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Clinical letter

A novel truncating mutation of *DOCK7* gene with an early-onset non-encephalopathic epilepsy

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DOCK7 (MIM:615730) plays a key role in neurogenesis by promoting the differentiation and transition of radial glial cells to basal progenitors and neurons [1]. *DOCK7* also regulates tangential neuroblast migration in the postnatal mouse forebrain [2].

Recently, a new phenotype of early infantile epileptic encephalopathies (EIEE23, MIM: 615859) was reported in 3 girls from 2 families with 4 different compound heterozygous truncating mutations in *DOCK7* [3]. Here, we report a boy with infantile onset well-controlled non-encephalopathic epilepsy and severe neurodevelopmental delay associated with a novel homozygous truncating mutation in DOCK7.

1. Case report

The proband, aged 35 months, born at 40 weeks with an uneventful history. The Turkish parents are healthy and first cousins once removed (Fig. 1A). They did not notice any issues regardingthe neurological development of the baby until 3.5 months of age when he presented with a generalized tonic-clonic seizure evolving to status epileptics. Neurological examination showed severe neurodevelopmental delay and lack of eye contact. Ophthalmologic examination was normal except prolonged latencies of flash VEP commented as 'cortical blindness'. He had frequent focal motor seizures which stopped after clobazam add on therapy at 13 months of age after being referred to our hospital and has been seizure free since then. Initial EEG examinations showed generalized sharp waves. Resolution of EEG progressively occurred: focal epileptiform discharges were recorded at 18 months of age and he has had normal EEG findings for the past 16 months.

Neurological examination currently shows delayed gross and fine motor functions(about at the developmental level of 15 and 8 months, respectively), lack of any visual contact with faces or objects, joint attention, social jests, or pretend play. He has intense mouthing objects. He notices the strangers and follows some simple verbal commands but no speech even vocalization is present. Dysmorphic features include normo-brachycephaly, narrow forehead, low anterior hairline, wide and anteverted nasal tip, prominent ears, full cheeks, long eyelashes, smooth and short philtrum and thin upper lip.

Cranial MRI examination at 33 months of age showed an abnormally marked pontobulbar sulcus associated with pontine hypoplasia, a thin corpus callosum, absence of interventricular septum, slight interdigitation of gyri across the interhemispheric fissure, and atrophy in the white and gray matter of the occipital lobe with increased signal on both T2 and FLAIR images (Fig. 2).

Metabolic screening and chromosomal microarray testing were unrevealing. He was analyzed by whole exome sequencing as a part of a project aimed at genetic analysis of early onset epilepsy patients. Details of the analysis are given as supplementary data.

A novel homozygous nonsense variant (Chr 1: 63003683T&gt,A GRCh37/hg19, NM_033407: c.3257T&gt,A, NP_212132:p.Leu1086*) in exon 27 of *DOCK7* was identified (Fig. 1B). The present variant confirmed by Sanger sequencing was not found in ESP, ExAC, 1000G, and gnomAD. His unaffected parents were heterozygous for this variant.

Family history did not comprise any similar epilepsy phenotype or febrile seizures.

All experimental procedures were conducted in accordance with recommendations of Ethics Committee of Marmara University and informed consent was obtained from parents

2. Discussion

The present variant, classified as pathogenic according to ACMG criteria [4], leads to a premature stop codon and is predicted to result in

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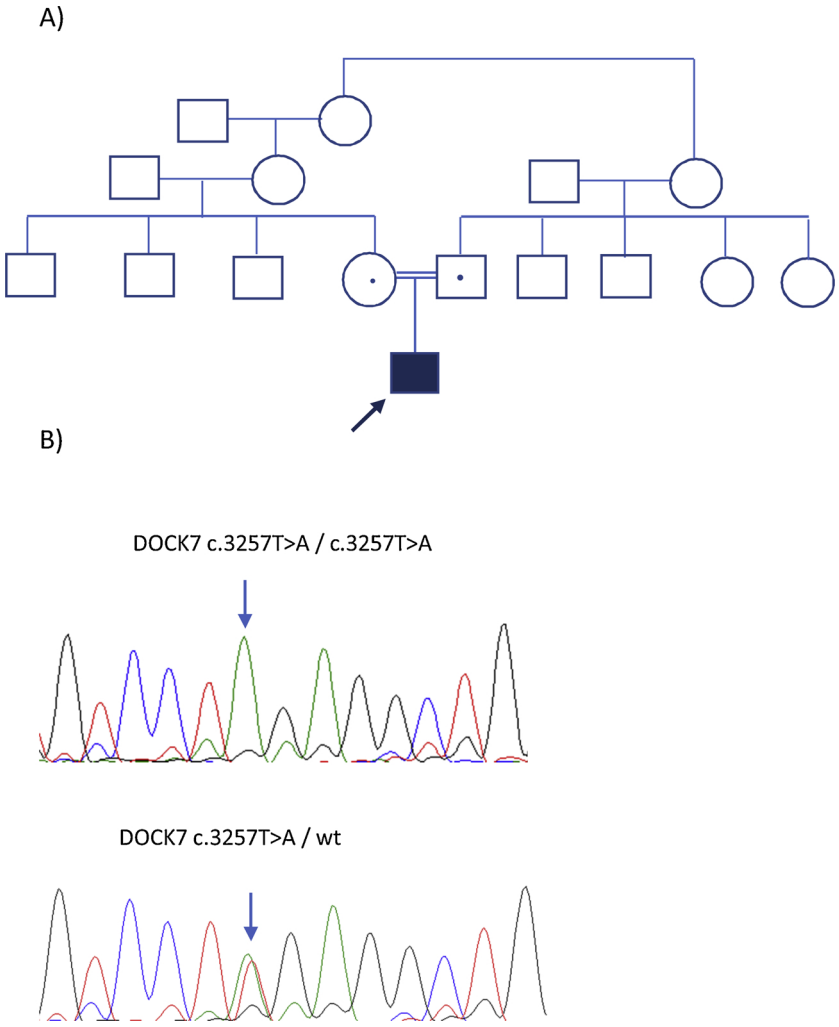

Fig. 1. A) Pedigree of the family B) Top: Index case mutation (c.3257 T > A homozygous) Bottom: parents' mutation (c.3257 T > A heterozygous) wt: wild-type.

a truncation of *DOCK7* after 1086 of 2109 amino acids and/or in nonsense-mediated mRNA decay (NMD). As a stop gain mutation locates in exon 27, post-transcriptional mRNA quality control mechanism (nonsense mediated decay) eliminates the mRNA of *DOCK7* containing this premature termination codon. Similarly, the reported 4 compound heterozygote mutations are located in upstream exons, and are proposed as having the potential to induce nonsense-mediated decay of the corresponding mRNA [3].

Our patient gained some developmental skills with regard to motor and limited nonverbal interactions, but the presence of some autistic features and lack of verbal skills imply a specific clinical picture associated with truncating mutations of *DOCK7*. The dysmorphic features and structural brain abnormalities are the main complementary findings of this rare entity. Contrary to 3 intractable EIEE patients firstly reported by Perrault et al. [3], our patient presents a drug-responsive non-encephalopathic epilepsy despite remaining similar clinical features. However, we do not have the long-term prognosis of epilepsy in our case.

The radiological findings in 2 of 3 original cases were marked pontobulbar sulcus and abnormal MRI signals with atrophy in the occipital lobe [3]. We found the same findings as well as interdigitation of gyri across the interhemispheric fissure and absence of interventricular septum. The presence of various brain abnormalities affecting both cortical and myelin formation in that phenotype may be related with the distinct roles of *DOCK7* in different cell types by interacting with a variety of protein complexes during the embryonic neurogenesis and

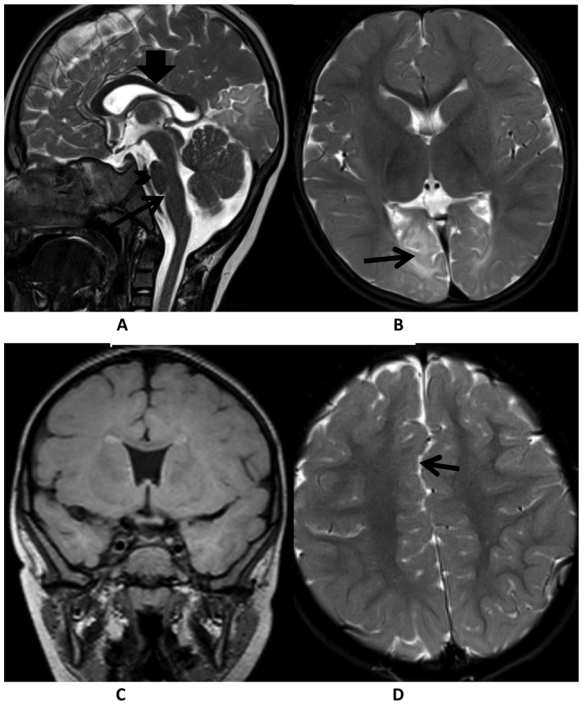

Fig. 2. MR images of the patient; Sagital T2 weighted image (A) shows abnormally marked pontobulbar sulcus (arrow) associated with pontine hypoplasia (arrow head), and thin corpus callosum (thick arrow). Axial T2 weigted image (B) reveals increased signal and atrophy in the white and gray matter of the occipital lobe (arrow). Coronal T1 weighted image (C) shows absence of interventricular septum. Axial T2 weigted image (D) shows mild interdigitation of gyri across the interhemispheric fissure (arrow).

also in the postnatal migration [1–3].

We presented a new case with a novel homozygous truncating mutation of *DOCK7* displaying specific clinical and radiological features similar to the original report except for a well-controlled infantile-onset epilepsy.

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Conflict of interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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