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Original article

SLC35A2-related congenital disorder of glycosylation: Defining the phenotype

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ABSTRACT

We aim to further delineate the phenotype associated with pathogenic variants in the *SLC35A2* gene, and review all published literature to-date. This gene is located on the X chromosome and encodes a UDP-galactose transporter. Pathogenic variants in *SLC35A2* cause a congenital disorder of glycosylation. The condition is rare, and less than twenty patients have been reported to-date. The phenotype is complex and has not been fully defined.

Here, we present a series of five patients with *de novo* pathogenic variants in *SLC35A2*. The patients' phenotype includes developmental and epileptic encephalopathy with hypsarrhythmia, facial dysmorphism, severe intellectual disability, skeletal abnormalities, congenital cardiac disease and cortical visual impairment.

Developmental and epileptic encephalopathy with hypsarrhythmia is present in most patients with *SLC35A2* variants, and is drug-resistant in the majority of cases. Adrenocorticotropic hormone therapy may achieve partial or complete remission of seizures, but the effect is usually temporary. Isoelectric focusing of transferrins may be normal after infancy, therefore a congenital disorder of glycosylation should still be considered as a

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diagnosis in the presence of a suggestive phenotype. We also provide evidence that cortical visual impairment is part of the phenotypic spectrum.

1. Introduction

Over 100 glycosylation-related human genetic disorders have been reported in the literature. These result from disruption of the normal N-glycosylation pathway which involves adding complex sugar chains (glycans) to proteins.[1] Congenital disorders of glycosylation (CDG) can result in a complex phenotype, including intellectual disability and seizures.[2,3] Variants in the *SLC35A2* gene (MIM #300896), on the X chromosome, coding for the only known transporter of UDP-galactose to the Golgi apparatus, have been found to result in a congenital disorder of glycosylation.[4] To the authors' knowledge, less than twenty patients with variants in this gene have been reported in detail to-date.[3–10] The associated phenotype includes developmental and epileptic encephalopathy (DEE), severe intellectual disability (ID), hypotonia, dysmorphic features, and shortening of the distal limbs.

Here, we present five new patients with *de novo* pathogenic variants in *SLC35A2*, who have DEE with hypsarrhythmia, severe ID, skeletal abnormalities and cortical visual impairment. We further define the phenotypic spectrum, in particular the epilepsy phenotype. With increasing use of next generation sequencing in patients with epilepsy, it is likely that more patients will be identified with this phenotype and

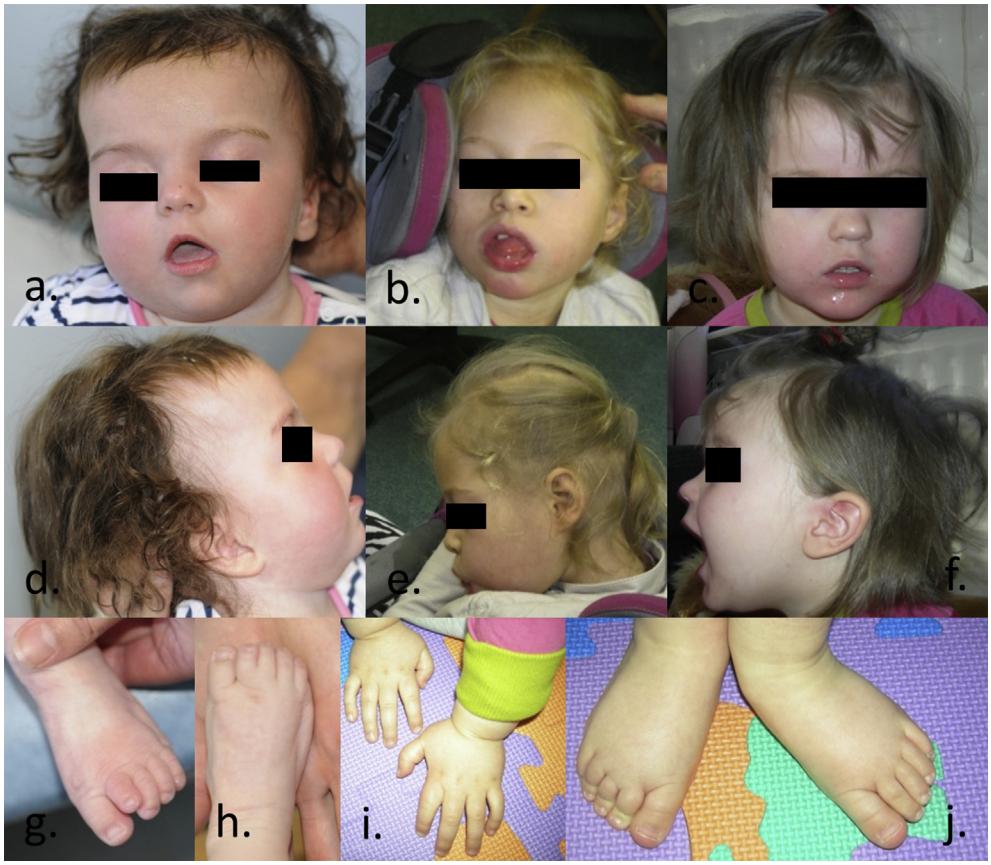

Fig. 1 – Patients 1 (a,d,g,h), 2 (b,e) and 3 (c,f,i,j) at ages 11-months, 8-years and 11-months, and two-years respectively. Patient 1: dysmorphic features include brachycephaly, hypertelorism, and low-set ears. Note 2–3 toe syndactyly (R foot) and proximally placed 2nd toe (L foot). Patient 2: dysmorphic features include high-set eyebrows, long, narrow palpebral fissures, mid-face hypoplasia with depressed nasal bridge, open mouth with full, tented upper lip and a protruding tongue. Patient 3: dysmorphic features include elongated palpebral fissures, large blue irises; eversion of the lower lids; long and prominent eyelashes; broad eyebrows; short nose and hypoplastic alae nasi; short, grooved philtrum; tented upper lip and posteriorly-rotated ears. Also note tapering fingers and broad great toes. (For interpretation of the references to color/colour in this figure legend, the reader is referred to the Web version of this article.)

Table 1 – Features of patients in this cohort. Isf Tf isoelectric focusing of transferrins; n/a not applicable; nd not done; AED antiepileptic medication. All variants are according to the NM_005660.2 transcript.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Gender	F	F	F	F	F
Age at evaluation (yr; mo)	3	8; 11	8; 0	3; 4	0; 10
***SLC35A2* variant (predicted protein change)**	c.889A > G (p.Lys297Glu)	c.327T > G (p.Tyr106*)	c.195C > A (p.Phe65Leu)	c.515T > C (p.Leu172Pro)	c.923C > T (p.Ser308Phe)
ACMG pathogenicity criteria	PS2, PM2 and PP3 (Likely pathogenic)	PVS1, PS2 (Pathogenic)	PS2, PM2, PP3, PP4 (Likely pathogenic)	PS2, PM2 and PP3 (Likely pathogenic)	PS2, PM2, PP2, PP3 (Likely pathogenic)
Family history	Cousin X-linked agammaglobulinaemia	Brother single febrile seizure	Unremarkable	Unremarkable	Unremarkable
Antenatal findings	Tetralogy of Fallot	Nil	Nil	Nuchal thickening	Nil
Gestational age at birth (weeks)	40	34	43	40	38
Birth weight	50th centile	25–50th centile	25th centile	40th centile	75th–91st centile
Admission to NICU	Yes – Tetralogy of Fallot	Yes – Weight loss, jaundice, skin ulcers	No	No	Yes – CPAP
Dev. delay	Yes	Yes	Yes	Yes	Yes
ID	n/a	Severe	Severe	Severe	n/a
Age of seizure onset	6 weeks	5 months	6 months	6 weeks	Possible at age 4 months
Initial seizure type	Infantile spasms	Infantile spasms	Infantile spasms	Infantile spasms	Eye rolling/chewing episodes
Evolving seizure phenotype	Myoclonic & tonic seizures; and ongoing spasms with clusters	Drop attacks, tonic spasms, change in visual attention	n/a	n/a	n/a
EEG	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	Hypsarrhythmia	Focalised epileptic activity
AED response	Partial	Pharmacoresistant	Seizure free, off medication	Seizure free on Vigabatrin, Nitrazepam and ketogenic diet	AED stopped with no clinical change
Dysmorphic	Yes	Yes	Yes	Yes	Yes
Hypotonia	No	No	Yes	Yes	Yes
Head circumference centile (age)	9th (11 mo)	<<0.4th (9 yr)	98th–99.6th (birth)	40th (3 y 4 mo)	50th (10 mo)
Visual defect	Severe cortical visual impairment	No	Myopia, astigmatism, intermittent exotropia of the right eye and amblyopia ex anopsia	No	Strabismus
Skeletal abnormality	Thoracic scoliosis, bilateral coxa valga and generalised osteopenia. Unusual defects involving the right proximal and distal tibia, with right tibia shorter than the left. Possible similar early changes in the left distal tibia	Bilateral coxa valga with partial hip subluxation	Joint hypermobility, genu valga, asymmetric chest deformity	Camptodactyly of the 2nd right finger	n/a

(*continued on next page*)

Table 1 – (continued)

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
MRI abnormality (age)	Asymmetry of the lateral ventricles and a thin corpus callosum (7 mo)	Normal (5 mo). Delayed cerebral white matter myelination (18 & 31 mo). Normalised with some residual hyperintensity posterior to the trigones of the lateral ventricles (4 yr). Hippocampi small and malrotated	No	Normal (2 mo). Thinning of the corpus callosum with delayed myelination and slight enlargement of the lateral ventricles (2.5 yr).	No
Isf Tf (age -yr; mo)	nd	normal (8; 11)	normal (3; 4)	normal (2; 6)	nd

hence, it is important to better understand the disease course and potential treatment options in this group of disorders.

2. Patient reports

Our cohort consists of five female patients born to non-consanguineous White European parents (Fig. 1). All patients had normal chromosomal microarray analysis (Patient 1 was found to have a paternally inherited 320 kb deletion at 6q26, classified as likely benign). All were found to have heterozygous *de novo* variants in *SLC35A2* with no additional variants. Patient 4 was also found to have a skewed X chromosome inactivation profile (100:0). Three patients had normal isoelectric focusing of transferrins, performed between the ages of 2 and 8 years. In addition to the reports here, Table 1 provides further clinical information. Further details are included in the supplementary material.

2.1. *Patient 1*

This 3-year old patient developed infantile spasms at 6-weeks of age. EEG (electroencephalogram) demonstrated hypsarrhythmia. Magnetic Resonance Imaging (MRI) of the brain at 7-months of age demonstrated asymmetry of the lateral ventricles and a thin corpus callosum (Supp Fig. 1). She had a partial response to Vigabatrin and Prednisolone. Her seizures subsequently evolved to myoclonic and tonic seizures in addition to ongoing spasms with clusters. These were resistant to several different treatment regimens including combinations of Vigabatrin, steroids, Sodium Valproate, Levetiracetam, and Topiramate. Seizure control improved on classical ketogenic diet therapy at 12-months of age, together with cessation of all anti-epileptic medications. A course of ACTH (adrenocorticotropic hormone) therapy resulted in a definite, but short-lived, improvement in seizure control. Response to a second course of ACTH was less effective.

She had significant developmental impairment. Tetralogy of Fallot was noted on antenatal ultrasound (USS), which subsequently required surgery. On assessment at the age of 3-years, she was noted to be dysmorphic and had right lower limb shortening.

Radiological review of a skeletal survey demonstrated thoracic scoliosis, bilateral coxa valga and generalised osteopenia. There were unusual defects involving the right proximal and distal tibia, with the defect in the proximal tibia being larger. Overall, the right tibia was shorter than the left. Possible similar early changes were seen in the left distal tibia (Fig. 2). The significance of these radiological findings remains uncertain.

She also has severe cortical visual impairment, with no response to formal visual acuity assessment but some brief fixation. Electroretinogram (ERG) confirmed no evidence of diffuse retinal dysfunction.

2.2. *Patient 2*

This 8-year old patient developed infantile spasms at the age of 5-months. EEG showed hypsarrhythmia and an MRI brain scan was normal. Initial treatment was with Prednisolone and

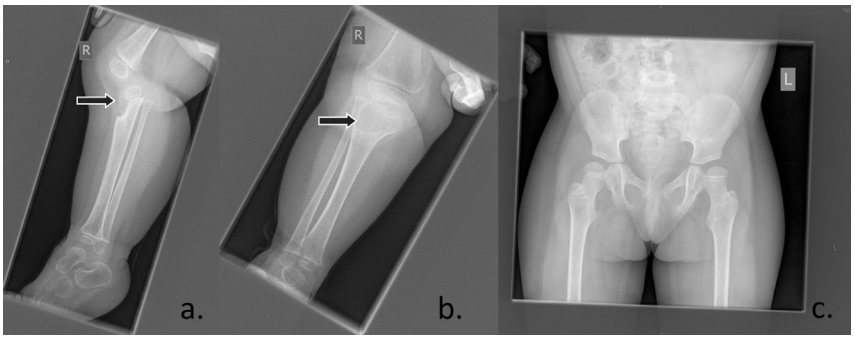

Fig. 2 – Patient 1 (a–b): radiographs at 11-months of age demonstrating non-specific defects involving the right proximal and distal tibia, with the proximal tibia being larger. Patient 2 (c): radiograph of pelvis demonstrates bilateral coxa valga with partial hip subluxation.

subsequently Vigabatrin with partial response. Over the course of the next few years she developed drop attacks, tonic spasms, and changes in visual attention associated with an unusual cry.

Her seizures were resistant to ketogenic diet, as well as combinations of Lamotrigine, Zonisamide, Nitrazepam, Rufinamide, and Topiramate. Repeat EEG at the age of 4-years and 3-months showed hypsarrythmia. Repeat MRI brain imaging at the ages of 18 and 31 months showed significantly delayed cerebral white matter myelination. This normalised by age 4-years, with some residual hyperintensity posterior to the trigones of the lateral ventricles. The hippocampi appeared small and malrotated (Supp Fig. 2).

She had severe developmental delay. On assessment at the age of 8-years she had severe ID and was able to walk a few steps with support. She was dysmorphic. A pelvis X-ray showed bilateral coxa valga with partial hip subluxation (Fig. 2).

2.3. *Patient 3*

This 8-year old patient developed infantile spasms at 6-months of age. EEG demonstrated hypsarrhythmia. Her seizures responded to Vigabatrin in combination with ACTH. She was then treated with Valproate monotherapy. From the age of 3½ years, medication was withdrawn and she remained seizure-free. Neonatal nystagmus was noted, which ceased as seizure control improved. She had myopia, astigmatism, intermittent exotropia of the right eye and amblyopia ex anopsia. ERG performed at 14-months of age was normal. MRI brain and echocardiogram at the age of 8-months was normal.

On assessment at the age of 3-years and 4-months, she had severe hypotonia and severe global developmental delay. She was dysmorphic. At the age of 8-years, she has severe ID with no spoken language. She can walk with support if helped to a standing position.

2.4. *Patient 4*

This 3-year old patient developed infantile spasms at 6-weeks of age and EEG demonstrated hypsarrhythmia. Her spasms were partially controlled with a combination of Vigabatrin, steroids and ACTH therapy. She was treated unsuccessfully with Phenobarbital, Valproate, Levetiracetam and Topiramate. Her spasms ceased with a combination of Vigabatrin, Nitrazepam and ketogenic diet at 2-years and 3-months of age.

MRI brain scan at two months was normal. A second MRI brain at 2½ years of age demonstrated thinning of the corpus callosum with delayed myelination and slight enlargement of the lateral ventricles. On assessment at 3-years and 4-months of age, she had global hypotonia. She could sit and stand with help. She had no spoken language. She had severe ID. She was dysmorphic. There were no ophthalmic abnormalities.

2.5. *Patient 5*

This 10-month old patient developed eye rolling and chewing episodes at the age of four months, as well as unilateral myoclonic jerks. There was one episode of opisthotonus. Focal epileptic activity was noted on EEG at the age of five months, however this did not correlate with clinical episodes. Carbamazepine and then Levetiracetam monotherapy was trialled, but did not have a significant effect and was discontinued. MRI brain was normal.

On assessment at the age of 10-months, she had moderate to severe developmental delay. She had hypotonia, and was dysmorphic. There were no ophthalmic abnormalities.

3. Methods

All patients were ascertained through routine referral to their local Clinical Genetics service. The cohort was formed through personal communication (Patient 2), interrogation of the DECIPHER database[11] (Patient 3) and through the GeneMatcher website[12] (Patients 4 and 5). Genomic DNA was extracted from peripheral blood leukocytes from patients using standard procedures. All patients underwent chromosomal microarray-analysis. Patients 1–2 and 4–5 were thought to have epilepsy as a predominant part of their phenotype. They therefore had targeted epilepsy gene panels performed. A wider differential was considered for Patient 3, therefore whole genome sequencing (WGS) was performed.

For patients 1 & 2, sequencing of 72 genes associated with early infantile epileptic encephalopathy was carried out using targeted whole exome sequencing (WES) (Agilent SureSelect and MiSeq). Trio-based WGS was carried out for patient 3 using the Illumina HiSeqX system (Illumina). For patient 4, sequencing of a 93 gene panel for monogenic epileptic

disorders was performed on a NextSeq500 (Illumina). Analysis of 569 genes associated with ID, autism and epilepsy was performed via targeted WES for patient 5 using NovaSeq 6000 Agilent SureSelect All Human Exon v6. All data was analysed against GRCh37. All variants reported are according to the NM_005660.2 transcript. Variants were verified by Sanger sequencing using standard protocols. Methods are described in further detail in the supplementary material.

4. Discussion

We present here a series of five patients with *de novo* pathogenic variants in *SLC35A2* and phenotypic features including epilepsy with hypsarrhythmia, severe ID, non-specific dysmorphism, visual and skeletal abnormalities.

Comparison of our cohort with those previously reported[3–10] allows us to define the phenotype associated with *SLC35A2*, particularly in relation to epilepsy, which affects 16/18 (89%) patients (Table 2). Seizures start in early infancy, with 8/11 (73%) of those reported developing before the age of 3-months and all before 6-months. The presentation was with infantile spasms in 8/10 (80%). Two patients presented with tonic seizures and partial motor seizures respectively. The phenotype was reported, in six patients, to progress to a combination of tonic seizures plus spasms. Two patients were also reported to have myoclonic seizures. Hypsarrhythmia is common (13/16; 81%). Given that all affected patients have developmental delay, this means most meet the criteria for West syndrome (triad of infantile spasms, hypsarrhythmia and developmental delay). Epilepsy in this group is usually resistant to treatment with 7/11 (64%) of patients having ongoing seizures.

There does not appear to be a definite pattern to response in treatment, but our experience suggests that partial and/or temporary seizure control may be achieved with either Vigabatrin ± steroids, the ketogenic diet or ACTH. Four previously reported patients have had a temporary response to ACTH, with a further patient achieving seizure control with this therapy.[3,6,7] As these are standard treatments for infantile spasms, further work is needed to determine optimal epilepsy medication in this group of patients.

All patients reported have severe ID. None of the five patients reported here had developed spoken language. Non-specific dysmorphic features are present in 16/17 (94%). Hypotonia (12/18; 67%) and microcephaly (6/13; 46%) are common. Fifteen out of 18 (83%) patients have abnormalities on brain MRI. The most common findings are thinning of the

Table 2 – Summary of patients with pathogenic SLC35A2 variants previously reported, including this study cohort.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Ng et al. (Patient 1)	Ng et al. (Patient 2)	Ng et al. (Patient 3)	Kodera et al. (Patient 1)
Gender	F	F	F	F	F	M	F	M	F
Age (yr; mo)	3	8; 11	8; 0	3; 4	0; 10	3	3	6	8; 10
Inher.	*de novo*	*de novo*	*de novo*	*de novo*	*de novo*	*de novo*	*de novo*	*de novo*	*de novo*
***SLC35A2* variant**	c.889A > G	c.327T > G	c.195C > A	c.515T > C	c.923C > T	c.15_91 + 48delinsA	c.3G > A	c.991G > A	c.433_434del
Predicted protein change	p.Lys297Glu	p.Tyr106*	p.Phe65Leu	p.Leu172Pro	p.Ser308Phe	p.Gly8Serfs*9	p.Met1?	p.Val331Ile	p.Tyr145Profs*76
Isf Tf (age -yr; mo)	Nd	nml (8; 11)	nml (3; 4)	nml (2; 6)	nd	abn (0; 5), nml (3; 2)	abn (0; 7), nml (2; 9)	abn (0; 5–7), nml (5; 0)	nml (8; 10)
Dev. delay	S	S	S	S	M-S	Y	Y	Y	S
ID	n/a	S	S	S	n/a	n/a	n/a	nd	S
Seizures	Y	Y	Y	Y	N	Y	Y	N	Y
Age seizure onset	6 wk	5 mo	6 mo	6 wk	n/a	nd	nd	nd	6 days
Initial seizure type	Infantile spasms	Infantile spasms	Infantile spasms	Infantile spasms	n/a	nd	nd	nd	Tonic
Evolving seizure phenotype	Myoclonic and tonic + ongoing spasms with clusters	Drop attacks + tonic spasms	n/a	n/a	n/a	nd	nd	nd	Infantile spasms + tonic seizures
Seizures ctrl	N	N	Y	Y	n/a	nd	nd	nd	N
Hypsarrhythmia	Y	Y	Y	Y	N	Y	Y	N	Y
Dysmorphism	Y	Y	Y	Y	Y	N	Y	Y	Y
Hypotonia	N	N	Y	Y	Y	Y	Y	Y	Y
Microcephaly	N	Y	N	N	N	N	Y	Y	nd
MRI abn.	TC, AV	DM	N	DM, TC	N	Small cerebellum	DM, TC	CA	TC, DM, CA
Visual defect	CV	N	RA	N	EM	EM	RA	EM	N
Skeletal abn.	SC	CV	JH, GV	N	N	N	SE	SE	N

Brain abnormalities: TC: thin corpus callosum, AV: abnormal ventricles, DM: delayed myelination, CA: cerebral/cerebellar atrophy.
Ophthalmic abnormalities: CV: cortical visual impairment, RA: refractive error, EM: abnormal eye movements, RA: retinal abnormality.
Skeletal abnormalities: SC: scoliosis, CV: coxa valga, GV: genu valga, SE: shortened extremities, HD: hip dislocation, JH: joint hypermobility.
Abbreviations: Inher. – inheritance, yr – year, mo – months, dn – *de novo*, mat – maternal, Y – yes, N – no, ACMG-AMP – American College of Medical Genetics and Genomics – Association for Molecular Pathology, Isf Tf – Isoelectric focusing of transferrins, S – severe, M-S – moderate to severe, ctrl – controlled, nd – not documented, Dev – developmental, ID – intellectual disability, nml – normal, abn – abnormality, ophthal – ophthalmic.

corpus callosum (8/18; 44%), cerebral and/or cerebellar atrophy (8/18; 44%) and delayed myelination (6/18; 33%). One patient in our cohort had a normal MRI brain scan at the age of 8-months. Interestingly, however, two previously reported patients[3] initially had normal MRI-brain scans in infancy. Subsequent imaging at the ages of 4 and 8 years respectively was abnormal. Therefore, it is possible that *SLC35A2*-associated brain abnormalities develop over time, and this may well prove to be the case in our patient with an early normal MRI brain scan.

Visual defects are present in 11/16 (69%) individuals. Of note, one other patient has been previously reported with cortical visual impairment,[5] although the patient of Dörre et al.[6] had severe visual impairment of unspecified cause. Therefore, our report provides further evidence that this specific visual abnormality is part of the phenotypic spectrum associated with *SLC35A2* pathogenic variants. However, it is also possible that in view of DEE, visual impairment may be a part of the phenotype rather than a specific issue.

Skeletal abnormalities are found in 9/14 (64%) patients. Features include short stature, non-specific limb shortening, scoliosis and bilateral coxa valga. The X-rays of the pelvis in both patients 1 and 2 showed bilateral coxa valga with high migration index on both sides, suggesting this may be a specific finding. Further imaging of patients with *SLC35A2* is required to ascertain the skeletal findings in this group.

Our cohort includes one patient with Tetralogy of Fallot. This has not been reported in association with *SLC35A2* and may represent a novel feature. However, this cardiac abnormality can occur in isolation and further reports are required to determine if congenital cardiac disease is part of the *SLC35A2* phenotypic spectrum.

Transferrin isoelectric focusing was normal for those tested in our cohort at ages 3-years 4-months and 2-years 6-months respectively (Patients 3 & 4). The majority of reported patients, including our cohort, had normal transferrin profiles after the age of 2-years (Table 2). Ng et al.[4] demonstrated galactosylation-deficient transferrin profiles in their patient series between the ages of 5–7 months, with normalisation after the age of 3 years. Therefore, there is likely to be an age-related time period for transferrin testing in relation to *SLC35A2*-related CDG, emphasising the importance of early diagnosis. Ng et al.[4] hypothesised this is related to selection against hepatocytes with abnormal *SLC35A2* during early development; however, this has not been conclusively demonstrated. Our data suggest that isoelectric focusing of transferrins is a useful diagnostic test in females presenting with early onset infantile spasms. This analysis should be performed before three years of age if feasible.

SLC35A2 is located on the X chromosome; all of our patients are females, in keeping with majority of patients

Kodera et al. (Patient 2)	Kodera et al. (Patient 3)	Bosch et al.	Kimizu et al.	Dorre et al.	Lopes et al.	EuroEPINOMICS et al. (Patient 1)	EuroEPINOMICS et al. (Patient 2)	Evers et al.	Total (reported)
F	F	F	F	F	M	F	F	F	–
12; 8	10; 5	23	2	5	8	3	13	2	–
de novo	*de novo*	*de novo*	*de novo*	*de novo*	mat	*de novo*	*de novo*	mat	–
c.972del	c.638C > T	c.800A > G	c.950delG	c.797G > T	c.772G > A	c.683C > A	c.502C > T	c.831C > G	–
p.Phe324Leufs*25	p.Ser213Phe	p.Tyr267Cys	p.Gly317Alafs*32	p.Gly266Val	p.Val258Met	p.Ser228*	p.Gln168*	p.Asn277Lys	–
nml (12; 8)	nml (10; 5)	nd	mass spectrometry nml (1; 0), (2; 6)	abn (0; 1), (5; 0)	nml (8; 0)	nd	nd	abn (2; 0)	–
S	S	Y	S	S	S	nd	S	S	17 of 17 (100%)
S	S	S	n/a	nd	S	Y	S	nd	10 of 10 (100%)
Y	Y	Y	Y	Y	Y	Y	Y	Y	16 of 18 (89%)
1 mo	3 mo	nd	2 mo	3 mo	nd	3 mo	4.5 mo	nd	–
Infantile spasms	Infantile spasms	nd	Partial motor seizures upper limbs	nd	nd	Infantile spasms	Infantile spasms	nd	–
Tonic seizures, spasms, focal seizure	Tonic seizure, spasms	nd	Spasms	nd	nd	Spasms + tonic seizures	Myoclonic, tonic-clonic, tonic	nd	–
N	N	nd	Y	Y	nd	N	N	nd	4 of 11 (36%)
Y	Y	nd	Y	Y	N	Y	Y	nd	13 of 16 (81%)
Y	Y	Y	Y	Y	Y	Y	Y	nd	16 of 17 (94%)
N	Y	Y	Y	Y	N	Y	N	N	12 of 18 (67%)
nd	nd	Y	N	Y	Y	nd	nd	N	6 of 13 (46%)
AV	CA, TC	DM	TC, CA, AV	CA, TC	CA, TC, periventricular heterotopia	N	DM, CA	CA	15 of 18 (83%)
RA	N	CV	N	'severe visual impairment'	nd	nd	EM	Cataract	11 of 16 (69%)
N	HD	SC	nd	JH	nd	nd	SC	nd	9 of 14 (64%)

reported thus far. Ng et al.[4] reported two male patients who were mosaic for *SLC35A2* pathogenic variants. It is likely that the presence of a functional allele is required for survival. There have been two reports of maternal inheritance in the literature[8,10]; otherwise all the pathogenic variants reported are *de novo*. Our cohort includes three novel missense variants and one novel nonsense variant. Overall, including our cohort, missense and truncating variants have been reported in the literature at approximately equal frequency.

In summary, we present a series of five patients with pathogenic *SLC35A2* variants and review the features of patients previously reported, with particular focus on the drug-resistant epilepsy phenotype and MRI brain findings. This allows us to further define the phenotype of this rare disorder. Early onset epilepsy presenting with infantile spasms and hypsarrhythmia predominates, in association with severe developmental delay and ID. Interestingly, severe early-onset epilepsy is unusual in CDGs in general. This appears to be a feature unique to *SLC35A2*-related CDG.

Additional common features include non-specific dysmorphism, microcephaly, hypotonia and MRI-brain abnormalities (e.g. thinning of the corpus callosum and cerebral atrophy). Visual and skeletal defects may be present, but further data is required to determine how specific these are in relation to *SLC35A2*.

In this respect, we provide evidence that cortical visual impairment is part of the phenotypic spectrum. Additionally, congenital cardiac disease may be part of the extended phenotype. Further patient series of this nature are required to understand the natural history and course of the seizure phenotype in patients with rare genotypes, such as those with pathogenic variants in *SLC35A2*.

Conflicts of interest

None to declare for all authors.

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This study makes use of data generated by the DECIPHER community. A full list of centres who contributed to the generation of the data is available from http://decipher.sanger.ac.uk and via email from decipher@sanger.ac.uk. Funding for the project was provided by the Wellcome Trust.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ejpn.2018.08.002.

REFERENCES

1. Freeze HH, Chong JX, Bamshad MJ, Ng BG. Solving glycosylation disorders: fundamental approaches reveal complicated pathways. *Am J Hum Genet* 2014;**94**:161–75.
2. Freeze HH, Eklund EA, Ng BG, Patterson MC. Neurological aspects of human glycosylation disorders. *Annu Rev Neurosci* 2015;**38**:105–25.
3. Kodera H, Nakamuer K, Osaka H, et al. De novo variants in *SLC35A2* encoding a UDP-galactose transporter cause early-onset epileptic encephalopathy. *Hum Mutat* 2013;**34**:1708–14.
4. Ng BG, Buckingham KJ, Raymond K, et al. Mosaicism of the UDP-galactose transporter SLC35A2 causes a congenital disorder of glycosylation. *Am J Hum Genet* 2013;**92**(4):632–6.
5. Bosch DG, Boonstra FN, de Leeuw N, et al. Novel genetic causes for cerebral visual impairment. *Eur J Hum Genet* 2016;**24**(5):660–5.
6. Dörre K, Olczak M, Wada Y, et al. A new case of UDP-galactose transporter deficiency (SLC35A2-CDG): molecular basis, clinical phenotype, and therapeutic approach. *J Inherit Metab Dis* 2015;**38**(5):931–40.
7. Kimizu T, Takahashi Y, Oboshi T, et al. A case of early onset epileptic encephalopathy with de novo variant in SLC35A2: clinical features and treatment for epilepsy. *Brain Dev* 2017;**39**(3):256–60.
8. Lopes F, Barbosa M, Ameur A, et al. Identification of novel genetic causes of Rett syndrome-like phenotypes. *J Med Genet* 2016;**53**(3):190–9.
9. EuroEPINOMICS-RES Consortium, Epilepsy Phenome/Genome Project, and Epi4K Consortium. De novo mutations in synaptic transmission genes including DNM1 cause epileptic encephalopathies. *Am J Hum Genet* 2014;**95**:360–70.
10. Evers C, Staufner C, Granzow M, et al. Impact of clinical exomes in neurodevelopmental and neurometabolic disorders. *Mol Genet Metab* 2017;**121**:297–307.
11. Firth HV, Richards SM, Bevan AP, et al. DECIPHER: database of chromosomal imbalance and phenotype in humans using ensembl resources. *Am J Hum Genet* 2009;**84**:524–33.
12. Sobreira N, Schiettecatte F, Valle D, Hamosh A. GeneMatcher: a matching tool for connecting investigators with an interest in the same gene. *Hum Mutat* 2015;**36**:928–30.