

ORIGINAL ARTICLE

De novo *DYNC1H1* mutation causes infantile developmental and epileptic encephalopathy with brain malformations

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Abstract

Background: The human dynein cytoplasmic 1 heavy chain 1 (*DYNC1H1*) gene encodes a large subunit of the cytoplasmic dynein complex. *DYNC1H1* mutations are associated with various neurological diseases involving both the peripheral and central nervous systems.

Methods: The clinical characteristics and genetic data of an infant carrying the de novo *DYNC1H1* variant identified by trio exome sequencing were analyzed. Patients with epilepsy with *DYNC1H1* mutations were summarized by reviewing the literature.

Results: We first identified an infant presenting with epileptic spasms harboring a de novo missense mutation in *DYNC1H1* (c.874C>T; p. Arg292Trp), once reported in an adult case, and further summarized another 54 patients with seizures or epilepsy caused by *DYNC1H1* pathogenic variants in the literature. Refractory epilepsy, intellectual disability, and cortical developmental malformations are crucial characteristics of patients with developmental and epileptic encephalopathy (DEE) caused by *DYNC1H1* variants. Notably, epileptic spasms in this case were resistant to multiple anti-seizure medications, corticosteroids, ketogenic diet, and vagus nerve stimulation treatment. The child also showed cortical gyrus malformation and global developmental delay.

Conclusion: *DYNC1H1* variants can cause infantile developmental and epileptic encephalopathy, in which Arg292Trp is a mutation hotspot of the *DYNC1H1* gene. Epileptic seizures in this type of *DYNC1H1*-related DEE are mostly resistant to multiple antiepileptic strategies and need to explore optimized treatments.

KEYWORDS

developmental and epileptic encephalopathy, dynein cytoplasmic 1 heavy chain 1, epileptic spasms, ketogenic diet, vagus nerve stimulation

1 | INTRODUCTION

Dynein cytoplasmic 1 heavy chain 1 (*DYNC1H1*, MIM #600112) encodes the heavy chain protein of the cytoplasmic

dynein 1 motor protein complex that transports organelles, vesicles, and macromolecules to the minus ends of microtubules. Mutations in *DYNC1H1* are associated with various clinical manifestations, including spinal muscular atrophy,

Tangfeng Su and Yu Yan contributed equally to this work.

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lower extremity-predominant 1 (SMALED1; MIM #158600) (Harms et al., 2010), Charcot-Marie-Tooth (CMT) disease, axonal type 20 (CMT20; MIM #614228) (Strickland et al., 2015; Weedon et al., 2011), mental retardation, autosomal dominant 13 (MRD13; MIM #614563) (Willemsen et al., 2012), and other phenotypes reported in the literature, including hereditary spastic paraplegia (Strickland et al., 2015), malformations of cortical development (MCD) (Poirier et al., 2013), and epileptic encephalopathies (EE) (Lin et al., 2017).

To the best of our knowledge, up to October 2021, at least 24 articles had reported 54 cases with seizures or epilepsy due to *DYNC1H1* variants, including seven infants with epileptic spasms (Table 1) (Amabile et al., 2020; Becker et al., 2020; Benson et al., 2020; Das et al., 2018; Di Donato et al., 2018; Gelineau-Morel et al., 2016; Gou et al., 2019; Helbig et al., 2016; Hertecant et al., 2016; Hu et al., 2018; Jamuar et al., 2014; Li et al., 2019; Lin et al., 2017; Matsumoto et al., 2021; Otten et al., 2017; Palmer et al., 2018; Poirier et al., 2013; Punetha et al., 2015; Rohtus et al., 2020; Scoto et al., 2013; Singh et al., 2015; Strickland et al., 2015; Tumiené et al., 2018; Willemsen et al., 2012). Most of these patients have brain developmental malformations and severe intellectual disability (ID). Developmental and epileptic encephalopathies (DEEs) are genetically heterogeneous conditions often characterized by early onset drug-refractory epilepsy, frequent epileptiform activity, and neurodevelopmental impairments (Scheffer et al., 2016). Here, we report the first case of a de novo p. Arg292Trp change caused by the *DYNC1H1* gene that exhibited epileptic spasms, intellectual disability, and brain malformation in a Chinese family, further summarizing the clinical characteristics of this kind of DEE related to *DYNC1H1* variants and its treatment and prognosis. Our observation of epileptic spasms in this patient further broadens the clinical spectrum of the known mutation p. Arg292Trp. However, this case was unable to become seizure-free through multiple treatment methods, including anti-seizure medications (ASMs), corticosteroids, ketogenic diet (KD), and vagus nerve stimulation (VNS).

2 | MATERIALS AND METHODS

2.1 | Ethical compliance

This study was approved by the Medical Ethics Committee of the Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, China. Written informed consent was obtained from the patient for publication of this case report and the accompanying images.

2.2 | Whole exome and Sanger sequencing

Whole exome sequencing (WES) was performed by the WuXi NextCODE Genomics, Shanghai, China (CLIA Lab ID: 99D2064856) using a previously described protocol (Su et al., 2020).

2.3 | Literature review

Literature search was performed to identify relevant articles using the terms “*DYNC1H1* AND epilepsy”, or “*DYNC1H1* AND seizure” up to October 19, 2021, in the following databases: PubMed, Google Scholar, China National Knowledge Infrastructure, and WANFANG DATA.

3 | RESULTS

3.1 | Case presentation

The female infant, born at 39 weeks, was the first child of a non-consanguineous Chinese couple. Pregnancy and delivery were uncomplicated. Her birth weight was 2850 g, and her head circumference (HC) was within the normal range. The family history of the infant was negative for epilepsy and other neurological and muscle disorders. Parents had few complaints about the development of this infant during the first 4 months of her life. At the age of 5 months, she presented with epileptic spasms. At that time, the patient was found to have poor head control. Her electroencephalogram (EEG) showed hypsarrhythmia (Figure 1a), confirming the diagnosis of West syndrome. Metabolic screening, including electrolytes and glucose, serum and urine organic acids, and blood amino acid levels were all normal. Brain magnetic resonance imaging (MRI) revealed that the bilateral parieto-occipital gyri decreased, the flattened cortex and related cortex thickened (oligogyri), and the frontotemporal extracerebral space widened (Figure 2). In addition to oral topiramate (TPM; 12.5 mg a.m. & 25 mg p.m.; weight, 7 kg), she was initially given high-dose oral prednisone (10 mg qid for the first week and the same dose for the second week after epileptic seizures stopped, then tapering off every week, that is, 10 mg tid, 10 mg bid, 10 mg qd, and 5 mg qd, for a total of 6 weeks), which was followed by seizure-free for 3 months. At the age of 10 months, wakefulness EEG displayed small occipital sharp waves, while background hypsarrhythmia faded (Figure 1b).

TABLE 1 Comparison of clinical phenotypes in *DYNC1H1* mutation patients with seizure or epilepsy

Author year (N)	No.	Case, gender	Age	cDNA	Protein	Inherit-ance	ID/DD	Cerebral MRI/CT	Seizure onset	Seizure types
Willemsen (2012) (1)	1	Patient 2/F	51y	c.452G>A	p.Glu1518Lys	De novo	Severe ID	MCD	3y	GS
Poirier (2013) (11)	2	P144 NA	15y	c.del1976-1987	p.del659-662	De novo	Bedridden	Pachygyria (P>A)	Early onset	NA
	3	P582 NA	10y	c.386A>T	p.Lys129Ile	De novo	Severe ID	Pachygyria (P>A)	Late onset	NA
	4	P122 NA	12y	c.10008G>T	p.Lys3336Asn	De novo	Bedridden	Pachygyria (P>A)	Early onset	NA
	5	P217 NA	10y	c.10151G>A	p.Arg3384Gln	De novo	Bedridden	Pachygyria (P>A)	Early onset	NA
	6	P398 NA	7y	c.4700G>A	p.Arg1567Gln	De novo	Severe ID	PMG (A>P)	NA	Absent
	7	P535 NA	5y	c.10031G>A	p.Arg3344Gln	De novo	Severe ID, autistic	Agyria (P>A)	NA	LGS
	8	360J NA	19y	c.5884C>T	p.Arg1962Cys	De novo	Severe ID	Pachygyria (P>A)	2 m	Focal
	9	346D1/M	11y	c.9722A>C	p.Lys3241Thr	Familial	Normal	Pachygyria (P>A)	2y5 m	Focal
	10	346D2/M	8y	c.9722A>C	p.Lys3241Thr	Familial	Mild ID	Pachygyria (P>A)	1y2 m	Focal
	11	346Dmother	39y	c.9722A>C	p.Lys3241Thr	Familial	Normal	Pachygyria (P>A)	10y	Focal
	12	574C NA	3y	c.10031G>A	p.Arg3344Gln	De novo	Moderate ID	Pachygyria (P>A)	5 m	Focal
Jamaur (2014) (1)	13	BFP-601/M	NA	NA	p.Glu561Gly	De novo	Mental and motor retardation	Pachygyria (P>A)	5y	NA
Strickland (2015) (1)	14	IHG26107/F	36y	c.3185 A>G	p.Asp1062Gly	De novo	Cognitive deficits	PMG (perisylvian)	17y	Focal, sGS
Punetha (2015) (1)	15	F	3.6y	c.1792C>T	p.Arg598Cys	De novo	Normal	Normal	NA	Febrile seizures
Singh (2015) (1)	16	F	NA	c.4259T>G	p.Leu1420Arg	De novo	EE	PMG (perisylvian)	7 m	Myoclonic, atonic
Scoto (2015) (2)	17	UK8-INA	2.5y	NA	p.Arg1603Thr	De novo	Delay	NA	NA	NA
	18	US1-IIINA	9y	NA	p.Ile584Leu	NA	Mild ID	NA	Neonatal	NA
Gelineau-Morel (2016) (1)	19	F	10y	c.6994C>T;	p.Arg2332Cys	De novo	Severe ID	PMG (A>P)	2y	NA
Hertecant (2016) (1)	20	M	16m	c.10973G>A	p.Gly3658Glu	De novo	Severe ID	Pachygyria/agyria	3 m	flexor spasms
Helbig (2016) (1)	21	ID32/ NA	NA	c.3278T>C	p.Phe1093Ser	De novo	EE	NA	Infantile	Spasms
Lin (2017) (1)	22	E3P/M	NA	c.10174A>G	p.Met3392Val	De novo	Autism, ID	NA	NA	Spasms
Otten (2017) (2)	23	Twins/F	NA	c.11015C>T	p.Ser3672Leu	De novo	Severe ID	PMG	4y	NA
	24	Twins/F	NA	c.11015C>T	p.Ser3672Leu	De novo	Severe ID	Multiple cortical dysplasia	6 m	NA

(Continues)

TABLE 1 (Continued)

Author year (N)	No.	Case, gender	Age	cDNA	Protein	Inherit-ance	ID/DD	Cerebral MRI/CT	Seizure onset	Seizure types
Di Donato (2018)	25	LR15-028/F	4y	c.915A>T	p.Lys305Asn	De novo	Mild	Pachygyria (P>A)	1y	NA
	26	LR15-025/M	2y 3m	c.926G>A	p.Arg309His	De novo	Severe ID	Pachygyria (P>A)	5m	NA
	27	LP98-088/F	1y 4m	c.926G>A	p.Arg309His	NA	Severe	Pachygyria/agyria (P>A)	3m	NA
	28	LR13-015/M	1y 11m	c.926G>A	p.Arg309His	De novo	Severe DD	Pachygyria (P>A)	3m	NA
	29	LP97-114/M	1y 8m	c.2003T>A	p.Val668Asp	De novo	Severe	Pachygyria (P>A)	1y7m	NA
	30	LR01-087/F	9m	c.4868G>A	p.Arg1623Gln	De novo	Mild DD	Pachygyria (A>P)	4m	NA
	31	LR15-140/F	4y	c.7813_7815del	p.Leu2605del	De novo	Severe	Pachygyria (A>P)	9m	NA
	32	LR07-192/M	2y 6m	c.9954G>T	p.Lys3318Asn	NA	Severe	Pachygyria (P>A)	6w	NA
	33	LR00-012/M	2y 6m	c.10030C>T	p.Arg3344Trp	NA	DD	Dysgyria (P>A) perisylvian	3m	NA
	34	LR12-456/M	2y	c.10031G>A	p.Arg3344Gln	De novo	Severe	Pachygyria (P>A)	7m	NA
	35	LP99-041/F	3y 8m	c.10888G>A	p.Gly3630Ser	NA	Severe DD	Pachygyria (P>A)	1y?	NA
	36	LR15-095/M	1y 4m	c.11311G>A	p.Glu3771Lys	De novo	Mild-moderate DD	Pachygyria (P>A)	8m	NA
	37	LR03-176/M	6y 6m	c.11941+2T>A	NA	NA	Moderate	Dysgyria (P>A)	3y	myoclonic
Das (2018) (1)	38	II 1/M	60y	c.1809A>T	p.Glu603Asp	Familial	Learning difficulties	NA	NA	NA
Tumiené (2018) (1)	39	No.3/ NA	NA	c.6994C>T	p.Arg2332Cys	De novo	Autism, ID	NA	NA	Focal
Palmer (2018) (1)	40	Fam10/M	4y	c.5884C>T	p.Arg1962Cys	De novo	Severe DD	Focal pachygyria.	3m/6m	Focal/spasms
Hu (2018) (1)	41	NA	NA	c.1682A>G	p.Glu561Gly	De novo	EOEE	Pachygyria (A-P)	N/A	Focal, spasms
Gou (2019) (2)	42	Twins/F	10m	c.10213A>C	p.Met3405Leu	De novo	Severe ID	Brain dysplasia	7m	Spasms
	43	Twins/F	10m	c.10213A>C	p.Met3405Leu	De novo	Severe ID	Brain dysplasia	7m	Spasms
Li (2019) (1)	44	M	3y	c.4075-2A>T	NA	De novo	MRD13	Normal (1y3m), FCD (6y)	1y5m	LGS
Rochtus (2020) (1)	45	F	17y	c.11095G>A	p.Val3699Ile	Familial	Severe DD	Atrophy	1 day	Ohtahara syndrome
Benson (2020) (1)	46	F	Adult	c.874C>T	p.Arg292Trp	De novo	ID	FCD	13-18m	GAS, GTCS
Amabile (2020) (2)	47	Patient 1/F	4y	NA	p.Val1116Ala	De novo	DD	PMG (A>P)	NA	NA
	48	Patient 4/M	4y 5m	NA	p.Gly3658Glu	De novo	ID, DD	Enlarged ventricle	NA	Focal
Becker (2020) (4)	49	P2/	NA	c.10432C>T	p.Leu3478Phe	De novo	Severe ID	Enlarged ventricle	11-48m	Focal

TABLE 1 (Continued)

Author year (N)	No.	Case, gender	Age	cDNA	Protein	Inheritance	ID/DD	Cerebral MRI/CT	Seizure onset	Seizure types
	50	P4/	NA	c.6880G>A	p.Glu2294Lys	De novo	Severe ID	Pachygyria (A>P)	11–48 m	Focal
	51	P8/	NA	c.9518C>G	p.Pro3173Arg	De novo	DD, ID	Pachygyria (A>P)	11–48 m	Focal
	52	P10/	NA	c.1998A>T	p.Glu666Asp	De novo	DD, Severe ID	Pachygyria (A>P)	11–48 m	Focal
Matsumoto (2021) (2)	53	P1/F	6y	c.4691A>T	p.Glu1564Val	De novo	Severe ID	Pachygyria (P>A)	2 m	Myoclonic, focal, GTS
	54	P2/M	13y	c.12536T>C	p.Leu4179Ser	De novo	Severe ID, ASD	Normal	7y	GTCs, Myoclonic
This case (1)	55	F	3y 2m	c.874C>T	p.Arg292Trp	De novo	Moderate ID	Oligogyri (P>A)	5 m	Spasms

Abbreviations: A, anterior; CC, corpus callosum; DD, developmental delay; EE, epileptic encephalopathy; EOE, early onset epileptic encephalopathy; FCD, frontal cortical dysplasia; GAS, generalized tonic seizures; GS, generalized seizures; GTCS, generalized tonic-clonic seizures; ID, intellectual disability; IS, infant spasms; LGS, Lennox-Gastaut syndrome; m, months; MRD13, Mental retardation, autosomal dominant 13; NA, not available; No., patient number; P, posterior; PMG, polymicrogyria; sGS, secondary generalized seizures; y, year.

However, 3 months after withdrawal of corticosteroids, epileptic spasms in clusters occurred again in this infant. Oral levetiracetam (LEV; 0.125 g bid; weight, 8 kg) was administered as an adjunct to TPM; however, she still had two or three clusters of epileptic spasms per day. At 11 months of age, oral drugs were continued, and the infant began to receive KD treatment (Jiantong, Kinton Medical Food Ltd., Guangzhou, China). After a 3:1 ketogenic ratio of fat to protein plus carbohydrate (in grams), the patient experienced a 50% reduction in seizure frequency, while blood ketone levels were 2.5–3 mmol/L, and blood glucose levels were normal. However, after 529 days of treatment, KD was discontinued when the child was 2 years and 9 months old due to <50% reduction in spasm frequency in subsequent long-term follow-up.

At the age of 2 years, seizures decreased significantly in the first week after VNS treatment (PINS Medica, Beijing, China; 30 Hz and 0.5–2.0 mA, 30 s on and 5 min off), but 1 week later, the frequency of seizures returned to the level before VNS treatment. At the last follow-up, the child had been treated with VNS for nearly 13 months; however, the seizures had not diminished. At the age of 3 years and 2 months, her physical measurements were as follows: height, 89 cm (10th–25th centile), weight, 11 kg (10th–25th centile), and HC, 43 cm (<3rd centile). She was unable to walk independently for up to 5 m, had an unstable gait and easily fell, had hypotonia of her lower extremities, and had severe delays in language skills.

3.2 | Molecular analysis

When the infant was 14 months old, WES identified a heterozygous variant (NM_001376.4:c.874C>T; p.Arg292Trp) in *DYNC1H1* located on chromosome 14q32.31. We submitted this variant to ClinVar (accession SCV001244188). The mutation was absent in the parental DNA and thus arose de novo (Figure 3). In silico analyses using PolyPhen-2 and Mutation Taster also predicted that the p.Arg292Trp mutation is functionally “probably damaging” (a HumanVar score of 0.986) and “disease causing”, respectively, which was also consistent with the data from the PROVEAN server (http://provean.jcvi.org/protein_batch_submit.php?species=human, PROVEAN score: −4.64, Prediction [cutoff = −2.5]: Deleterious; SIFT score: 0.01, Damaging). In accordance with the American College of Medical Genetics and Genomics (ACMG) guidelines, sequence variants were classified as likely pathogenic.

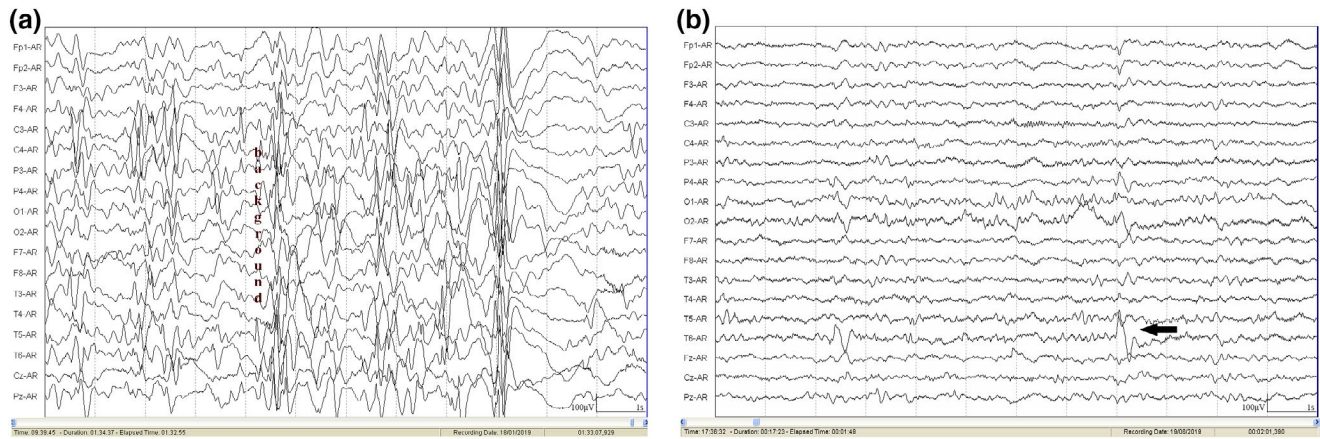


FIGURE 1 Wakefulness EEG at 5 (a) and 10 months (b). (a) Interictal EEG showed a background of hypsarrhythmia with asymmetrical or asynchronous high-amplitude, multifocal spike and wave discharges. (b) Interictal EEG showed a normal EEG background with a small amount of sharp and slow waves in right posterior head region, as shown by the arrow

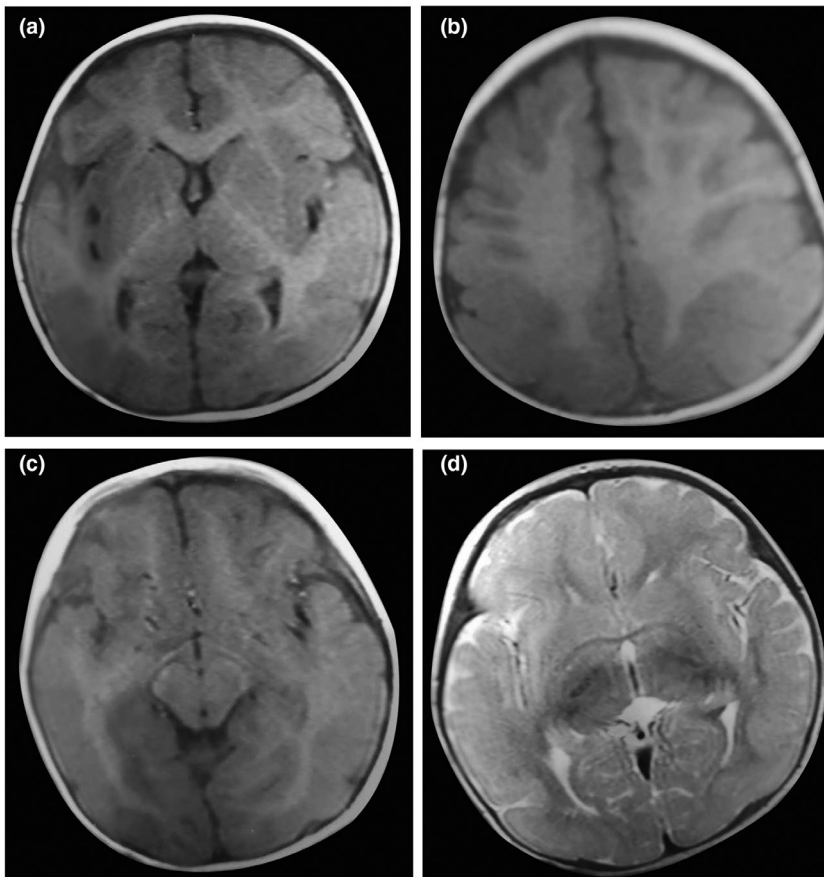


FIGURE 2 Brain MRI at 5 months. (a, b) Dilated bilateral frontotemporal extracerebral space. (c, d) Bilateral parieto-occipital gyri are diminished and flattened, and the related cortex is thickened (oligogyri)

4 | DISCUSSION

Dynein can be divided into two types: axonemal and cytoplasmic. Cytoplasmic dynein is an important motor protein complex in the nervous system and is responsible for the retrograde transport of important substances in axons from the end to the cell body. Cytoplasmic

DYNC1H1 is a key subunit of the cytoplasmic dynamic protein complex, and its normal expression is closely related to the development of the nervous system (Eschbach & Dupuis, 2011).

DYNC1H1 mutations have been reported in a series of neurological diseases, including peripheral and central nervous system disorders. Vissers et al. first reported in

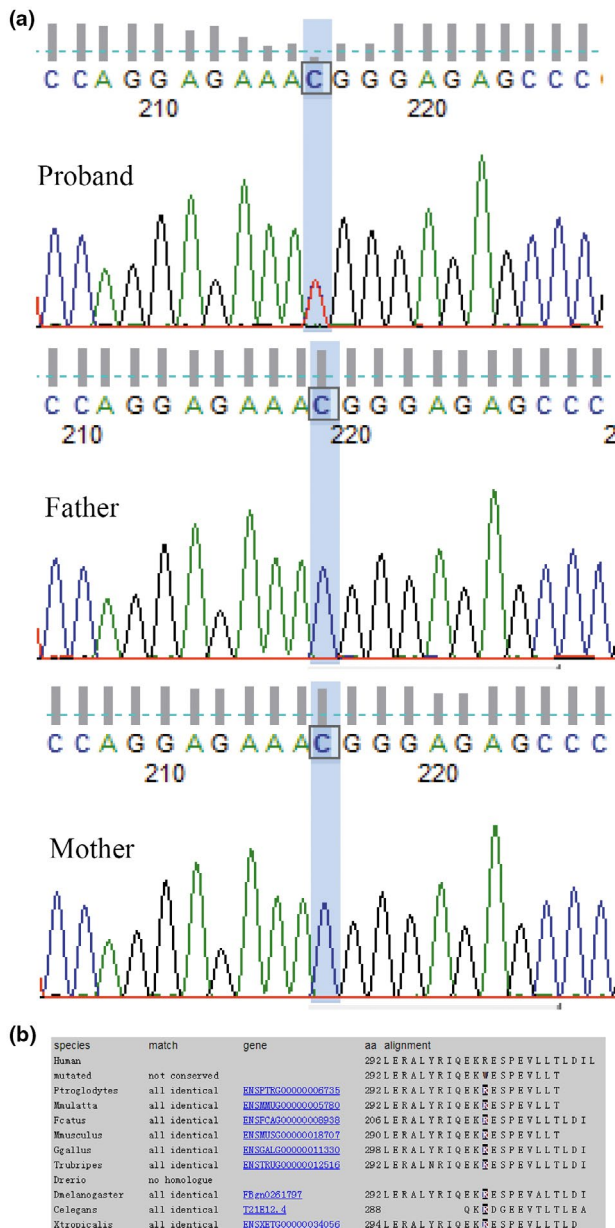


FIGURE 3 Sanger sequencing of *DYNC1H1* variants in the infant and her healthy parents. (a) The shadow in the electrophoretic pattern shows the site of the mutation. Exome sequencing identified a de novo heterozygous mutation in the *DYNC1H1* gene (NM_001376.4: c.874C>T) in exon 5. (b) The amino acid sequence alignment of the *DYNC1H1* protein from different species shows that the Arg292 residue is highly conserved during evolution

2010 that *DYHC1H1* mutation was associated with mental retardation in a 2-year-old boy. He had mild facial deformities, while his brain MRI was normal (Vissers et al., 2010). In 2013, Poirier et al. reported that 11 patients with a *DYHC1H1* mutation had posterior pachygyria and seizures, about half of them had early onset epilepsy, and one proband had Lennox–Gastaut syndrome (LGS) (Poirier et al., 2013). DEE is a group of heterogeneous

neurodevelopmental disorders characterized by early onset intractable seizures, abundant EEG epileptiform activity, intellectual disability, or regression. West syndrome and LGS are representative of DEE in both infants and children. To the best of our knowledge, including this reported case, eight infants with *DYNC1H1* variants had epileptic spasms (including a pair of twins) (Table 1), and the age of seizure onset was 3–7 months. All of these children had intellectual disability and brain dysplasia, mainly manifesting as gyrus malformations (Table 1). It should be mentioned that a total of three children described autism or autism-like features in the literature (P7, P39, P54).

DYNC1H1 encodes a large protein (>530 kDa and 4646 amino acid residues), which consists of three main domains. The C-terminal motor domain region (residues 1846–4646, ~380 kDa) contains six ATPases associated with diverse cellular activities (AAA) and a microtubule-binding stalk located between AAA4 and AAA5 (Pfister et al., 2006). The N-terminal region (~160 kDa) is known as the stem domain (tail domain) and contains binding positions for light intermediate and light chains (Figure 4). Previous studies have shown that *DYNC1H1* variants have obvious phenotypic heterogeneity and that mutations in different domains or at different locations in the same domain also show different clinical phenotypes. Mutations in the tail domain of *DYNC1H1* cause mutations in SMALED1 (Harms et al., 2012) and CMT20 (Weedon et al., 2011). Damage caused by motor domain mutations is mainly caused by MCD and intellectual impairments, such as MRD13 (Poirier et al., 2013; Vissers et al., 2010). Mutations in both tail and motor domains have also been reported to cause SMALED (Fiorillo et al., 2014) and MRD13 (Jamuar et al., 2014).

In this case, the c.874C>T mutation is located in the tail domain of *DYNC1H1*, near the N-terminus, which is a de novo missense mutation. The phenotypes of this case mostly consisted of brain malformations, global developmental delays, and seizures. Compared with an adult case reported by Benson et al., both patients had intellectual disability, abnormal MRIs, and early onset epilepsy, while there were no epileptic spasms or hypsarrhythmia EEG background in Benson's case (Benson et al., 2020). As shown in Figure 4, the *DYNC1H1* mutation sites in patients with seizures were found in both the motor and tail domains, mainly clustering in and around the stalk region of the motor domain, junction area of the motor and tail domain, and N-terminal region of the tail domain. In addition, this patient had decreased muscle strength of her lower limbs, and she was unable to achieve independent walking at the age of 2 years, which was, to a certain extent, similar to the phenotypes of spinal muscular atrophy, lower extremity-predominant 1 caused by a *DYNC1H1* mutation.

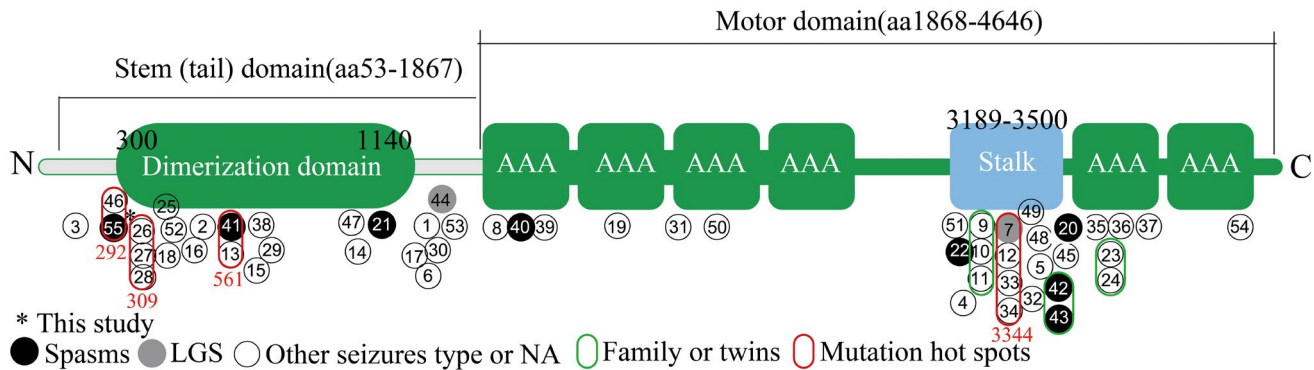


FIGURE 4 Schematic representation of human *DYNC1H1* and mutations in patients with seizures or epilepsy. The *DYNC1H1* mutation sites in patients with seizures were found in both motor domain and tail domain, mainly clustering in and around the stalk region of the motor domain, the junction area of motor and tail domain, and the N-terminal region of the tail domain

ID	Seizure onset	Seizure type	Drugs	Seizure < 50%
P20	3 m	Spasms	Prednisolone, VGB	NA
P41	NA	Spasms	PB, LEV, CZP, VPA	NA
P42/43	7 m	Spasms	LEV, TPM, VPA	Vigabatrin
P44	1 y 5 m	LGS	LEV, VPA, RUF	LEV + KD
P55	5 m	Spasms	Prednisolone, TPM	LEV + KD + VNS

TABLE 2 Treatments in *DYNC1H1* mutation patients with epileptic encephalopathy

Abbreviations: CZP, clonazepam; KD, ketogenic diet; LEV, levetiracetam; LGS, Lennox–Gastaut syndrome; m, month; NA, not available; PB, phenobarbital; RUF, rufinamide; TPM, topiramate; VGB, vigabatrin; VNS, vagus nerve stimulation; VPA, valproate; y, year.

Epileptic spasms are often accompanied by hypsarrhythmia on EEG, and the use of standard first-line drugs, such as ACTH, vigabatrin, and prednisolone, may provide the greatest benefit in terms of seizures, EEG changes, and long-term prognosis in children (Knupp et al., 2016). Regarding the seizure treatments in these 55 patients, 27 had no information available in the literature, 13 were reported as refractory epilepsy, seven were reported as controlled seizures, eight cases mentioned specific treatment drugs, and all were drug-resistant epilepsy (P20, P41, P42/43, P44, P53, P54, P55, see Table 2). Five of these eight patients were diagnosed with epileptic spasms, and one with LGS. Similar to Li's case report (Li et al., 2019), seizures were reduced by more than 50% after introduction of KD in our case (8 months follow-up for Li's case, and 33 months in this study). Although combined with oral ASMs, KD, and VNS, our case still had at least one cluster of spasms per day and global development delay, including physical growth, motor, and language skills. These results indicate that the existing encephalopathy in this infant, due to a *DYNC1H1* mutation, was not only caused by epileptic spasms, but also by the developmental consequences of the gene variant itself, known as one type of DEE.

In summary, *DYNC1H1* mutations can cause lesions in the central and peripheral nervous systems with various heterogeneous manifestations. Mutations in both the motor and tail domains of *DYNC1H1* can cause cortical developmental malformations and refractory seizures. Epileptic spasms were resistant to multiple treatments (ASMs, corticosteroids, KD, and VNS) in this p.Arg292Trp mutation patient. Refractory epilepsy, developmental retardation, and brain malformations are core symptoms of *DYNC1H1*-related DEE.

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CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

TS prepared the original draft, YY did literature searching, YY, QH, YL revised the manuscript, TS and SX edited the

final manuscript. All authors have read and approved the final manuscript.

ETHICAL APPROVAL

This study was approved by the ethics committee of the Tongji Hospital of Huazhong University of Science and Technology.

PATIENT CONSENT STATEMENT

The parents agreed to the publication of the WES results and some of the data related to the medical history and signed an informed consent form.

PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES

None.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

- Amabile, S., Jeffries, L., McGrath, J. M., Ji, W., Spencer-Manzon, M., Zhang, H., & Lakhani, S. A. (2020). Dync1h1-related disorders: A description of four new unrelated patients and a comprehensive review of previously reported variants. *American Journal of Medical Genetics. Part A*, *182*(9), 2049–2057.
- Becker, L. L., Dafsari, H. S., Schallner, J., Abdin, D., Seifert, M., Petit, F., Smol, T., Bok, L., Rodan, L., Krapels, I., Spranger, S., Weschke, B., Johnson, K., Straub, V., Kaindl, A. M., di Donato, N., von der Hagen, M., & Cirak, S. (2020). The clinical-phenotype continuum in dync1h1-related disorders-genomic profiling and proposal for a novel classification. *Journal of Human Genetics*, *65*(11), 1003–1017.
- Benson, K. A., White, M., Allen, N. M., Byrne, S., Carton, R., Comerford, E., Costello, D., Doherty, C., Dunleavy, B., El-Naggar, H., Gangadharan, N., Heavin, S., Kearney, H., Lench, N. J., Lynch, J., McCormack, M., Regan, M. O., Podesta, K., Power, K., ... Cavalleri, G. L. (2020). A comparison of genomic diagnostics in adults and children with epilepsy and comorbid intellectual disability. *European Journal of Human Genetics*, *28*(8), 1066–1077.
- Das, J., Lilleker, J. B., Jabbal, K., & Ealing, J. (2018). A missense mutation in DYNC1H1 gene causing spinal muscular atrophy - lower extremity, dominant. *Neurologia i Neurochirurgia Polska*, *52*(2), 293–297.
- Di Donato, N., Timms, A. E., Aldinger, K. A., Mirzaa, G. M., Bennett, J. T., Collins, S., Olds, C., Mei, D., Chiari, S., Carvill, G., Myers, C. T., Rivière, J. B., Zaki, M. S., Gleeson, J. G., Rump, A., Conti, V., Parrini, E., Ross, M. E., Ledbetter, D. H., ... Dobyns, W. B. (2018). Analysis of 17 genes detects mutations in 81% of 811 patients with lissencephaly. *Genetics in Medicine*, *20*(11), 1354–1364.
- Eschbach, J., & Dupuis, L. (2011). Cytoplasmic dynein in neurodegeneration. *Pharmacology & Therapeutics*, *130*(3), 348–363.
- Fiorillo, C., Moro, F., Yi, J., Weil, S., Brisca, G., Astrea, G., Severino, M., Romano, A., Battini, R., Rossi, A., Minetti, C., Bruno, C., Santorelli, F. M., & Vallee, R. (2014). Novel dynein DYNC1H1 neck and motor domain mutations link distal spinal muscular atrophy and abnormal cortical development. *Human Mutation*, *35*(3), 298–302.
- Gelineau-Morel, R., Lukacs, M., Weaver, K. N., Hufnagel, R. B., Gilbert, D. L., & Stottmann, R. W. (2016). Congenital cataracts and gut dysmotility in a DYNC1H1 Dyneinopathy patient. *Genes*, *7*(10), 85. <https://doi.org/10.3390/genes7100085>
- Gou, M., Fan, J., Zhou, Q., Fu, R., He, J., & Liu, J. (2019). A de novo mutation of the DYNC1H1-related infantile spasms in a family and literature review. *Chinese Journal of Applied Clinical Pediatrics*, *34*(13), 1022–1024.
- Harms, M. B., Allred, P., Gardner, R., Jr., Fernandes Filho, J. A., Florence, J., Pestronk, A., Al-Lozi, M., & Baloh, R. H. (2010). Dominant spinal muscular atrophy with lower extremity predominance: Linkage to 14q32. *Neurology*, *75*(6), 539–546.
- Harms, M. B., Ori-McKenney, K. M., Scoto, M., Tuck, E. P., Bell, S., Ma, D., Masi, S., Allred, P., Al-Lozi, M., Reilly, M. M., Miller, L. J., Jani-Acsadi, A., Pestronk, A., Shy, M. E., Muntoni, F., Vallee, R. B., & Baloh, R. H. (2012). Mutations in the tail domain of DYNC1H1 cause dominant spinal muscular atrophy. *Neurology*, *78*(22), 1714–1720.
- Helbig, K. L., Farwell Hagman, K. D., Shinde, D. N., Mroske, C., Powis, Z., Li, S., Tang, S., & Helbig, I. (2016). Diagnostic exome sequencing provides a molecular diagnosis for a significant proportion of patients with epilepsy. *Genetics in Medicine*, *18*(9), 898–905.
- Hertcant, J., Komara, M., Nagi, A., Suleiman, J., Al-Gazali, L., & Ali, B. R. (2016). A novel de novo mutation in DYNC1H1 gene underlying malformation of cortical development and cataract. *Meta Gene*, *9*, 124–127.
- Hu, C., Sun, D., Deng, X., Hu, J., & Liu, Z. (2018). Clinical features and genetic analysis of early-onset epileptic encephalopathy with pachygyria-lissencephaly. *Chinese Journal of Applied Clinical Pediatrics*, *33*(24), 1864–1868.
- Jamuar, S. S., Lam, A. T., Kircher, M., D'Gama, A. M., Wang, J., Barry, B. J., Zhang, X., Hill, R. S., Partlow, J. N., Rozzo, A., Servattalab, S., Mehta, B. K., Topcu, M., Amrom, D., Andermann, E., Dan, B., Parrini, E., Guerrini, R., Scheffer, I. E., ... Walsh, C. A. (2014). Somatic mutations in cerebral cortical malformations. *New England Journal of Medicine*, *371*(8), 733–743.
- Knupp, K. G., Coryell, J., Nickels, K. C., Ryan, N., Leister, E., Loddenkemper, T., Grinspan, Z., Hartman, A. L., Kossoff, E. H., Gaillard, W. D., Mytinger, J. R., Joshi, S., Shellhaas, R. A., Sullivan, J., Dlugos, D., Hamikawa, L., Berg, A. T., Millichap, J., Nordli, D. R., Jr., ... Pediatric Epilepsy Research Consortium. (2016). Response to treatment in a prospective national infantile spasms cohort. *Annals of Neurology*, *79*(3), 475–484.
- Li, X. L. S., Jiang, L., Wang, F., Feng, X., & Yuan, X. (2019). A case of mental retardation, autosomal dominant 13 with Lennox-Gastaut syndrome. *Journal of Epilepsy*, *5*(4), 320–322 [in Chinese].
- Lin, Z., Liu, Z., Li, X., Li, F., Hu, Y., Chen, B., Wang, Z., & Liu, Y. (2017). Whole-exome sequencing identifies a novel de novo

- mutation in DYNC1H1 in epileptic encephalopathies. *Scientific Reports*, 7(1), 258.
- Matsumoto, A., Kojima, K., Miya, F., Miyauchi, A., Watanabe, K., Iwamoto, S., Kawai, K., Kato, M., Takahashi, Y., & Yamagata, T. (2021). Two cases of dync1h1 mutations with intractable epilepsy. *Brain & Development*, 43(8), 857–862.
- Otten, K., Bauder, F., Kroell, J., Roethlisberger, B., & Schmitt-Mechelke, T. (2017). Severe cortical malformation and acquired cataract—An unusual presentation of DYNC1H1 mutation in twins. *European Journal of Paediatric Neurology*, 21, e75–e76.
- Palmer, E. E., Schofield, D., Shrestha, R., Kandula, T., Macintosh, R., Lawson, J. A., Andrews, I., Sampaio, H., Johnson, A. M., Farrar, M. A., Cardamone, M., Mowat, D., Elakis, G., Lo, W., Zhu, Y., Ying, K., Morris, P., Tao, J., Dias, K. R., ... Sachdev, R. K. (2018). Integrating exome sequencing into a diagnostic pathway for epileptic encephalopathy: Evidence of clinical utility and cost effectiveness. *Molecular Genetics & Genomic Medicine*, 6(2), 186–199.
- Pfister, K. K., Shah, P. R., Hummerich, H., Russ, A., Cotton, J., Annuar, A. A., King, S. M., & Fisher, E. M. (2006). Genetic analysis of the cytoplasmic dynein subunit families. *PLoS Genetics*, 2(1), e1.
- Poirier, K., Lebrun, N., Broix, L., Tian, G., Saillour, Y., Boscheron, C., Parrini, E., Valence, S., Pierre, B. S., Oger, M., Lacombe, D., Geneviève, D., Fontana, E., Darra, F., Cances, C., Barth, M., Bonneau, D., Bernadina, B. D., N'Guyen, S., ... Chelly, J. (2013). Mutations in TUBG1, DYNC1H1, KIF5C and KIF2A cause malformations of cortical development and microcephaly. *Nature Genetics*, 45(6), 639–647.
- Punetha, J., Monges, S., Franchi, M. E., Hoffman, E. P., Cirak, S., & Tesi-Rocha, C. (2015). Exome sequencing identifies DYNC1H1 variant associated with vertebral abnormality and spinal muscular atrophy with lower extremity predominance. *Pediatric Neurology*, 52(2), 239–244.
- Rochtus, A., Olson, H. E., Smith, L., Keith, L. G., El Achkar, C., Taylor, A., Mahida, S., Park, M., Kelly, M., Shain, C., Rockowitz, S., Rosen Sheidley, B., & Poduri, A. (2020). Genetic diagnoses in epilepsy: The impact of dynamic exome analysis in a pediatric cohort. *Epilepsia*, 61(2), 249–258.
- Scheffer, I. E., French, J., Hirsch, E., Jain, S., Mathern, G. W., Moshé, S. L., Perucca, E., Tomson, T., Wiebe, S., Zhang, Y. H., & Zuberi, S. M. (2016). Classification of the epilepsies: New concepts for discussion and debate—special report of the ILAE classification task force of the Commission for Classification and Terminology. *Epilepsia Open*, 1(1–2), 37–44.
- Scoto, M., Rossor, A., Harms, M. B., Calissano, M., Cirak, S., Foley, A. R., Sewry, C., Hafezparast, M., Robb, S., Manzur, A. Y., Baloh, R. H., Reilly, M. M., & Muntoni, F. (2013). Wide phenotypic spectrum of SMA with lower limbs predominance due to mutations in the tail domain of DYNC1H1 gene: A case series. *Neuromuscular Disorders*, 23(9–10), 772–772.
- Singh, J., Illingworth, M., Whitney, A., Konn, D., Foulds, N., Allen, D., & Uglow, M. (2015). Spinal muscular atrophy—lower extremity dominant (SMA-LED), with bilateral perisylvian polymicrogyria and infantile epileptic encephalopathy, due a novel DYNC1H1 mutation. *Neuromuscular Disorders*, 25, S222–S223.
- Strickland, A. V., Schabhüttl, M., Offenbacher, H., Synofzik, M., Hauser, N. S., Brunner-Krainz, M., Gruber-Sedlmayr, U., Moore, S. A., Windhager, R., Bender, B., Harms, M., Klebe, S., Young, P., Kennerson, M., Garcia, A. S. M., Gonzalez, M. A., Züchner, S., Schule, R., Shy, M. E., & Auer-Grumbach, M. (2015). Mutation screen reveals novel variants and expands the phenotypes associated with DYNC1H1. *Journal of Neurology*, 262(9), 2124–2134.
- Su, T., Yan, Y., Xu, S., Zhang, K., & Xu, S. (2020). Early onset epileptic encephalopathy caused by novel compound heterozygous mutation of WWOX gene. *International Journal of Developmental Neuroscience*, 80(2), 157–161.
- Tumienè, B., Maver, A., Writzl, K., Hodžić, A., Čuturilo, G., Kuzmanić-Šamija, R., Čulić, V., & Peterlin, B. (2018). Diagnostic exome sequencing of syndromic epilepsy patients in clinical practice. *Clinical Genetics*, 93(5), 1057–1062.
- Vissers, L. E., de Ligt, J., Gilissen, C., Janssen, I., Stehouwer, M., de Vries, P., van Lier, B., Arts, P., Wieskamp, N., del Rosario, M., van Bon, B. W., Hoischen, A., de Vries, B. B., Brunner, H. G., & Veltman, J. A. (2010). A de novo paradigm for mental retardation. *Nature Genetics*, 42(12), 1109–1112.
- Weedon, M. N., Hastings, R., Caswell, R., Xie, W., Paszkiewicz, K., Antoniadis, T., Williams, M., King, C., Greenhalgh, L., Newbury-Ecob, R., & Ellard, S. (2011). Exome sequencing identifies a DYNC1H1 mutation in a large pedigree with dominant axonal Charcot-Marie-tooth disease. *American Journal of Human Genetics*, 89(2), 308–312.
- Willemsen, M. H., Vissers, L. E. L., Willemsen, M. A. A. P., van Bon, B. W. M., Kroes, T., de Ligt, J., de Vries, B. B., Schoots, J., Lugtenberg, D., Hamel, B. C. J., van Bokhoven, H., Brunner, H. G., Veltman, J. A., & Kleefstra, T. (2012). Mutations in DYNC1H1 cause severe intellectual disability with neuronal migration defects. *Journal of Medical Genetics*, 49(3), 179–183.

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