



## Sporadic and familial glut1ds Italian patients: A wide clinical variability



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### ABSTRACT

**Purpose:** GLUT1 deficiency syndrome is a treatable neurological disorder characterized by developmental delay, movement disorders and epilepsy. It is caused by mutations in the SLC2A1 gene inherited as an autosomal dominant trait with complete penetrance, even if most detected SCL2A1 mutations are de novo. Our aim is to present a wide series of Italian patients to highlight the differences among subjects with de novo mutations and those with familial transmission.

**Methods:** We present clinical and genetic features in a series of 22 GLUT1DS Italian patients. Our patients were classified in two different groups: familial cases including GLUT1DS patients with genetically confirmed affected relatives and sporadic cases with detection of SLC2A1 de novo mutation.

**Results:** We found remarkable differences in the severity of the clinical picture regarding the type of genetic inheritance (sporadic versus familial): sporadic patients were characterized by an earlier epilepsy-onset and higher degree of intellectual disability. No significant differences were found in terms of type of movement disorder, whilst Paroxysmal Exertion-induced Dyskinesia (PED) is confirmed to be the most characteristic movement disorder type in GLUT1DS. In familial cases the clinical manifestation of the disease was particularly variable and heterogeneous, also including asymptomatic patients or those with minimal-symptoms.

**Conclusion:** The finding of a "mild" phenotype in familial GLUT1DS gives rise to several questions: the real incidence of the disease, treatment option with ketogenic diet in adult patients and genetic counseling.

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## 1. Introduction

GLUT1 deficiency syndrome (GLUT1DS, OMIM 606777) is a treatable neurological disorder caused by a deficiency of glucose transporter type 1 (GLUT1) at the blood–brain barrier and in brain cells which results in impaired glucose transport into the brain. The clinical manifestations of GLUT1DS include developmental delay, movement disorders, epilepsy and acquired microcephaly.

GLUT1DS was first described in 1991 by De Vivo<sup>1</sup> and seven years later, a molecular basis for the defect in GLUT1-mediated

glucose transport was found.<sup>2</sup> GLUT1DS is still an often under-diagnosed condition but it benefits from rapid recognition because an early introduction of the ketogenic diet (KD) could reduce the frequency of seizures, the severity of the movement disorders, and improve patients' behavior and alertness.<sup>3</sup>

GLUT1DS is caused by mutations in the SLC2A1 gene (OMIM 138140) which maps to the short arm of chromosome 1 (1p35–31.3).<sup>4</sup> This is the only gene associated with GLUT1DS so far. The condition is inherited as an autosomal dominant trait with complete penetrance, however most detected SCL2A1 mutations are de novo.<sup>5</sup>

We hereby present the clinical and genetic features in a series of 22 GLUT1DS Italian patients and compare their clinic-genetic characteristics in order to find any difference and significant features.

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## 2. Materials and methods

### 2.1. Patients

56 Italian patients satisfying the clinical criteria for diagnosis of GLUT1DS<sup>6–9</sup> underwent the genetics test from 2006 to 2014 at our Institutes and 22 patients were found positive at SLC2A1 mutation.

Our study was approved by the Ethic Committee of our Institutes.

At recruitment the study sample includes 16 females and 6 males, aged 2–57 (average 21.3) born to non-consanguineous parents.

In some previous papers the clinical, biochemical and genetic features of patients #1, #2, #3 and #7<sup>10–12</sup> and patients #15 and #16<sup>13</sup> have already been described.

In 14/22 patients lumbar puncture (LP) was performed in the fasting state (after 5–6 h of fasting), and the blood sample for glucose measurement was obtained immediately before the procedure to avoid stress-related hyperglycemia.<sup>7</sup> A CSF-to-blood glucose ratio below 0.6 was considered indicative for GLUT1DS.

In the remaining 8 patients, presenting high suggestive clinical signs of the disease (intellectual disability, epilepsy and/or movement disorder), LP was not performed for various reasons (non-compliance, investigation failure, 5 patients were relatives of probands) and they were directly submitted to SLC2A1 mutation analysis.

All the blood and CSF samples were collected, after obtaining written informed consent, from patients and/or the parents. The investigations fulfilled our institution's ethical rules for human studies.

All GLUT1DS patients were subjected to our diagnostic and follow-up protocol including blood tests for the KD monitoring, sleep EEG, neuropsychological assessments.<sup>7</sup>

All patients were classified in two different groups: familial cases including GLUT1DS cases with genetically confirmed affected relatives and sporadic cases due to SLC2A1 de novo mutation.

We compared the two groups in order to identify some possible clinical and genetic peculiarities.

### 2.2. Mutation analysis of SLC2A1

After obtaining written informed consent to genetic test collected at "C. Mondino" National Neurological Institute, genomic DNA from probands and relatives were extracted from peripheral blood using standard procedures (Maxwell<sup>®</sup> 16 Blood DNA – Promega, Milan, Italy).

All 10 exons of SLC2A1 gene were screened for sequence variations by direct sequencing using the Big-Dye Terminator v. 3.1

sequencing kit (Applied Biosystems, Milan, Italy) and ABI 3130 Genetic Analyzer (Applied Biosystems, Milan, Italy). Each fragment was sequenced on both strands. The alignment to reference sequence (NG 008232.1) was performed using Sequencher 4.8 software.

The effect of the newly detected SLC2A1 mutations on protein structure or function was analyzed with the prediction programs ExPASy (<http://www.expasy.org>).

## 3. Results

The clinical signs and laboratory data are presented in Tables 1 and 2.

### 3.1. Clinical and genetic features in sporadic patients

The age range of sporadic cases (9 females and 2 males) at the time of diagnosis and study enrollment was 2–20 (mean 13.5). Their clinical signs and laboratory data are detailed in Table 1 and summarized below.

Pregnancy, delivery and the neonatal period were uneventful in all. Five patients (45%) had microcephaly (head circumference below or equal to the 25th percentile for age at the time of enrollment). Eight patients (73%) presented intellectual disability, severe in 3 of these; 3 patients (27%) presented a borderline Intellectual Quotient (IQ).

Epilepsy represented a main feature and the first symptom in all patients. Seizure onset was in the first years of life (mean 24.1 months) and 6 patients (55%) developed a drug resistant condition. Seizure types varied and included absence seizures (64%), usually atypical or drug-resistant, discognitive seizures (36%), generalized tonic-clonic (27%), myoclonic (27%), focal seizure without discognitive features (18%), myoclonic-atonic (9%).

Ten patients (91%) presented a movement disorder (MD) consisting of paroxysmal exercise-/stress-/fasting-induced MD (73%) and/or paroxysmal kinesigenic MD (9%) and/or non-paroxysmal MD (36%). In most cases it began in childhood (age range: 8–168 months; mean 80.4 months) after seizure onset.

Dysarthria, reported to be a common sign in GLUT1DS,<sup>6,8</sup> was present in 55% of the patients, with halting speech, pauses, articulation errors and dropping of word endings. Other associated clinical signs included spasticity (45%), weakness on awakening or in the fasting state (36%), migraine (27%), myoclonias (27%) and prognathism with dental malocclusion (18%).

**Table 1**

Clinical and laboratory data in GLUT1DS sporadic patients.

Pt	Gender	Age (y)	Ratio	HC (p)	IQ	Spasticity	Seizure	Seizure onset (m)	Seizure type	DR	EEG	MD	MD type	MD subtype	MD onset (m)	Other	KD response
1	F	20	0.33	>50°	<45	Y	Y	6	ABS GTC MS	Y	SB G	Y	C	a	12	Ds Pr W Mi	EEG E MD W
2	F	19	0.33	>50°	<45	Y	Y	3	FS, ABS, GTC MS	Y	SB G F	Y	C	a c	8	Ds	EEG E MD
3	F	20	0.38	25–50°	<45	Y	Y	4	ABS FS MS	Y	SB G F	Y	C	a	18	Ds Pr W Mi	EEG E MD W
4	F	14	0.44	<25°	53	Y	Y	18	DS	Y	SB F	Y	C	a	20	Ds	EEG E MD
5	F	6	0.54	<25°	76	N	Y	11	GTC ABS	N	SB G	Y	PED	d	36	W	E MD W
6	F	10	0.34	<25°	40	N	Y	30	MAS, DS, ABS	Y	SB G F	Y	PED	d	72	Ds W	E MD W*
7	F	13	NA	<25°	84	N	Y	11	ABS	Y	SB G	Y	N	N	NA	M	NA
8	F	17	0.41	>50°	62	Y	Y	72	ABS	N	G	Y	PND	a m	72	Mi	E EEG
9	M	17	0.51	<25°	57	N	Y	72	CFS	N	F	Y	PED	d	168	Ds	E MD
10	M	11	0.51	<25°	82	N	Y	30	CFS	N	F	Y	PED	c d	96	M	MD
11	F	2	0.37	25–50°	50	N	Y	9	MAS	NA	SB G	N	–	–	–	–	E EEG

**Abbreviations:** Pt, patient; F, female; M, male; Ratio, CSF/blood glucose ratio; NA, not available; Y, yes; N, no; HC, head circumference (percentiles); m, months; DS, discognitive seizures; ABS, absence seizure; GTC, generalised tonic-clonic seizure; DR, drug resistance; SB, slow background activity; G, generalised discharges; F, focal discharges; N, normal; MD, movement disorder; C, chronic; PED, paroxysmal exertion-induced dyskinesia; PND, paroxysmal non exertion-induced dyskinesia; a, ataxia; d, dystonia; c, choreoatetosis; Mi, migraine; Pr, Prognathism with dental malocclusion and/or supernumerary teeth; W, weakness; M, myoclonias; KD, ketogenic diet.

**Table 2**  
Clinical and laboratory data in GLUT1DS familial patients.

Pt	Gender	Age (y)	Ratio	CC	IQ	Spasticity	Seizure	Seizure onset (m)	Seizure type	DR	EEG	MD	MD type	MD subtype	MD onset (m)	Other	KD response
12	F	5	0.39	<25°	104	N	Y	NA	DS, GTC, ABS	N	SB G F	Y	C	a	16	–	EEG E MD
13	M	10	0.47	25–50°	75	N	Y	72	DS	Y	SB F	Y	PED	c	60	W Mi	EEG E MD IQ
14	F	43	NA	>50°	78	N	Y	72	ABS	N	SB	N	–	–	–	Mi Pr	NA
15	M	35	NA	>50°	60	N	Y	8	DS	N	N	Y	PED	d/c	240	M	NA
16	F	57	NA	>50°	74	N	Y	60	ABS	N	N	N	–	–	–	M	NA
17	M	28	NA	>50°	85	N	Y	48	ABS	N	N	Y	PED	d/c	60	–	NA
18	M	49	NA	>50°	75	N	Y	–	–	–	N	Y	PED	d	144	W	NA
19	F	10	0.38	<25°	66	N	N	–	–	–	N	Y	PED	d/c	36	–	MD
20	F	29	0.44	>50°	55	N	Y	12	ABS/GTC	N	SB G	Y	PED	–	NA	–	NA
21	F	24	NA	>50°	76	N	Y	72	ABS	N	G	N	–	–	–	–	NA
22	F	27	NA	>50°	72	N	Y	74	ABS	N	G	Y	PED	–	NA	–	NA

**Abbreviations:** Pt, patient; F, female; M, male; Ratio, CSF/blood glucose ratio; NA, not available; Y, yes; N, no; HC, head circumference (percentiles); m, months; DS, dyscognitive seizures; ABS, absence seizure; GTC, generalised tonic-clonic seizure; DR, drug resistance; SB, slow background activity; G, generalised discharges; F, focal discharges; N, normal; MD, movement disorder; C, chronic; PED, paroxysmal exertion-induced dyskinesia; PND, paroxysmal non exertion-induced dyskinesia; a, ataxia; d, dystonia; c, choreoatetosis; Mi, migraine; Pr, Prognathism with dental malocclusion and/or supernumerary teeth; W, weakness; M, myoclonias; KD, ketogenic diet.

### 3.2. Genetics

**Table 3** summarizes the results of the SLC2A1 gene analysis. Direct sequencing of SLC2A1 revealed 7 missense mutations (64%), 3 nonsense mutations (27%) and 1 splice site mutation (9%).

### 3.3. EEG and imaging

At the time of diagnosis, interictal EEG showed diffuse slowing of background activity in 8 patients (73%), epileptiform discharges with generalized 2–3.5 Hz spike-wave pattern in 8 patients (73%) and focal/multifocal discharges in 6 patients (55%).

On MRI non-specific data were found in 4 patients and included: moderate generalized cortical atrophy (#3), an arachnoid cyst (#2), moderate atrophy of the cerebellar vermis (#4) and delayed myelination (#11).

Two patients (#10, #11) in particular need to be mentioned; their parents and relatives were negative to SLC2A1 gene mutation but their siblings presented epileptic seizures (absences and generalized tonic-clonic seizures) suggestive of epilepsy with possible genetic origin.

The first patient (#9) is a male presenting a normal IQ, generalized tonic clonic epilepsy with onset at the age of 30 months, and PED (onset at 96 months); his CSF/blood glucose ratio was 0.51 while direct sequencing of SLC2A1 revealed a missense

**Table 3**  
Genetic data in GLUT1DS Italian patients.

Proband	Protein mutation	Gene location	Type of mutation	References
#1	W48X	Exon 3	Nonsense	Zorzi et al. <sup>10</sup>
#2	Q283X	Exon 6	Nonsense	Zorzi et al. <sup>10</sup>
#3	R126C	Exon 4	Missense	Zorzi et al. <sup>10</sup>
#4	P36R	Exon 2	Missense	Novel mutation
#5	c 1457delG_1delG SPL	Intron-Exon 10	Splice site	Novel mutation
#6	R126C	Exon 4	Missense	Zorzi et al. <sup>10</sup>
#7	A275T	Exon 6	Missense	Weber et al. <sup>25</sup>
#8	R92W	Exon 3	Missense	Schneider et al. <sup>26</sup>
#9	R458W	Exon 10	Missense	Arsov et al. <sup>27</sup>
#10	R223W	Exon 5	Missense	Leen et al. <sup>30</sup>
#11	R249Afs131X	Exon 6	Nonsense	Novel mutation
F-1 (#12)	R153C	Exon 4	Missense	Pascual et al. <sup>29</sup>
F-2 (#9, #13, #14)	R458W	Exon 10	Missense	Arsov et al. <sup>27</sup>
F-3 (#15, #16)	R153C	Exon 4	Missense	Pascual et al. <sup>29</sup>
F-4 (#17, #18)	G91A	Exon 3	Missense	Gagliardi et al. <sup>13</sup>
F-4 (#19, #20, #21, #22)	V165I	Exon 4	Missense	Urbizu et al. <sup>28</sup>

mutation. His brother presented a generalized tonic-clonic epilepsy with onset at 3 months and respondent to a single antiepileptic drug (valproic acid). So far, after discontinuation of AED at 7 years of age, his follow-up (current age 21) is completely negative for any type of neurological disorder. In this person LP was not performed and SLC2A1 gene analysis revealed no mutations (like in the parents).

The second patient (#10) is a female, presenting a mild MR, myoclonic atonic epilepsy with early onset at 9 months and no other clinical signs; her CSF/blood glucose ratio was 0.37, direct sequencing of SLC2A1 revealed a nonsense mutation. In this patient cerebral MRI showed delayed myelination, as previously described in other GLUT1DS patients.<sup>14</sup> Her brother is now 5 years old, at the age of 3 he presented absence epilepsy with good response to valproic acid. Now he is seizure free and he does not present any neurological symptom after a follow-up of 2 years. Also in this case LP was not performed and direct sequencing of SLC2A1 revealed no mutation (like in the parents).

### 3.4. Clinical and genetic features in familial patients

Four males and seven females, aged from 5 to 57 (mean 28.8) were found positive to SLC2A1 mutation in five families. The clinical signs and laboratory data for this group are listed in **Table 2** and presented below.

Pregnancy, delivery and the neonatal period were uneventful in all. Two patients (18%) had microcephaly. IQ was normal in 2 patients (18%), borderline in 6 (55%) and indicative of mild intellectual disability in 3 (27%).

Epilepsy was present in 9 patients (82%) with age of onset from 8 to 74 months (mean: 52.25 months). Only 1 patient presented a drug-resistant condition (9%). Seizure types included absence (64%), dyscognitive seizures (27%), generalized tonic-clonic (18%). Three adult patients (#14, #21, #22) had epilepsy during infancy respondent to common AEDs, but at the time of study enrollment did not have any seizure.

MD was present in 8 patients (73%) with an age of onset from 16 to 240 months (mean: 92.6 months).

Associated clinical signs included weakness on awakening or in the fasting state (18%), migraine (18%), myoclonias (18%) and prognathism with dental malocclusion (18%).

### 3.5. Genetics

**Table 3** and **Fig. 1** summarize the results of the SLC2A1 gene analysis in these five families. Direct sequencing of SLC2A1 detected missense mutations in all patients (100%).

Proband	Protein Mutation	Gene Location	Type of mutation	Reference
F-1 (#12)	R153C	Exon 4	missense	(Pasqual et al. <sup>29</sup> )
F-2 (#13 #14)	R458W	Exon 10	missense	(Arsov et al. <sup>27</sup> )
F-3 (#15 #16)	R153C	Exon 4	missense	(Pasqual et al. <sup>29</sup> )
F-4 (#17 #18)	G91A	Exon 3	missense	(Gagliardi et al. <sup>13</sup> )
F-4 (#19 #20 #21 #22)	V165I	Exon 4	missense	(Urbizu et al. <sup>28</sup> )

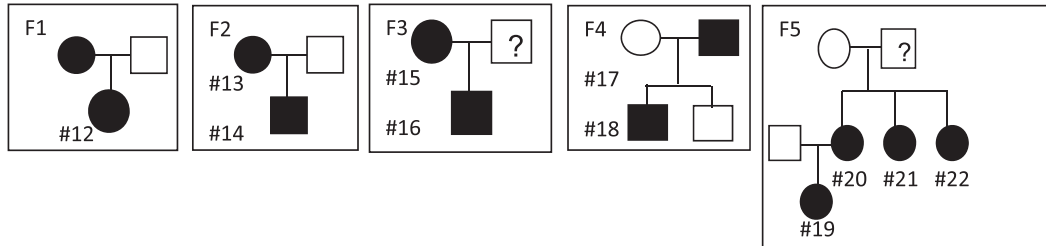


Fig. 1. Pedigree of familial patients.

### 3.6. EEG and imaging

In the SLC2A1-family patients, interictal EEG showed a lower frequency of epileptiform and non-epileptiform abnormalities compared to sporadic cases; in particular EEG showed diffuse slowing of background activity in 4 patients (36%), generalized spike and wave epileptiform discharges in 4 patients (36%) and focal/multifocal discharges in 2 patients (18%). No abnormalities were detected on neuroimaging.

### 3.7. Response to the ketogenic diet

13 patients underwent KD treatment (10 sporadic and 3 familial patients). Patients were initially started on the classical 3:1 ketogenic ratio (3 g lipids: 1 g carbohydrates + proteins) but when possible we reduced the ratio (in #11 to 1.8:1 ratio), maintaining the same therapeutic efficacy with stable beta-hydroxybutyrate levels around 2 Mmol/l.

The efficacy of KD treatment was noticeable. PED episodes disappeared in a few weeks; this dramatic result was not replicated for chronic MD like ataxia or chorea, although in 3 patients (#1, #2, #3) a mild improvement was noticed.

Focal and/or generalized EEG abnormalities disappeared in 8/10 (80%) patients. We also noticed the disappearance of seizures in the 2 patients (#6, #10) who presented clinical seizures at the study enrollment. As a result, 7 patients were able to come off AEDs after approximately the first year of treatment. Patient or parent-perceived improvements in cognitive function, alertness and activity after starting the KD were reported in 5 patients (37%). An IQ improvement – albeit not statistically significant – in patient #12, is also worth noting. It is documented by an increase from 79 to 89 on the Wechsler Infant Intelligence Scale after 2 years on the KD.

The clinical improvement was maintained with time under KD in all but 1 patient (#6), leading us to recommend permanent continuation of this therapy as previously reported.<sup>14–16</sup>

## 4. Discussion

In this series of 22 GLUT1DS patients remarkable differences were found in the severity of the clinical picture regarding the type of genetic inheritance (sporadic versus familial).

In fact it was possible to detect the association of various severe clinical manifestations and symptoms (epilepsy, MD and intellectual disability) in almost all sporadic patients, thus suggesting a more severe phenotype in this group; conversely in the familial group the clinical expression of the disease was widely variable

and heterogeneous. Moreover in familial patients the evolution over the years seems to be spontaneously more favorable: compared to sporadic patients they are affected by a more “benign” epilepsy, intellectual disability is less compromising and other symptoms are less frequent, for this reason KD was tested less in this group (3/11 patients).

The mental development was more compromised with a higher intellectual disability in sporadic patients (sporadic mean IQ 58; familial mean IQ: 74.5).

Regarding the epilepsy, all sporadic patients presented an earlier epilepsy-onset (mean age onset 24.1 months versus familial mean age onset 52.25 months) and higher tendency to become refractory to conventional AEDs treatment (55% versus 9% in familial group) even though in the second decade they experienced a reduction in the intensity and frequency of their seizures. In familial cases epilepsy (present in 82% of patients) was not a severe disabling symptom, seizures were rare and disappeared in adulthood.

Regarding MD we found no significant difference between the two groups (91% in sporadic and 73% in familial group), we noticed only a mild later onset of MD in familial cases (92.6 months versus 80.4 months in sporadic group).

As outlined in literature PED also remains the most characteristic MD type in GLUT1DS<sup>17,18</sup> in our sample too. Furthermore weakness and intermittent worsening of the MD during exercise or fasting was a peculiarity in our case series<sup>19,20</sup> (50% in sporadic and 18% in familial patients).

Nearly all our sporadic cases (91%) had both epilepsy and MD, whereas familial cases presented only seizures (27%), or only MD (18%) or both (55%).

In both sporadic and familial cases MD onset occurred later than seizures (in sporadic group 80.4 versus 24.1 months for seizures; in familial group 92.6 versus 52.25 months) and it tended to replace epilepsy over the years. Sporadic patients reported that MD was the clinical symptom which most compromised the quality of life before the introduction of KD. On the contrary in familial group MD was not a severe disabling symptom, episodes were rare – even without KD treatment – they persisted in adulthood but only after a very prolonged physical activity.

Regarding the other symptoms we noticed that only in the sporadic group spasticity (45%) and dysarthric speech (55%) were present. Neither microcephaly nor migraine was a key feature in GLUT1DS. Prognathism was evident in 18% of sporadic patients and in 18% of familial patients; even if it is not essential for the GLUT1DS diagnosis we suggest keeping it in mind as a possible gestalt sign of the disease.



As far as diagnostic workout is concerned no correlation between clinical severity, mutation type and glucose ratio or degree of hypoglycorrhachia was detectable, as already reported in literature.<sup>21</sup>

With regard to treatment, we could not compare the two groups: in familial patients KD was less tested (3/11) because of the minor severity in their symptoms.

In all our sporadic patients KD was effective for epilepsy (when present), in epileptic discharges and against MD. On the contrary no improvement in the cognitive impairment was noticed even after years of treatment, a possible explanation is that they only underwent this etiological therapy in adulthood.

The clinical improvement was maintained with time in all but 1 patient (#6), leading us to recommend permanent continuation of the KD therapy as previously reported.<sup>14–16</sup>

Patients #10 and #11 are genetically confirmed GLUT1DS patients, their siblings have a similar type of epilepsy but they are negative for the SLC2A1 gene. Rushing to the conclusion that this is a random association could be a general explanation. The possible presence of an additional unknown gene involved in clinical manifestation of the disease may be assumed.<sup>22,23</sup>

## 5. Conclusion

In conclusion, the present study delineates a wide heterogeneity in GLUT1DS, in particular our experience shows some important differences between sporadic and familial inheritance in terms of severity of the clinical picture. Familial patients allow us to affirm that in GLUT1DS a “mild” phenotype could be present. This mild phenotype only shows a “benign” epilepsy, and/or a slight MD, and/or a borderline IQ.

These findings necessarily raise several questions, first of all the real incidence of the disease: patients having a mild phenotype are currently under-diagnosed.

Secondly we wonder if KD is suitable in asymptomatic or minimally symptomatic patients bearing in mind that the diet, while effective, has frequent difficulties in acceptance and compliance. No suggestion is given in literature so far. This lack of experience induces reserves in setting up such dietary therapy in adults in which the anti-epileptic treatment achieves good results<sup>16</sup> even if no data are given about cognitive long-term outcome without alternative fuel to the brain.

The marked differences in phenotypes among relatives or patients sharing the same genetic mutation remain a challenging issue to explain, for this reason giving a reasonably accurate genetic counseling<sup>23</sup> is difficult.

A possible first step to answer these questions could be the creation of an international GLUT1DS registry in order to collect a large series of patients to improve the knowledge regarding the clinical variability of the disease.<sup>24</sup>

In patients without SLC2A1 mutation but with clinical symptoms suggesting GLUT1DS a wide genetic screening should be done in order to find other genes associated with the disease. The presence of other genes could enable us to explain the great clinical variability found.

## Conflict of interest

None of the authors has any conflict of interest to disclose.

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