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**Research Article**

**Keywords:** GLUT1 deficiency, intellectual disability, seizures, ketogenic diet, ataxia

**Posted Date:** September 10th, 2026

**DOI:** https://doi.org/10.21203/rs.3.rs-10327622/v1

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**Additional Declarations:** No competing interests reported.

**Version of Record:** A version of this preprint was published at Orphanet Journal of Rare Diseases on November 6th, 2026. See the published version at https://doi.org/10.1186/s13023-026-04703-w.

# Phenotypic spectrum and diagnostic evolution in GLUT1 deficiency syndrome: a single-centre adult cohort experience

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Word count: 5825

Tables: 4

Figures: 5

Supplementary files: 1

# Abstract

**Background**

Glucose transporter type 1 deficiency syndrome (GLUT1-DS) is a rare neurometabolic disorder caused by pathogenic variants in the *SLC2A1* gene. It is classically described as an infantile-onset condition; however, an expanding phenotypic spectrum is increasingly recognised, including diagnoses in adulthood. In this retrospective review of an adult cohort with GLUT1-DS, we explore the phenotypic diversity and diagnostic evolution within this cohort.

**Methods**

This retrospective case series was a single-centre study conducted at one adult metabolic centre and included adult patients with confirmed clinical, biochemical or genetic GLUT1-DS.

**Results**

Thirty-one individuals were identified with a median age of 27 years (IQR: 22-37). Median age at symptom onset was 3 years (IQR: 0-7). Median diagnostic delay was 6.5 years (IQR: 0.75-27.25) with a maximal delay of 47 years. 56% of individuals were diagnosed via genetic testing, most commonly by targeted single gene sequencing, with a shift towards exome and whole genome sequencing (WGS) in more recent cases. Individuals with a mixed phenotype (seizure and movement disorder) had the lowest median diagnostic delay (3.5 years, IQR: 1-13). The longest diagnostic delay was seen in movement-disorder predominant phenotypes (10 years, IQR: 2.5-37). Loss-of-function *SLC2A1* variants tended to present earlier and with seizure-predominant or mixed phenotypes, whereas missense variants more commonly presented later with movement disorder-predominant phenotypes.

**Conclusion**

This case series demonstrates the marked phenotypic heterogeneity in GLUT1-DS. It also charts the evolution in diagnostic methods over the last few decades, illustrating how the increased availability of WGS and cascade testing has identified milder and atypical phenotypes. Widespread adoption of cascade testing would help identify individuals with undiagnosed GLUT1-DS and further define the full spectrum of GLUT1 deficiency.



**Key words:** GLUT1 deficiency, intellectual disability, seizures, ketogenic diet, ataxia

# Introduction

Glucose Transporter Type 1 deficiency syndrome (GLUT1-DS; OMIM #606777) is a rare monogenic neurometabolic disorder characterised by a failure of cerebral glucose delivery secondary to GLUT1 transporter hypofunction.[1] GLUT1 is the principal transporter for insulin-independent glucose transport across the blood-brain barrier.[2] Dysfunction of this transporter reduces glucose delivery to neurons, resulting in cerebral energy failure and giving rise to neurological sequelae.[3]

GLUT1-DS arises from pathogenic variants of the *SLC2A1* (solute carrier family 2 member 1) gene, located on chromosome 1p34.2.[4,5] GLUT1-DS exhibits both autosomal dominant and sporadic transmission, with approximately 10% of cases being inherited.[6] In these instances the parent is usually asymptomatic or only mildly affected. The other 90% of GLUT1 presentations are due to *de novo* pathogenic variants.[7]

Symptoms of GLUT1-DS typically emerge within the first 6 months of life, as the rising central glucose requirement of the growing brain surpasses GLUT1 transporter-mediated delivery mechanisms. Symptoms include paroxysmal eye or head movements, treatment-resistant seizures, developmental delay, movement disorders, acquired microcephaly and neurocognitive symptoms.[8]

A broader, atypical GLUT1-DS phenotype is being increasingly diagnosed.[9] Symptoms are generally more subtle with a later onset, and as a result are associated with delayed diagnosis. These symptoms may include exercise-induced limb weakness, and neuropsychiatric or cognitive symptoms.[10] These symptoms can vary greatly between individuals, even within the same family.[11,12]

Diagnosis of GLUT1-DS involves clinical history, lumbar puncture and genetic testing. The mainstay of treatment is ketogenic diet therapy (KDT), response to which can be quantified by monitoring seizure control, cognitive function and presence/severity of movement disorders. Once KDT is established, anti-seizure medication can often be successfully withdrawn, however patients on KDT may develop steatosis or struggle to tolerate the diet long-term.[13] Monitoring is also required for carnitine deficiency, which may develop over time.[14]

Improved clinician awareness of atypical GLUT1-DS presentations, coupled with wider availability of WGS, is leading to the recognition of an increasingly broad phenotype[1,15]. This change in practice creates an opportunity to better understand this disease, particularly in the case of milder phenotypes.

# Methods

### 2.1 Study design

A retrospective case series was conducted of patients with GLUT1-DS under the care of the general metabolic clinic at a tertiary Adult Inherited Metabolic Diseases centre and neurology clinics in Salford Royal Hospital (NCA) in the UK.

### 2.2 Participants

Eligibility criteria included either:

1. Clinical diagnosis of GLUT1-DS based on characteristic features (developmental delay, paroxysmal exertion-induced dyskinesia, movement disorders or seizures), or:

2. Diagnostic confirmation by one or more of the following:

a. Cerebrospinal fluid (CSF) analysis demonstrating hypoglycorrhachia (CSF:serum glucose ratio interpreted on age-specific basis)

b. Genetic identification of a pathogenic/likely pathogenic variant in the *SLC2A1* gene

c. Clinical symptoms of GLUT1-DS and a first-degree family member with a genetic diagnosis

### 2.3 Data collection

Clinical data were extracted from electronic health records and clinic letters, covering patient demographics, presenting features, age at onset, symptoms, and method of diagnosis.

Genetic information included the *SLC2A1* variant, predicted protein domain or transmembrane region, inheritance pattern where parental testing was available, and the presence of affected family members. Variants were annotated using the canonical *SLC2A1* transcript (NM_006516.4), and protein domain localisation was determined based on published GLUT1 protein topology models.

Neurological and psychiatric data included movement disorders, dysphagia, speech impairment, headache, sleep disorders, developmental delay, memory impairment, autism spectrum disorder, attention deficit hyperactive disorder, depression, anxiety and fatigue. The initiation of, and adherence to a ketogenic diet was also recorded.

### 2.4 Outcomes

The primary outcome was the clinical phenotype description of the Salford GLUT1-DS cohort. Secondary outcomes included seizure burden, neurological profile, neurodevelopmental profile, medications and association of genotype with phenotype severity.

### 2.5 Statistical analysis

All statistics were calculated using R, version 4.6.0.

### 2.6 Ethical consideration

This project was approved by Northern Care Alliance (NCA) Research and Innovation Department as a health improvement project (25HIP56). No formal ethics permission or consenting of patients was deemed necessary due to the aggregate presentation of anonymised data, collected retrospectively as part of routine patient care. The study was conducted in accordance with the Declaration of Helsinki.

# Results

**Demographics**

This cohort describes 31 adults with GLUT1-DS. The median age at the time of analysis is 27 years of age (IQR: 22-37). The age of symptom onset was 3 years (IQR 0-7). The median age at diagnosis was 11 years (IQR 6-29). The median delay in diagnosis (time from symptoms to diagnosis) was 6.5 years (IQR 0.75-27.25). The longest diagnostic delay was 47 years (figure 3). 8 patients were diagnosed in adulthood (>18 years) (Table 1). There is a degree of missingness in our data due to the retrospective nature of this study.

**Table 1. Demographic and phenotype summary for 31 patients;** *Some patients have multiple symptoms listed below. Denominators are stated where they differ from the full cohort (n=31).*

| **Category** | **n (%)** | |
|---|---|---|
| **Age, years (n=31)** | | |
| | ***Onset*** | ***Diagnosis*** |
| 0–9 | 23 (74%) | 10 (32%) |
| 10–19 | 6 (19%) | 7 (22%) |
| 20–29 | 0 (0%) | 6 (19%) |
| 30–39 | 0 (0%) | 3 (10%) |
| 40–49 | 0 (0%) | 3 (10%) |
| 50–59 | 0 (0%) | 1 (3%) |
| Missing data | 2 | 1 |
| Median age at time of analysis | 27 years (IQR 22–37) | |
| Median diagnostic delay | 6.5 years (IQR 0.75–27.25) | |
| **Gender (n=31)** | | |
| Male | 13 (42%) | |
| Female | 18 (58%) | |
| **Primary diagnostic method (n=31)** | | |
| **Genetics** | **26 (84%)** | |
| *— of which reports available* | *21/26 (81%)* | |
| *— of which cascade diagnosis* | *2/26 (8%)* | |
| CSF | 5 (16%) | |
| **Predominant phenotype (n=31)** | | |
| Seizure-predominant | 8 (26%) | |
| Movement disorder-predominant | 14 (45%) | |
| Mixed phenotype | 9 (29%) | |
| **Median diagnostic delay by phenotype (years, IQR)** | | |
| Seizure + movement disorder | 3.5 (IQR 0–13) | |
| Seizure only | 9 (IQR 1–28) | |
| Movement disorder only | 10 (IQR 2.5–37) | |
| **Primary seizure type (n=17)** | | |
| Focal aware | 2 (12%) | |
| Focal impaired awareness | 3 (18%) | |
| Generalised tonic-clonic | 6 (35%) | |
| Absence | 3 (18%) | |
| Not recorded | 3 (18%) | |

| | |
|---|---|
| **Type of movement disorder (n=31)** | |
| Tremor | 6 (19%) |
| Ataxia | 9 (29%) |
| Dystonia | 20 (65%) |
| Dyskinesia | 11 (35%) |
| Exercise-induced weakness | 12 (39%) |
| **Associated neurodevelopmental phenotypes (n=31)** | |
| Intellectual disability | 24 (77%) |
| Developmental delay | 15 (48%) |
| Autism spectrum disorder | 6 (19%) |
| ADHD | 3 (10%) |
| Sleep disorder | 3 (10%) |
| **Additional neurological features** | |
| Migraine | 8 (26%) |
| Depression | 9 (29%) |
| Anxiety | 8 (26%) |
| Fatigue | 5 (16%) |
| **Functional outcome (n=31)** | |
| | |
| Speech issues | 12 (39%) |
| Mobility issues | 8 (26%) |
| **Ketogenic diet (n=31)** | |
| **Initiated** | **26 (84%)** |
| *— stability** | *16/26 (62%)* |
| *— adherent* | *11/26 (42%)* |
| *— poor adherence* | *5/26 (19%)* |
| *— discontinued* | *5/26 (19%)* |
| **Pregnancy** | |
| Pregnancy | 6/18 (33%) |
| Complications during pregnancy | 1/6 (17%) |

**Disease stability as reflected in minimal clinical change of symptoms recorded in clinical notes (in relation to seizure, movement disorder or cognition).*

**Diagnostic pathways**

Diagnosis occurred through a range of methods (figure 1). Some patients received only biochemical testing (n=4), others only genetic testing (n=19). Some patients who received biochemical testing went on to receive genetic testing also. For some patients, especially those who had transferred between services, it was not possible to track the method of diagnosis (n=6), however they met inclusion criterion 1. Genetic methods included targeted single gene sequencing (n=7), targeted mutation testing (n=2), exome sequencing (ES) (n=1), microarray testing (n=1), and whole genome sequencing (WGS) (n=2).

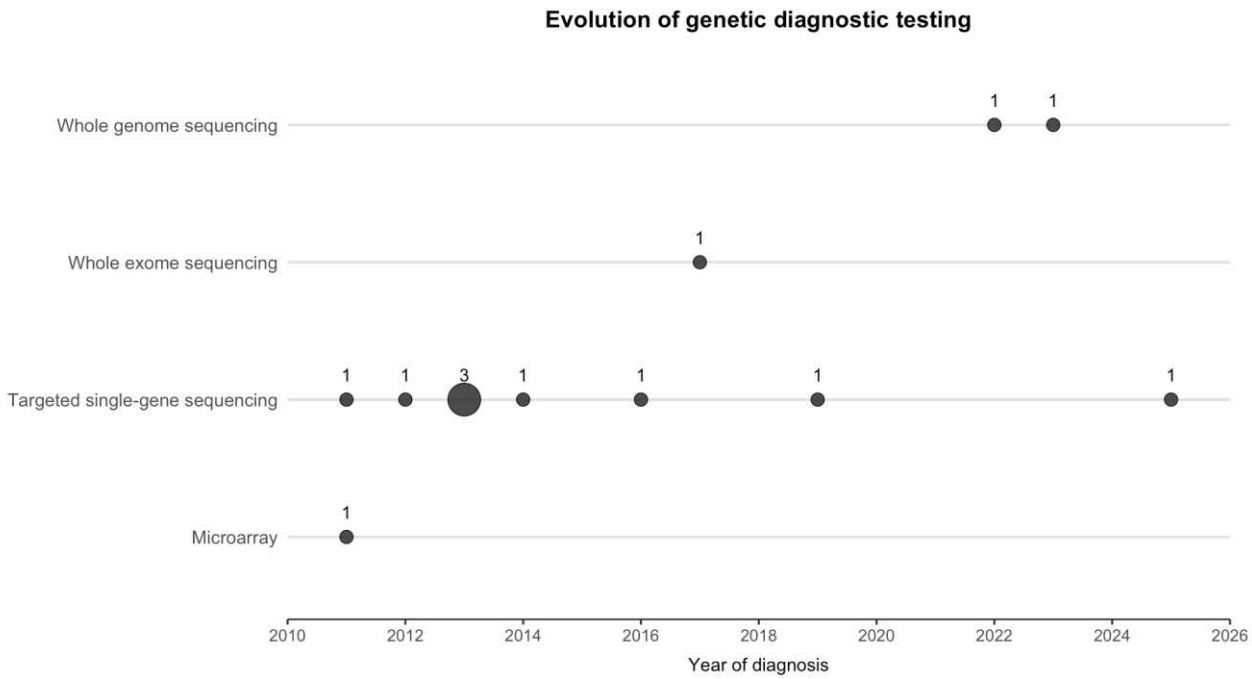



**Figure 1:** Diagnostic method evolution over time (data for n=13 patients)

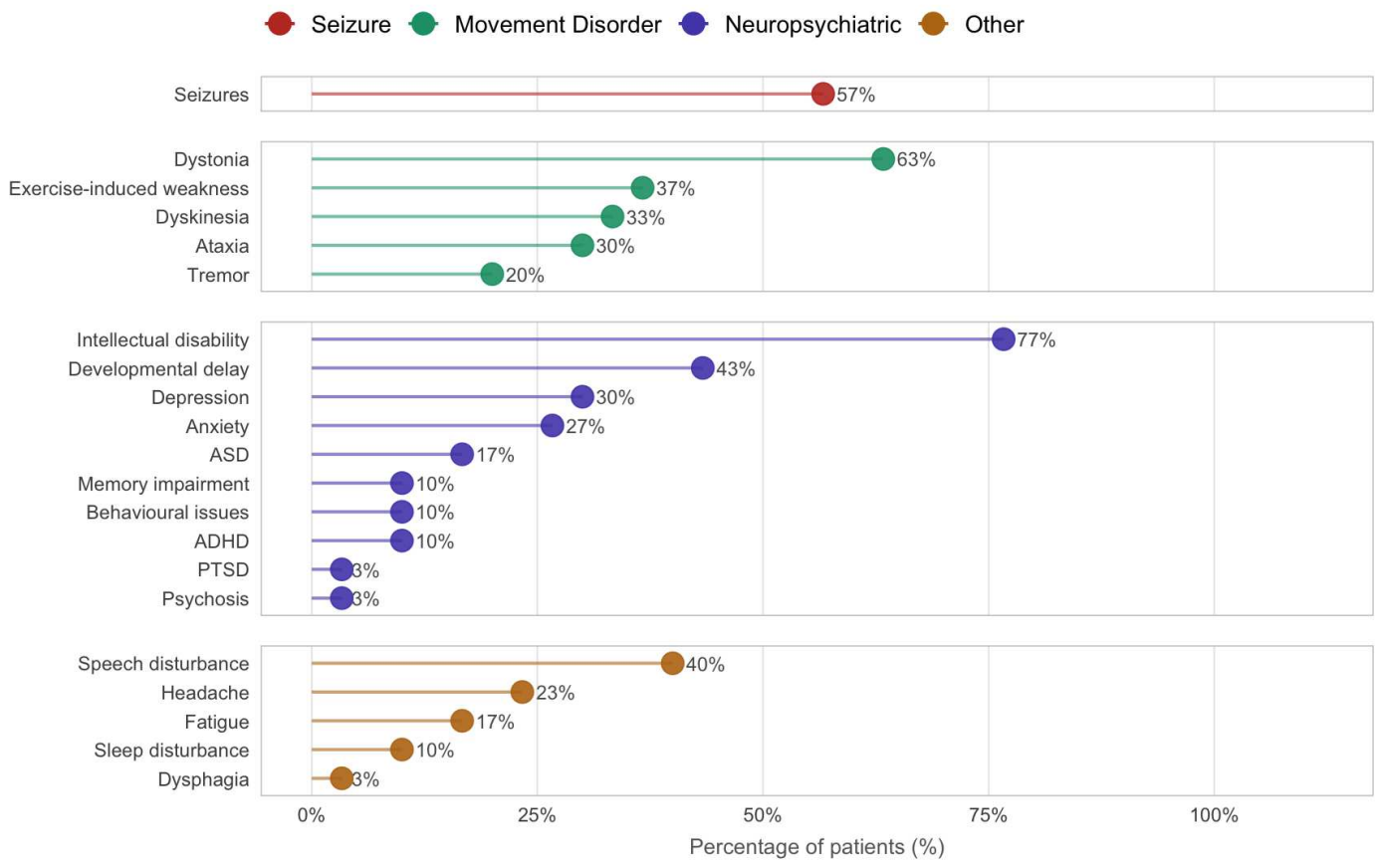
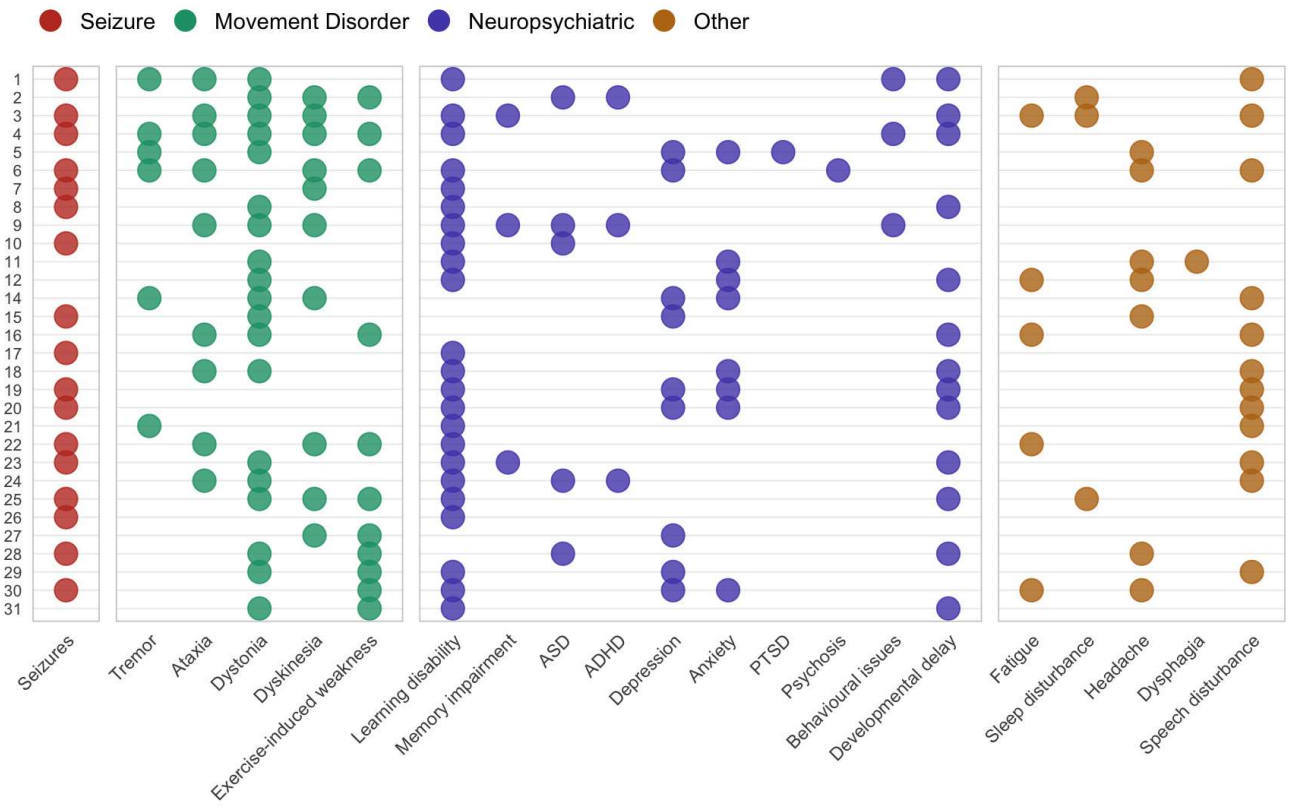



**Figure 2a:** Symptom prevalence throughout cohort




**7b:** Symptom map of cohort by patient

**Phenotype data**

*Epilepsy*

57% of patients in this cohort experienced seizures (figure 2a), with seizure types including focal impaired awareness, absence, myoclonic, and generalised tonic-clonic seizures. The median age of diagnosis amongst seizure-predominant phenotype patients was 9 years (IQR 0.75-28) (figure 3). 57% of patients established on KDT had documentation that reported an improvement in seizure control on KDT.

*Movement disorders*

Movement disorders were highly prevalent in this cohort (figure 2b), with 81% of patients reporting some manifestation of a movement disorder (tremor, ataxia, dystonia, dyskinesia and gait instability) and 23% of patients presenting with an exercise-induced movement disorder as their primary feature. The median diagnostic delay amongst movement-disorder predominant phenotypes was 10 years (IQR: 2.5-37) (figure 3). 3/24 (12.5%) patients with movement disorders were prescribed medication to treat them. One patient was prescribed baclofen and botulinum toxin injections, and another two patients were prescribed acetazolamide. Acetazolamide was documented as being inferior to KDT initiation in one patient. No further comments on medication use for movement disorders in this cohort.

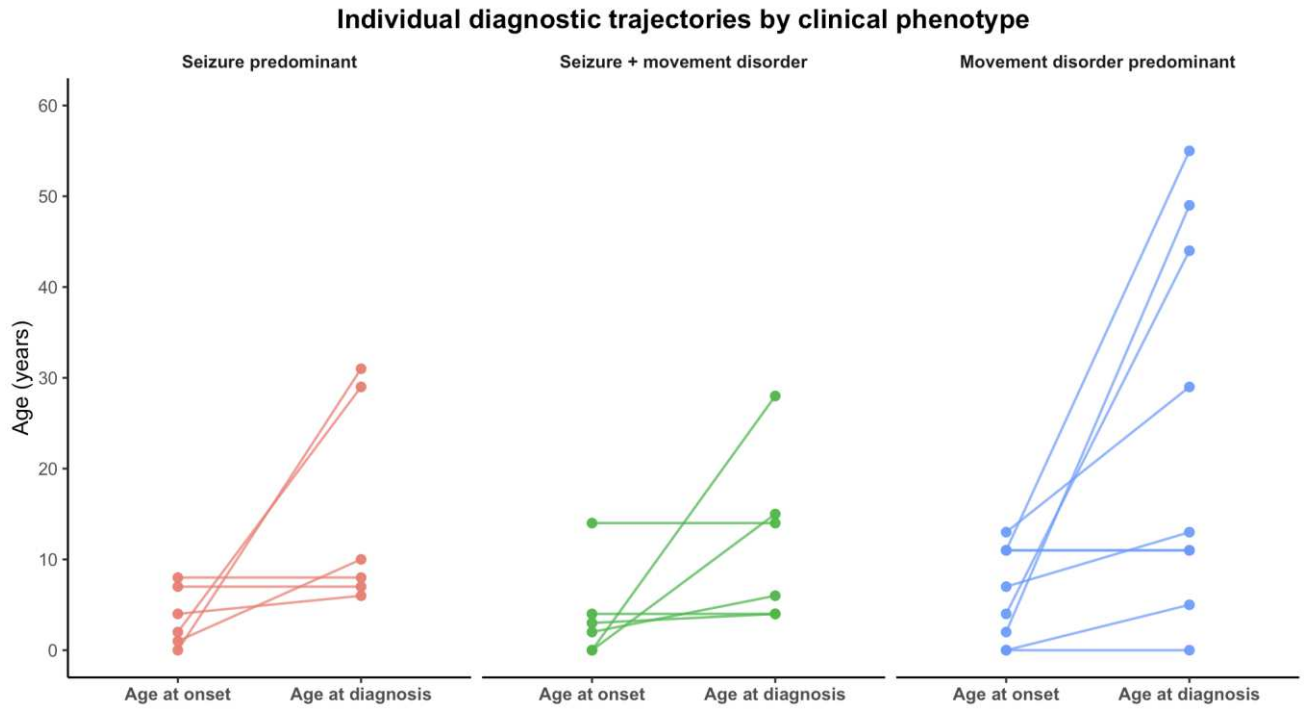



**Figure 3**: GLUT1DS age of onset and diagnosis by clinical phenotype (data for n=21 patients). $p$ = 0.689 (Kruskal-Wallis chi-squared)

*Neurodevelopmental and psychiatric features*

Developmental delay was reported in 12 patients (35%). 6 patients (19%) experienced global developmental delay, and a further 6 patients (19%) had a delay in their motor development. One patient (3%) experienced a delay in speech development. 23 patients (74%) were documented as having an intellectual disability. Patients also experienced migraine (n=8), anxiety (n=8), depression (n=9), fatigue (n=5) and insomnia (n=3). 5 patients (16%) had a formal diagnosis of autism spectrum disorder, and 3 patients (10%) had a formal diagnosis of Attention Deficit Hyperactivity Disorder (ADHD).

Seizure-predominant phenotypes were associated with greater neurodevelopmental burden: intellectual disabilities were present in 88% of patients with seizure-predominant phenotypes (n=7/8) and 89% of patients with combined seizure and movement disorder phenotypes (n=8/9), compared to only 64% of movement-disorder phenotypes (n=9/14). Developmental delay was present in 7/8 patients (87%) with seizure and movement disorder phenotype, 3/4 patients (75%) with a seizure predominant phenotype, and only 5/11 patients (45%) with a movement disorder predominant phenotype.

*Functional outcomes and mobility*

Functional status varied widely between patients. 5/31 patients (16%) were wheelchair dependent, and a further 4/31 patients (13%) were ambulant with support (e.g. reduced walking distance or use of walking aids). 12/21 patients (57%) were independent or physically active. The remainder did not have sufficient documentation pertaining to their activity status. Pronounced ataxia was prevalent with recurrent falls in 6/31 patients (20%). SARA score was available for 8/31 patients and showed median 11.75 (8.5-20.5) indicating moderate ataxia.

29% of patients were documented as being independent in their activities of daily living (ADLs). 13% were dependent, with fine motor skill difficulties (feeding, writing, fastening buttons) being the most cited reason for ADL dependency.

Whilst educational attainment was not universally recorded in patient notes, 7 patients were undertaking college-level study with a further patient undertaking a university degree. One patient was documented as requiring specialist education, whereas other patients were in mainstream education.

*Social context*

4 patients (13%) were adopted, with another patient being cared for by their extended family. For 2 of the adopted cases (50%), the patient's biological parents had received a diagnosis of GLUT1-DS.

***Pregnancy***

Pregnancy was documented in 6 women with the disorder in this cohort, with only one documented as having a complication (status epilepticus near term) and the other 5 pregnancies leading to normal deliveries. The individual who had status epilepticus near term had a movement-disorder predominant phenotype and was fully adherent with KDT. Only one proband had an epilepsy-predominant phenotype and they had a normal delivery and were not adherent to KDT. All other probands who were pregnant had a movement-disorder predominant phenotype.

**Genotype**

26 patients (77%) received a genetic diagnosis, of which 21 patients (68%) had retrievable genetic reports (5 patients received their genetic diagnosis at another centre and their report was not accessible). Genetic testing was the primary method of diagnosis in 17 patients. Five patients (16%) were diagnosed biochemically based on CSF hypoglycorrhachia. Eighteen unique variants were identified, and variant types included missense (n=11 unique variants) in 15 patients, frameshift indels (n=3), stop-gain (n=1), intronic (n=1), large deletion (n=1), and intragenic duplication (n=1). Fourteen variants were classified as pathogenic, and four as likely pathogenic. Nine patients had a family history of GLUT1-DS with a familial *SLC2A1* identified, while inheritance was unknown in the remaining patients. Nine patients had a family history of GLUT1-DS, while inheritance was unknown in the remaining patients. Seven variants were not previously reported in the literature or public databases. The genotype findings in the study were detailed in table 2, supplemental table 1 and figure 5.

**Phenotype-genotype correlations**

Recurrent pathogenic variants were identified at codon 153, with p.(Arg153Cys) and p.(Arg153Leu) affecting two patients each. All four patients with Arg153 variants had variants localised to the intracellular loop connecting transmembrane helices TM4 and TM5, a region critical for transporter gating, and three of four presented with a movement disorder-predominant phenotype. The p.(Met96Val) variant in TM3 was identified in two unrelated patients, both presenting with movement disorder-predominant phenotypes and exercise-induced features. Together, recurrent variants accounted for 6 of 22 (27%) genotyped patients.

Among the 15 patients with missense variants, those with variants in the N-terminal transmembrane domains and loops (TM1-TM6 region; n=10) predominantly presented with movement disorder-predominant phenotypes (8/10, 80%), with one patient presenting with a seizure-predominant

phenotype p.(Arg153Cys) and variant, and one with a combined seizure and movement disorder phenotype and p.(Leu12Phe) variant. Patients with missense variants in C-terminal domains (TM7-TM11 region; n=5) showed a more varied phenotype presentation, with two presenting with a movement disorder-predominant phenotype, two with a seizure-predominant phenotype, and one with a mixed phenotype. The intronic variant c.680-11G>A in patient 3 predicts utilisation of a cryptic splice acceptor within intron 5, resulting in an in-frame insertion of three amino acids in the intracellular loop connecting TM6 and TM7, without truncation of the GLUT1 protein. Based on this, it was classified as protein-altering rather than truncating.

We compared the phenotypes in the patients with missense and protein-altering variants (n=17) with those with truncating/loss-of-function (LoF) (n=5) (table 3). Patients with truncating/LoF variants tended to present at an earlier age at onset, and more frequently exhibited seizure-predominant or mixed phenotypes compared to those with missense variants. Exercise-induced neurological features were documented in at least 8/22 genotyped patients and included paroxysmal exercise-induced dyskinesia, lower limb weakness triggered by exertion, and post-exertional ataxia or dystonia, and were more frequent in the protein-altering group (7/17) than in the LoF group (1/5) ($p$=0.603).

Neurodevelopmental features showed associations with both variant class and phenotypic category. Learning difficulties were present in all five patients with LoF variants (100%), compared to 12/17 patients with protein-altering variants (71%), ($p$ = 0.290). Developmental delay was reported in 3/5 LoF patients (60%) versus 5/17 protein-altering patients (29%) ($p$ = 0.309). Intellectual disability was present in the majority of patients with any seizure involvement, including those with seizure-predominant phenotypes, and mixed seizures and movement disorders phenotypes, compared to 7/12 patients (58%) of those in the movement disorder-predominant group. Early onset of symptoms (age ≤4 years) was associated with a higher frequency of developmental delay (4/9; 44%) compared to later onset (>4 years) (1/9; 11%), ($p$ = 0.294). Intellectual disability were similarly prevalent in both groups (78% in the early-onset group vs 67% of the later-onset group). All p values were calculated by Fisher's exact test.

**Biochemistry**

Six patients were diagnosed by lumbar puncture, with 1 patient receiving WGS following this. Given the retrospective nature of this study, detailed CSF biochemistry results were not accessible.

**Neuroimaging**

Nine participants received MRI scans (figure 4). Three individuals had abnormal findings, including high T2 signal change in the paravermian cerebellum and multiple discrete foci of high T2 signal change in the subcortical white matter.

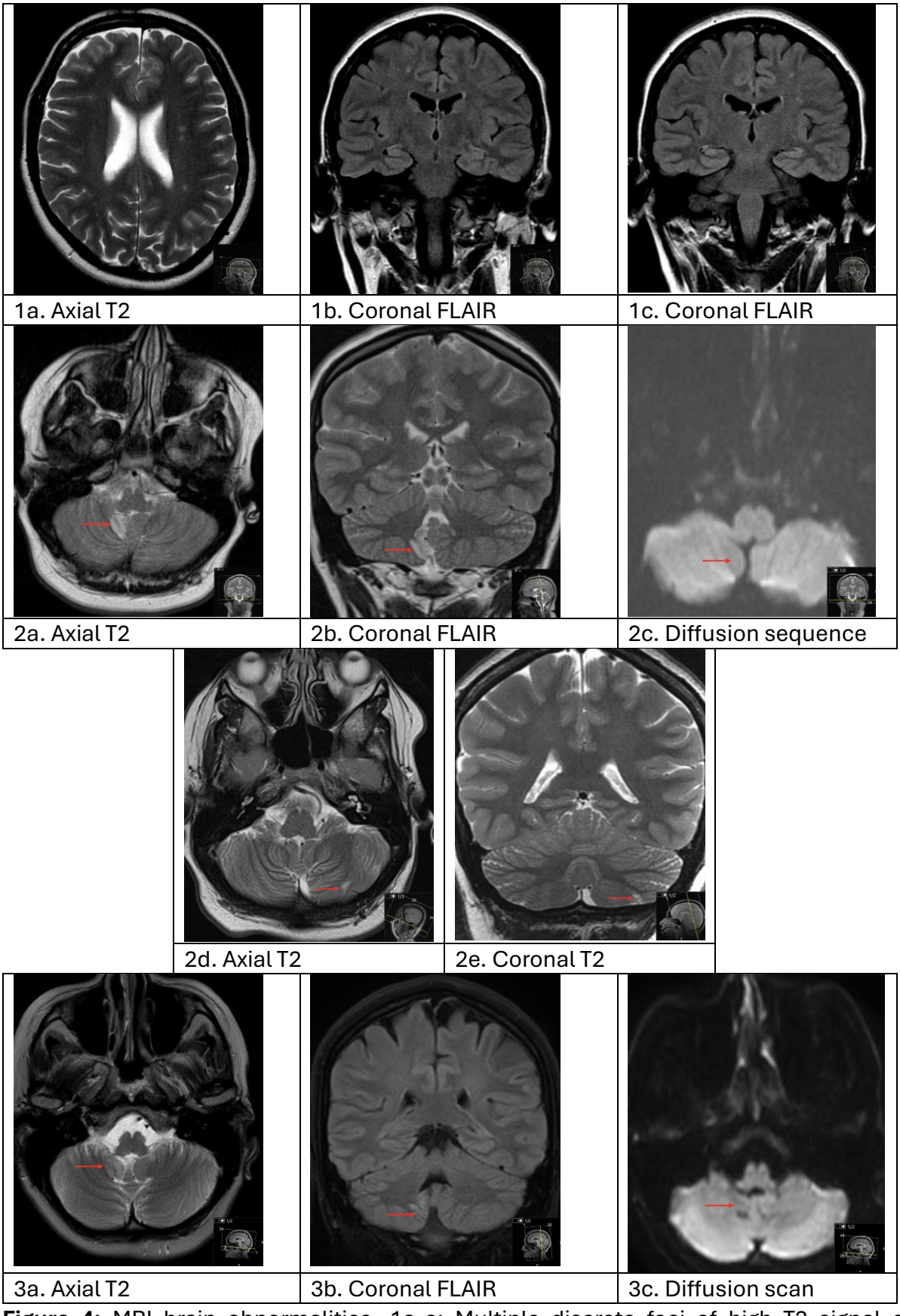



**Figure 4:** MRI brain abnormalities. 1a-c: Multiple discrete foci of high T2 signal changes in the subcortical white matter of both frontal lobes; 2a-c: High T2 signal change in the paravermian right cerebellar hemisphere without diffusion restriction; 2d-e: Axial and coronal T2 sequences show focal high T2 signal change in the inferior aspect of the left cerebellar cortex consistent with an old infarct. 3a-c: High T2 signal in the paravermian cerebellar hemisphere without diffusion restriction

**Table 2:** The genotype characteristics of the study cohort

| Patient ID | Variant | Mutation type | Protein domain | Inheritance | Pathogenicity |
|---|---|---|---|---|---|
| Movement Predominant | | | | | |
| 2 | c.352T>C (p.Ser118Pro) | Missense | EC loop (TM3-TM4) | Unknown | Likely pathogenic |
| 5 | Exon 2 Duplication | Duplication | TM1 (in-frame duplication) | Familial (Mat) | Likely pathogenic |
| 9 | c.458G>T (p.Arg153Leu) | Missense | IC loop (TM4-TM5) | Unknown | Pathogenic |
| 11 | c.376C>T (p.Arg126Cys) | Missense | TM4 | Unknown | Pathogenic |
| 12 | c.354_355insT p.(Glu120*) | Stop-Gain | EC loop (TM3-TM4) | Unknown | Pathogenic |
| 13 | c.286A>G (p.Met96Val) | Missense | TM3 | Familial (Mat) | Pathogenic |
| 15 | c.1258A>G (p.Met420Val) | Missense | TM11 | Familial (Mat) | Pathogenic |
| 16 | c.457C>T (p.Arg153Cys) | Missense | IC loop (TM4-TM5) | Unknown | Pathogenic |
| 21 | c.493G>A (p.Val165Ile) | Missense | TM5 | Unknown | Pathogenic |
| 24 | c.458G>T (p.Arg153Leu) | Missense | IC loop (TM4-TM5) | Unknown | Pathogenic |
| 27 | c.286A>G (p.Met96Val) | Missense | TM3 | Familial (Pat) | Pathogenic |
| 29 | c.940G>A (p.Gly314Ser) | Missense | TM8 | Unknown | Pathogenic |
| Mixed phenotype (Seizure and Movement disorder) | | | | | |
| 1 | Whole Gene Deletion | Deletion | - | Unknown | Pathogenic |
| 3 | c.680-11G>A | Intronic | IC loop (TM6-TM7) | Familial | Pathogenic |
| 6 | c.975delins (p.Val327Cysfs*54) | Frameshift | TM8 | Unknown | Pathogenic |

| | | | | | |
|---|---|---|---|---|---|
| 22 | c.1126G>C (p.Val376Leu) | Missense | TM10 | Unknown | Likely pathogenic |
| 30 | c.34C>T p.(Leu12Phe) | Missense | TM1 | Familial | Likely pathogenic |
| Seizure predominant | | | | | |
| 7 | c.97dup (p.Ile33Asnfs*56) | Frameshift | TM1 | Unknown | Pathogenic |
| 8 | c.616_623del (p.Phe206Argfs*28) | Frameshift | TM6 | Unknown | Pathogenic |
| 10 | c.971C>T (p.Ser324Leu) | Missense | TM8 (Pore) | Unknown | Pathogenic |
| 20 | c.457C>T (p.Arg153Cys) | Missense | IC loop (TM4-TM5) | Familial | Pathogenic |
| 26 | c.884C>T (p.Thr295Met) | Missense | EC loop (TM7-TM8) | Unknown | Pathogenic |

Abbreviations: EC: extracellular, IC: intracellular, TM: transmembrane domain

**Table 3:** Phenotype comparison between the patients with missense and Truncating / LoF variants in the study

| | **Protein-Altering Variants† (n=17)** | **LoF Variants‡ (n=5)** | ***p-value*** |
|---|---|---|---|
| **Predominant phenotype, n (%)** | | | |
| Seizure predominant | 3 (18%) | 2 (40%) | 0.186* |
| Movement disorder predominant | 11 (65%) | 1 (20%) | 0.186* |
| Combined seizure and movement disorder | 3 (18%) | 2 (40%) | 0.186* |
| **Age of onset** | | | |
| Mean (SD), years | 8.0 (5.1) | 1.8 (3.0) | 0.046** |
| Median (range), years | 8 (0.5–16) | 0 (0–7) | 0.046** |
| **Neurodevelopmental features, n (%)** | | | |
| Developmental delay | 5 (29%) | 3 (60%) | 0.309* |
| Intellectual disability | 12 (71%) | 5 (100%) | 0.290* |

| **Movement disorder features, n (%)** | | | |
|---|---|---|---|
| Any movement disorder | 14/17 (82%) | 3/5 (60%) | 0.548* |
| Exercise-induced features | 7/17 (41%) | 1/5 (20%) | 0.613* |

*p-value calculated using Fisher's exact test

** p-value retained from original analysis (Mann-Whitney U test for age of onset)

† Protein-altering variants: missense variants, the intronic variant c.680-11G>A (predicting an in-frame PPV amino acid insertion in the IC loop TM6–TM7 without protein truncation), and the intragenic exon 2 duplication (in-frame; predicted to produce an internal amino acid repeat within TM1). These variants are predicted to produce a structurally altered but non-truncated GLUT1 protein, with variable degrees of residual transport function.

‡ Loss-of-function (LoF) variants: frameshift variants (c.97dup, c.616_623del, c.975delinsTT), stop-gain variant (c.354_355insT), and whole-gene chromosomal deletion (1p34.2-p34.1). These variants are predicted to result in nonsense-mediated mRNA decay and GLUT1 haploinsufficiency, with an approximately 50% reduction in functional GLUT1 protein.

Abbreviations: IQR, interquartile range; IC, intracellular; LoF, loss-of-function; MD, movement disorder; SD, standard deviation; TM, transmembrane domain.

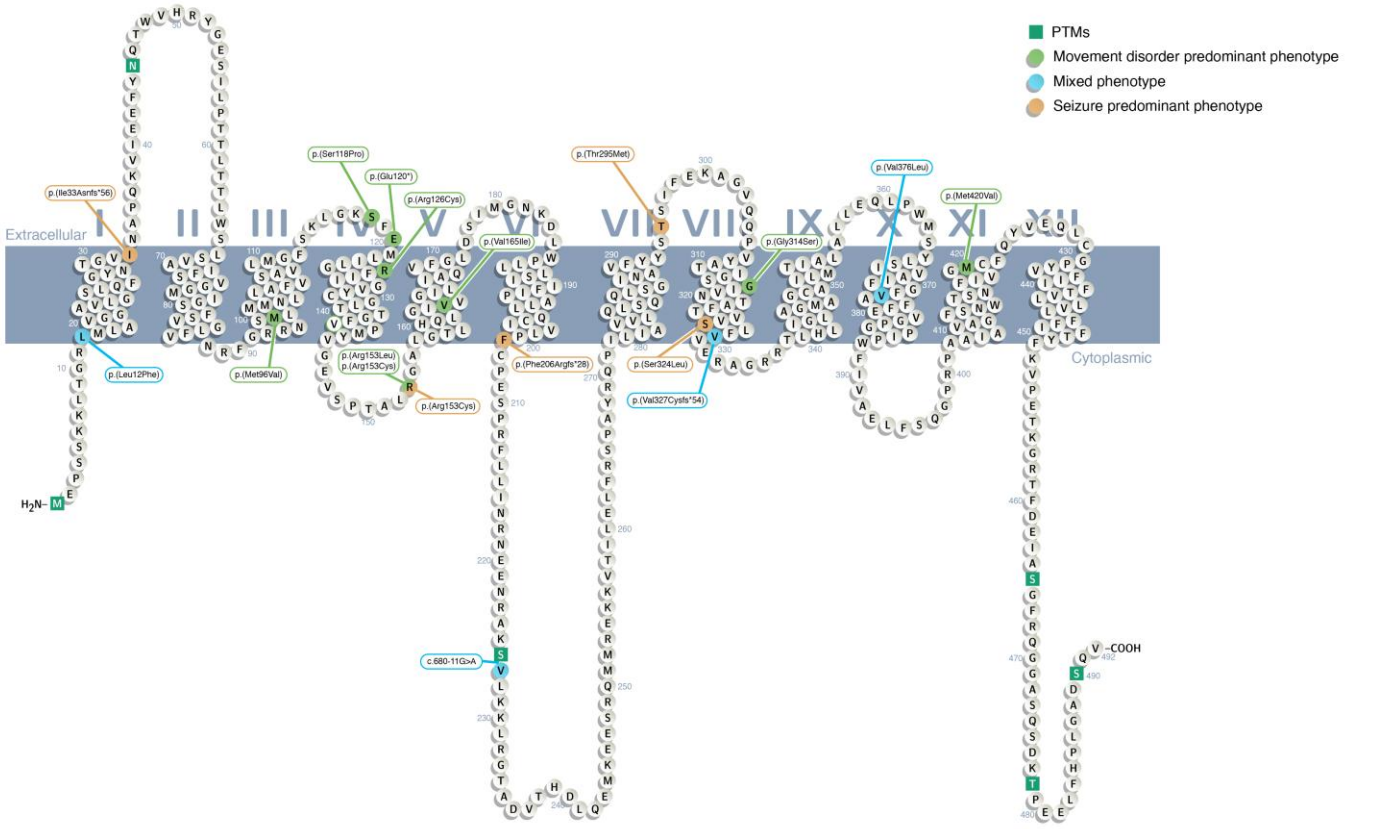



**Figure 5**: Transmembrane topology of GLUT1 with mapped *SLC2A1* variants; Two-dimensional topology of the GLUT1 protein (UniProt P11166 · GTR1_HUMAN), illustrating the 12 transmembrane helices (I–XII), with extracellular loops above and intracellular loops below. Each residue is represented as a circle. Residues harbouring pathogenic or likely pathogenic SLC2A1 variants identified in this cohort

are colour-coded by predominant clinical phenotype: blue (movement disorder-predominant), red (seizure-predominant), and purple (combined seizure and movement disorder). An enlarged circle indicates loss-of-function variants (frameshift, stop-gain). The gold circle in the intracellular loop connecting TM4 and TM5 denotes the Arg153 mutational hotspot, at which four patients harbour two distinct pathogenic substitutions (p.Arg153Leu ×2 and p.Arg153Cys ×2). A dashed orange-outlined circle represents the variant of uncertain significance (p.Val376Leu). The intronic variant c.680-11G>A (Patient 3), which predicts an in-frame amino acid insertion in the intracellular loop connecting TM6 and TM7, is indicated at its approximate loop position. The whole-gene chromosomal deletion (Patient 1) and the in-frame exon 2 duplication (Patient 5) are not represented at the individual residue level and are described in Table *. Variants are annotated using the canonical *SLC2A1* transcript NM_006516.4. The figure is illustrated using Protter.[16]

**Management**

*Anti-seizure medications*

35% of patients were documented as being established on anti-seizure medications (ASMs) which included lamotrigine (n=4), levetiracetam (n=4), sodium valproate (n=1) and perampanel and lamotrigine combination (n=1). 29% of patients had previous discontinued ASMs, which included: carbamazepine, ethosuximide, topiramate, sodium valproate, levetiracetam, zonisamide, lacosamide and lamotrigine. 32% of patients had trialled 2 or more ASMs. One patient developed exercise-induced dystonia when switched from levetiracetam to lamotrigine.

*Ketogenic diet*

87% of patients were documented as having previously adhered to, or continuing to adhere to KDT. Of these 27 patients, 8 were fully adherent, 3had partial adherence, 7 patients using a tailored MCT based supplement and restricting carbohydrates but not following the ketogenic diet in full, 4 had poor adherence, 4 had discontinued KDT and 5 had unknown adherence. Common reasons for KDT cessation were lack of enjoyment of food, preference for higher carbohydrate foods, disliked ketogenic food options, struggled to tolerate ketogenic diet supplements, daily burden of managing the diet, need to prepare all foods and plan ahead when eating out of the home due to lack of ketogenic options from most shops and food outlets, weight loss, constipation and fatty liver disease.

Patients adhering to KDT benefitted from improved seizure control, reduced paroxysmal movement disorders, improved cognition and feeling more alert, improved energy levels, improved ability to manage activities of daily life and greater mobility. One patient was noted to have an increase in seizure frequency since stopping KDT.

41% of epileptic patients adhering to KDT were documented as having improved seizure control (n=7/17), with one of these patients becoming seizure-free. Other benefits included reduced paroxysmal movement disorders (n=1), improved cognition (n=3) and greater mobility (n=2).

48% of patients were prescribed a nutritional supplement, including KVita (n=8), Phlexy vits (n=4), vitamin B drops (n=1), forceval (n=1), MCT oil (n=3), Ketocal (n=1), Ketovie (n=1), Keyo semisolid feed (n-1), Nutricia liquigen (n=1), Nutricia calogen (n=1).

# Discussion

This observational study outlines the clinical phenotypes of a large cohort of adults with GLUT1-DS. Diagnostic pathways, neurological sequelae and response to treatment are presented in the context of genotype data.

**Phenotype**

In this case series of 31 individuals with GLUT1-DS, a broad spectrum of phenotypes were displayed. Although historically characterised as a condition presenting with treatment-resistant seizures in infancy, this paper supports the growing evidence base around extended phenotype presentations.[11]

**Seizure type**

Patients suffering from seizures had a mean age of onset of 3.4 years. This is comparable other studies (2-3.2 years).[15,17] Seizure types within this cohort included focal impaired awareness, absence seizures, myoclonic and generalised tonic-clonic seizures, which is comparable to previously published cohorts.[13,15] Seizures were frequently resistant to anti-seizure medications but improved with KDT initiation. The diverse seizure semiology seen in this cohort highlights the global nature of cerebral glucose deficiency and supports the classification of GLUT1DS as a diffuse metabolic encephalopathy rather than a focal epileptic disorder.

**Movement disorder phenotype**

Movement disorder-predominant phenotypes were associated with the longest diagnostic delays in this cohort, with a median delay of 10 years (IQR: 2.5-37) compared to 9 years (IQR: 1-28) in seizure-predominant phenotypes and 3.5 years (IQR: 0-13) in combined phenotypes. This difference likely stems from the under-recognition of movement disorders as a key feature of GLUT1-DS diagnosis, even in the absence of epilepsy. Increased awareness of paroxysmal movement disorders and exercise-induced weakness or dystonia in neurology clinics may help to reduce this delay in diagnosis in future.

**Neurodevelopmental burden**

Psychiatric features such as anxiety, depression, Autism Spectrum Disorder (ASD) and ADHD were more prevalent in this cohort than in the population average. ADHD was present in 10% of patients in this cohort compared to a population prevalence of 2.6-6.8%.[18] ADHD has previously been identified in children with GLUT1-DS,[19] and is likely underreported as it is not routinely screened for in GLUT1-DS patients. ADHD has been associated with copy number variation in the SLC2A3 gene that codes for GLUT3, the primary transporter channel for glucose uptake into neurons.[20] It is possible that dysregulation of cerebral glucose transport leads to neurodevelopmental divergence.

ASD was observed at a higher prevalence in this cohort (19%) compared to the population prevalence (0.72%).[21] Although epilepsy and ASD are known to co-occur, the prevalence of ASD in this cohort is higher than in the general epilepsy population (12.1%).[22]

Whilst the exact pathogenesis of ASD remains unknown, the culmination of environmental and genetic factors are thought to affect the development of neuronal circuits involved in behaviour, cognition and communication.[23] ASD in general has been associated with aberrant mitochondrial function[24],

which in the case of GLUT1-DS may occur as a sequalae of chronic cerebral energy failure in the developing brain.

Of the patients in this cohort with a formal diagnosis of ASD, 50% had a movement-disorder predominant phenotype, 17% had a seizure-predominant phenotype and 33% had a combined phenotype. This suggests that the relationship between ASD and GLUT1-DS is not solely epilepsy-mediated.

Depression was prevalent in 29% of patients in this cohort compared to a population prevalence of 3-5%. It has previously been reported at 10-57% in other GLUT1-DS cohorts.[1,25] These findings add weight to the emerging evidence of neuropsychiatric phenotypes in GLUT1-DS.

**Developmental delay and intellectual disability**

Seizure-predominant and seizure-associated phenotypes were associated with more frequent neurodevelopmental burden including both intellectual disability and developmental delay. This suggests that seizure activity carries an independent neurodevelopmental burden beyond cerebral glucose deprivation alone. It is possible that epileptic activity during critical periods of cerebral development contributes to neuronal dysfunction and impaired cognition. In our cohort, symptom onset ≤4 years was strongly associated with developmental delay (50%) compared to later onset (11%). This is consistent with previous studies which identified a link between early-onset epilepsy and intellectual disability.[1]

**Functional outcome**

The degree of heterogeneity seen in this cohort in relation to mobility, including within families sharing the same pathogenic variant, illustrates the intrafamilial phenotype variation. The reasons for this phenotype variation are not well understood.[26] GLUT1-DS does not uniformly result in a significant level of disability: in many patients in this cohort it was compatible with an active lifestyle. Gait abnormality was reported in this cohort, in concordance with existing literature.[27] Fine motor skill difficulties, particularly affecting feeding, writing and fastening buttons, were the most frequently cited reason for dependency in activities of daily living. This is consistent with the high prevalence of dystonia and ataxia in this cohort and highlights the importance of occupational therapy input as a key component of multidisciplinary care, even in individuals without significant gross motor impairment. Despite the high prevalence of intellectual disability in this cohort, we observed that educational attainment was not uniformly limited and seven patients were undertaking college-level study and one a university degree. This suggests that that individuals with GLUT1-DS can still achieve significant educational development and highlights the importance of individualised educational support rather than making assumptions about educational and functional abilities based solely on their diagnosis.

**Pregnancy**

This small series suggests that pregnancy in GLUT1-DS may be generally well tolerated, though a single case of status epilepticus near term is a reminder that the increased metabolic demands of pregnancy may trigger seizures in GLUT1-DS patients who have no previous history of seizures, or increase the frequency of existing seizures. This highlights the importance of multidisciplinary team input in optimising GLUT1-DS control in pregnancy, in particular epilepsy with KDT as a monotherapy or in conjunction with antiepileptic medications.[28]

There are no guidelines on the management of pregnancy in GLUT1-DS and the evidence available in the literature is scarce. It is worth emphasizing that the management of nutrition and seizure control in the mother is key to optimize the clinical outcomes in the foetus who is at risk of GLUT1-DS as well. Mothers who follow strict KDT are likely to develop plasma carnitine deficiency,[29] required for beta-oxidation in mitochondria. Pregnant women require frequent dietetic review and nutritional status monitoring (once per trimester; personal observations). During active labour, any form of starvation will potentially impact ketosis (initially lowering via gluconeogenesis and latterly increasing through starvation). IV sodium chloride or Hartmans for hydration and 2-4 hourly monitoring of ketones and blood glucose during the entire starvation period (pre, peri and post baby delivery) is recommended.

If possible, home monitoring of betahydroxybutyrate (BHB) should be provided for the woman during pregnancy and after the childbirth. In addition, children at birth have been reported to have lower BHB <2 mmol/L, as they are able to extract and their ketone bodies utilisation is four-fold higher as compared to adults.[30]

**Genotypes and phenotype genotype correlations**

In keeping with previous reports,[7,31,32] patients in our cohort with truncating or LoF *SLC2A1* variants tended to present at an earlier age, and were more likely to exhibit seizure-predominant or mixed seizure and movement disorder phenotypes compared to those with missense variants, and were more likely to present with developmental delay and learning difficulties. Truncating variants result in GLUT1 haploinsufficiency, leading to significantly reduced glucose transport across the blood–brain barrier and a more severe neurological phenotype, often presenting with early-onset epilepsy and developmental impairment,[1,31,33] as observed in four out of five (80%) patients with LoF variants in our cohort who had a seizure-predominant or mixed phenotype, and all five (100%) who had learning difficulties.

We observed that the N-terminal missense variants were more frequently associated with movement disorder-predominant phenotypes. This is consistent with the structural architecture of GLUT1 as characterised by crystal structures of GLUT1 and GLUT3.[32,34] GLUT1 operates via an alternating-access mechanism in which the transporter cycles between outward-facing, occluded, and inward-facing conformations to facilitate glucose translocation. The C-terminal domains contribute key residues to the substrate-binding site and mediate exofacial access, while the N-terminal domains form the cytoplasmic gate whose relative motion drives the alternating-access cycle.[32,34] Missense variants within the N-terminal gating region are therefore more likely to impair the kinetics of the conformational transition rather than outright abolishing substrate binding, resulting in partial preservation of basal transport capacity.

The p.(Arg153Leu) and p.(Arg153Cys) variants identified in this cohort, both affecting the intracellular loop connecting TM4 and TM5, have been shown in functional studies to markedly reduce erythrocyte glucose transport without abolishing it.[35] Similarly, the p.(Arg126Cys) variant in TM4 shows significantly impaired but residual transport activity.[36,37] This residual functional activity is sufficient to meet cerebral glucose demand under resting conditions, but becomes inadequate with an acute rise in demand, such as during exercise, fasting, or febrile illness, resulting in the paroxysmal movement disorder phenotype associated with these variants.[13,38]

In this cohort, C-terminal missense variants clustered in TM8–TM11 and the extracellular loop between TM7 and TM8, and showed more heterogeneous phenotypes than their N-terminal counterparts. Two variants directly affecting this region — p.(Thr295Met) in the TM7–TM8 extracellular loop and p.(Ser324Leu) in TM8 — were both associated with seizure-predominant phenotypes. C-terminal variants, clustering around TM7–TM10, may more directly disrupt the extracellular gating mechanism and substrate-binding in particular the rearrangement of TM7 that mediates opening and closing of the exofacial access channel,[34,39] thereby reducing net glucose uptake more uniformly across metabolic states and lowering the seizure threshold rather than producing a threshold-dependent paroxysmal phenotype. Notably, p.(Gly314Ser) in TM8, previously reported in association with childhood-onset paroxysmal exertion-induced dyskinesia,[40] presented with a movement disorder-predominant and exercise-induced phenotype in our cohort, illustrating that even within the C-terminal domains, residue-specific effects can produce a threshold-dependent phenotype more typical of N-terminal variants. These observations support the view that domain-level structural localisation provides a useful but imperfect framework for phenotypic prediction, and residue-specific functional studies remain necessary to resolve the mechanistic basis of individual variant effects.

**Neuroimaging**

Two of the three patients with abnormal MRI findings had paravermian cerebellar changes, which raises the possibility that chronically low cerebral glucose levels can lead to structural changes in the cerebellum. The cerebellum has a high metabolic demand and so may be more susceptible to chronically low cerebral glucose.[41,42] We also identified white matter changes in one patient, although the clinical significance of this is unclear. It is important to interpret these results with caution given the small size of this cohort.

**Diagnostic pathway**

Individuals with GLUT1-DS can present at any age, through a number of services, such as adult neurology, paediatric neurology, genetic clinics, metabolic clinics, or through family screening. In this cohort, 6% of patients were identified through familial cascade testing, which occurred more recently, reflecting increased uptake of this approach. The broader use of cascade testing has the potential to identify individuals with mild, subclinical or atypical phenotypes.

**Diagnostic mechanism**

The majority of individuals in this cohort received a genetic diagnosis, and the methods used to achieve this reflect the evolution of diagnostic practice in GLUT1-DS. Historically, diagnosis was primarily achieved biochemically on lumbar puncture demonstrating hypoglycorrhachia (CSF: plasma glucose <0.40),[1,43] supplemented where available by the erythrocyte glucose uptake assay as a functional surrogate for GLUT1 haploinsufficiency, a test highly specific when reduced below 74% of control values, but limited to tertiary centres due to its requirement for fresh blood and specialist processing.[13] Molecular diagnosis initially relied on targeted gene sequencing of the *SLC2A1* coding sequence, supplemented by chromosomal microarray or Multiplex Ligation-dependent Probe Amplification (MLPA) for structural variants, both of which are represented in this cohort.[44,45] During the 2010s, targeted gene panels progressively replaced single-gene testing, enabling identification of *SLC2A1* variants in individuals not primarily suspected of GLUT1-DS.[3] ES subsequently became a

standard first-line investigation, allowing re-analysis of previously uninformative exomes as an additional diagnostic route as variant annotation databases expanded.[3,46] More recently, whole genome sequencing has emerged as the recommended approach when coding-region analysis is uninformative, capturing non-coding *SLC2A1* variants, including deep intronic and 5'-UTR changes that are undetectable by exome-based methods.[3,47,48]

Negative genetic testing of the *SLC2A1* gene is reported in about 5% to 15% of cases with a typical Glut1DS phenotype and GSF hypoglycorrhachia. This could be due to variants in non-coding or regulatory regions, which could be difficult to detect by routine genetic testing.[49] More recently, diagnostic blood testing for GLUT1-DS by quantification of erythrocyte surface GLUT1 by flow cytometry with the METAglut1 assay has been described.[50]

In a prospective multicentre validation across 33 French centres, it demonstrated sensitivity of approximately 80% and specificity exceeding 99%, comparable to lumbar puncture combined with molecular analysis.[51] It is not yet routinely available in the United Kingdom, and its main limitation is a false-negative rate of approximately 20%, particularly among individuals with missense variants and milder phenotypes, meaning a negative result does not exclude the diagnosis.[51]

**Diagnostic delay**

The median diagnostic delay for this cohort was 6.5 years, however in some individuals (particularly those with a milder phenotype without features of epilepsy), this diagnostic delay could be over 20 years. A broader awareness of the classical GLUT1 phenotype amongst paediatricians and neurologists specialising in epilepsy or movement disorders would help reduce the delay in diagnosis. Similarly, a more widely recognised atypical phenotype (for example, paroxysmal movement disorder + intellectual disability/developmental delay) would help clinicians more easily consider the possibility of a metabolic disorder. The shorter diagnostic delay observed in the combined movement disorder and seizure phenotype group likely reflects that the simultaneous presence of seizures and movement disorders phenotypes is more readily recognised as suggestive of a genetic or metabolic aetiology warranting metabolic and/or genetic investigations than either phenotype alone.

A number of adult patients only received a diagnosis after a first-degree relative (usually their child) received a genetic diagnosis of GLUT1-DS. This stresses the importance of cascade testing, where the patient or their legal guardians give consent, particularly in cases where a child with GLUT1-DS has been adopted.

**Inheritance**

Current evidence suggests that most of the SLC2A1 variants are de novo, while only around 10% are inherited.[6] In this cohort, nine patients (29%) had a confirmed family history of GLUT1-DS. This could be attributed to the cohort being recruited from a tertiary adult metabolic service, which disproportionately includes familial cases through cascade testing. However, the estimation of the prevalence of inherited variants in GLUT1-DS may be underestimated due to a lack of recognition of the broad range of GLUT1DS phenotypes in adults, milder phenotypes including isolated paroxysmal dyskinesia or psychiatric presentations, and incomplete penetrance.[6,19] It is increasingly likely that transmitting parents with mild or no phenotypes were historically not genetically investigated and therefore classified as unaffected. We observed in our cohort inheritance through both maternal and

paternal lines with intrafamilial phenotypic variability, a pattern previously reported in GLUT1-DS, where a familial SLC2A1 variant can result in a broad range of phenotypic severity within the same family.[12,52]

**Antiseizure medications**

Antiseizure medications have previously been associated with impaired GLUT1 function, including barbiturates[53] and benzodiazepines.[54] These agents were shown to reduce GLUT1-mediated erythrocyte glucose uptake, whereas carbamazepine and phenytoin were not associated with a reduction in uptake.[54] Whether this translates to cerebral glucose uptake is not known. Sodium valproate has been shown to reduce GLUT1-mediated glucose transport by 20-40%.[55] In our cohort, one patient experienced dystonia on switching from levetiracetam (synaptic vesicle 2A (SV2A) agonist) to lamotrigine (sodium channel inhibitor). It is possible that sodium channel blockade affects GLUT1 function, however GLUT1 is a facilitative glucose transporter and therefore its function is not sodium-dependent.[56] The mechanism underlying this observation is unclear, as GLUT1 is a facilitative transporter and its function is not directly sodium-dependent; this single case should be interpreted with caution

**Ketogenic diet**

This study showed that the best therapy for patients with GLUT1DS is the ketogenic diet, often supported with supplements including MCT based supplements which can further reduce symptoms of GLUT1DS and aid the induction of ketosis. This is in alignment with previously published literature.[29,30,57]

Improvements in GLUT1DS symptoms included reduced seizure frequency, with some patients becoming seizure-free on the KDT. Other patients experienced improvements in mobility and cognition. However, KDT is very burdensome. In this study, 4 patients had fully discontinued the diet and 7 patients had moderately restricted carbohydrates and were reliant on MCT based supplements to achieve the positive effects of the ketogenic diet. In this study reasons for discontinuation included lack of enjoyment of food, gastrointestinal intolerance, preference for higher carbohydrate foods, disliked ketogenic food options, struggled to tolerate ketogenic diet supplements, daily burden of managing the diet, need to prepare all foods and plan ahead when eating out of the home due to lack of ketogenic options from most shops and food outlets.

Adherence to the diet in young children is heavily influenced by caregivers. This changes as the patient grows older. Teenagers can rebel against the strict limitations of the diet and the obvious difference to the diet their peers are consuming. As patients become older managing all the specific daily requirements of the KDT can become less of a priority in the context of the demands of daily life. Changes in their support structure also often mean they have less support than previously: in one case the passing away of a patient's main caregiver led to discontinuation of the diet.

For those starting the diet as an adult the diet is unpalatable, limited and difficult to manage. The use of MCT based supplements can be very helpful to achieve the effects of the KDT in the context of a less severe restriction of carbohydrate intake when compared to the classic form of KDT. Broader nutritional needs must also be considered so individually tailored dietetic support is essential These findings are in keeping with reports from the wider literature of the effectiveness of KDT.[58,59]

**Multi-disciplinary team**

The management of adult patients with GLUT1-DS requires multi-disciplinary input from metabolic medicine, dietetics, genetics, and neurology. Long-term follow up should include monitoring of seizure control, movement disorders, cognitive function, nutritional status, and monitoring of adherence to and complications from ketogenic diet therapy. The recent increase in adult presentation seen in this cohort highlights a need for the development of adult care pathways and further understanding of GLUT1-DS in adult life, including during pregnancy.

**Strengths and limitations**

This study captures a broad range of symptomatology in both paediatric and adult patients, which allows it to add to the emerging literature around extended phenotypes experienced by people living with GLUT1-DS. However, the retrospective nature of the study limits the completeness of the data, as some patients' records lack documentation in various fields. One such example is the reporting of genetics, which is not complete for every patient and would require prospective data collection to achieve. It also likely results in an underreporting of various comorbidities such as ASD and ADHD, as not all patients have received a formal neuropsychiatric workup around these conditions. The small size of the cohort limits the ability to make phenotype-genotype correlations, and a larger pooled study may be required in future to examine this in sufficient detail. The lack of completeness in data collection highlights the need for standardised data collection in patients with GLUT1-DS, such as in the form of a minimum data set. Routine collection of this data would help expand the quality of data collected about the condition and possibly lead to a better understanding of the disease and treatments relating to it.

# Conclusion

This study demonstrates the diverse range of phenotypes present in GLUT1-DS. It adds to the emerging notion that GLUT1-DS is not just a disorder associated with treatment-resistant seizures, but one that affects individuals more broadly. Improved awareness amongst clinicians of exercise-induced dyskinesia and learning disabilities in the presence or absence of epilepsy is important to improve the rate of diagnosis. Further prospective and pooled analyses would be beneficial to further understand the broader phenotype, and phenotype-genotype correlations.

**Abbreviations:**

ADHD – Attention Deficit Hyperactivity Disorder

ADL – Activities of Daily Living

ASD – Autism Spectrum Disorder

ASM – Anti-Seizure Medication(s)

BHB – Beta-Hydroxybutyrate

CMA – Chromosomal Microarray Analysis

CSF – Cerebrospinal Fluid

ES –Exome Sequencing

GLUT1-DS – Glucose Transporter Type 1 Deficiency Syndrome

KDT – Ketogenic Diet Therapy

MCT – Medium-Chain Triglyceride

LoF – Loss-of-Function

LP – Lumbar Puncture

MLPA – Multiplex Ligation-dependent Probe Amplification

PED – Paroxysmal Exercise-Induced Dyskinesia

SARA – Scale for the Assessment and Rating of Ataxia

SLC2A1 – Solute Carrier Family 2 Member 1

TM – Transmembrane Domain

WGS – Whole Genome Sequencing

**Declarations:**

Ethical considerations: This project was approved by the Northern Care Alliance Research and Innovation Department as a health improvement project (25HIP56). Formal research ethics committee approval was not required as all data were collected retrospectively from routine clinical records and are presented in an anonymised and aggregated format.

Funding: No funding was received for this work

Guarantor: Dr Alastair Paterson is the guarantor of this work and accepts full responsibility for the integrity of the data and the accuracy of the analysis.

Conflict of interest: No conflicts of interest were declared in relation to this work

Acknowledgment: The authors would like to thank all the patients and their families for their support with the clinical research, and all clinicians and caregivers involved in the care of these patients.

**LEGENDS:**

**Tables:**

**Table 1**. Demographic and phenotype summary for 31 patients

**Table 2:** The genotype characteristics of the study cohort

**Table 3:** Phenotype comparison between the patients with missense and Truncating / LoF variants in the study

**Figures:**

**Figure 1:** Diagnostic method evolution over time (data for n=13 patients)

**Figure 2:** Symptom prevalence throughout cohort

**Figure 3:** GLUT1DS age of onset and diagnosis by clinical phenotype (data for n=21 patients). $p$ = 0.689 (Kruskal-Wallis chi-squared)

**Figure 4:** MRI brain abnormalities. 1a-c: Multiple discrete foci of high T2 signal changes in the subcortical white matter of both frontal lobes; 2a-c: High T2 signal change in the paravermian right cerebellar hemisphere without diffusion restriction; 2d-e: Axial and coronal T2 sequences show focal high T2 signal change in the inferior aspect of the left cerebellar cortex consistent with an old infarct; 3a-c: High T2 signal in the paravermian cerebellar hemisphere without diffusion restriction

**Figure 5**: Transmembrane topology of GLUT1 with mapped *SLC2A1* variants; Two-dimensional topology of the GLUT1 protein (UniProt P11166 · GTR1_HUMAN), illustrating the 12 transmembrane helices (I–XII), with extracellular loops above and intracellular loops below. Each residue is represented as a circle. Residues harbouring pathogenic or likely pathogenic SLC2A1 variants identified in this cohort are colour-coded by predominant clinical phenotype: blue (movement disorder-predominant), red (seizure-predominant), and purple (combined seizure and movement disorder). An enlarged circle indicates loss-of-function variants (frameshift, stop-gain). The gold circle in the intracellular loop connecting TM4 and TM5 denotes the Arg153 mutational hotspot, at which four patients harbour two distinct pathogenic substitutions (p.Arg153Leu ×2 and p.Arg153Cys ×2). A dashed orange-outlined circle represents the variant of uncertain significance (p.Val376Leu). The intronic variant c.680-11G>A (Patient 3), which predicts an in-frame amino acid insertion in the intracellular loop connecting TM6 and TM7, is indicated at its approximate loop position. The whole-gene chromosomal deletion (Patient 1) and the in-frame exon 2 duplication (Patient 5) are not represented at the individual residue level and are described in Table *. Variants are annotated using the canonical *SLC2A1* transcript NM_006516.4. The figure is illustrated using Protter.[16]

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