], caffeine [56], and red wine [57]. The caffeine binding site has recently been allocated to amino acid residues Q161 and P385 (see Figure 1) [56]. Ethanol and antiepileptic drugs (AEDs) such as diazepam, chloralhydrate, and ethanol have been shown to inhibit GLUT1-mediated glucose transport in vitro [58].

3 | Current Challenges in Clinical Practice

3.1 | Incidence

Glut1DS is much more frequent than previously thought: the prevalence estimates have ranged from 1:90 000 to 1:24 000 suggesting that there are several thousand cases of Glut1DS in the United States (NORD: https://rarediseases.org/rare-diseases/glucose-transporter-type-1-deficiency-syndrome/). A prospective national epidemiological cohort study in Scotland over a 3-year period described the incidence and phenotypic spectrum of the most common single-gene epilepsies in young children. For *SLC2A1* variants, the authors reported an incidence of 1 per 24 300 (4.13/100 000; 95% confidence interval = 1.07–7.19) [59]. Of note, Glut1DS was among the five most common single-gene epilepsies and the only one treatable by KDT, highlighting the need to identify these patients.

3.2 | Patient Voices

Much has been learned by listening to patients, parents, and caretakers. Paroxysmal eye-head movements in infancy as a specific, early sign of Glut1DS have been known in individual cases among experts, but it took increasing parental reports and mobile phone videos to eventually recognize it as an important novel feature of this entity [60]. Likewise, it took patients and parents two decades to bring dysarthria and the associated significant impairment of life quality into the focus of clinicians, with publications appearing only recently [61–63]. Parent support groups have significantly accelerated research and awareness of GlutDS in the medical community by supporting international meetings, grant proposals, homepages, and chat groups. The *Glut1 Deficiency Collective Voices Project*, designed to have a better understanding of the patient and family experience across a broad range of areas, exemplifies the importance of these contributions to understanding Glut1DS (https://www.g1dfoundation.org/collective-voices/). Also, web-based, worldwide patient registries are available and first results from these databanks have been published [64, 65].

3.3 | Phenotype

The clinical spectrum of Glut1DS ranges from severe impairment to asymptomatic cases [66]. The classical phenotype features three cardinal symptoms: epilepsy, movement disorders, and developmental delay. Increasing patient numbers resulted in the recognition of highly variable, sometimes atypical, and age-specific clinical features [67, 68]. Paroxysmal eye-head

movements [60] often represent the first sign of Glut1DS in infants. Epilepsy is predominant in infancy and childhood and often stabilizes during the course of the disease. Constant or paroxysmal movement disorders and speech disturbances (dysarthria) increase in puberty and contribute to impaired life quality in adolescents and adults with Glut1DS [69]. Defining and classifying dysarthria in Glut1DS in order to establish effective speech therapy remains a challenge [61]. Equally important are the recognition of novel symptoms, long-term adverse effects of KDT, and potential means to improve quality of life [70].

Specific age groups that have recently come to attention include pregnant women, infants, and elderly people. KDT in pregnancy remains an unsolved issue of public health, as the effects of ketonemia affect Glut1DS pregnancies, pregnant women with diabetes, and healthy women following low-carbohydrate lifestyle diets. Ketosis in pregnancy is more pronounced due to changes in maternal metabolism. Diabetic ketoacidosis is a rare but potentially life-threatening complication of diabetes. Results regarding elevated maternal ketone levels and childhood IQ are conflicting (for review, see [71, 72]). In Glut1DS, currently, no recommendations exist on whether pregnant patients should remain on KDT. Case reports suggest that in Glut1DS mothers, intrauterine ketosis may in fact be protective if the child is carrying the same *SLC2A1* variant [66]. As such, prenatal or neonatal screening would be a "game-changer" for early diagnosis and treatment, especially as the use of KDT in infants, even when breastfed, has been shown to be safe and effective [73–75]. However, neither the extent of hypoglycorrhachia determined by a lumbar puncture nor recently developed GLUT1 immunoassays [76] or *SLC2A1* variants are currently suitable for neonatal screening. Genomic newborn screening is on the rise. Glut1DS would be among the targeted treatable diseases, but screening concepts are hampered by poor genotype–phenotype correlations and the complexity of Glut1DS, variable outcomes despite KDT, as well as general limitations of screening programs [77]. For example, *SLC2A1* variants are absent in about 5%–10% of patients with Glut1DS, and diagnosis is based on clinical grounds and hypoglycorrhachia—genetic newborn screening would miss this subgroup [3, 78]. Posttranslational modification, impaired GLUT1 trafficking, activation, or translocation from intracellular pools to the cell membrane are potential mechanisms in *SLC2A1*-negative patients but have not been elucidated to date.

In adult Glut1DS, data on the clinical presentation and response to KDT are limited. When entering adolescence, epilepsy often diminishes or even disappears, while paroxysmal movement disorders emerge or increase in duration and frequency. Other tissues and organs rich in GLUT1, such as the retina, might be affected by Glut1DS in adults [79]. Cognition appears to be stable throughout life [63, 80]. KDT can be applied successfully in adult Glut1DS [81], and international recommendations for treating adult Glut1DS have recently been published [82]. No data on the benefit of KDT in patients diagnosed late in adulthood or in the elderly are available.

3.4 | Treatment

Response to KDT in Glut1DS, especially in children, is impressive, but mainly defined by epilepsy control. Seizures are usually pharmacoresistant [3], and there is not enough data to recommend a specific AED as superior to others. Also, there is limited data on the interaction of AEDs with KDT [83]. A recent concern is the emerging subgroup of epileptic patients with Glut1DS unresponsive to KDT [84, 85]. Here, treatment can only be empirical and on an individual basis, as the efficacy of individual AEDs in Glut1DS-associated epilepsy is unknown. For movement disorders, KDT appears to be less effective. This is particularly true for paroxysmal exertion-induced dystonia (PED) and dysarthria [3, 86]. In these situations, physicians have few options except for a trial with acetazolamide [87–89]. Triheptanoin, an odd-carbon, medium-chain triglyceride that is an anaplerotic substrate of calories and fatty acids, has been shown to be ineffective in Glut1DS for both epilepsy and paroxysmal exertion-induced dystonia in randomized multicenter trials [90, 91]. Two reports have described diazoxide ($n=1$) [92] and L-Dopa ($n=1$) [93] as an effective treatment for movement disorder in Glut1DS, but this has not yet been confirmed by others. Emerging therapies for protein and gene replacement, small molecules, and biologics to enhance GLUT1 expression are not available in the near future and are beyond the scope of this review and are discussed in detail elsewhere [94, 95].

4 | Current Challenges in Research

In 1991, impaired GLUT1-specific glucose transport across the BBB was originally considered the main pathogenic mechanism in Glut1DS. To date, the metabolic interactions of different brain cells and their cell-specific transport systems for metabolites that are essential for neuronal function, such as glucose, glycogen, and lactate, have come into focus [96].

4.1 | Cerebral Transport Systems and Metabolites

In the brain, a concert of transporters regulates the flux of substrates for cerebral energy metabolism. The impact of low glucose levels in untreated Glut1DS on these pathways remains unclear. Likewise, in treated Glut1DS, the effects of increased ketones from KDT on cerebral energy metabolism have not been studied. As such, the interaction of different cell types, predominantly neurons and astrocytes, and the impact on other GLUT and MCT transporters in Glut1DS is unclear. In recent years, the focus of research in brain energy metabolism has shifted from neurons to astrocytes. Astrocytes, with their tight proximity to the BBB, may play a critical role in brain energy metabolism [97]. Lactate, generated predominantly in astrocytes from glucose or glycogen, is transferred to neurons to generate ATP and provide neuronal functions, termed the astrocyte-lactate-shuttle [98, 99] (Figure 3). Recently, lactate was safely administered intravenously to patients with Glut1DS [100]. CSF concentrations of glucose and lactate, as well as the CSF blood/glucose ratio, have shown their value as reliable biomarkers in this entity [101]. A study analyzing CSF, plasma, and urine metabolites in three patients with GLUT1DS treated with KDT indicated that metabolomics may provide new insights into disease mechanisms in the future [102]. Recently, comparing CSF profiles from 12 patients to those of 116 controls identified Gluconic + galactonic acid, xylose-α1-3-glucose, and xylose-α1-3-xylose-α1-3-glucose as potential biomarkers for Glut1DS [101–103], but further data are needed.

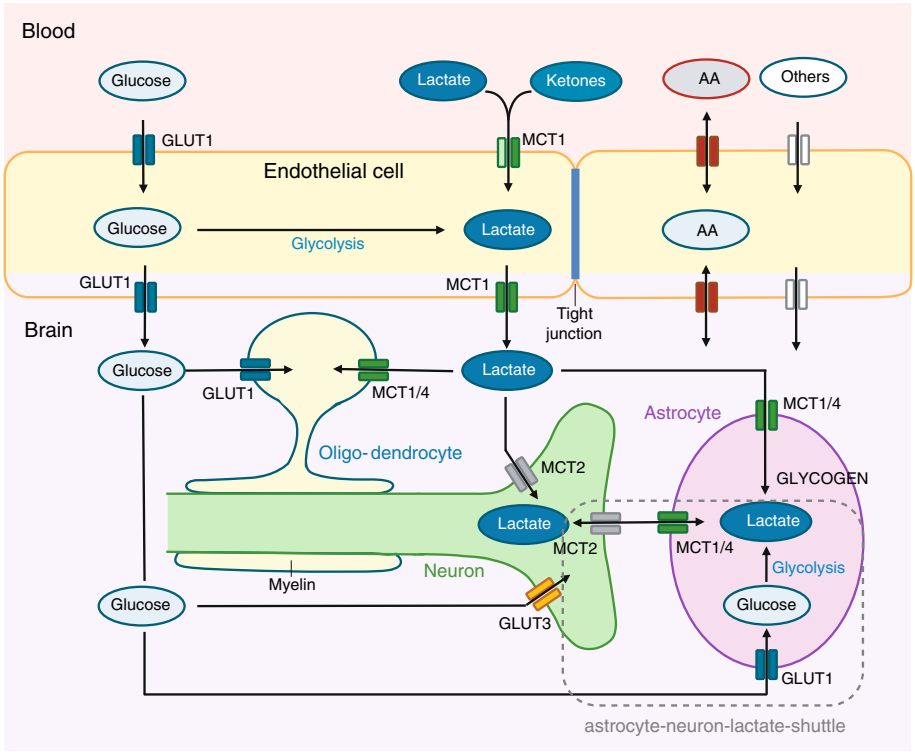

FIGURE 3 | Schematic diagram of glucose transporters (GLUTs) and monocarboxylate transporters (MCTs) at the blood–brain barrier (BBB) and in brain cells (adapted from [96]). *Glucose*. GLUT1: Facilitated glucose diffusion via GLUT1 across the endothelial cells in the BBB. In brain, entry into astrocytes and oligodendrocytes. GLUT3: Glucose entry in neurons. *Lactate*. Glucose is converted into lactate via glycolysis in endothelial cells and astrocytes. MCT 1: Facilitated diffusion of lactate and ketones across endothelial cells in the BBB. MCT1/4: Release/entry of lactate and ketones in astrocytes and oligodendrocytes. MCT2: Lactate and ketone entry in neurons. *Others*. Amino acid transporters, lipid transporters, and further solute transporters (others) are also expressed in the BBB. Astrocyte neuron lactate shuttle provides lactate to neurons, derived from glycolysis in astrocytes (dotted line).

Unraveling such mechanisms in health and disease could offer opportunities for therapeutic interventions in Glut1DS.

Other energy metabolites, such as glucogenic amino acids, lipids, or even glycogen, may also play a substantial role in Glut1DS. Amino acids in the brain are essential for neurotransmitter synthesis and function. In theory, glucogenic amino acids may provide glucose as gluconeogenesis takes place in astrocytes [104]. Medium-chain fatty acids are metabolized in astrocytes to generate lactate and do not affect ketone metabolism [105]. Cerebral glycogen is a critical component of cerebral metabolism [106]. It is metabolized in astrocytes [107]. In Glut1DS, the normal production of glycogen from glucose is impaired, as shown in Glut1DS-deficient mouse brains [108, 109]. In short, increasing or adding such metabolites to KDT as an auxiliary fuel might be beneficial in Glut1DS.

GLUT1 does not exclusively transport glucose. In 1998, we described the deficient transport of dehydroascorbic acid, the oxidized form of vitamin C, in Glut1DS [110]. Recently, eight GLUT1 residues involved in glucose and dehydroascorbic acid have been described (i.e., F26, Q161, I164, Q282, Y292, and W412) [111]. Potentially, the accumulation of this antioxidant by the brain could thus be impaired, but it remains speculative and has never been studied in vivo. GLUT1 was also recently identified as an L-fucose transporter non-competitive with millimolar levels of D-glucose [112]. In the brain, fucose is linked to proteins (fucosylation), a process reported to affect learning and memory, neurite outgrowth and migration, synapse formation, and others [113]. L-fucose itself has been shown to act as a neuromodulator, enhancing synaptic transmission and long-term potentiation [114]. Diseases associated with fucose are fucosidosis, a rare lysosomal storage disease [115], and five defects of congenital disorders of glycosylation (CDG) related to an impaired fucosylation of N- and O-glycans [116]. Again, the implications of fucose as a GLUT1 substrate are currently unclear, particularly as about 90% of GDP-fucose originates from the de novo *s*ynthesis [117].

Another focus currently lies on the vascular effects of Glut1DS. Tang et al. showed that hypoglycorrhachia impairs brain angiogenesis. Hypoglycorrhachia may trigger a severe neuroinflammatory response and the reduction of brain-derived neurotrophic factor (BDNF), potentially resulting in fewer neurons in the Glut1DS brain [118].

5 | Summary and Conclusion

The 34 years since the initial description by De Vivo et al. [1] have been a success story—delineating a novel entity with a clear pathomechanism, establishing reliable diagnostic tools, and an effective treatment by KDT. Progress in understanding Glut1DS was achieved by international conferences, consensus guidelines, and growing research networks providing awareness

in the medical community, patient registries, education, and support for patients and families, conducting clinical trials, and sharing information. Glut1DS also helped KDT achieve international recognition and acceptance.

5.1 | What Needs to Be Done?

This review summarizes the current answers and "loose ends" in this complex entity in order to develop new ideas to understand and treat Glut1DS. We need to unravel the mechanisms of cell-specific interactions of substrates and transporters causing disruptions at the cellular level beyond the concept of energy failure. Reliable biomarkers and predictors for outcome and response to KDT are needed. The complexity of *SLC2A1* variants in relation to phenotype has to be delineated, as well as the potential of genomic newborn screening and gene therapy for Glut1S. We have to extend our knowledge about Glut1DS in pregnancy and in adults. We have to listen to patients and parents regarding novel symptoms, adverse effects, potential involvement of other GLUT1-rich tissues and how to improve life quality. Finally, we have to develop safe, lasting, and efficient therapies along with and beyond KDT. We need to understand and identify KDT nonresponders. Further challenges remain and are beyond the scope of this review. Potential therapeutic strategies, including gene therapy, are outlined in a comprehensive review by Tang et al. [94]. Much has been understood, but there is so much more to learn about this entity—we need to be ready. Or, in respect to Darryl De Vivo, who described Glut1DS, and to Louis Pasteur: "Chance favors the prepared mind."

Acknowledgements

We thank the German Glut1DS parent support group (www.glut1.de) for helpful discussions and continuing support, as well as all patients and families who participated in the study.

Ethics Statement

The author has nothing to report.

Consent

The author has nothing to report.

Conflicts of Interest

Joerg Klepper has sat on Conference Scientific Advisory Panels for Nutricia and Vitaflo for which remuneration has been paid. He has received travel expenses from Nutricia and Vitaflo for invited lectures and for the Clinical Training Fellowship in KDT (KetoCollege by Matthews Friends, UK). He is currently a board member of the International Neurological Ketogenic Society (INKS) as well as Clinical Advisor to US, UK, German, and Austrian Glut1DS parent support groups.

Data Availability Statement

The author has nothing to report.

References

1. D. C. De Vivo, R. R. Trifiletti, R. I. Jacobson, G. M. Ronen, R. A. Behmand, and S. I. Harik, "Defective Glucose Transport Across the Blood-Brain Barrier as a Cause of Persistent Hypoglycorrhachia, Seizures, and Developmental Delay," *New England Journal of Medicine* 325, no. 10 (1991): 703–709.

2. D. Wang, J. M. Pascual, and D. de Vivo, "Glucose Transporter Type 1 Deficiency Syndrome," in *GeneReviews((R))*, ed. M. P. Adam, J. Feldman, G. M. Mirzaa, et al. (1993).

3. J. Klepper, C. Akman, M. Armeno, et al., "Glut1 Deficiency Syndrome (Glut1DS): State of the Art in 2020 and Recommendations of the International Glut1DS Study Group," *Epilepsia Open* 5, no. 3 (2020): 354–365.

4. K. Brockmann, D. Wang, C. G. Korenke, et al., "Autosomal Dominant Glut-1 Deficiency Syndrome and Familial Epilepsy," *Annals of Neurology* 50, no. 4 (2001): 476–485.

5. J. Klepper, M. Willemsen, A. Verrips, et al., "Autosomal Dominant Transmission of GLUT1 Deficiency," *Human Molecular Genetics* 10, no. 1 (2001): 63–68, https://doi.org/10.1093/hmg/10.1.63.

6. J. Klepper, H. Scheffer, M. F. Elsaid, E. J. Kamsteeg, M. Leferink, and T. Ben-Omran, "Autosomal Recessive Inheritance of GLUT1 Deficiency Syndrome," *Neuropediatrics* 40, no. 5 (2009): 207–210, https://doi.org/10.1055/s-0030-1248264.

7. M. Rotstein, K. Engelstad, H. Yang, et al., "Glut1 Deficiency: Inheritance Pattern Determined by Haploinsufficiency," *Annals of Neurology* 68, no. 6 (2010): 955–958.

8. D. Aktas, E. G. Utine, K. Mrasek, et al., "Derivative Chromosome 1 and GLUT1 Deficiency Syndrome in a Sibling Pair," *Molecular Cytogenetics* 3, no. 1 (2010): 10.

9. S. Vermeer, D. A. Koolen, G. Visser, et al., "A Novel Microdeletion in 1(p34.2p34.3), Involving the SLC2A1 (GLUT1) Gene, and Severe Delayed Development," *Developmental Medicine and Child Neurology* 49, no. 5 (2007): 380–384.

10. M. Mueckler and C. Makepeace, "Model of the Exofacial Substrate-Binding Site and Helical Folding of the Human Glut1 Glucose Transporter Based on Scanning Mutagenesis," *Biochemistry* 48, no. 25 (2009): 5934–5942.

11. N. Walsh, A. Cooper, A. Dockery, and J. J. O'Byrne, "Variant Reclassification and Clinical Implications," *Journal of Medical Genetics* 61, no. 3 (2024): 207–211.

12. N. Tayebi, B. Leon-Ricardo, K. McCall, et al., "Quantitative Determination of SLC2A1 Variant Functional Effects in GLUT1 Deficiency Syndrome," *Annals of Clinical Translational Neurology* 10, no. 5 (2023): 787–801.

13. Y. C. Liu, J. W. Lee, S. T. Bellows, et al., "Evaluation of Non-Coding Variation in GLUT1 Deficiency," *Developmental Medicine and Child Neurology* 58, no. 12 (2016): 1295–1302, https://doi.org/10.1111/dmcn.13163.

14. M. A. Willemsen, L. E. L. M. Vissers, M. M. Verbeek, et al., "Upstream SLC2A1 Translation Initiation Causes GLUT1 Deficiency Syndrome," *European Journal of Human Genetics* 25, no. 6 (2017): 771–774.

15. O. Sanchez-Lijarcio, D. Yubero, F. Leal, et al., "The Clinical and Biochemical Hallmarks Generally Associated With GLUT1DS May Be Caused by Defects in Genes Other Than SLC2A1," *Clinical Genetics* 102, no. 1 (2022): 40–55.

16. E. M. Morrow and M. F. Pescosolido, "Christianson Syndrome," in *GeneReviews((R))*, ed. M. P. Adam, J. Feldman, G. M. Mirzaa, et al. (1993).

17. M. Srour, N. Shimokawa, F. F. Hamdan, et al., "Dysfunction of the Cerebral Glucose Transporter SLC45A1 in Individuals With Intellectual Disability and Epilepsy," *American Journal of Human Genetics* 100, no. 5 (2017): 824–830.

18. L. Mayorga, B. Gamboni, A. Mampel, and M. Roqué, "A Frame-Shift Deletion in the PURA Gene Associates With a New Clinical Finding:

Hypoglycorrhachia. Is GLUT1 a New PURA Target?," *Molecular Genetics and Metabolism* 123, no. 3 (2018): 331–336.

19. M. R. F. Reijnders, R. Janowski, M. Alvi, et al., "PURA Syndrome: Clinical Delineation and Genotype-Phenotype Study in 32 Individuals With Review of Published Literature," *Journal of Medical Genetics* 55, no. 2 (2018): 104–113.

20. S. A. Baldwin, "Mammalian Passive Glucose Transporters: Members of an Ubiquitous Family of Active and Passive Transport Proteins," *Biochimica et Biophysica Acta* 1154, no. 1 (1993): 17–49.

21. Y. Oka, T. Asano, Y. Shibasaki, et al., "C-Terminal Truncated Glucose Transporter Is Locked Into an Inward-Facing Form Without Transport Activity," *Nature* 345, no. 6275 (1990): 550–553.

22. P. Lange, E. Gertsen, I. Monden, J. Klepper, and K. Keller, "Functional Consequences of an In Vivo Mutation in Exon 10 of the Human GLUT1 Gene," *FEBS Letters* 555, no. 2 (2003): 274–278.

23. A. Salas-Burgos, P. Iserovich, F. Zuniga, J. C. Vera, and J. Fischbarg, "Predicting the Three-Dimensional Structure of the Human Facilitative Glucose Transporter glut1 by a Novel Evolutionary Homology Strategy: Insights on the Molecular Mechanism of Substrate Migration, and Binding Sites for Glucose and Inhibitory Molecules," *Biophysical Journal* 87, no. 5 (2004): 2990–2999.

24. J. Klepper and B. Leiendecker, "GLUT1 Deficiency Syndrome—2007 Update," *Developmental Medicine and Child Neurology* 49, no. 9 (2007): 707–716.

25. H. Y. Wong, P. Y. Law, and Y. Y. Ho, "Disease-Associated Glut1 Single Amino Acid Substitute Mutations S66F, R126C, and T295M Constitute Glut1-Deficiency States In Vitro," *Molecular Genetics and Metabolism* 90, no. 2 (2007): 193–198.

26. D. Deng, C. Xu, P. Sun, et al., "Crystal Structure of the Human Glucose Transporter GLUT1," *Nature* 510, no. 7503 (2014): 121–125.

27. M. Raja and R. K. H. Kinne, "Mechanistic Insights Into Protein Stability and Self-Aggregation in GLUT1 Genetic Variants Causing GLUT1-Deficiency Syndrome," *Journal of Membrane Biology* 253, no. 2 (2020): 87–99.

28. T. Asano, H. Katagiri, K. Takata, et al., "The Role of N-Glycosylation of GLUT1 for Glucose Transport Activity," *Journal of Biological Chemistry* 266, no. 36 (1991): 24632–24636.

29. T. Asano, K. Takata, H. Katagiri, et al., "The Role of N-Glycosylation in the Targeting and Stability of GLUT1 Glucose Transporter," *FEBS Letters* 324, no. 3 (1993): 258–261.

30. A. Olsowski, I. Monden, G. Krause, and K. Keller, "Cysteine Scanning Mutagenesis of Helices 2 and 7 in GLUT1 Identifies an Exofacial Cleft in Both Transmembrane Segments," *Biochemistry* 39, no. 10 (2000): 2469–2474.

31. J. Klepper, A. Salas-Burgos, E. Gertsen, and J. Fischbarg, "Bench Meets Bedside: A 10-Year-Old Girl and Amino Acid Residue Glycine 75 of the Facilitative Glucose Transporter GLUT1," *Biochemistry* 44, no. 38 (2005): 12621–12626.

32. J. Klepper, I. Monden, E. Guertsen, T. Voit, M. Willemsen, and K. Keller, "Functional Consequences of the Autosomal Dominant G272A Mutation in the Human GLUT1 Gene," *FEBS Letters* 498, no. 1 (2001): 104–109.

33. G. D. Holman, "Structure, Function and Regulation of Mammalian Glucose Transporters of the SLC2 Family," *Pflügers Archiv* 472, no. 9 (2020): 1155–1175.

34. M. Sato and M. Mueckler, "A Conserved Amino Acid Motif (R-X-G-R-R) in the Glut1 Glucose Transporter Is an Important Determinant of Membrane Topology," *Journal of Biological Chemistry* 274, no. 35 (1999): 24721–24725.

35. M. Mueckler and C. Makepeace, "Identification of an Amino Acid Residue That Lies Between the Exofacial Vestibule and Exofacial Substrate-Binding Site of the Glut1 Sugar Permeation Pathway," *Journal of Biological Chemistry* 272, no. 48 (1997): 30141–30146.

36. Z. Zhang, X. Li, F. Yang, et al., "DHHC9-Mediated GLUT1 S-Palmitoylation Promotes Glioblastoma Glycolysis and Tumorigenesis," *Nature Communications* 12, no. 1 (2021): 5872.

37. M. Wellner, I. Monden, and K. Keller, "The Role of Cysteine Residues in Glucose-Transporter-GLUT1-Mediated Transport and Transport Inhibition," *Biochemical Journal* 299, no. Pt 3 (1994): 813–817.

38. R. J. Zottola, E. K. Cloherty, P. E. Coderre, A. Hansen, D. N. Hebert, and A. Carruthers, "Glucose Transporter Function Is Controlled by Transporter Oligomeric Structure. A Single, Intramolecular Disulfide Promotes GLUT1 Tetramerization," *Biochemistry* 34, no. 30 (1995): 9734–9747.

39. E. E. Lee, J. Ma, A. Sacharidou, et al., "A Protein Kinase C Phosphorylation Motif in GLUT1 Affects Glucose Transport and Is Mutated in GLUT1 Deficiency Syndrome," *Molecular Cell* 58, no. 5 (2015): 845–853.

40. D. Wang, J. M. Pascual, P. Iserovich, et al., "Functional Studies of Threonine 310 Mutations in Glut1: T310I Is Pathogenic, Causing Glut1 Deficiency," *Journal of Biological Chemistry* 278, no. 49 (2003): 49015–49021.

41. J. Z. Zhang, H. Hayashi, Y. Ebina, R. Prohaska, and F. Ismail-Beigi, "Association of Stomatin (Band 7.2b) With Glut1 Glucose Transporter," *Archives of Biochemistry and Biophysics* 372, no. 1 (1999): 173–178.

42. J. F. Flatt, H. Guizouarn, N. M. Burton, et al., "Stomatin-Deficient Cryohydrocytosis Results From Mutations in SLC2A1: A Novel Form of GLUT1 Deficiency Syndrome," *Blood* 118, no. 19 (2011): 5267–5277.

43. W. M. Bawazir, E. F. Gevers, J. F. Flatt, et al., "An Infant With Pseudohyperkalemia, Hemolysis, and Seizures: Cation-Leaky GLUT1-Deficiency Syndrome due to a SLC2A1 Mutation," *Journal of Clinical Endocrinology and Metabolism* 97, no. 6 (2012): E987–E993.

44. B. Fricke, H. G. Jarvis, C. D. L. Reid, et al., "Four New Cases of Stomatin-Deficient Hereditary Stomatocytosis Syndrome: Association of the Stomatin-Deficient Cryohydrocytosis Variant With Neurological Dysfunction," *British Journal of Haematology* 125, no. 6 (2004): 796–803.

45. A. Furia, L. Muccioli, M. Santucci, L. Licchetta, and F. Bisulli, "Pseudohyperkalemia due to Cryohydrocytosis in GLUT1 Deficiency Syndrome. A Case Report and Literature Review," *Epileptic Disorders* 25, no. 3 (2023): 410–415.

46. Y. G. Weber, A. Storch, T. V. Wuttke, et al., "GLUT1 Mutations Are a Cause of Paroxysmal Exertion-Induced Dyskinesias and Induce Hemolytic Anemia by a Cation Leak," *Journal of Clinical Investigation* 118, no. 6 (2008): 2157–2168.

47. K. Meyer, M. Kirchner, B. Uyar, et al., "Mutations in Disordered Regions Can Cause Disease by Creating Dileucine Motifs," *Cell* 175, no. 1 (2018): 239–253.e17.

48. H. L. Wieman, S. R. Horn, S. R. Jacobs, B. J. Altman, S. Kornbluth, and J. C. Rathmell, "An Essential Role for the Glut1 PDZ-Binding Motif in Growth Factor Regulation of Glut1 Degradation and Trafficking," *Biochemical Journal* 418, no. 2 (2009): 345–367.

49. K. S. Heard, N. Fidyk, and A. Carruthers, "ATP-Dependent Substrate Occlusion by the Human Erythrocyte Sugar Transporter," *Biochemistry* 39, no. 11 (2000): 3005–3014.

50. K. B. Levine, E. K. Cloherty, N. J. Fidyk, and A. Carruthers, "Structural and Physiologic Determinants of Human Erythrocyte Sugar Transport Regulation by Adenosine Triphosphate," *Biochemistry* 37, no. 35 (1998): 12221–12232.

51. K. B. Levine, S. Hamill, E. K. Cloherty, and A. Carruthers, "Alanine Scanning Mutagenesis of the Human Erythrocyte Glucose Transporter Putative ATP Binding Domain," *Blood Cells, Molecules & Diseases* 27, no. 1 (2001): 139–142.

52. Q. Liu, J. C. Vera, H. Peng, and D. W. Golde, "The Predicted ATP-Binding Domains in the Hexose Transporter GLUT1 Critically Affect Transporter Activity," *Biochemistry* 40, no. 26 (2001): 7874–7881.

53. D. M. Blodgett, J. K. de Zutter, K. B. Levine, P. Karim, and A. Carruthers, "Structural Basis of GLUT1 Inhibition by Cytoplasmic ATP," *Journal of General Physiology* 130, no. 2 (2007): 157–168.

54. R. J. Naftalin, I. Afzal, P. Cunningham, et al., "Interactions of Androgens, Green Tea Catechins and the Antiandrogen Flutamide With the External Glucose-Binding Site of the Human Erythrocyte Glucose Transporter GLUT1," *British Journal of Pharmacology* 140, no. 3 (2003): 487–499.

55. D. Ni, Z. Ai, D. Munoz-Sandoval, et al., "Inhibition of the Facilitative Sugar Transporters (GLUTs) by Tea Extracts and Catechins," *FASEB Journal* 34, no. 8 (2020): 9995–10010.

56. J. M. Sage, A. J. Cura, K. P. Lloyd, and A. Carruthers, "Caffeine Inhibits Glucose Transport by Binding at the GLUT1 Nucleotide-Binding Site," *American Journal of Physiology. Cell Physiology* 308, no. 10 (2015): C827–C834.

57. O. A. Ojelabi, K. P. Lloyd, J. K. de Zutter, and A. Carruthers, "Red Wine and Green Tea Flavonoids Are Cis-Allosteric Activators and Competitive Inhibitors of Glucose Transporter 1 (GLUT1)-Mediated Sugar Uptake," *Journal of Biological Chemistry* 293, no. 51 (2018): 19823–19834.

58. J. Klepper, A. Flörcken, J. Fischbarg, and T. Voit, "Effects of Anticonvulsants on GLUT1-Mediated Glucose Transport in GLUT1 Deficiency Syndrome In Vitro," *European Journal of Pediatrics* 162, no. 2 (2003): 84–89.

59. J. D. Symonds, S. M. Zuberi, K. Stewart, et al., "Incidence and Phenotypes of Childhood-Onset Genetic Epilepsies: A Prospective Population-Based National Cohort," *Brain* 142, no. 8 (2019): 2303–2318.

60. T. S. Pearson, R. Pons, K. Engelstad, S. A. Kane, M. E. Goldberg, and D. C. de Vivo, "Paroxysmal Eye-Head Movements in Glut1 Deficiency Syndrome," *Neurology* 88, no. 17 (2017): 1666–1673.

61. M. Barthold, A. Jurkutat, R. Goetz, et al., "Timing of Ketogenic Dietary Therapy (KDT) Introduction and Its Impact on Cognitive Profiles in Children With Glut1-DS-A Preliminary Study," *Children (Basel)* 10, no. 4 (2023): 681.

62. M. Corradini, M. P. Zanaboni, C. Varesio, et al., "GLUT1DS Focus on Dysarthria," *European Journal of Paediatric Neurology* 51 (2024): 62–70.

63. S. Olivotto, A. Duse, S. M. Bova, et al., "Glut1 Deficiency Syndrome Throughout Life: Clinical Phenotypes, Intelligence, Life Achievements and Quality of Life in Familial Cases," *Orphanet Journal of Rare Diseases* 17, no. 1 (2022): 365.

64. J. Hao, D. I. Kelly, J. Su, and J. M. Pascual, "Clinical Aspects of Glucose Transporter Type 1 Deficiency: Information From a Global Registry," *JAMA Neurology* 74, no. 6 (2017): 727–732.

65. C. Varesio, V. de Giorgis, P. Veggiotti, et al., "GLUT1-DS Italian Registry: Past, Present, and Future: A Useful Tool for Rare Disorders," *Orphanet Journal of Rare Diseases* 18, no. 1 (2023): 63.

66. J. Kramer and L. Smith, "Ketogenic Diet in Glut 1 Deficiency Through the Life Cycle: Pregnancy to Neonate to Preschooler," *Child Neurology Open* 8 (2021): 2329048X211034655, https://doi.org/10.1177/2329048X211034655.

67. M. Hully, S. Vuillaumier-Barrot, C. le Bizec, et al., "From Splitting GLUT1 Deficiency Syndromes to Overlapping Phenotypes," *European Journal of Medical Genetics* 58, no. 9 (2015): 443–454.

68. V. De Giorgis, F. Teutonico, C. Cereda, et al., "Sporadic and Familial Glut1DS Italian Patients: A Wide Clinical Variability," *Seizure* 24 (2015): 28–32.

69. T. S. Pearson, C. Akman, V. J. Hinton, K. Engelstad, and D. C. de Vivo, "Phenotypic Spectrum of Glucose Transporter Type 1 Deficiency Syndrome (Glut1 DS)," *Current Neurology and Neuroscience Reports* 13, no. 4 (2013): 342.

70. C. Varesio, L. Pasca, S. Parravicini, et al., "Quality of Life in Chronic Ketogenic Diet Treatment: The GLUT1DS Population Perspective," *Nutrients* 11, no. 7 (2019): 1650.

71. H. L. Tanner, M. Dekker Nitert, L. K. Callaway, and H. L. Barrett, "Ketones in Pregnancy: Why Is It Considered Necessary to Avoid Them and What Is the Evidence Behind Their Perceived Risk?," *Diabetes Care* 44, no. 1 (2021): 280–289.

72. H. L. Tanner, M. D. Nitert, L. K. Callaway, and H. L. Barrett, "Erratum. Ketones in Pregnancy: Why Is It Considered Necessary to Avoid Them and What Is the Evidence Behind Their Perceived Risk?. Diabetes Care 2021;44:280–289," *Diabetes Care* 44, no. 6 (2021): 1456.

73. A. Dressler, C. Häfele, V. Giordano, et al., "The Ketogenic Diet Including Breast Milk for Treatment of Infants With Severe Childhood Epilepsy: Feasibility, Safety, and Effectiveness," *Breastfeeding Medicine* 15, no. 2 (2020): 72–78.

74. E. van der Louw, P. Trimmel-Schwahofer, A. Devlin, et al., "Human Milk and Breastfeeding During Ketogenic Diet Therapy in Infants With Epilepsy: Clinical Practice Guideline," *Developmental Medicine and Child Neurology* 66, no. 10 (2024): 1276–1288.

75. E. J. van der Louw, T. J. Williams, B. J. Henry-Barron, et al., "Ketogenic Diet Therapy for Epilepsy During Pregnancy: A Case Series," *Seizure* 45 (2017): 198–201.

76. F. Mochel, D. Gras, M. P. Luton, et al., "Prospective Multicenter Validation of a Simple Blood Test for the Diagnosis of Glut1 Deficiency Syndrome," *Neurology* 100, no. 23 (2023): e2360–e2373, https://doi.org/10.1212/WNL.0000000000207296.

77. U. Spiekerkoetter, D. Bick, R. Scott, et al., "Genomic Newborn Screening: Are We Entering a New Era of Screening?," *Journal of Inherited Metabolic Disease* 46, no. 5 (2023): 778–795.

78. J. Klepper, "Absence of SLC2A1 Mutations Does Not Exclude Glut1 Deficiency Syndrome," *Neuropediatrics* 44, no. 4 (2013): 235–236.

79. M. Henry, J. Kitchens, J. M. Pascual, and R. S. Maldonado, "GLUT1 Deficiency: Retinal Detrimental Effects of Gliovascular Modulation," *Neurology Genetics* 6, no. 4 (2020): e472.

80. W. G. Leen, M. Taher, M. M. Verbeek, E. J. Kamsteeg, B. P. van de Warrenburg, and M. A. Willemsen, "GLUT1 Deficiency Syndrome Into Adulthood: A Follow-Up Study," *Journal of Neurology* 261, no. 3 (2014): 589–599.

81. M. C. Cervenka, "Keto Is Not Just for Kids: A Randomized Trial of a Modified Atkins Diet for Adolescents and Adults With Anti-Seizure Medication-Resistant Epilepsy," *Epilepsy Currents* 23, no. 3 (2023): 147–149.

82. M. C. Cervenka, S. Wood, M. Bagary, et al., "International Recommendations for the Management of Adults Treated With Ketogenic Diet Therapies," *Neurology Clinical Practice* 11, no. 5 (2021): 385–397.

83. M. L. Armeno and E. H. Kossoff, "Let Food Be Thy Medicine. The Interaction Between Ketogenic Diet Therapy and Anti-Seizure Medications: A Systematic Review," *Epileptic Disorders* 25, no. 1 (2023): 18–27.

84. Y. A. C. Bekker, D. A. Lambrechts, J. S. Verhoeven, et al., "Failure of Ketogenic Diet Therapy in GLUT1 Deficiency Syndrome," *European Journal of Paediatric Neurology* 23, no. 3 (2019): 404–409.

85. R. Falsaperla, V. Sortino, G. J. Kluger, et al., "Exploring Ketogenic Diet Resistance in Glucose Transporter Type 1 Deficiency Syndrome: A Comprehensive Review and Critical Appraisal," *Epilepsia Open* 10, no. 1 (2025): 31–39.

86. J. Klepper, B. Leiendecker, C. Eltze, and N. Heussinger, "Paroxysmal Nonepileptic Events in Glut1 Deficiency," *Movement Disorders Clinical Practice* 3, no. 6 (2016): 607–610.

87. M. Anheim, E. Maillart, S. Vuillaumier-Barrot, et al., "Excellent Response to Acetazolamide in a Case of Paroxysmal Dyskinesias due to GLUT1-Deficiency," *Journal of Neurology* 258, no. 2 (2011): 316–317.

88. R. Chambon, S. Vuillaumier-Barrot, N. Seta, S. Wagner, and C. Sarret, "Partial Effectiveness of Acetazolamide in a Mild Form of GLUT1 Deficiency: A Pediatric Observation," *Movement Disorders* 28, no. 12 (2013): 1749–1751.

89. D. Tchapyjnikov and M. A. Mikati, "Acetazolamide-Responsive Episodic Ataxia Without Baseline Deficits or Seizures Secondary to GLUT1 Deficiency: A Case Report and Review of the Literature," *Neurologist* 23, no. 1 (2018): 17–18.

90. V. De Giorgis, K. P. Bhatia, O. Boespflug-Tanguy, et al., "Triheptanoin Did Not Show Benefit Versus Placebo for the Treatment of Paroxysmal Movement Disorders in Glut1 Deficiency Syndrome: Results of a Randomized Phase 3 Study," *Movement Disorders* 39, no. 8 (2024): 1386–1396.

91. P. Striano, S. Auvin, A. Collins, et al., "A Randomized, Double-Blind Trial of Triheptanoin for Drug-Resistant Epilepsy in Glucose Transporter 1 Deficiency Syndrome," *Epilepsia* 63, no. 7 (2022): 1748–1760.

92. S. N. Logel, E. L. Connor, D. A. Hsu, R. J. Fenske, N. J. Paloian, and D. C. de Vivo, "Exploring Diazoxide and Continuous Glucose Monitoring as Treatment for Glut1 Deficiency Syndrome," *Annals of Clinical Translational Neurology* 8, no. 11 (2021): 2205–2209.

93. F. Baschieri, A. Batla, R. Erro, C. Ganos, C. Cordivari, and K. P. Bhatia, "Paroxysmal Exercise-Induced Dystonia due to GLUT1 Mutation Can Be Responsive to Levodopa: A Case Report," *Journal of Neurology* 261, no. 3 (2014): 615–616.

94. M. Tang and U. R. Monani, "Glut1 Deficiency Syndrome: New and Emerging Insights Into a Prototypical Brain Energy Failure Disorder," *Neuroscience Insights* 16 (2021): 26331055211011507.

95. M. Tang, S. H. Park, D. C. de Vivo, and U. R. Monani, "Therapeutic Strategies for Glucose Transporter 1 Deficiency Syndrome," *Annals of Clinical Translational Neurology* 6, no. 9 (2019): 1923–1932.

96. Y. T. K. Nguyen, H. T. T. Ha, T. H. Nguyen, and L. N. Nguyen, "The Role of SLC Transporters for Brain Health and Disease," *Cellular and Molecular Life Sciences* 79, no. 1 (2021): 20, https://doi.org/10.1007/s00018-021-04074-4.

97. E. Beard, S. Lengacher, S. Dias, P. J. Magistretti, and C. Finsterwald, "Astrocytes as Key Regulators of Brain Energy Metabolism: New Therapeutic Perspectives," *Frontiers in Physiology* 12 (2021): 825816.

98. P. J. Magistretti and I. Allaman, "Lactate in the Brain: From Metabolic End-Product to Signalling Molecule," *Nature Reviews. Neuroscience* 19, no. 4 (2018): 235–249.

99. J. E. Rinholm and L. H. Bergersen, "Neuroscience: The Wrap That Feeds Neurons," *Nature* 487, no. 7408 (2012): 435–436.

100. L. A. van Gemert, N. van Alfen, L. Gaal, S. Wortmann, and M. A. Willemsen, "Effects of Sodium Lactate Infusion in Two Girls With Glucose Transporter 1 Deficiency Syndrome," *Neuropediatrics* 54, no. 6 (2023): 365–370, https://doi.org/10.1055/a-2134-8766.

101. M. Mastrangelo, F. Manti, G. Ricciardi, et al., "The Diagnostic and Prognostic Role of Cerebrospinal Fluid Biomarkers in Glucose Transporter 1 Deficiency: A Systematic Review," *European Journal of Pediatrics* 183, no. 9 (2024): 3665–3678.

102. G. Cappuccio, M. Pinelli, M. Alagia, et al., "Biochemical Phenotyping Unravels Novel Metabolic Abnormalities and Potential Biomarkers Associated With Treatment of GLUT1 Deficiency With Ketogenic Diet," *PLoS One* 12, no. 9 (2017): e0184022.

103. T. M. A. Peters, J. Merx, P. C. Kooijman, et al., "Novel Cerebrospinal Fluid Biomarkers of Glucose Transporter Type 1 Deficiency Syndrome: Implications Beyond the Brain's Energy Deficit," *Journal of Inherited Metabolic Disease* 46, no. 1 (2023): 66–75.

104. J. Yip, X. Geng, J. Shen, and Y. Ding, "Cerebral Gluconeogenesis and Diseases," *Frontiers in Pharmacology* 7 (2016): 521, https://doi.org/10.3389/fphar.2016.00521.

105. W. Xu and K. Borges, "Case for Supporting Astrocyte Energetics in Glucose Transporter 1 Deficiency Syndrome," *Epilepsia* 65, no. 8 (2024): 2213–2226.

106. K. H. Markussen, M. Corti, B. J. Byrne, C. W. Vander Kooi, R. C. Sun, and M. S. Gentry, "The Multifaceted Roles of the Brain Glycogen," *Journal of Neurochemistry* 168, no. 5 (2024): 728–743.

107. L. F. Obel, M. S. Müller, A. B. Walls, et al., "Brain Glycogen-New Perspectives on Its Metabolic Function and Regulation at the Subcellular Level," *Frontiers in Neuroenergetics* 4 (2012): 3, https://doi.org/10.3389/fnene.2012.00003.

108. S. S. Ellingwood and A. Cheng, "Biochemical and Clinical Aspects of Glycogen Storage Diseases," *Journal of Endocrinology* 238, no. 3 (2018): R131–R141, https://doi.org/10.1530/JOE-18-0120.

109. K. Rajasekaran, Q. Ma, L. B. Good, et al., "Metabolic Modulation of Synaptic Failure and Thalamocortical Hypersynchronization With Preserved Consciousness in Glut1 Deficiency," *Science Translational Medicine* 14, no. 665 (2022): eabn2956.

110. J. Klepper, J. C. Vera, and D. C. De Vivo, "Deficient Transport of Dehydroascorbic Acid in the Glucose Transporter Protein Syndrome," *Annals of Neurology* 44, no. 2 (1998): 286–287.

111. M. Villagran, C. F. Burgos, C. I. Rivas, and L. Mardones, "Identification of Structural Determinants of the Transport of the Dehydroascorbic Acid Mediated by Glucose Transport GLUT1," *Molecules* 28, no. 2 (2023): 521.

112. B. G. Ng, P. Sosicka, Z. Xia, and H. H. Freeze, "GLUT1 Is a Highly Efficient L-Fucose Transporter," *Journal of Biological Chemistry* 299, no. 1 (2023): 102738.

113. M. Schneider, E. Al-Shareffi, and R. S. Haltiwanger, "Biological Functions of Fucose in Mammals," *Glycobiology* 27, no. 7 (2017): 601–618.

114. W. Wetzel, N. Popov, B. Lössner, S. Schulzeck, R. Honza, and H. Matthies, "Effect of L-Fucose on Brain Protein Metabolism and Retention of a Learned Behavior in Rats," *Pharmacology, Biochemistry, and Behavior* 13, no. 6 (1980): 765–771.

115. B. Pekdemir, M. Bechelany, and S. Karav, "Fucosidosis: A Review of a Rare Disease," *International Journal of Molecular Sciences* 26, no. 1 (2025): 353.

116. A. Hullen, K. Falkenstein, C. Weigel, et al., "Congenital Disorders of Glycosylation With Defective Fucosylation," *Journal of Inherited Metabolic Disease* 44, no. 6 (2021): 1441–1452.

117. P. D. Yurchenco and P. H. Atkinson, "Equilibration of Fucosyl Glycoprotein Pools in HeLa Cells," *Biochemistry* 16, no. 5 (1977): 944–953.

118. M. Tang, G. Gao, C. B. Rueda, et al., "Brain Microvasculature Defects and Glut1 Deficiency Syndrome Averted by Early Repletion of the Glucose Transporter-1 Protein," *Natural Communications* 8 (2017): 14152.