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ORIGINAL ARTICLE

Characteristic facial features and cortical blindness distinguish the *DOCK7*-related epileptic encephalopathy

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Abstract

Background: The epileptic encephalopathies display extensive locus and allelic heterogeneity. Biallelic truncating *DOCK7* variants were recently reported in five children with early-onset epilepsy, intellectual disability, and cortical blindness, indicating that DOCK7 deficiency causes a specific type of epileptic encephalopathy.

Methods: We identified 23- and 27-year-old siblings with the clinical pattern reported for DOCK7 deficiency, and conducted genome-wide linkage analysis and WES. The consequences of a *DOCK7* variant were analyzed on the transcript and protein level in patients' fibroblasts.

Results: We identified a novel homozygous *DOCK7* frameshift variant, an intragenic tandem duplication of 124-kb, previously missed by CGH array, in adult patients. Patients display atrophy in the occipital lobe and pontine hypoplasia with marked pontobulbar sulcus, and focal atrophy of occasional cerebellar folia is a novel finding. Recognizable dysmorphic features include normo-brachycephaly, narrow forehead, low anterior and posterior hairlines, prominent ears, full cheeks, and long eyelashes. Our patients function on the level of 4-year-old children, never showed signs of regression, and seizures are largely controlled with multi-pharmacotherapy. Studies of patients' fibroblasts showed nonsense-mediated RNA decay and lack of DOCK7 protein.

Conclusion: DOCK7 deficiency causes a definable clinical entity, a recognizable type of epileptic encephalopathy.

KEYWORDS

cortical blindness, *DOCK7*, epileptic encephalopathy, nonsense-mediated RNA decay, recognizable syndrome

Edda Haberlandt and Taras Valovka contributed equally to this work.

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1 | INTRODUCTION

The early infantile epileptic encephalopathies (EIEE) represent a large and genetically heterogeneous group of neurodevelopmental disorders diagnosed during early childhood. Variable degrees of social, cognitive, motor, language, and behavioral impairments are observed. Seizures supposedly contribute to developmental impairment and regression (Scheffer et al., 2017). Whole exome sequencing (WES) or targeted gene panels enable a genetic diagnosis in about 30% of EIEE patients. Genetic diagnoses can lead to more accurate treatment in up to 25% of the epilepsy patients, that is, they are required for precision medicine (Heyne et al., 2019; Moller et al., 2019). However, genes whose mutations are known to cause EIEE are most often associated with overlapping and non-specific phenotypes, complicating the establishment of etiological diagnoses.

Recently, a specific phenotype of EIEE (EIEE23, OMIM 615859) was suggested based on the findings in five children aged 3–10 years, who harbored biallelic truncating mutations in the *DOCK7* (dedicator of cytokinesis 7) gene (OMIM 615730), that were supposed but not shown to trigger nonsense-mediated mRNA decay (NMD) (Bai et al., 2019; Perrault et al., 2014; Turkdogan et al., 2019). *DOCK7* encodes a guanine nucleotide exchange factor (GEF) that plays a role in axon formation and neuronal polarization (Watabe-Uchida et al., 2006).

We report an adult sibling-pair displaying the pattern of EIEE23; these patients function on the level of 4-year-old children with largely controlled seizures. We identify a novel homozygous truncating *DOCK7* variant, and show that it abrogates protein production.

2 | MATERIALS AND METHODS

2.1 | Ethical compliance

Written informed consent for molecular genetic studies and publication of data was obtained, and the ethics committee of the Medical University of Innsbruck approved the study. Linkage analysis and WES were performed as reported (Baumann et al., 2017; Waich et al., 2020), and breakpoint sequencing and functional studies are described in Supporting Information.

3 | RESULTS

3.1 | Clinical characteristics

The two female patients (P1 and P2) are 27 and 23 years old. They were born at term after unremarkable pregnancy and delivery to healthy, consanguineous Austrian parents. Their neonatal course was uneventful, except for the discovery of an atrial septal defect in P2, for which the child was operated on at 5 years of age. Both sisters presented with infantile spasms at 6 months of age, which occurred as many as 50 times a day. Over the next months, both patients showed different types of seizures, including myoclonus, partial complex seizures with rotation of the head, drop attacks, and tonic seizures. Control was initially poor in both sisters despite the administration of multiple antiepileptic drugs in various combinations. Electroencephalography (EEG) performed at 11 months of age in P1 and at 5 months of age in P2 showed a pattern consistent with hypsarrhythmia. Subsequent EEG studies showed multifocal epileptic activity in both sisters. Current antiepileptic therapy consists of levetiracetam, clobazam, zonisamide, and midazolam to terminate prolonged seizures.

Lack of reaction to visual stimuli was evident during the first months of life; a fine horizontal and vertical nystagmus in both eyes and lack of object fixation first suggested Leber congenital amaurosis (LCA) in both patients. However, pupillary reactions and fundoscopy were normal in both sisters, and the scotopic flash evoked visual potentials (FEVP) showed a normal waveform of markedly decreased amplitude in both patients, which led to a diagnosis of cortical blindness. A photopic Ganzfeld electroretinogram (GF-ERG) showed mildly reduced amplitudes in P1 at 20 years of age, indicating some degree of retinal dysfunction; scotopic testing was not possible due to lack of cooperation. Currently, both individuals still display grossly abnormal visual pursuit, but can ambulate with moderate speed in known environment. P1 correctly identifies large objects and colors, and P2 has nearly no vision.

Patients' adult body height and occipitofrontal head circumference measures are 163, 164, 56 and 54 cm, respectively, and they are mildly obese. Patients show recognizable facial features (Figure 1, P1 and P2). Both patients entered and completed puberty at appropriate age.

P1 and P2 started to walk at 20 months of age, and today patients require assistance to ambulate in unknown environment. Both patients can eat by themselves, can brush their teeth unaided, and are continent by day since age 12 years. Both patients rarely point or use their hands to communicate, but can use objects and perform easy tasks in a sheltered workshop; P1 can assemble a 48-piece puzzle, and P2 can cut vegetables in the community kitchen. Both patients speak grammatically correct sentences, referring to simple subjects, and understand simple commands, and can designate body parts on demand. They can smile in and out of social context. They display nearly no visual contact. Overall, their skills were rated as on the level of 4-year-old children by using the SON-R 2½-7 non-verbal intelligence test, and by non-formal clinical assessment, and they never showed

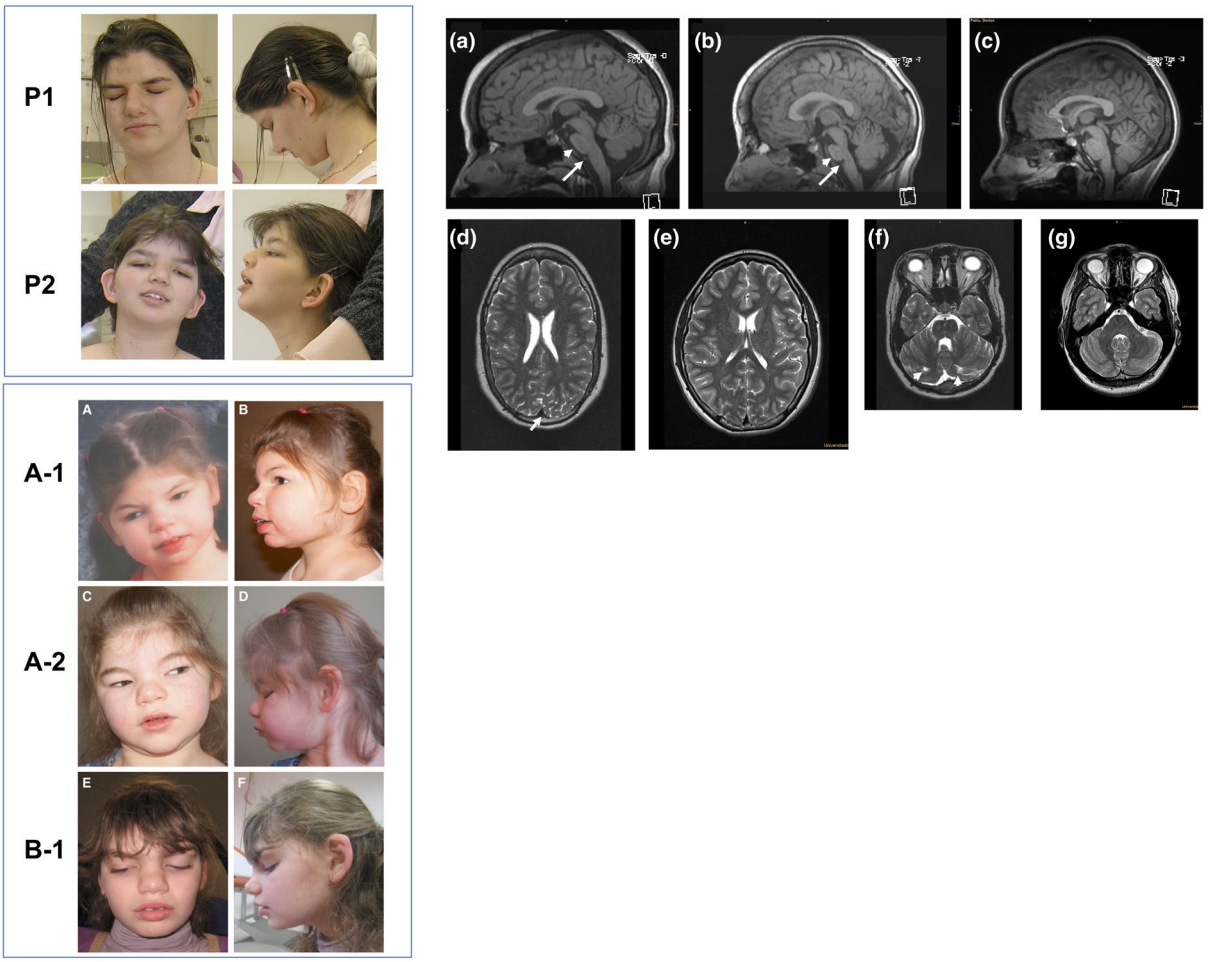

FIGURE 1 Typical dysmorphic facial features and typical brain MRI abnormalities in EIEE23. Photographs of P1 and P2 at 19 and 15 years of age. Normo-brachycephaly, narrow forehead, low anterior and posterior hairlines, protruding and low-set ears, wide and anteverted nasal tip, full cheeks and periorbital fullness, long eyelashes, smooth and short philtrum and thin upper lip, and highly arched palate are present in P1 and P2, as in three reported patients (A1, A2, and B1, reprinted with permission). Pontine hypoplasia of different degree (arrow heads) with abnormally marked pontobulbar sulci (arrows) in P1 at age 20 years (a) and P2 at age 16 years (b) as compared to age-matched control (c) (T1, sagittal sections). (d) Cortical and subcortical atrophy of occipital gyri in P2 at age 16 years as compared to age-matched control (e), and (f) focal atrophy of cerebellar folia in P2, and (g) age-matched control (T2, transverse section)

signs of regression. Neurological examination was otherwise unremarkable.

A metabolic work-up, including plasma triglycerides, cholesterol, amino acid concentrations, and urine organic acid chromatography, was normal in both sisters.

All previously reported structural brain abnormalities were present in both siblings, but the focal atrophy of cerebellar folia is a novel finding (Figure 1a–g).

Major clinical findings of our and of reported patients are compiled in Table 1.

3.2 | Genetic and protein studies

Linkage analysis with all individuals in generations III-V excluded 97% of the genome to harbor the disease locus (Figure 2a,b). WES analysis in P1 identified homozygosity for an intragenic 124-kb tandem duplication in *DOCK7* (NC_000001.11:g.62527474_62651054dup, NM_001271999.1:c.390_3936dup), comprising exons 5–31, as determined by genomic breakpoint and by fibroblast cDNA sequencing (Figure 2c,d). The duplication causes a frameshift and DOCK7 deficiency (Figure 2e) via NMD, as demonstrated by partial mRNA rescue with NMD inhibitor puromycin prior to fibroblast culture harvesting. To detect residual DOCK7 protein in whole-cell lysates, a polyclonal antibody raised in Rabbit with a synthetic peptide corresponding to a region within amino acids 175–225 of human DOCK7 was used.

This duplication also contains the complete *ANGPTL3* gene, which resides within exon 14 of *DOCK7* and is transcribed from the other strand. ANGPTL3 deficiency

TABLE 1 *DOCK7* variants in patients with a recognizable type of epileptic encephalopathy

Reference	This study		Bai et al. (2019)	Perrault et al. (2014)			Turkdogan et al. (2019)
Patient ID	P1	P2	C	Patient A-1	Patient A-2	Patient B-1	D
Age (years)	27	23	3	7	5	10	3
Sex	Female	Female	Female	Female	Female	Female	Male
Ethnicity	Austrian	Austrian	Chinese	French-Canadian	French-Canadian	French	Turkish
Parental consanguinity	Yes	Yes	No	No	No	No	Yes
DOCK7 variants[a]	Homozygous	Homozygous	Compound-het.	Compound-het.	Compound-het.	Compound-het.	Homozygous
Variant type	Intragenic 124 kb tandem duplication	Intragenic 124 kb tandem duplication	Splice/stop	Stop/frameshift	Stop/frameshift	Stop/stop	Stop
cDNA variant[b]	c.390_3936dup	c.390_3936dup	c.5929-1G>C/c.2479C>T	c.3709C>T/c.2510delA	c.3709C>T/c.2510delA	c.983C>G/c.6232G>T	c.3350T>A
Protein variant	Loss of protein[c]	Loss of protein[c]	p.?/p.Arg827[a]	p.Arg1237[a]/p.Asp837Alafs[a]48	p.Arg1237[a]/p.Asp837Alafs[a]48	p.Ser328[a]/p.Glu2078[a]	p.Leu1117[a]
hg19 position	NC_000001.10:g.62993145_63116725dup	NC_000001.10:g.62993145_63116725dup	NC_000001.10:g.62941023C>G /	NC_000001.10:g.62995020G>A/ NC_000001.10:g.63021582delT	NC_000001.10:g.62995020G>A/ NC_000001.10:g.63021582delT	NC_000001.10:g.63100496G>C/ NC_000001.10:g.62923324	NC_000001.10:g.63003683A>T
Age of onset and initial frequency of seizures	6 months 100 times/day	6 months 100 times/day	6 months 20 times/day	Between 2 and 4 months	Between 2 and 4 months 50 times/day	6 months	3.5 months
Types of observed seizures	BNS, myoclonus, partial complex seizures with rotation of the head, drop attacks, and tonic seizures	BNS, myoclonus, partial complex seizures with rotation of the head, drop attacks, and tonic seizures	Infantile spasm	Tonic seizures infantile spasms seizures, despite antiepileptic therapy	Tonic seizures myoclonus partial complex seizures with rotation of the head, drop attacks, and tonic seizures seizures, despite antiepileptic therapy	Eye revulsion, rhythmic arm and body movements. Short absences	Status epilepticus frequent focal motor seizures
	Currently, seizure-free under antiepileptic therapy	Currently, short absences despite antiepileptic therapy		Ineffective ketogenic diet	Ineffective ketogenic diet	When last seen, repeated tonic-clonic seizures, despite antiepileptic therapy	Seizure-free from 13 months with clobazam
EEG, initial and on follow-up	Hypsarrhythmia, multifocal epileptic activity	Hypsarrhythmia, multifocal epileptic activity	Hypsarrhythmia, multifocal epileptic activity	Hypsarrhythmia, multifocal epileptic activity	Multifocal epileptic activity	Multifocal epileptic activity with occasional electroclinical spasms	Initial EEG examinations showed generalized sharp waves
cMRI	(at age 20 years) Abnormally marked pontobulbar sulcus, mild pontine hypoplasia, atrophy in occipital white and gray matter	(at age 16 years) Abnormally marked pontobulbar sulcus, mild pontine hypoplasia, atrophy in occipital white and gray matter. Focal atrophy of occasional cerebellar folia	(at age 3 years) Abnormally marked pontobulbar sulcus, mild pontine hypoplasia, thin corpus callosum, dilation of lateral ventricles, pachygyria	(at age 25 months) Abnormally marked pontobulbar sulcus, mild pontine hypoplasia, a thin and short corpus callosum, and abnormal signals (T2 hyperintensities) with atrophy in the occipital white and gray matter	(at age 8 months) Mild hypoplasia of the corpus callosum	(at age 2 years) Abnormally marked pontobulbar sulcus, mild pontine hypoplasia, and abnormal signals (T2 hyperintensities) with atrophy in the occipital white and gray matter	(at age 33 months) Marked pontobulbar sulcus, pontine hypoplasia, and thin corpus callosum. Increased signal and atrophy in the white and gray matter of the occipital lobe. Absence of interventricular septum. Mild interdigitation of gyri across the interhemispheric fissure

(Continues)

TABLE 1 Continued

Facial features	Low anterior and posterior hairline, highly arched palate, some periorbital fullness, telecanthus, long eyelashes, a broad nasal tip. Low-set and protruding ears. Smooth and short philtrum and thin upper lip	Low anterior and posterior hairline, highly arched palate, periorbital fullness, telecanthus, long eyelashes, a broad nasal tip with anteverted nares. Low-set and protruding ears	Low posterior hairlines, highly arched palate, gingival maldevelopment, telecanthus, long eyelashes, low-set, abnormally shaped and protruding ears, periorbital fullness, broad nasal tip, large nasal root	Low anterior hairline, some periorbital fullness, telecanthus, long eyelashes, a broad nasal tip with anteverted nares	Low anterior hairline, some periorbital fullness, telecanthus, long eyelashes, a broad nasal tip with anteverted nares	Bitemporal narrowness, a low anterior hairline, thick eyebrows, synophrys, telecanthus, long eyelashes, enophthalmia, large and prominent nasal root, a bulbous nasal tip, a thick helix and earlobes, a short philtrum, full lips and everted lower lip, spaced incisors	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
Eye abnormality	Lack of reaction to visual stimuli during the first months of life; a fine horizontal and vertical nystagmus in both eyes, and lack of object fixation. Normal pupillary reactions and fundoscopy. FEVP: normal waveform of markedly decreased amplitude, cortical blindness. Photopic GF-ERG: mildly reduced amplitudes. Identifies large objects and colors	Lack of reaction to visual stimuli during the first months of life; a fine horizontal and vertical nystagmus in both eyes, and lack of object fixation. Normal pupillary reactions and fundoscopy. FEVP: normal waveform of markedly decreased amplitude, cortical blindness. Nearly no vision	Lack of ocular reaction to visual stimulus, binoculus optometric obstacles, horizontal optokinetic nystagmus, left strabismus. Flash evoked visual potentials (FEVP) show abnormal waveform including a longer latency in right eye and decreased amplitude in both eyes cortical blindness	Normal eye movements, pupillary reaction, and fundus. Lack of ocular reaction to visual stimulus, binoculus optometric obstacles, cortical blindness. Currently, grossly normal visual pursuit, although with difficulty following objects in the upper visual fields	Normal eye movements, pupillary reaction, and fundus. Lack of ocular reaction to visual stimulus, binoculus optometric obstacles, cortical blindness. Can follow a moving object, but does not see well enough to play with toys	Lack of ocular reaction to visual stimulus, cortical blindness. Evoked visual potentials were unremarkable, but electroretinographic (ERG) traces were ambiguous. Ophthalmological examinations repeated at 2 and 9 years of age showed unchanged retinal aspect and normal ERG traces, leading to the diagnosis of cortical blindness. Currently, there are wandering eye movements and a complete absence of reaction to visual threat and light stimulation	Normal ophthalmologic examination except for prolonged latencies of FVEP, cortical blindness
Heart	Normal	Atrial septal defect	Atrial septal defect	Aortic supravalvular stenosis, bicuspid valve	Normal		
Language	Understands and speaks grammatically correct sentences of a few words, make use of cell phones, follow simple commands, can designate body parts on demand	Understands and speaks grammatically correct sentences of a few words, make use of cell phones, follow simple commands, can designate body parts on demand	Lack of speech	Lack of speech, understands a few simple commands	Speaks 30 words and associates two words. She can designate body parts on demand and understand simple commands	Repeating three words, understands simple commands	Lack of speech, follows some simple verbal commands

(Continues)

TABLE 1 Continued

Psychomotor development	Started to walk at 20 months of age. Today, requires assistance to ambulate in unknown environment. Can eat by herself, can brush her teeth unaided, and is continent by day since age 12 years. Rarely point or uses her hands to communicate, but can use objects and perform easy tasks in a sheltered workshop; can assemble a 48-piece puzzle. Displays nearly no visual contact	Started to walk at 20 months of age. Today, requires assistance to ambulate in unknown environment. Can eat by herself, can brush her teeth unaided, and is continent by day since age 12 years. Rarely point or uses her hands to communicate, but can use objects and perform easy tasks in a sheltered workshop; Displays nearly no visual contact	Walking unstably at 28 months, sits, crawls and stands by herself	Walking at 20 months, with help. Cannot eat by herself, does not point or use her hands to communicate	Walking at 28 months, can run, cannot jump. Eats with a spoon and has a pincer grasp but cannot point to objects	Moderate hypotonia, walking at 22 months, can walk without help in known environments. Can grasp objects, but not point or communicate with hands. Brings a spoon to her mouth, but cannot eat by herself	At 35 months 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.

[a]None of these variants is listed in gnomAD.

[b]Coding sequence nomenclature refers to NCBI reference NM_001271999.1/Ensembl reference ENST00000454575.6.

[c]Loss of protein as determined in patients' fibroblasts; FEVP, Scotopic flash evoked visual potentials; GF-ERG, Ganzfeld electroretinogram.

was associated with a form of hypobetalipoproteinemia (Musunuru et al., 2010); our patients apparently have four intact copies of ANGPTL3 and repeatedly normal serum lipid levels.

Conventional karyotyping after GTG-banding at a 500 band resolution showed normal female karyotypes, 46,XX. Chromosomal microarray analysis (Illumina HumanCytoSNP-12v2 BeadChip SNP array with 300 k markers) in P1 had missed the homozygous *DOCK7* duplication due to a sparsity of markers in the region.

4 | DISCUSSION

We report here, to the best of our knowledge, for the first time the outcome of DOCK7 deficiency in two adult patients and corroborate the hypothesis that there is a distinctive EIEE23 phenotype that consists of an infantile-onset epilepsy, severe neurodevelopmental delay, cortical blindness, and the typical facial features and common brain abnormalities described above. Additional developmental brain abnormalities were present in single patients each, such as focal atrophy of cerebellar folia in P2, the interdigitation of gyri across the interhemispheric fissure and the absence of the interventricular septum (Turkdogan et al., 2019), and pachygyria and dilation of lateral ventricles (Bai et al., 2019).

In six of seven patients reported to date, epilepsy was largely controlled by multi-pharmacotherapy, onward from the ages of 16 months to 6 years. Importantly, our two patients continuously acquired skills, in particular attention span and social communication skills over the years, and participate in daily life at home and outside.

This outcome appears encouraging with respect to the five children previously described with biallelic truncating *DOCK7* mutations, at ages 3–10 years, and who all showed severe psychomotor retardation; there was no speech development in three of five patients, 30 words at age 5 years in one patient and repeating the last three words of sentences at age 10 years in another patient. Only one patient was able to eat with a spoon at age 7 years.

CNV calling in WES data identified a frameshifting triplication of exons 5–31 of the DOCK7 gene in the proband. To the best of our knowledge, we are the first to demonstrate NMD and DOCK7 deficiency in patients' fibroblasts as the consequence of a truncating *DOCK7* variant, although biallelic truncating mutations were identified in all five previously reported patients (Bai et al., 2019; Perrault et al., 2014; Turkdogan et al., 2019).

DOCK7 plays a key role in neurogenesis by promoting the differentiation and transition of radial glial cells to basal progenitors and neurons (Yang et al., 2012). *DOCK7* also regulates tangential neuroblast migration in the postnatal mouse forebrain given that knockdown of *DOCK7* alone

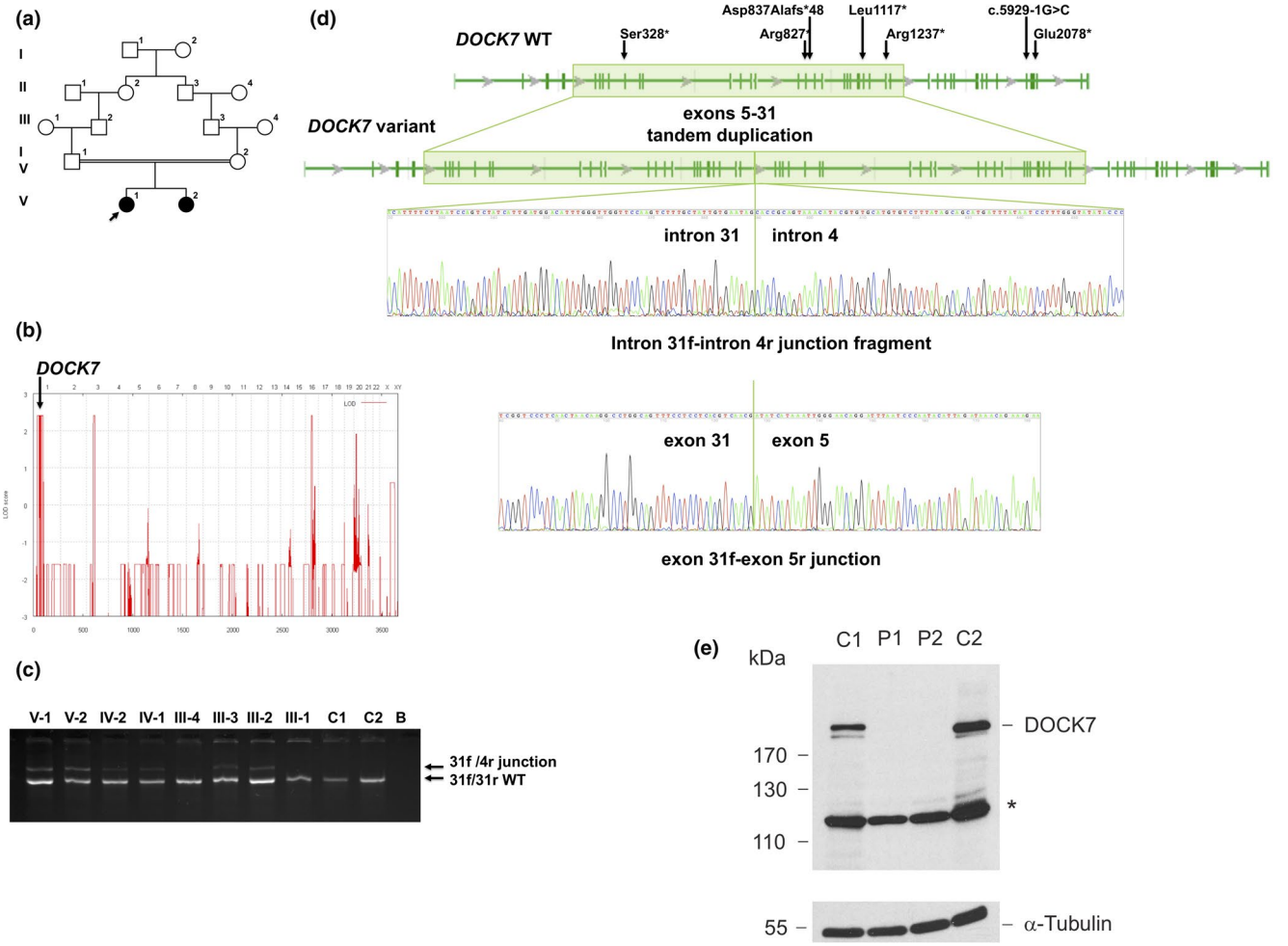

FIGURE 2 Identification of a novel truncating *DOCK7* variant in EIEE23. (a) Family under study and (b) homozygosity mapping results. (c) Duplex PCR amplifies part of *DOCK7* intron 31 and an abnormal intron 31-intron 4 junction fragment in heterozygotes and homozygotes for a large intragenic tandem duplication in *DOCK7* (d); previously identified *DOCK7* variants are indicated. (e) DOCK7 protein is lacking in patients' fibroblasts

is sufficient to cause defects in neurogenesis (Nakamuta et al., 2017). *DOCK7* is expressed in GABAergic interneurons in the central nervous system. The reduced ERG amplitudes in our patient might indicate the involvement of GABAergic retinal amacrine cells as well as *DOCK7* expression in the retina, which would need to be addressed with further studies.

It is of interest that a strong conserved craniofacial-specific enhancer (identifier: GH01J062686) localizes within and around exon 1 of *DOCK7* (Wilderman et al., 2018). It remains highly speculative to suggest that premature stop codons in the downstream coding sequence alter the pattern of transcription factor binding to this craniofacial-specific enhancer and thereby lead to the recognizable syndromic features of patients with DOCK7 deficiency.

Altogether, our observation validates the hypothesis that loss of DOCK7 function causes a recognizable form of EIEE, with the hallmarks of cortical blindness and common developmental brain abnormalities, and might potentially be clinically diagnosed based on the shared facial features.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

AUTHOR CONTRIBUTIONS

EH and ARJ participated in the conception of the study. ARJ drafted the manuscript. All authors collected and analyzed data, interpreted the results, and revised the manuscript. All authors read and approved the final manuscript.

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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SUPPORTING INFORMATION

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

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