CASE REPORT: DOCK7 MUTATION AS A RARE CAUSE OF EPILEPTIC ENCEPHALOPATHY, CORTICAL BLINDNESS, DYSMORPHIC FINDINGS

Özlem Özsoy[1], Didem Soydemir[1], Çağatay Günay[1], Gamze Sarıkaya Uzan[1], Mehmet Can Yeşilmen[1], Ayşe Semra Hız[1], Uluç Yiş[1]

[1]Department of Pediatric Neurology, Dokuz Eylül University Faculty of Medicine, İzmir, Turkey

ICNC 2022
17th INTERNATIONAL CHILD NEUROLOGY CONGRESS
ANTALYA, TURKEY | OCTOBER 3-7, 2022

INTRODUCTION:

Epileptic encephalopathies (EE) are a heterogeneous group of disorders characterized by epileptic seizures causing cognitive and behavioral disturbances (1). EIEE, on the other hand, represents the group diagnosed in the early childhood period that is genetically heterogeneous and progresses with neurodevelopmental delays. Cases have social, cognitive, motor, language and behavioral impairment at varying levels as well as seizures. The genetic origin of EIEE patients can be identified in only half the patients with WES or targeted gene panels (2, 3, 4).

DOCK7 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 is known to regulate the neurogenesis of radial glial cells and enterokinetic nuclear migration during cortical development in interaction with *TACC3* (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) genetic autosomal disorder of recessive inheritance (OMIM #615859) (7). Patients are generally characterized by stubborn seizures occurring between 2 and 6 months, multifocal epileptic activity in 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, which was followed by other case reports (1,2,4,7,8,9). Characteristic features of our case are closely related with most of the findings reported for previous cases.

OBJECTIVE

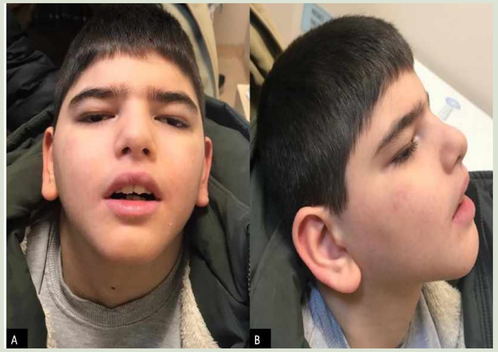
The present article aimed to present a pediatric patient diagnosed with EIEE23 associated with a novel homozygous, frameshift and pathogenic variant in *DOCK7* gene and to review the literature briefly in order to make it more familiar for clinicians.

MATERIALS & METHODS

Whole exome sequencing (WES) was performed in our case, which is consistent with the clinical pattern reported for DOCK7 deficiency, and data were analyzed with variant prioritization algorithms.

RESULTS

Our case, currently aged 7, was born to healthy parents of Turkish origin in a first-cousin marriage. He was born on the due date after a smooth pregnancy. No complication developed during delivery. He first applied as his parents noticed he did not have eye contact when he was 5 months old. His ophthalmologic examination revealed horizontal nystagmus in both eyes. Severe conduction defect was found in bilateral visual pathways in the VEP. Fundus examination and pupillary reactions were normal bilaterally. LHON was considered first and no mutation was seen in the whole mitochondrial genome analysis. When he was 6 months old, he had his first afebrile seizure characterized by eyelid myoclonia and clonic seizure of the right arm and leg after vaccination. Metabolic evaluations were normal. His EEG revealed epileptiform activity in the left fronto-centro-temporal region. No pathologic findings were detected on Echocardiogram (EKO), Cranial Magnetic Resonance (CMR) and MR spectroscopy. His *SCN1A* and *SCN2A* tests and chromosome analysis results were normal. Different types of seizures were seen in follow-ups like gelastic, drop head, versive, tonic-clonic, tonic, behavior arrest and impaired awareness. EEG recordings showed multifocal epileptic activity. Our 7-year-old case has delayed neuro-motor development and he is unable to sit without support, crawl, stand up without help, walk and eat. He has horizontal nystagmus and does not have visual communication with others. 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. The patient has 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 (Figures 1A and 1B). His repeated Cranial MRG 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 2A, 2B, 2C, 2D). The results of the WES showed that the c.5669dup (p.Cys1891ValfsTer2, C1891Vfs*2) mutation in exon 44 of *DOCK7* gene was homozygous. This frameshift variant has not been reported on the Clinvar database. It was evaluated as a pathogenic variant according to ACMG criteria (10). The pathogenic variants of *DOCK7* gene were associated with developmental and epileptic encephalopathy (OMIM#615859) indicating autosomal and recessive heredity.



Figures 1A and 1B

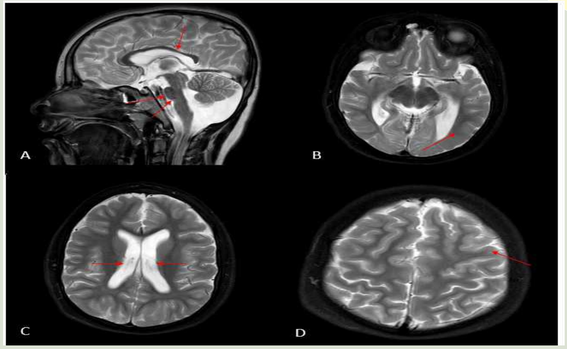


Figure 2A, 2B, 2C, 2D

CONCLUSIONS

DOCK7 function loss has been described in the genetic etiology for EIEE23 that shows infantile-onset epilepsy, severe neurodevelopmental delay, cortical blindness, typical facial features and structural abnormalities in the brain (1,2,4,7,8,9).

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.

REFERENCES

1-Perrault I, Hamdan FF, Rio M, Capo-Chichi JM, Boddaert N, Décarie JC, Maranda B, Nabbout R, Sylvain M, Lortie A, Roux PP, Rossignol E, Gérard X, Barcia G, Berquin P, Munnich A, Rouleau GA, Kaplan J, Rozet JM, Michaud JL. Mutations in DOCK7 in individuals with epileptic encephalopathy and cortical blindness. Am J Hum Genet. 2014 Jun 5;94(6):891-7

2- Kivrak Pfiffner F, Koller S, Ménétrey A, Graf U, Bähr L, Maspoli A, Hackenberg A, Kottke R, Gerth-Kahlert C, Berger W. Homozygosity for a Novel *DOCK7* Variant Due to Segmental Uniparental Isodisomy of Chromosome 1 Associated with Early Infantile Epileptic Encephalopathy (EIEE) and Cortical Visual Impairment. Int J Mol Sci. 2022 Jul 2;23(13):7382.

3-Epi4K Consortium; Epilepsy Phenome/Genome Project, Allen AS, Berkovic SF, Cossette P, Delanty N, Dlugos D, Eichler EE, Epstein MP, Glauser T, Goldstein DB, Han Y, Heinzen EL, Hitomi Y, Howell KB, Johnson MR, Kuzniecky R, Lowenstein DH, Lu YF, Madou MR, Marson AG, Mefford HC, Esmaeeli Nieh S, O'Brien TJ, Ottman R, Petrovski S, Poduri A, Ruzzo EK, Scheffer IE, Sherr EH, Yuskaitis CJ, Abou-Khalil B, Alldredge BK, Bautista JF, Berkovic SF, Boro A, Cascino GD, Consalvo D, Crumrine P, Devinsky O, Dlugos D, Epstein MP, Fiol M, Fountain NB, French J, Friedman D, Geller EB, Glauser T, Glynn S, Haut SR, Hayward J, Helmers SL, Joshi S, Kanner A, Kirsch HE, Knowlton RC, Kossoff EH, Kuperman R, Kuzniecky R, Lowenstein DH, McGuire SM, Motika PV, Novotny EJ, Ottman R, Paolicchi JM, Parent JM, Park K, Poduri A, Scheffer IE, Shellhaas RA, Sherr EH, Shih JJ, Singh R, Sirven J, Smith MC, Sullivan J, Lin Thio L, Venkat A, Vining EP, Von Allmen GK, Weisenberg JL, Widdess-Walsh P, Winawer MR. De novo mutations in epileptic encephalopathies. Nature. 2013 Sep 12;501(7466):217-21

4-Haberlandt E, Valovka T, Janjic T, Müller T, Blatsios G, Karall D, Janecke AR. Characteristic facial features and cortical blindness distinguish the DOCK7-related epileptic encephalopathy. Mol Genet Genomic Med. 2021 Mar;9(3):e1607

5-Watabe-Uchida, M., John, K. A., Janas, J. A., Newey, S. E., & Van Aelst, L. (2006). The Rac activator DOCK7 regulates neuronal polarity through leocal phosphorylation of stathmin/Op18. Neuron, 51, 727–739 (2)

6-Yang YT, Wang CL, Van Aelst L. DOCK7 interacts with TACC3 to regulate interkinetic nuclear migration and cortical neurogenesis. Nat Neurosci. 2012 Sep;15(9):1201-10.

6-Yang YT, Wang CL, Van Aelst L. DOCK7 interacts with TACC3 to regulate interkinetic nuclear migration and cortical neurogenesis. Nat Neurosci. 2012 Sep;15(9):1201-10.

7-Bai B, Guo YR, Zhang YH, Jin CC, Zhang JM, Chen H, Zhu BS. Novel DOCK7 mutations in a Chinese patient with early infantile epileptic encephalopathy 23. Chin Med J (Engl). 2019 Mar 5;132(5):600-603.

8-Turkdogan D, Turkyilmaz A, Gormez Z, Sager G, Ekinci G. A novel truncating mutation of DOCK7 gene with an early-onset non-encephalopathic epilepsy. Seizure. 2019 Mar;66:12-14.

9-Nashabat M, Al Qahtani XS, Almakdob S, Altwaijri W, Ba-Armah DM, Hundallah K, Al Hashem A, Al Tala S, Maddirevula S, Alkuraya FS, Tabarki B, Alfadhel M. The landscape of early infantile epileptic encephalopathy in a consanguineous population. Seizure. 2019 Jul;69:154-172.