



# The phenotypic spectrum of X-linked, infantile onset *ALG13*-related developmental and epileptic encephalopathy

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**Abstract**

**Objective:** Asparagine-linked glycosylation 13 (*ALG13*) deficiencies have been repeatedly described in the literature with the clinical phenotype of a developmental and epileptic encephalopathy (DEE). Most cases were females carrying the recurrent *ALG13* de novo variant, p.(Asn107Ser), with normal transferrin electrophoresis.

**Methods:** We delineate the phenotypic spectrum of 38 individuals, 37 girls and one boy, 16 of them novel and 22 published, with the most common pathogenic *ALG13* variant p.(Asn107Ser) and additionally report the phenotype of three individuals carrying other likely pathogenic *ALG13* variants.

**Results:** The phenotypic spectrum often comprised pharmaco-resistant epilepsy with epileptic spasms, mostly with onset within the first 6 months of life and with spasm persistence in one-half of the cases. Tonic seizures were the most prevalent additional seizure type. Electroencephalography showed hypsarrhythmia and at a later stage of the disease in one-third of all cases paroxysms of fast activity with electrodecrement. *ALG13*-related DEE was usually associated with severe to profound developmental delay; ambulation was acquired by one-third of the cases, whereas purposeful hand use was sparse or completely absent. Hand stereotypies and dyskinetic movements including dystonia or choreoathetosis were relatively frequent. Verbal communication skills were absent or poor, and eye contact and pursuit were often impaired.

**Significance:** X-linked *ALG13*-related DEE usually manifests as West syndrome with severe to profound developmental delay. It is predominantly caused by the recurrent de novo missense variant p.(Asn107Ser). Comprehensive functional studies will be able to prove or disprove an association with congenital disorder of glycosylation.

**KEY WORDS**

*ALG13*, developmental and epileptic encephalopathy, epileptic spasms, West syndrome

## 1 | INTRODUCTION

Epileptic encephalopathy is defined as a condition in which epileptic activity itself contributes to cognitive and behavioral impairment beyond what is expected from the underlying pathology alone.<sup>1</sup> However, in many of the severe epilepsies of infancy and childhood, abnormal development may not just be due only to seizures and interictal epileptiform abnormalities but arises as a direct consequence of the underlying etiology. In some diseases, developmental impairment results from the combination of both mechanisms. Disorders in which developmental impairment results from the underlying cause as well as from the epileptic encephalopathy are now termed developmental and epileptic encephalopathies (DEEs).<sup>2</sup>

Deficiency of asparagine-linked glycosylation 13 (*ALG13*) was first identified in 2012 in a boy with a de novo likely pathogenic variant c.280A > G, p.(Lys94Glu) as a cause of congenital disorder of glycosylation (CDG), a defect in the synthesis and attachment of glycoprotein and

**Key Points**

- *ALG13*-related DEE is solely caused by X-linked de novo missense variants, predominantly by p.(Asn107Ser)
- The phenotype of *ALG13*-related DEE comprises epilepsy, global developmental delay, and often dyskinetic movements and hand stereotypies
- Epilepsy in *ALG13*-related DEE consists of West syndrome, often pharmaco-resistance, and a recognizable EEG pattern

glycolipid glycans.<sup>3</sup> He presented with pharmaco-resistant seizures, microcephaly, nystagmus, bilateral optic nerve atrophy, extrapyramidal signs, hepatomegaly, edemas and a bleeding tendency and died at 1 year of age.<sup>4</sup>

In 2013, *ALG13* variant c.320A > G, p.(Asn107Ser) was found in a female with epileptic spasms, global developmental delay, hypotonia, and some facial dysmorphisms. She had normal transferrin electrophoresis, and no clear evidence of CDG was identified<sup>5</sup>; the same variant has now been reported in at least 21 females and one male,<sup>6–22</sup> including one patient reported twice.<sup>5,23</sup> Where segregation was performed, the pathogenic variant always arose de novo. One patient was published with a different de novo *ALG13* variant of the same amino acid p.(Asn107Thr).<sup>14</sup> In addition, six male index patients have been reported with maternally inherited variants of unknown significance (VUS).<sup>24–29</sup> Several of these VUS were identified in healthy individuals, such as p.(Tyr1074Cys), 112/176489 alleles ([https://gnomad.broadinstitute.org/gene/ENSG0000101901?dataset=gnomad\\_r2\\_1](https://gnomad.broadinstitute.org/gene/ENSG0000101901?dataset=gnomad_r2_1)).<sup>24,30</sup>

Most reported patients with *ALG13*-related DEEs are female and have epileptic spasms (ES) with onset in the first year of life as well as severe to profound global developmental delay with regression as well as hypotonia, movement disorders, and sometimes dysmorphic features, consistent with a DEE.<sup>5,9–13,17–19,23</sup> However, less than one-half of the reported cases had detailed phenotypic information.

Many of these affected females underwent transferrin testing, likely due to the *ALG13* case published in 2012 that had been linked to CDG.<sup>4</sup> However, all of these tested female patients with the recurrent variant had normal transferrin isoelectric focusing.

In mouse models, the expression of *ALG13* in the central nervous system was shown to have histologically and cellular specificity, mainly in the neurons in the cortex and hippocampus, and deficient *ALG13* increased the susceptibility to epileptic seizures.<sup>31</sup>

Here, we delineate the phenotypic spectrum of *ALG13*-related DEE, focusing on the predominant recurrent pathogenic variant, p.(Asn107Ser), but also on three individuals carrying other likely pathogenic variants in *ALG13*. We analyze the phenotypic data of 38 individuals with the recurrent de novo variant p.(Asn107Ser), including 16 novel and 22 published cases.

## 2 | MATERIALS AND METHODS

We recruited patients from pediatric neurology and genetics centers in Marseille, Lyon, Paris, and Strasbourg in France, Basel, Bern, and Geneva in Switzerland, Utrecht in the Netherlands, Radeberg, Leipzig, and Tübingen in Germany, London in the UK, Wellington in New Zealand, and Melbourne in Australia.

Eighteen individuals had the recurrent *ALG13* de novo missense variant c.320A>G, p.(Asn107Ser). For two previously reported patients, we provide additional phenotypic data.<sup>9,11</sup>

We obtained comprehensive phenotypic data on each individual. All patients were seen by a pediatric neurologist or epileptologist who provided information on epilepsy, development, movement disorders, general medical history, electroencephalographic (EEG) and magnetic resonance imaging (MRI) findings, and metabolic and other test results.

Developmental delay was divided according to clinical severity into profound, severe, moderate, and mild global delay. Intellectual disability was diagnosed after the age of 6 years. Profound was defined as the patient being unable to sit or walk and nonverbal at age 4 years. Severe referred to a child who walked after 4 years and spoke single words or was nonverbal. Moderate was defined as the child walking by 3 years and speaking simple sentences, whereas mild delay meant walking by 2 years and being able to hold a conversation but delayed compared with typical development.

This study was approved by the ethics committee of the University of Leipzig (224/16-ek, 402/16-ek) as well as the collaborating institution of the referring clinician. For all patients, their parents or legal guardians gave written informed consent for research participation.

In addition, we reviewed the clinical data of 22 published patients with the *ALG13* missense variant p.(Asn107Ser). The literature (PubMed, Human Gene Mutation Database, ClinVar) was searched for reports of the recurrent *ALG13* variant until April 2020. All published variants were assessed according to the guidelines of the American College of Medical Genetics and Genomics,<sup>32</sup> and only individuals with pathogenic or likely pathogenic variants were considered for further analysis. Patients with VUS were not included in this study.

## 3 | RESULTS

We characterized the phenotypic spectrum of *ALG13*-related DEE, primarily focusing on the recurrent *ALG13* variant c.320A > G, p.(Asn107Ser). We also report four patients with novel likely pathogenic missense variants.

### 3.1 | Recurrent pathogenic variant *ALG13* p.(Asn107Ser)

We ascertained 18 patients (16 new and two previously reported patients with additional clinical information<sup>9,11</sup>) with the recurrent *ALG13* variant p.(Asn107Ser) (Tables 1 and S1, supplement) and compared them with 20 published

**TABLE 1** Overview of 37 female patients with the recurrent *ALG13* variant c.320A > G, p.(Asn107Ser), the only male patient with this recurrent variant,<sup>13</sup> and three patients with likely pathogenic new *ALG13* variants

	Female patients with c.320A > G, p.(Asn107Ser)	Male patient with c.320A > G, p.(Asn107Ser) <sup>13</sup>	Female patients with most likely pathogenic mutations and similar clinical phenotype	Female patient with most likely pathogenic mutations and different clinical phenotype
Variation, inheritance, n	c.320A > G, p.(Asn107Ser); de novo; n = 37	c.320A > G, p.(Asn107Ser); de novo; n = 1	c.86A > G, p.(Asn29Ser); c.120A > C, p.(Gln40His); c.169A > C, p.(Thr57Pro); 13% mosaic; n = 2	c.23T > C, p.(Val8Ala); n = 1
Epilepsy syndrome, seizure type, onset, course	Epilepsy: 100% (37/37); epileptic spasms: 97% (32/33); tonic seizures: 21% (7/33); median onset of ES: 5.3 mo; seizure onset by 6 mo: 80% (25/31)	Epileptic spasms; onset of spasms: 4.5 mo; GTCS later	Epileptic spasms: 2/2; mean onset of ES: 5 mo	Epilepsy with febrile seizures; onset first at 14 mo; nonfebrile seizure at 6 y 8 mo
Antiepileptic treatment, pharmacoresistance	VGB: 65% (15/23); oral steroids: 48% (11/23); ACTH: 39% (9/23); ketogenic diet: 35% (8/23); pharmacoresistance: 60% (15/25)	VGB, oral steroids, VPA, LEV; seizure-free (on LEV)	VGB: 1/2; oral steroids: 2/2; ketogenic diet: 1/2; pharmacoresistance: 2/2	LEV; seizure-free (on LEV)
EEG-specific pattern	Hypsarrhythmia: 100% (29/29); multifocal epileptiform activity: 45% (13/29); pattern paroxysms of fast activity with electrodecree: 34% (10/29) <sup>a</sup>	Hypsarrhythmia; pattern of paroxysms of fast activity with electrodecree: no	Hypsarrhythmia: 1/2; bilateral posterior spikes; background slowing: 1/3; pattern of paroxysms of fast activity with electrodecree: 0	Normal; pattern of paroxysms of fast activity with electrodecree: no
Motor development, regression, dysmorphic features	Global delay: 100% (35/35). – profound: 47% (10/21) – severe: 19% (4/21) – moderate: 24% (5/21) – mild: 10% (2/21).walking: 38% (8/21); mean: 3.3 y; regression: 80% (18/22); dysmorphic features: 17% (3/18)	Global delay; asymmetrical hearing loss; dysmorphic features: yes	Global delay: 2/2; severe: 1/2; mild: 1/2; walking without help at 3.5 y in 1/2; walk with help at 9 y in 1/2; regression: 1/2; dysmorphic features: 1/2.	Global delay: mild; regression: no; dysmorphic features: no
Stereotypies, dyskinetic movements	Hand stereotypies: 68% (13/19); limited purposeful hand use: 90% (17/19); dyskinetic movements: 41% (9/22)	Hand stereotypies: no; limited purposeful hand use: not reported; dyskinetic movements: yes	Hand stereotypies: 1/2; purposeful hand use: 1/2; dyskinetic movements: no	Hand stereotypies: no; purposeful hand use: yes; dyskinetic movements: no
Language	Poor language skills: 21% (5/24); nonverbal: 79% (19/24)	Not reported	Poor language skills: 1/2; nonverbal: 50% (1/2)	Delayed language development
Visual contact, social	Delayed and limited eye contact: 96% (26/27); autistic spectrum disorder: 15% (4/27)	Delayed eye contact	Delayed eye contact: 2/2; autistic spectrum disorder: 1/2	Normal

(Continues)

**TABLE 1** (Continued)

	Female patients with c.320A > G, p.(Asn107Ser)	Male patient with c.320A > G, p.(Asn107Ser) <sup>13</sup>	Female patients with most likely pathogenic mutations and similar clinical phenotype	Female patient with most likely pathogenic mutations and different clinical phenotype
Head growth	Microcephaly: 18% (4/22); plateauing in head growth: 64% (14/22)	Not reported	Normocephaly: 1/2; microcephaly: 1/2	N/A
MRI	Nonspecific anomalies: 26% (7/27); thinning of corpus callosum: 7% (2/27); delayed white matter myelination: 11% (3/27)	Hypoplasia corpus callosum	Normal: 2/2	Normal
Transferrin electrophoresis	Normal transferrin electrophoresis: 11; N/A: 24	Slightly abnormal (inconclusive)	N/A	N/A

Abbreviations: ACTH, adrenocorticotropic hormone; EEG, electroencephalography; ES, epileptic spasms; GTCS, generalized tonic-clonic seizures; LEV, levetiracetam; N/A, not available; VGIB, vigabatrin; VPA, valproic acid; y, years.

<sup>a</sup>See Figure 1.

cases (Tables 1 and Table S2, supplement). The mean age of all 38 patients was 6 years (median = 4.5 years, range = 2-23 years); 37 were female and one was male. The clinical phenotype of the only male patient reported<sup>13</sup> with this variant does not significantly differ from the female patients.

### 3.2 | Epilepsy

All 38 (100%) patients had epilepsy; however, the seizure type was not reported for four.<sup>16,17,19</sup> In 32 patients (18 novel, 14 published), epilepsy onset was known; 31 of 32 had onset by age 10 months, with 26 of 32 (80%) beginning by age 6 months. Only one female patient had later onset at 13 years.

ES were the most common seizure type, occurring in 33 of 34 (97%) patients. Mean age at onset of ES was 5.3 months (median = 4.5 months, range = 1-10 months). In two patients, ES were associated with inappropriate laughing. Hypsarrhythmia occurred in infancy in 30 of 33 (90%) individuals with ES. Among the 25 patients for whom data about the duration of ES were available, ES persisted beyond 2 years of age (up to 12 years of age) in 15 of 25 (60%) individuals. Only 10 of 25 (40%) patients with ES became seizure-free; eight of 10 (80%) became seizure-free within the first 6 months of treatment. Drug-resistant epilepsy was associated with more severe delay, with 80% of those profoundly impaired having ongoing seizures.

Three of 33 (9%) girls had seizures prior to onset of ES. One had bilateral tonic seizures, and two had focal seizures; one had recurrent staring episodes and the other became apneic with cyanosis.

Overall, tonic seizures were observed in seven of 34 (24%) individuals. The girl with later seizure onset at 13 years presented with refractory generalized tonic seizures. In the remaining six patients, tonic seizures persisted at mean age 4.5 years (median = 4 years, range = 2-9 years), associated with ongoing ES in five and as the sole seizure type in one. Less frequent seizure types included absence seizures (3/34, 8%), focal seizures including focal impaired awareness seizures (2/34, 6%), myoclonic seizures (4/34, 12%), and tonic-clonic seizures (3/34, 9%). The presence of other seizure types resulted in drug-resistant epilepsy in two-thirds of cases.

In terms of epilepsy syndrome, 30 of 33 (90%) individuals had West syndrome with series of ES, hypsarrhythmia, and developmental delay.<sup>33</sup> In the remaining three of 33 (9%) ES patients, the EEGs were not available. One patient evolved from West syndrome to Lennox-Gastaut syndrome with tonic, myoclonic, and atonic seizures.<sup>6</sup>

In 24 patients with West syndrome for whom information on treatment was available, antiepileptic therapy comprised

vigabatrin in 16 of 24 (66%), oral steroids in 12 of 24 (50%), adrenocorticotrophic hormone in nine of 24 (37%), and ketogenic diet in eight of 24 (33%); in all patients with successfully treated spasms, these drugs were used. Individuals with either drug-resistant ES or other seizure types also received valproic acid (9/24, 37%), topiramate (9/24, 37%), levetiracetam (8/24, 33%), and other drugs.

### 3.3 | Electroencephalography

Hypsarrhythmia was seen in all (30/30, 100%) patients with ES where EEG data were available (not reported for seven cases).<sup>5,15-18</sup> Multifocal epileptiform activity occurred in 13 of 30 (43%) cases. After age 2 years, a distinctive EEG pattern comprising paroxysms of fast activity with electrodecrement lasting a few seconds without clinical correlate was observed in 10 patients (10/29, 34%; eight new and two published cases<sup>6,8</sup>; Figure 1). Activation of epileptiform activity in sleep occurred in four of 30 (13%), with loss of normal sleep architecture in one. Background slowing was noted in four of 30 (13%) individuals, most probably not reported in many other cases. Only one-half of the patients who became seizure-free had a normal EEG, and EEG recordings remained abnormal in all drug-resistant individuals.

### 3.4 | Development

All (34/34, 100%) children with available data had global developmental delay, which was not further specified in 11 cases. The remaining had profound (11/23, 48%), severe (5/23, 22%), moderate (5/23, 22%), or mild (2/23, 9%) delay.

Eighteen of 23 (78%) cases presented with developmental regression in the first year of life, which preceded ES onset in three (13%) patients, and coincided with onset of ES in all other 15 (65%) cases.

#### 3.4.1 | Motor development

For the 24 patients with documented developmental motor milestones, sitting was delayed until 9 months in one of 24 (4%) and 10-24 months in seven of 24 (29%) children. Walking was achieved by nine of 24 (38%) patients, mostly in the second or third year of life.

Seventeen of 19 (90%) patients had limited or no purposeful hand use. Thirteen of 19 (68%) had hand stereotypies, mostly involving hand-to-mouth or hand-to-face movements, and also hand-washing movements, flapping, and rocking. Only two of 19 (11%) patients had purposeful hand use on a background of moderate developmental delay.

Ten of 23 (43%) children had dyskinetic movement disorders. These included chorea, dystonia, and athetosis.

Movement abnormalities were not mentioned in 15 cases. One patient had eye movement stereotypies with recurrent eye rolling, and two patients had intermittent strabismus.

#### 3.4.2 | Language development

Language development was reported for 24 individuals and was delayed in all. Five of 24 (21%) spoke a few single words, and 19 of 24 (79%) were nonverbal.

#### 3.4.3 | Social development

Eye contact was delayed and remained limited in 27 of 28 (96%) patients. Four of 28 (14%) children had autism spectrum disorder.

#### 3.4.4 | Head growth

Four of 22 (18%) individuals had acquired microcephaly, 14 of 22 (64%) showed plateauing in head growth, and one of 22 (5%) was macrocephalic. Three of 22 (14%) had normocephaly.

### 3.5 | Dysmorphic features

Patients with *ALG13*-related DEE did not have a distinctive or recognizable dysmorphic facial gestalt. Dysmorphic features were present in eight of 38 (21%) individuals, including micrognathia (n = 4)<sup>5,12,13,19</sup> and hypertelorism (n = 2).<sup>5</sup> The one male patient with the recurrent variant p.(Asn107Ser) had micrognathia, mild torticollis, and hemivertebra L1-L2 as well as asymmetrical hearing loss.<sup>13</sup> Other sporadic dysmorphic features are described in Tables S1 and S2.

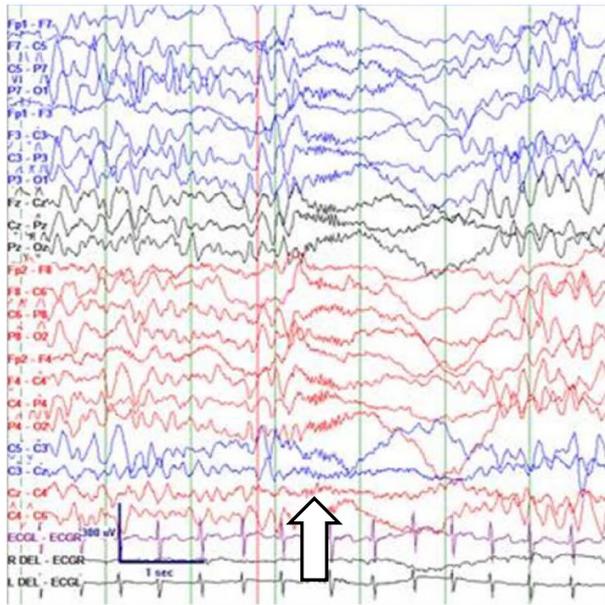
### 3.6 | Magnetic resonance imaging

Nonspecific anomalies were observed in eight of 28 (28%) patients. They included hypoplasia of the corpus callosum (n = 2; one novel),<sup>13</sup> delayed white matter myelination (n = 2; one novel),<sup>5</sup> reduced volume of white matter (n = 1, novel), and cortical atrophy.<sup>2,10,19</sup>

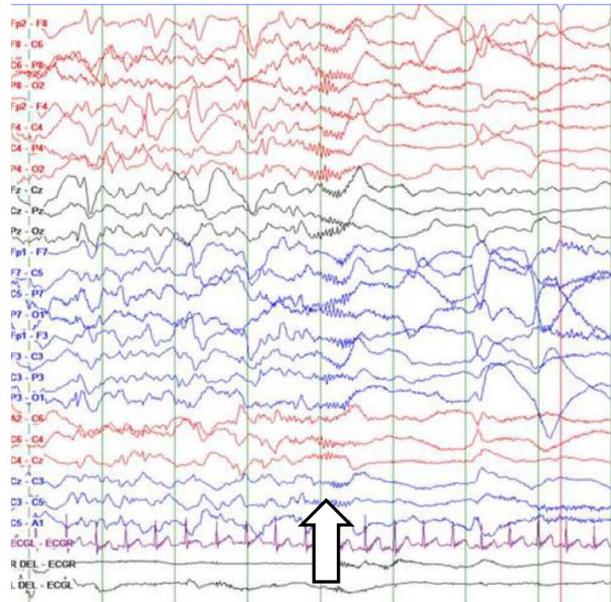
### 3.7 | Transferrin electrophoresis

Of the 38 patients, 12 had normal transferrin electrophoresis; 25 were either not tested or the test was not reported. One individual had mildly abnormal, inconclusive results.<sup>13</sup> No individual had clearly abnormal transferrin testing.

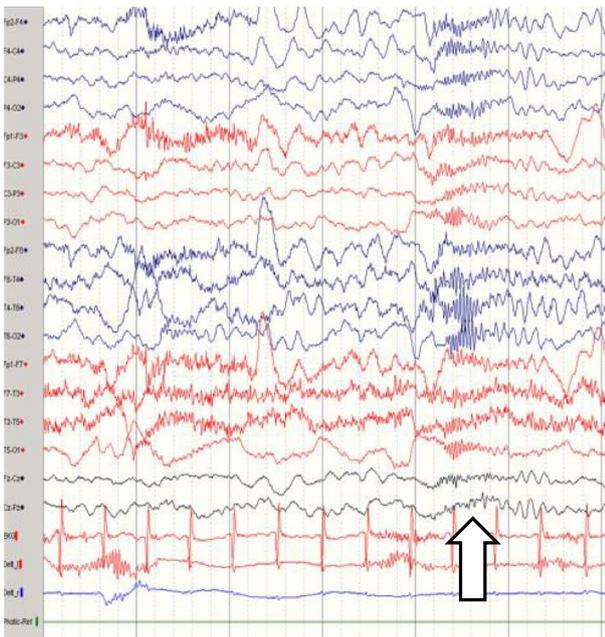
**A Patient 2, aged 5y**



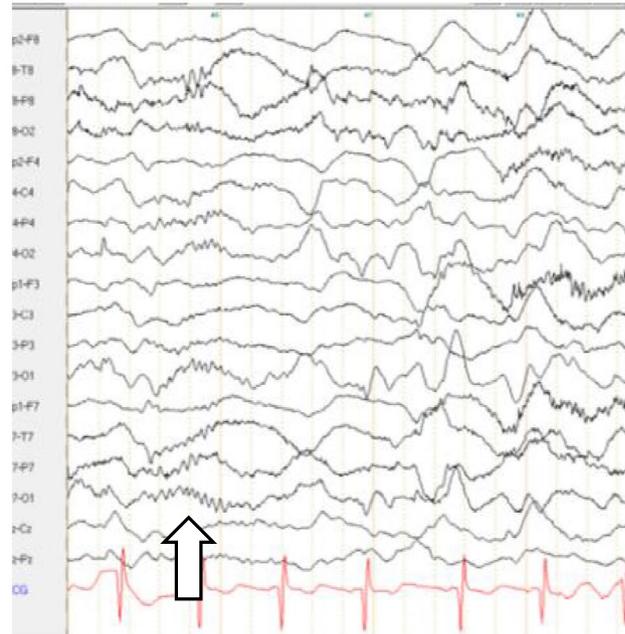
**B Patient 3, aged 3y**



**c Patient 14, aged 3 y**



**d Patient 15, aged 2y.**



**FIGURE 1** Electroencephalograms of Patients 2, 3, 14, and 15 with a distinct pattern of paroxysm of fast activity (arrows) with electrodecrement

### 3.8 | Additional likely pathogenic *ALG13* de novo missense variants

We identified three girls with different likely pathogenic *ALG13* de novo missense variants, all affecting residues in the C-terminal glycosyltransferase domain of *ALG13* (Table S3, supplement). None of these missense variants was described in the gnomAD database (<https://gnomad.broadinstitute.org/ge>

[ne/ENSG00000101901?dataset=gnomad\\_r2\\_1](https://gnomad.broadinstitute.org/ge)), and all were classified as likely pathogenic according to American College of Medical Genetics and Genomics criteria (PS2, PM2, PP3).<sup>32</sup> Patient 40 had p.(Gln40His), and Patient 41 was carrier of a 13% mosaic on blood-derived DNA for p.(Thr57Pro). Both cases had ES, beginning at 4 months in Patient 40, whereas Patient 41 had unclear episodes at 4 months followed by ES at 6 months. Both patients were pharmacoresistant; Patient 40

had severe developmental impairment, whereas Patient 41 had moderate delay with variable eye contact. Patient 40 had hand stereotypies and did not develop any language, whereas language was poor in Patient 41. All three had normal cerebral MRI and transferrin electrophoresis.

Patient 39, carried the *ALG13* de novo variant p.(Val8Ala) and showed a much milder clinical presentation; she had febrile seizures in the second year of life and afebrile seizures after 6 years of age. She was well controlled by antiepileptic drugs and had mild developmental delay.

## 4 | DISCUSSION

We describe a comprehensive genotype-phenotype correlation in individuals with pathogenic or likely pathogenic variants in *ALG13* and reveal that X-linked *ALG13*-related DEE affects mainly girls and is characterized by West syndrome, often with persisting ES that are frequently accompanied by other seizure types and, in more than one-half of the cases, remain drug-resistant. The EEG typically shows hypsarrhythmia and multifocal epileptiform activity that occasionally changes into a marked encephalopathic pattern of background slowing and in one-third of all cases paroxysms of fast activity with electrodecrement mostly without clinical correlate after the age of 3 years.

An additional hallmark of *ALG13*-related DEE is severe to profound developmental delay with developmental regression prior to or at ES onset, impaired eye contact and pursuit, and poor to absent verbal speech. Hand stereotypies, lack of purposeful hand use, and dyskinetic movement disorder including dystonia and choreoathetosis are frequent. Head growth often tends to stagnate.

Only three individuals with *ALG13*-related DEE had unique, likely pathogenic variants that differed from the predominant recurrent variant p.(Asn107Ser). Two females carried p.(Gln40His) or p.(Thr57Pro), respectively, and displayed a phenotype with DEE and epileptic spasms quite similar to carriers of p.(Asn107Ser). The milder degree of developmental delay of the girl with p.(Gln40His) can likely be attributed to the 13% mosaic status of this variant in blood. Moreover, a third female with a unique variant, p.(Val8Ala), also had a remarkably milder phenotype. Thus, it currently remains open whether the degree of developmental delay associated with variants in the C-terminal glycosyltransferase domain of *ALG13* may differ from the severity of *ALG13*-related DEE due to p.(Asn107Ser).

*ALG13*-related DEE shares phenotypic parallels with other X-linked DEEs mainly affecting girls, such as *CDKL5*-related disorders with ES and hypsarrhythmia, tonic seizures, pharmacoresistance, severe developmental delay, poor eye contact in the presence of cortical visual impairment, poor or absent speech, hand stereotypies, and deceleration of head

growth.<sup>34,35</sup> By contrast, Rett syndrome, one of the most common X-linked DEEs and mainly due to variants in *MECP2*, may be differentiated more easily from *ALG13*-related DEE; developmental regression is usually independent from epilepsy onset in Rett syndrome, whereas it is mostly present at the onset of ES in *ALG13*-related DEE. *MECP2*-related hand stereotypies are mostly washing-hand movements, whereas they comprise more hand mouthing and hand clapping in *ALG13*- as well as in *CDKL5*-related DEE. Purposeful hand use is acquired and then typically lost in *MECP2*-related DEE, whereas it is not or poorly developed in many cases of *ALG13*-related DEE. Breathing abnormalities including hyperventilation and apnea are typical for *MECP2*-related DEE and not seen in *ALG13*- and *CDKL5*-related DEE.<sup>30,34</sup>

The male patient reported by Timal and collaborators with the likely pathogenic de novo *ALG13* variant c.280A > G, p.(Lys94Glu) shared some features with CDG, including hepatomegaly, increased bleeding tendency, edemas, refractory epilepsy, microcephaly, nystagmus, bilateral optic nerve atrophy, and extrapyramidal signs.<sup>4</sup> The main link of the patient's phenotype to CDG was a 17% residual enzyme activity of UDP-GlcNAc:GlcNAc1-PP-dolichol GlcNAc-transferase in fibroblasts, an enzyme with a key role in the synthesis of the lipid linked oligosaccharide precursor for the N-glycan assembly.

None of the individuals in our cohort (published or novel cases) who underwent transferrin electrophoresis to verify the link to CDG<sup>4</sup> had abnormal transferrin electrophoresis. The only male individual with *ALG13*-related DEE due to p.(Asn107Ser)<sup>13</sup> had a normal transferrin electrophoresis and a lack of one glycan on mass spectroscopy. Comprehensive functional studies will be able to prove or disprove the association with CDG.

For the time being, X-linked *ALG13*-related DEE remains a disorder with a relatively homogenous phenotype exclusively related to de novo variants, first of all c.320A > G, p.(Asn107Ser). A number of male individuals have been reported with rare maternally inherited *ALG13* variants; however, all of them currently remain variants of uncertain significance and are not further considered in this study.<sup>24–26,28,29</sup>

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## CONFLICT OF INTEREST

A.N.D. has served on scientific advisory boards for UCB, Eisai, and Nutricia. He has consultancy activities for Roche, Idorsia, Neurocrine, and Epilog. He has received funding for travel from UCB, Sanofi, Eisai, and Nutricia. B.H. has received consulting fees and speaker honoraria from Actelion and Shire-Takeda, and travel expenses and congress fee reimbursements from

Shire-Takeda and Sanofi Genzyme, and is an investigator for industrial studies and trials for Abeona Therapeutics, Lysogene, Orphazyme A/S, Idorsia, and Mallinckrodt Pharmaceuticals. I.E.S. serves/has served on the editorial boards of the *Annals of Neurology*, *Neurology*, and *Epileptic Disorders*; may accrue future revenue on pending patent WO61/010176 (filed: 2008): Therapeutic Compound; has a patent for SCN1A testing held by Bionomics and licensed to various diagnostic companies; has a patent for molecular diagnostic/theranostic target for benign familial infantile epilepsy (PRRT2) 2011904493 & 2012900190 and PCT/AU2012/001321 (TECH ID: 2012-009) with royalties paid; has served on scientific advisory boards for UCB, Eisai, GlaxoSmithKline, BioMarin, Nutricia, Rogcon, and Xenon Pharmaceuticals; has received speaker honoraria from GlaxoSmithKline, UCB, BioMarin, Biocodex, and Eisai; has received funding for travel from UCB, Biocodex, GlaxoSmithKline, Biomarin, and Eisai; and has consulted for Zynerva Pharmaceuticals, Atheneum Partners, Ovid Therapeutics, and UCB. R.M.P. has served on scientific advisory boards for UCB and Eisai. She does consultancy activities for UCB. Her research is supported by the National Institute of Health Research (NIHR) Biomedical Research Centre at Great Ormond Street Hospital, NIHR, and GOSH Charity. J.H.C. has acted as an investigator for studies with GW Pharma, Zogenix, Vitaflo, and Marinius. She has been a speaker and on advisory boards for GW Pharma, Zogenix, and Nutricia; all remuneration has been paid to her department. Her research is supported by the NIHR Biomedical Research Centre at Great Ormond Street Hospital, NIHR, EPSRC, GOSH Charity, ERUK, and the Waterloo Foundation. None of the other authors has any conflict of interest to disclose.

## ETHICAL PUBLICATION STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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## REFERENCES

- Berg AT, Berkovic SF, Brodie MJ, Buchhalter J, Cross JH, van Emde BW, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005–2009. *Epilepsia*. 2010;51(4):676–85.
- Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L, et al. ILAE classification of the epilepsies: position paper of the ILAE Commission for Classification and Terminology. *Epilepsia*. 2017;58(4):512–21.
- Peanne R, de Lonlay P, Foulquier F, Kornak U, Lefeber DJ, Morava E, et al. Congenital disorders of glycosylation (CDG): quo vadis? *Eur J Med Genet*. 2018;61(11):643–63.
- Timal S, Hoischen A, Lehle L, Adamowicz M, Huijben K, Sykut-Cegielska J, et al. Gene identification in the congenital disorders of glycosylation type I by whole-exome sequencing. *Hum Mol Genet*. 2012;21(19):4151–61.
- De Ligt J, Willemsen MH, Van Bon BW, Kleefstra T, Yntema HG, Kroes T, et al. Diagnostic exome sequencing in persons with severe intellectual disability. *N Engl J Med*. 2012;367(20):1921–9.
- Epi4K Consortium; Epilepsy Phenome/Genome Project; Allen AS, Berkovic SF, Cossette P, Delanty N, et al. De novo mutations in epileptic encephalopathies. *Nature*. 2013;501(7466):217–21.
- Michaud JL, Lachance M, Hamdan FF, Carmant L, Lortie A, Diadori P, et al. The genetic landscape of infantile spasms. *Hum Mol Genet*. 2014;23(18):4846–58.
- Smith-Packard B, Myers SM, Williams MS. Girls with seizures due to the c.320A>G variant in ALG13 do not show abnormal glycosylation pattern on standard testing. *JIMD Rep*. 2015;22:95–8.
- Dimassi S, Labalme A, Ville D, Calender A, Mignot C, Boutry-Kryza N, et al. Whole-exome sequencing improves the diagnosis yield in sporadic infantile spasm syndrome. *Clin Genet*. 2016;89(2):198–204.
- Kobayashi Y, Tohyama J, Kato M, Akasaka N, Magara S, Kawashima H, et al. High prevalence of genetic alterations in early-onset epileptic encephalopathies associated with infantile movement disorders. *Brain Dev*. 2016;38(3):285–92.
- Myers CT, McMahon JM, Schneider AL, Petrovski S, Allen AS, Carvill GL, et al. De novo mutations in SLC1A2 and CACNA1A are important causes of epileptic encephalopathies. *Am J Hum Genet*. 2016;99(2):287–98.
- Hamici S, Bastaki F, Khalifa M. Exome sequence identified a c.320A > G ALG13 variant in a female with infantile epileptic encephalopathy with normal glycosylation and random X inactivation: review of the literature. *Eur J Med Genet*. 2017;60(10):541–7.
- Galama WH, Verhaagen-van den Akker SLJ, Lefeber DJ, Feenstra I, Verrips A. ALG13-CDG with infantile spasms in a male patient due to a de novo ALG13 gene mutation. *JIMD Rep*. 2018;40:11–6.
- Geisheker MR, Heymann G, Wang T, Coe BP, Turner TN, Stessman HAF, et al. Hotspots of missense mutation identify neurodevelopmental disorder genes and functional domains. *Nat Neurosci*. 2017;20(8):1043–51.
- Ortega-Moreno L, Giraldez BG, Soto-Insuga V, Losada-Del Pozo R, Rodrigo-Moreno M, Alarcón-Morcillo C, et al. Molecular diagnosis of patients with epilepsy and developmental delay using a customized panel of epilepsy genes. *PLoS One*. 2017;12(11):e0188978.
- Zhu X, Padmanabhan R, Copeland B, Bridgers J, Ren Z, Kamalakaran S, et al. A case-control collapsing analysis identifies epilepsy genes implicated in trio sequencing studies focused on de novo mutations. *PLoS Genet*. 2017;13(11):e1007104.

17. Deciphering Developmental Disorders Study. Prevalence and architecture of de novo mutations in developmental disorders. *Nature*. 2017;542(7642):433–8.
18. Fung CW, Kwong AK, Wong VC. Gene panel analysis for nonsyndromic cryptogenic neonatal/infantile epileptic encephalopathy. *Epilepsia Open*. 2017;2(2):236–43.
19. Bastaki F, Bizzari S, Hamici S, Nair P, Mohamed M, Saif F, et al. Single-center experience of N-linked congenital disorders of glycosylation with a summary of molecularly characterized cases in Arabs. *Ann Hum Genet*. 2018;82(1):35–47.
20. Palmer EE, Schofield D, Shrestha R, Kandula T, Macintosh R, Lawson JA, et al. Integrating exome sequencing into a diagnostic pathway for epileptic encephalopathy: evidence of clinical utility and cost effectiveness. *Mol Genet Genomic Med*. 2018;6(2):186–99.
21. Yuskaitis CJ, Ruzhnikov MRZ, Howell KB, Allen IE, Kapur K, Dlugos DJ, et al. Infantile spasms of unknown cause: predictors of outcome and genotype-phenotype correlation. *Pediatr Neurol*. 2018;87:48–56.
22. Madaan P, Negi S, Sharma R, Kaur A, Sahu JK. X-Linked ALG13 gene variant as a cause of epileptic encephalopathy in girls. *Indian J Pediatr*. 2019;86(11):1072–3.
23. Gilissen C, Hehir-Kwa JY, Thung DT, van de Vorst M, van Bon BWM, Willemsen MH, et al. Genome sequencing identifies major causes of severe intellectual disability. *Nature*. 2014;511(7509):344.
24. Bissar-Tadmouri N, Donahue WL, Al-Gazali L, Nelson SF, Bayrak-Toydemir P, Kantarci S. X chromosome exome sequencing reveals a novel ALG13 mutation in a nonsyndromic intellectual disability family with multiple affected male siblings. *Am J Med Genet A*. 2014;164A(1):164–9.
25. Farwell KD, Shahmirzadi L, El-Khechen D, Powis Z, Chao EC, Tippin Davis B, et al. Enhanced utility of family-centered diagnostic exome sequencing with inheritance model-based analysis: results from 500 unselected families with undiagnosed genetic conditions. *Genet Med*. 2015;17(7):578–86.
26. Moller RS, Larsen LH, Johannesen KM, Talvik I, Talvik T, Vaher U, et al. Gene panel testing in epileptic encephalopathies and familial epilepsies. *Mol Syndromol*. 2016;7(4):210–9.
27. Wei CM, Xia GZ, Ren RN. Gene mutations in unexplained infantile epileptic encephalopathy: an analysis of 47 cases. *Zhongguo Dang Dai Er Ke Za Zhi*. 2018;20(2):125–9.
28. Hino-Fukuyo N, Kikuchi A, Arai-Ichinoi N, Niihori T, Sato R, Suzuki T, et al. Genomic analysis identifies candidate pathogenic variants in 9 of 18 patients with unexplained West syndrome. *Hum Genet*. 2015;134(6):649–58.
29. Gadomski TE, Bolton M, Alfadhel M, Dvorak C, Ogunsakin OA, Nelson SL, et al. ALG13-CDG in a male with seizures, normal cognitive development, and normal transferrin isoelectric focusing. *Am J Med Genet A*. 2017;173(10):2772–5.
30. Kadam SD, Sullivan BJ, Goyal A, Blue ME, Smith-Hicks C. Rett syndrome and CDKL5 deficiency disorder: from bench to clinic. *Int J Mol Sci*. 2019;20(20):5098.
31. Gao P, Wang F, Huo J, Wan D, Zhang J, Niu J, et al. ALG13 deficiency associated with increased seizure susceptibility and severity. *Neuroscience*. 2019;409:204–21.
32. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med*. 2015;17(5):405–24.
33. Lux AL, Osborne JP. A proposal for case definitions and outcome measures in studies of infantile spasms and West syndrome: consensus statement of the West Delphi group. *Epilepsia*. 2004;45(11):1416–28.
34. Bahi-Buisson N, Bienvenu T. CDKL5-related disorders: from clinical description to molecular genetics. *Mol Syndromol*. 2012;2(3–5):137–52.
35. Demarest ST, Olson HE, Moss A, Pestana-Knight E, Zhang X, Parikh S, et al. CDKL5 deficiency disorder: relationship between genotype, epilepsy, cortical visual impairment, and development. *Epilepsia*. 2019;60(8):1733–42.

## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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