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Clinical diversity of different genetic variants changes the way we look at diseases; Two cases of ACTL6B gene-related DECAM syndrome

[1]Canan Üstün, [2]Ayşe Nur Coşkun, [3]Mutluay Arslan, [4]Deniz Torun, [3]Bülent Ünay

[1]Department of Pediatrics, Division of Child Neurology, Ankara Etlik City Hospital, Ankara, Türkiye; [2]Department of Pediatrics, Division of Child Neurology, Ankara Atatürk Sanatoryum Education And Research Hospital, Ankara, Türkiye; [3]Department of Pediatrics, Division of Child Neurology, University of Health Sciences, Gülhane Training and Research Hospital, Ankara, Türkiye; [4]Department of Medical Genetics, University of Health Sciences, Gülhane Training and Research Hospital, Ankara, Türkiye

Abstract

Developmental Delay, Epileptic Encephalopathy, Cerebral Atrophy, and Abnormal Myelination syndrome (DECAM syndrome) is a rare autosomal recessive neurodevelopmental disorder with developmental delay, epileptic encephalopathy, cerebral atrophy, severe intellectual disability, and autistic features. It is also called Developmental and Epileptic Encephalopathy 76 (DEE76). In this report, we present two cases of DECAM syndrome, a 5-year-old boy and a 9-year-old girl, who presented with refractory seizures, microcephaly and severe developmental delay. Although both patients had homozygous mutation in the ACTL6B gene, the time of onset and clinical severity of the disease were different. We attributed this to the mutations being in different regions and aimed to emphasize the importance of genotype-phenotype correlation.

Keywords: Developmental and epileptic encephalopathy, early infantile epileptic encephalopathy, ACTL6B gene, DECAM syndrome

INTRODUCTION

DECAM syndrome is a rare autosomal recessive neurodevelopmental disorder causing severe global motor and cognitive impairment. Affected children have growth failure, microcephaly, dysmorphic features, scoliosis, severe intellectual disability and autistic traits. Neurologically, early-onset drug-resistant epileptic encephalopathy leads to absence of speech and independent ambulation and may be fatal in childhood.[1,2]

We report here two unrelated children (a 5-year-old boy and a 9-year-old girl) with refractory seizures, microcephaly and severe developmental delay, both harboring homozygous ACTL6B variants and diagnosed with DECAM syndrome (DEE76, OMIM: 618468). Clinical characteristics are summarised in Table 1.

Patient 1

A 5-year-old boy first presented at 18 days of life with focal seizures (gaze fixation and spasms) evolving to generalized tonic–clonic events, occurring 6–7 times per day. He was born at term by caesarean section (2980 g) to non-consanguineous parents, with an unremarkable perinatal history and normal initial laboratory tests and cranial ultrasound. Levetiracetam (LEV) and vitamin B6 provided only partial seizure control.

He displayed global developmental delay with poor head growth and absent eye contact, tracking, speech and motor milestones. EEG at 2 years showed right temporo-occipital spikes and multifocal spike–wave discharges. Karyotype and microarray were normal. Whole-exome sequencing (WES) revealed a homozygous ACTL6B variant of uncertain significance, c.85G>A (NM_016188.5, p.G29R) in exon 2,

Address correspondence to: Canan Üstün, MD, Division of Pediatric Neurology, Department of Pediatrics, Ankara Etlik City Hospital, Ankara, Turkey. E-mail: drcananustun@hotmail.com

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Table 1: The characteristics of the patients

	Patient 1	Patient 2
cDNA	c.85G>A	c.1267C>T
Protein	p.G29R	p.Arg423*
Mutation type	Recessive, homozygos	Recessive, homozygos
Gender	Male	Female
Consanguinity of parents	No	Yes (cousins)
Family history	Mother, father heterozygos +	Mother, father, one of her brother heterozygos +
Motor delay	Yes	Yes
Hypotonia in infancy	Yes	Yes
Intellectual disability	Severe	Moderate
ASD	No	No
Epilepsy	Yes	Yes
Seizure type	Spasm, GTC	Hypotonic, GTC
Age of seizure onset	18 days of life	5 years
Status epilepticus	Yes	No
EEG	Right temporo-occipital multifocal spike-wave	Bilateral frontal and temporal spike-polispike-wave
Current ASMs	VPA+VGB	VPA+CLB
Previous ASMs	TPM, LEV, CLB, LCZ	CLN, LTG, LEV
Other findings	Thoracal scholiosis	No
Dysmorphic features	High arch palate, hypertelorizm, low set ears	High arch palate
Metabolic Investigation	Normal	Normal
Genetic Investigation	Chromozome analysis 46 XY Microarray 12p12.3 region 929 kb duplication	Chromozome analysis 46 XX Microarray normal
Brain MRI	At the age of 3, cerebral and cerebellar atrophy, ventricular dilatation	At the age of 8, cerebral and cerebellar atrophy

* Abbreviations: ASD: Autism Spectrum Disorder, GTC: Generalized tonic clonic, VPA: Valproic acid, VGB: Vigabatrin, TPM: Topiramate, LEV: Levetiracetam, CLB: Clobazam, LCZ: Lacozamide, LTG: Lamotrigine, CLN: Clonazepam

later re-classified as likely pathogenic using American College of Medical Genetics (ACMG) criteria (PP3, PM2, PP2).[3]

Brain MRI at 3 years showed cerebral and cerebellar atrophy with ventricular dilatation (Figure 1). At 5 years, head circumference was 48 cm (<3rd percentile), with dysmorphic features (high-arched palate, hypertelorism, low-set ears), thoracic scoliosis, axial hypotonia, limb spasticity and brisk reflexes. He never achieved independent sitting, walking or verbal/non-verbal communication. Despite multiple antiseizure drugs, including valproic acid (VPA) and vigabatrin (VGB), he continued to have 1–2 seizures per week.

ACTL6A and ACTL6B are alternative subunits of the SWI/SNF complex that originate from the same source, share an 83% similarity, but function in different cell types; ACTL6A promotes proliferation, while ACTL6B promotes neuronal differentiation.[4,5] Since there is no direct template for ACTL6B in the protein data bank (PDB), the PDB template for ACTL6A was used in protein modeling due to their similarity (PDB template ID: 9c4b). YASARA software was used for 3D modelling of the ACTL6B variant and subsequent analysis revealed the change in secondary protein structure (Figure 2).[6]

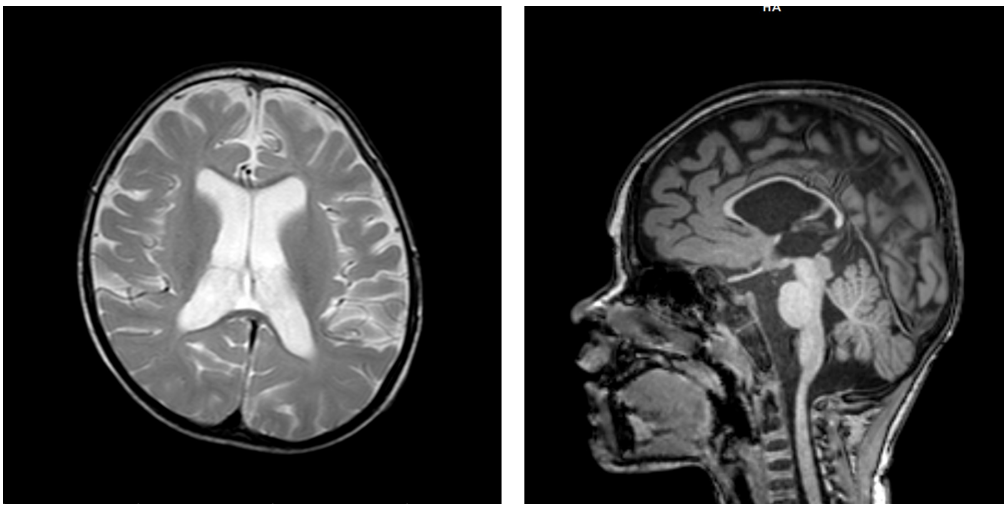

Figure 1. Brain MRI of the first patient: (a) T2-weighted axial image showing cerebral atrophy and ventricular dilatation; (b) T1-weighted sagital image showing cerebral, cerebellar atrophy and thinning of the corpus callosum

Glycine, with its minimal side chain, provides conformational flexibility, whereas arginine carries a bulky, positively charged side chain.[7] Substitution of glycine by arginine in this region is therefore expected to markedly alter protein conformation and protein–protein interactions. However, YASARA captures only a single energy-minimized conformation. As such, protein dynamics, solvent effects, and transient interactions are not fully represented, and long-range or allosteric effects cannot be assessed. Future molecular dynamics simulations could provide further insight into the dynamic behaviour of mutant BAF53b and its interaction with partner proteins.

Patient 2

A 9-year-old girl, born at term by caesarean section (3110 g) to consanguineous parents, was first evaluated for seizures at 5 years. Neuromotor milestones were markedly delayed: head control at 1 year, sitting with support at 4 years and independent sitting at 5 years; she had never walked or spoken. Earlier evaluation for infantile hypotonia had shown normal metabolic tests and cranial ultrasound.

EEG showed bilateral frontal and temporal spikes with multifocal spike–wave activity, and LEV was initiated. Repeat metabolic investigations, chromosomal analysis and microarray were normal. WES identified a homozygous ACTL6B nonsense variant,

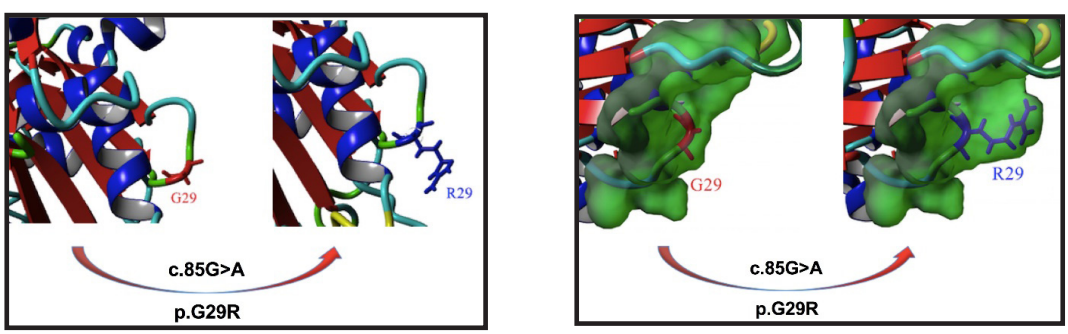

Figure 2. 3D modelling of ACTL6B gene c.85G>A (p.G29R) variant reveals the side chain and surface change of secondary structure of the protein. Gly29 is electrically neutral and contributes minimally to local electrostatic interactions. In contrast, substitution with arginine introduces a positively charged side chain, leading to an increased local positive electrostatic potential.

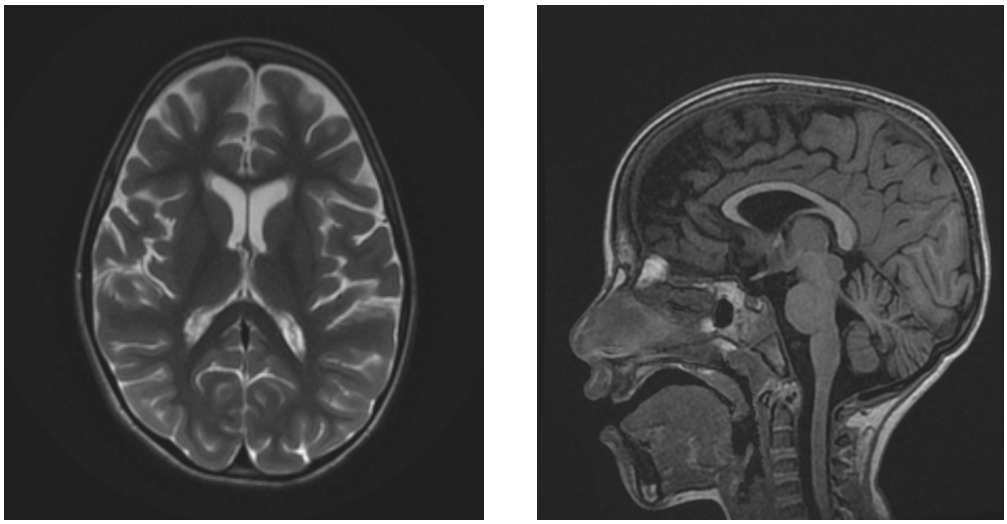

Figure 3. Brain MRI of the second patient: (a) T2-weighted axial image showing cortical thinning; (b) T1-weighted sagital image showing minimal cerebral and cerebellar atrophy

c.1267C>T (p.Arg423*) in exon 14. Variant was classified as pathogenic and confirmed DECAM syndrome (PS4, PVS1, PM2). Brain MRI at 8 years demonstrated cerebral and cerebellar atrophy (Figure 3).

At 9 years, head circumference was 46 cm (<3rd percentile). She had microcephaly, axial hypotonia, marked spasticity with hyperreflexia, profound intellectual disability and persistent absence of speech and ambulation. Multiple antiseizure medications were tried; on VPA and clobazam (CLB) she experienced 1–2 seizures per month.

DISCUSSION

The ACTL6B gene is located at 7q22.1, consists of 14 exons, and encodes BAF53b.[5] Intellectual Developmental Disorder with Severe Speech and Ambulation Defects (IDDSSAD, OMIM #618470) manifests with speech difficulties, hypotonia, neurodevelopmental delay, autistic features, and stereotypies in individuals with autosomal dominant forms of ACTL6B.[8] Conversely, autosomal recessive forms include Developmental and Epileptic Encephalopathy 76 (DEE76, DECAM syndrome, OMIM #618468), characterized by early-onset refractory seizures, neurodevelopmental delay, atypical facial appearance, hypotonia, and abnormalities in brain imaging.[2,8]

Chromatin structure is dynamically regulated by DNA methylation, histone modification and ATP-dependent chromatin-remodelling complexes such as Brg1/Brm-associated factors (BAF).[9,10] During neurogenesis, the neuronal progenitor BAF (npBAF) complex is replaced by the neuronal BAF (nBAF) complex, which controls neuron-specific transcription, dendritic growth, synaptic function and long-term memory.[1,8,11-13] Disruption of BAF53b, the ACTL6B-encoded subunit of nBAF, has been associated with autism spectrum disorder and cognitive dysfunction.[12-14]

In our first patient, the likely pathogenic p.G29R variant lies within the actin-binding domain of BAF53b, a region organised into four subdomains that mediate ATP-dependent conformational changes and interaction with actin filaments.[15,16] In contrast, the second patient carries a homozygous nonsense variant, p.Arg423, truncating the protein near its C-terminus (amino acid 423/426). We hypothesise that disruption of the actin-binding domain leads to earlier and more severe neurodevelopmental impairment, whereas near-terminal truncation results in later-onset but still profound disease.

In conclusion, we would like to highlight three important points. First, DECAM syndrome should be considered in children with intractable epilepsy accompanied by global developmental delay, hypertonia, microcephaly and delayed myelination. Second, in cases of developmental and epileptic encephalopathy (DEE), a comprehensive exploration into hereditary origins is warranted, and individuals exploring hereditary factors should expeditiously pursue

relevant genetic examinations. Our first patient's mutation was initially labeled as a variant of uncertain significance (VUS) but reclassified as possibly pathogenic at age 5. Continuous reevaluation of genetic data, considering clinical characteristics and treatment response, is crucial, even when initial test results are negative. Third, the importance of the region of the gene where the mutation is located as well as the mutation detection. Although the mutation in our first patient was classified as 'possibly pathogenic', it caused an earlier and more severe clinic because it affected the actin binding domain. However, the mutation in our second patient, although classified as 'pathogenic', caused a later and relatively milder clinic because it occurred when protein synthesis was about to be completed. Therefore, knowing which parts of the gene and their possible functions are affected by the mutation may be useful in predicting the clinic.

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DISCLOSURE

Ethics: Institutional Review Board Statement -- The study was conducted in accordance with the Declaration of Helsinki.The authors certify that they have obtained all appropriate patient consent forms, where the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal.

Data availability: The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Conflicts of interest: None

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