Neurology Asia 2023; 28(2) : 421 – 429

A novel *DOCK7* variant as a rare reason for epileptic encephalopathy, cortical blindness, dysmorphic features: A case report and brief review of the literature

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Abstract

Early infantile epileptic encephalopathy 23 (EIEE23; OMIM #615859) is a rare autosomal recessive disorder. It is characterized by refractory seizures, multifocal epileptic activity on electroencephalography, psychomotor development delay, dysmorphic facial features and cortical blindness/visual impairment. DOCK7 is involved in intracellular signaling networks and plays a role in axon formation and neuronal polarization. Function loss of this gene has previously been described in the molecular etiology of EIEE23. Here, we report a boy with a pathogenic novel variant in the *DOCK7* gene presenting with, infantile-onset epileptic encephalopathy, severe neurodevelopmental delay, dysmorphic facial features, cortical blindness as well as previously unreported minor dental and extremity anomalies. Few cases with *DOCK7* mutations have been reported in the literature. Due to its high genetic heterogeneity and scarcity, it is extremely important to report a novel and specific mutations and their associated clinical phenotypes. Whole exome sequencing revealed a novel pathogenic homozygous frameshift variant which has not been reported (c.5669dup (p.Cys1891ValfsTer2) mutation in the exon 44 of *DOCK7).*

Keywords: DOCK7, epileptic encephalopathy, cortical blindness, dysmorphism, novel mutation

INTRODUCTION

Epileptic encephalopathies (EE) are a heterogeneous group of disorders characterized by epileptic seizures causing cognitive and behavioral disturbances.[1] Cases have social, cognitive, motor, language, and behavioral impairment at varying levels as well as seizures. The genetic origin of early infantile epileptic encephalopathy (EIEE) patients can be identified in only half the patients with whole exome sequencing (WES) or targeted gene panels.[2-4]

DOCK7 (dedicator of cytogenesis 7) gene consists of 50 exons and codes for a guanine nucleotide exchange factor (GEF) that plays a role in axon formation and neuronal polarization.[2,5] In addition, it regulates the neurogenesis of radial glial cells and enterokinetic nuclear migration during cortical development in interaction with *TACC3* (transforming acidic coiled-coil-containing protein 3).[2,5,6] Biallelic pathogenic variants detected in *DOCK7* are known to cause EIEE23, a sub-group of EIEE in early childhood.[1,2,4,7,8] EIEE23 is a rare (<1/1,000,000) autosomal recessive disorder (OMIM #615859).[7] Patients present with refractory seizures between 2 and 6 months, multifocal epileptic activity in electroencephalography (EEG), psychomotor development delay, facial dysmorphism, specific structural brain anomalies and cortical blindness or visual impairment.[1,4,7,8] It was first defined by Perrault and colleagues in 2014, and was followed by other case reports.[1,2,4,7-9]

This article presents a pediatric patient diagnosed with EIEE23 associated with a novel homozygous, frameshift and pathogenic variant in

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Date of Submission: 30 January 2023; Date of Acceptance: 13 March 2023

https://doi.org/10.54029/2023exu

the *DOCK7* gene. We also reviewed the literature to make it more familiar for clinicians.

CASE REPORT

Our case, currently aged 8, was born to healthy consanguineous parents of Turkish origin. No complications developed during pregnancy and delivery. His birth weight, length and head circumference measures were within the normal percentile range. His failure to make eye contact was first noticed when he was 5 months old. Ophthalmologic examination revealed horizontal nystagmus in both eyes. Severe conduction defect was found in bilateral visual pathways in the visual evoked potential (VEP). Fundus examination and pupillary reactions were normal bilaterally. Leber hereditary optic neuropathy (LHON) was considered but no mutation was seen in the whole mitochondrial genome analysis.

At 6 months of age, he had his first afebrile seizure after vaccination characterized by eyelid myoclonia and a clonic seizure of the right arm and leg. A metabolic workup including plasma triglycerides, cholesterol, amino acid concentrations and urine organic acid chromatography was normal. First EEG revealed epileptiform activity in the left fronto-centro-temporal region. No pathologic findings were detected on echocardiogram, brain magnetic resonance imaging (MRI) and MR spectroscopy. *SCN1A* and *SCN2A* gene and chromosome analysis were normal. Different seizure types on the follow-up include gelastic, drop head, versive, tonic-clonic, tonic, behavior arrest and impaired awareness. EEG recordings showed multifocal epileptic activity.

He is currently 8 years old. On neurological examination hypotonic and delayed fine and gross motor functions. Unable to sit without support, crawl, stand up without help, walk and eat with pronounced muscular hypotonia. He cannot speak, but he smiles although not in the social context. He can use his hands to grasp objects; however, he is unable to use them to point to or communicate. Despite his normal results on the hearing test, he does not respond to his name. He exhibits autism-like behaviors such as rocking, hand-biting and making random noises. In the ophthalmologic examination, he has horizontal nystagmus. The pupillary reflex and aspect of the fundus are normal, but there is no visual communication. The other system examinations were normal.

He had dysmorphic facial features including low-set frontal hairline, bitemporal narrowness, plump lips, short philtrum, telecanthus, periorbital fullness, long eyelashes, protruding ears, anteverted nares and a broad nasal tip. He also had a previously unreported crooked teeth, syndactyly between the 2nd and 3rd toes, and pes planus in both feet (Figure 1).

Despite the use of antiepileptic drugs in several combinations, he had refractory seizures. He is currently receiving clobazam, sodium valproate and lamotrigine. The ketogenic diet was tried but was stopped as it made no change in seizure character and frequency.

Brain MRI at age 7 showed abnormally marked pontobulbar sulcus associated with pontine hypoplasia, thin corpus callosum, increased signal and atrophy in the white and gray matter of the occipital lobe, dilation of lateral ventricles and mild interdigitation of gyri across the interhemispheric fissure (Figure 2).

WES revealed a homozygous c.5669dup (p.Cys1891ValfsTer2, C1891Vfs*2) mutation in exon 44 of the *DOCK7* gene (ENST00000251157.5). This frameshift variant has not been reported in any public human genetic variants databases such as the 1000 Genomes Project, NHLBI/NIH Exome Sequencing Project, ExAC/gnomAD, ClinVar, or dbSNP. It was a pathogenic variant according to The American College of Medical Genetics and Genomics (ACMG) criteria.[10] The variant was confirmed by Sanger sequencing (Figure 3).

DISCUSSION

DOCK7 is expressed in GABAergic interneurons in the central nervous system.[4] It promotes the differentiation and transition of radial glial cells to basal progenitors and neurons, playing an important role in neurogenesis.[6] It has also been shown to regulate the tangential neuroblast migration in the mouse forebrain.[11] Thus, DOCK7 deficiency is thought to cause significant defects in neurogenesis. Moreover, visual problems may occur due to the involvement of GABAergic retinal amacrine cells.[4] It is of interest that the strongly conserved craniofacial specific enhancer (identifier: GH01J062686) is localized in and around exon 1 of *DOCK7*. Thus, it is considered that patients with DOCK7 deficiency have dysmorphic features.[4,12]

Nine patients have been reported with a mutation in *DOCK7* in the literature. Clinical presentations in patients, closely matched most of the previously reported cases of EIEE23. He was

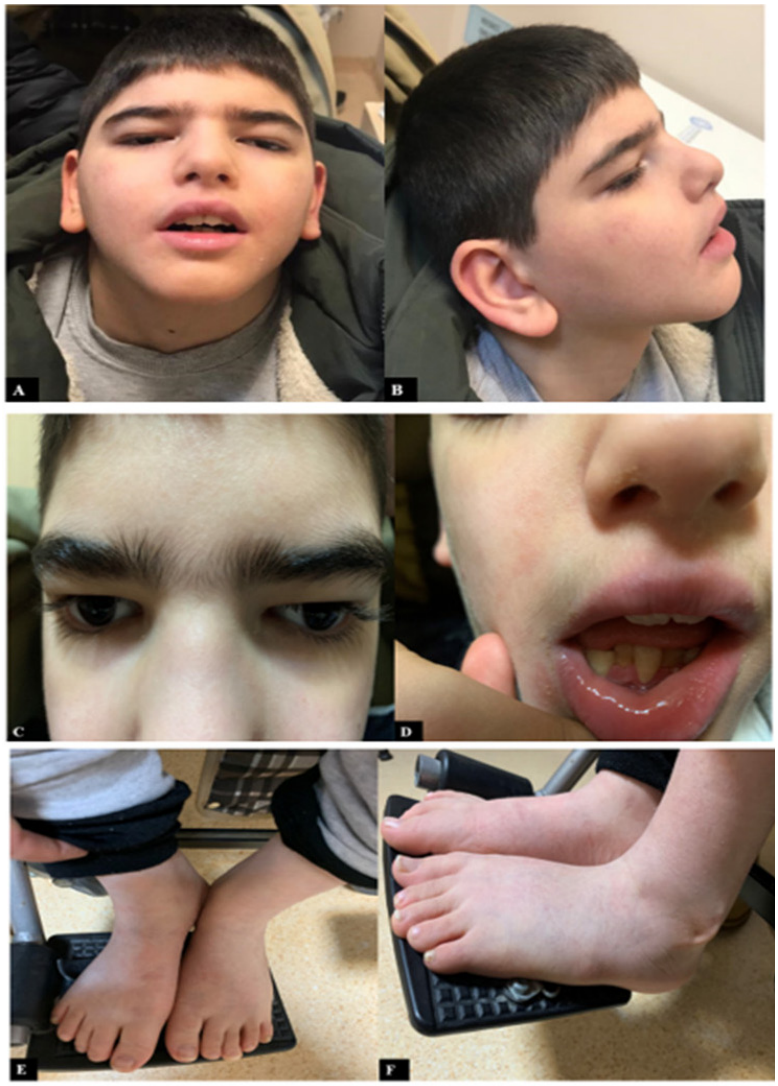

Figure 1. Facial and extremity anomalies of the patient with *DOCK7* mutation:
(a-b) Low anterior hairline, bitemporal narrowness, plump lips, short philtrum, telecanthus, periorbital fullness, long eyelashes, protruding ears, a broad nasal tip with anteverted nares **(c)** Telecanthus **(d)** Crooked teeth **(e)** Syndactyly between the 2nd and 3rd toes **(f)** Pes planus

presented with typical characteristics of EIEE23 such as lack of reaction to visual stimuli despite a normal anterior and posterior eye examination, eyelid myoclonia and focal clonic epileptic seizures with epileptiform discharges on EEG and typical dysmorphic features. Demographic, genetic and clinical data of patients are presented in Table 1.[1,2,4,7-9]

Speech and cognitive functions were affected in previously reported patients, and their fine and gross motor functions were retarded compared to their peers.[1,2,4,7,8] Two patients developed better language and social communication skills compared to previously published cases.[9] The findings in our case were similar to other cases, he did not speak any meaningful words and could never walk unaided. In addition, he exhibited autism-like behaviors such as hand clapping and senseless sounds. Therefore, psychomotor developmental delay, some autistic features and lack of verbal skills may indicate the clinical status associated with mutations in *DOCK7*.

Typical facial features were common in all affected patients, including periorbital fullness, low anterior hairline, broad nasal tip, long eyelashes and telecanthus is a significant dysmorphic finding that is present in most of the patients, as in our patient.[1,2,4,7-9] Telecanthus

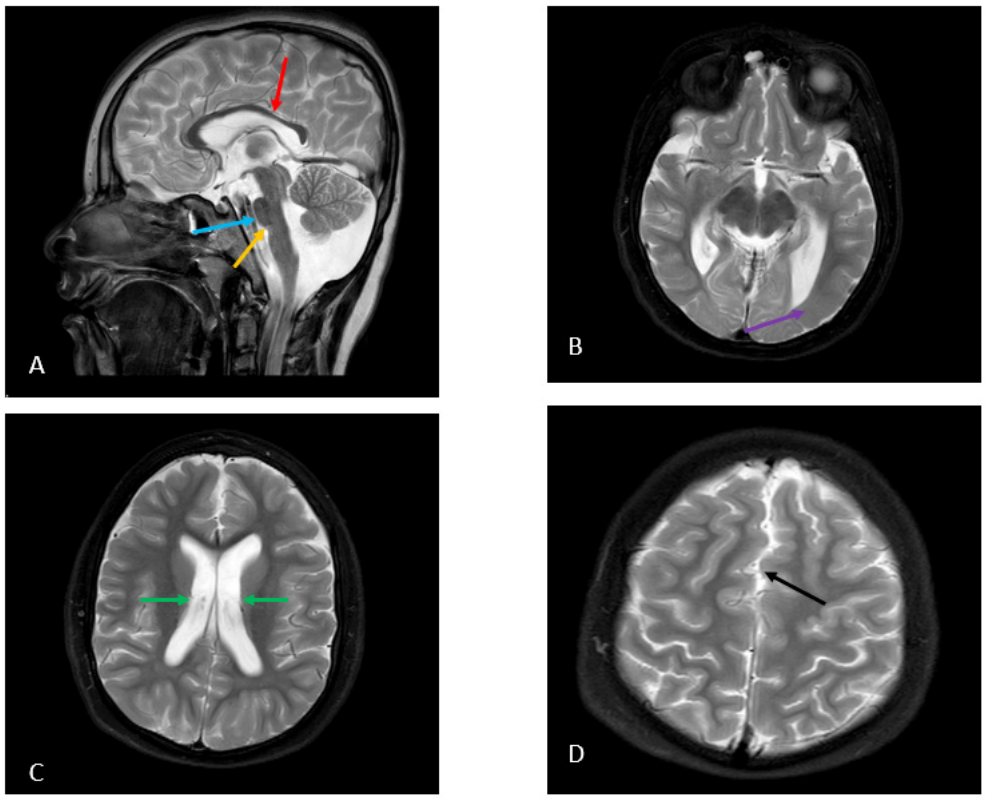

Figure 2. Brain MRI of the case with a mutation in *DOCK7*: **(a)** Shows abnormally marked pontobulbar sulcus (yellow arrow) associated with mild pontine hypoplasia (blue arrow) and thin corpus callosum (red arrow) **(b)** shows reveals increased signal and atrophy in the white and gray matter of the occipital lobe (purple arrow) **(c)** shows dilation of lateral ventricles (green arrows) **(d)** shows mild interdigitation of gyri across the interhemispheric fissure (black arrow)

is important because the dysmorphic eye findings that are noticeable in the first place, refer to the increased distance between the inner corners of the eyelids (medial canthi), while the inter-pupillary distance is normal. This is in contrast to hypertelorism, in which the distance between the whole eyes is increased.[13] Therefore, we think that these patients can be recognized more easily with their characteristic eye and facial appearance. In addition to the dysmorphic findings described in our patient, there was crooked teeth, syndactyly between the 2nd and 3rd toes and pes planus. These findings were not reported in previously described patients. Therefore, we think that dental and extremity anomalies can be seen in patients with *DOCK7* gene mutation.

Microcephaly was reported in only one patient.[9] Head circumference measurements of others[1,2,4,7,8]

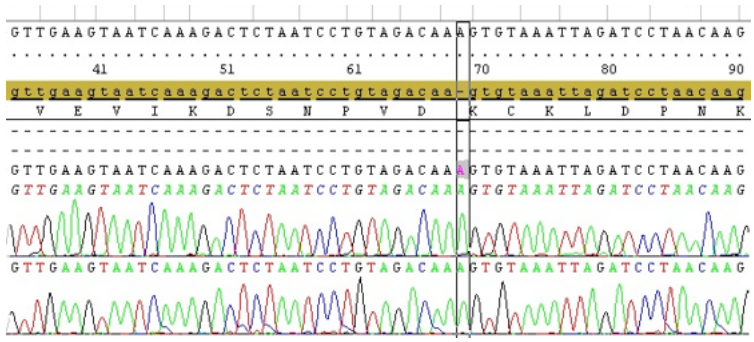

Figure 3. Index case mutation (c.5669dup (p.Cys1891ValfsTer2) homozygous)

Table 1: Demographic, genetic and clinical data of patients

Reference	No	Gender	Age (years)	Variant	Age of onset seizures (month)	Types of seizures	Antiseizure medication	Seizure prognosis	Facial dysmorphic findings and other anomalies	Ocular abnormality
Index case	P1	M	8	c.5669dup, p.Cys1891ValfsTer2, C1891Vfs*2	6	Eyelid myoclonus Focal clonic Generalize tonic-clonic Versive and drop head Gelastic	VPA CLB LTG KD	Uncontrolled seizure	Low anterior hairline Bitemporal narrowness Plump lips Short philtrum Telecanthus Periorbital fullness Long eyelashes Protruding ears Broad nasal tip Anteverted nares Crooked teeth Syndactyly Pes planus	Lack of reaction to visual stimulus Fine horizontal nystagmus Lack of object fixation Cortical blindness
Perrault *et al.* (2014)[1]	P2	F	7	c.3709C>T/c.2510delA, p.Arg1237a/p.Asp837A-lafsa48	2-4	Tonic Infantile spasm	NR KD	Uncontrolled seizure	Low anterior hairline Periorbital fullness Telecanthus Broad nasal tip Anteverted nares	Lack of reaction to visual stimulus Binocular optometric obstacles Cortical blindness
	P3	F	5	c.3709C>T/c.2510delA, p.Arg1237a/p.Asp837A-lafsa48	2-4	Myoclonic Focal onset impaired awareness Tonic	NR KD	Uncontrolled seizure	Low anterior hairline Periorbital fullness Telecanthus Broad nasal tip Anteverted nares	Lack of reaction to visual stimulus Binocular optometric obstacles, Cortical blindness
	P4	F	10	c.983C>G/c.6232G>T, p.Ser328a/p.Glu2078a	6	Tonic-clonic	NR	Uncontrolled seizure	Bitemporal narrowness Low anterior hairline Thick eyebrows Long eyelashes Synophrys Enophthalmia Large and prominent nasal root Bulbous nasal tip Thick and hammered helix Thick earlobes Short philtrum Full lips Everted lower lip Spaced incisors	Lack of reaction to visual stimulus Cortical blindness

Reference	No	Gender	Age (years)	Variant	Age of onset seizures (month)	Types of seizures	Antiseizure medication	Seizure prognosis	Facial dysmorphic findings and other anomalies	Ocular abnormality
Bai *et al.* (2019)[7]	P5	F	3	c.5929-1G>C/c.2479C>T, p.?/p.Arg827a	6	Infantile spasm	NR	NR	Low posterior hairlines Highly arched palate Gingival maldevelopment Protruding ears Low ear set Periorbital fullness Abnormally shaped ears Broad nasal tip Large nasal root	Lack of reaction to visual stimulus Horizontal optokinetic nystagmus Strabismus Cortical blindness
Turkdogan *et al.* (2019)[8]	P6	M	3	c.3350T>A, p.Leu1117a, p.Leu1117a	3.5	Focal Generalized tonic-clonic Status epi-lepticus	CLB	Seizure-free	Normo- brachycephaly Narrow forehead Low anterior hairline Wide and anteverted nasal tip Prominent ears Full cheeks Long eyelashes Smooth and short philtrum Thin upper lip	Cortical blindness
Nashabat M *et al.* (2019)[9]	P7	F	9 mont-hs	c.884del (p.Lys295Ar-gfs*15)	Neonatal	Generalized tonic-clonic	NR	Seizure-free	Microcephaly	NR
Haberlandt et al. (2020)[4]	P8	F	27	c.390_3936dup, Loss of protein	6	Myoclonic Versive and drop head Tonic	LEV CLB ZNS MDZ	Seizure-free	Low anterior-posterior hairline Highly arched palate Some periorbital fullness Telecanthus Long eyelashes Broad nasal tip Low-set and protruding ears Smooth and short philtrum Thin upper lip	Lack of reaction to visual stimulus Horizontal and vertical nystagmus Lack of object fixation Cortical blindness
	P9	F	23	c.390_3936dup, Loss of protein	6	Myoclonic Versive and drop head Tonic	LEV CLB ZNS MDZ	Uncontrolled seizure	Low anterior and posterior hairline Highly arched palate Periorbital fullness Telecanthus Long eyelashes Broad nasal tip Anteverted nares Low-set and protruding ears	Lack of reaction to visual stimulus Horizontal and vertical nystagmus Lack of object fixation Cortical blindness

Reference	No	Gender	Age (years)	Variant	Age of onset seizures (month)	Types of seizures	Antiseizure medication	Seizure prognosis	Facial dysmorphic findings and other anomalies	Ocular abnormality
Kivrak Pfiffner F *et al.* (2022)[2]	P10	F	NR	c.5391delA, p. (Ala1798Leufs*Ter59)	16	Myoclonic Infantil spasm	VPA	Uncontrolled seizure	Long eyelashes Broad nose tip Telecanthus	Wandering eye movements Absent fixation to light or objects Slow pupillary response to light

NR= Not reported
P patient, *F* female, *M* male
VPA Valproic acid, *CLB* Clobasam, *LTG* Lamotrigine, *KD* Ketogenic diet, *LEV* Levetiracetam *ZNS* Zonisamide, *MDZ* Midazolam

and our patient were normal. Like other reported cases[1,2,4,7-9], his ophthalmologic examination revealed normal pupillary reaction and fundus consistent with the diagnosis of cortical blindness. Nystagmus was among other previously described findings[4,7], as in our case.

Seizure was one of the most common clinical manifestations in the cases.[1,2,4,7-9] In our case, similar semiological features were observed and differently, gelastic seizures were also added in the follow-up. Focal epileptic activity was frequently found in EEG recordings. Levetiracetam, clobazam and zonisamide are the most effective antiseizure drugs for seizure control in patients with *DOCK7* mutations.[8,9] However, seizure control failed in our case despite-combination of valproate, clobazam and lamotrigine. Ketogenic diet was also ineffective. Similarly, the ketogenic diet was attempted in two reported cases, but seizure freedom was not achieved.[14]

Structural brain anomalies were identified in all previously reported cases.[1,2,4,7-9] In our case at the age of 6 months, neuroimaging was normal, and when repeated at the age of 7, neuroimaging findings were consistent with other reported cases (Figure 2). It is remarkable that the pontobulbar sulcus, which is located in the brainstem and forms the border between the pons and the medulla oblongata, becomes more prominent with pons hypoplasia in the brain MRI findings in most patients. This finding was supported by our case.[1,2,4,7,8] Mild interdigitation of gyri across the interhemispheric fissure was demonstrated in our patient, a rare and subtle sign that may be overlooked. The interdigitation of gyri arises when medial hemispheric gyri become interlocked across the interhemispheric fissure like the fingers of folded hands.[15] The presence of several brain abnormalities affecting both cortical and myelin formation may be related to different roles of *DOCK7* in diverse cell types via interacting with various protein complexes during both embryonic neurogenesis and postnatal migration.[1,8] We suggest that the normality of early brain MRI imaging in such cases does not exclude this particular diagnosis and should be repeated when necessary. In addition, although cardiac anomalies were rarely reported[1,4,7], echocardiographic assessment of our patient was normal. Electrophysiological, neuroimaging, and echocardiographic findings of the patients were provided in Table 2.

The variant c.5669dup causes frameshift mutation of exon 44 in the DHR2 domain of the *DOCK7* gene. We suggest that this variant might

Table 2: Electrophysiological, neuroimaging and echocardiographic findings of the patients

Reference	No	Electroencephalography	Brain MRI	Echocardiography
Index case	P1	Focal (left frontocentral) EA Generalize EA	Abnormally marked pontobulbar sulcus Mild pontine hypoplasia Thin and short corpus callosum Atrophy in the white and gray matter of the occipital lobe Dilation of lateral ventricles Mild interdigitation of gyri across the interhemispheric fissure	Normal
Perrault *et al.* (2014)[1]	P2	Hypsarrhythmia Multifocal EA	Abnormally marked pontobulbar sulcus Mild pontine hypoplasia Thin and short corpus callosum Atrophy in the white and gray matter of the occipital lobe	Aortic supravalvular stenosis Bicuspid aortic valve
	P3	Multifocal EA	Mild hypoplasia of the corpus callosum	Normal
	P4	Multifocal EA	Abnormally marked pontobulbar sulcus Mild pontine hypoplasia, Atrophy in the white and gray matter of the occipital lobe	NR
Bai *et al.* (2019)[7]	P5	Hypsarrhythmia Multifocal EA	Abnormally marked pontobulbar sulcus Mild pontine hypoplasia, Thin corpus callosum Dilation of lateral ventricles Pachygyria	Atrial septal defect
Turkdogan *et al.* (2019)[8]	P6	Generalized EA Focal EA	Abnormally marked pontobulbar sulcus Pontine hypoplasia Thin corpus callosum Atrophy in the white and gray matter of the occipital lobe Absence of interventricular septum The mild interdigitation of gyri across the interhemispheric fissure	NR
Nashabat *et al.* (2019) [9]	P7	Epileptic encephalopathy	NR	NR
Haberlandt *et al.* (2020)[4]	P8	Hypsarrhythmia Multifocal EA	Abnormally marked pontobulbar sulcus, Mild pontine hypoplasia, Atrophy in the white and gray matter of the occipital lobe	Normal
	P9	Hypsarrhythmia Multifocal EA	Abnormally marked pontobulbar sulcus Mild pontine hypoplasia Atrophy in occipital white and gray matter Focal atrophy of occasional cerebellar folia	Atrial septal defect
Kivrak Pfiffner *et al.* (2022)[2]	P10	Multifocal EA Generalized EA	Pontine hypoplasia Dilated pontine perivascular spaces anteriorly Concave posterior border of the pons Abnormally marked sulcus at the pontomedullary junction The occipital white matter in the region of the visual cortex showed increased high T2 signal compatible with a lower degree of myelination Diffuse cerebellar microcystic changes and severely hypoplastic olfactory bulbus	NR

MRI Magnetic resonance imaging, *EA* Epileptic activity, *NR* Not reported,

lead to the premature decay of the corresponding mRNA, and disable its DHR2 domain. Also, Rac1 activated by the DHR-2 domain regulates actin and microtubule network dynamics. In the literature, there are two cases with different variants in the same domain. When we compared the cases in terms of the DHR2 domain, we came across similar phenotypic features.[2,7] As a result, the catalytic DHR2 domain of *DOCK7* is necessary for cortical neurogenesis, axon development, and neuronal polarity.

In conclusion, by reporting a case with a novel frameshift, pathogenic mutation of *DOCK7*, and reminding the heterogeneous clinical symptoms of EIEE23 in line with the literature, we aim to make typical dysmorphic features and structural abnormalities recognizable and help genetic counseling.

ACKNOWLEDGMENT

We thank all the other departments of our hospital for their contributions to this article. We also thank the patient's parents for their cooperation.

DISCLOSURE

Ethics: Samples from the patient were obtained in accordance with the Helsinki Declaration. The paper is exempt from ethical committee approval. Ethical approval was not required for this study in accordance with local/national guidelines. Written informed consent for genetic testing was obtained from the patient parents. Written informed consent was obtained from the parent/legal guardian of the patient for publication of the details of their medical case and any accompanying images.

Financial support: None

Conflict of interest: None

Data Availability: All data generated or analyzed during this study are included in the references. Further inquiries can be directed to the corresponding author.

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