# A rare case of HNRNPU-related neurodevelopmental disorder

Mert Altıntaş*, Miraç Yıldırım*, Ömer Bektaş*, Serap Teber*

*Department of Pediatric Neurology, Ankara University Faculty of Medicine, Ankara, Turkey

## OBJECTIVES

Developmental and epileptic encephalopathies (DEEs) are a group of epilepsy syndromes characterized by developmental impairment related to both the underlying etiology and the frequent epileptic activity.[1,2] Developmental and epileptic encephalopathy-54 (DEE54), also called HNRNPU-related neurodevelopmental disorder (HNRNPU-NDD), is a recently identified extremely rare disease caused by pathogenic variations in the HNRNPU gene, characterized by developmental delay, intellectual disability, speech impairment, behavioral abnormalities, and early-onset epilepsy.[3] In DEE54, speech is particularly and disproportionately affected.[4]

Here, we aimed to present a case who presented with speech delay and in whom HNRNPU gene mutation, which is a rare cause of developmental delay, was found in its etiology.

## CASE PRESENTATION

A 10-year-old girl patient was admitted to our outpatient clinic due to speech delay and self-mutilation. She was born of non-consanguineous parents, after an uneventful term pregnancy, by emergency cesarean section due to preeclampsia with 3300g birth weight. On physical and neurological examinations, she had mild facial dysmorphic features, microcephaly and global developmental delay. Her speech delay was prominent, and she said her first words at the age of three. Head circumference measurements were -3.3SDS at the age of 20 months, -2.4SDS at the age of five, and -1.7SDS at the age of nine, respectively. The parents' head circumference measurements were within normal limits. The detailed biochemical and metabolic examinations revealed no pathologic findings suggestive of any specific neurometabolic disease. Electroencephalography (EEG) was normal, and cranial magnetic resonance imaging (MRI) showed inferior vermian hypoplasia and mega cisterna magna. Chromosomal analysis confirmed a normal female 46,XX karyotype and the array comparative genomic hybridization (array-CGH) analysis revealed normal. Whole exome sequencing (WES) idientified a de novo heterozygous inframe deletion of c.3643_645del (p.Lys215del) in the HNRNPU gene, and she was diagnosed with HNRNPU-NDD.

## DISCUSSION

The HNRNPU gene is located on chromosome 1 between bands q43 and q44, and encodes heterogeneous nuclear ribonucleoprotein U (hnRNP U), which is expressed in the brain (highest expression in the cerebellum), heart, kidney, and liver.[3,4] HNRNPU is involved in gene expression through transcription initiation and elongation, pre-mRNA processing and chromatin organization, and pathogenic loss-of-function variants in this gene cause DEE54.[3,5]

Neurodevelopmental problems caused by pathogenic variants in the HNRNPU gene was initially considered part of the 1q44 microdeletion syndrome, however was later recognized as a separate clinical entity.[6]

DEE54, is a recently identified extremely rare neurodevelopmental disorder, and is characterized by craniofacial dysmorphism (microcephaly, palpebral fissure and other various facial apperance abnormalities), global developmental delay (in which speech is disproportionately affected), febrile and afebrile seizures, intellectual disability, and behavioral abnormalities (aggressive outbursts, stereotypical movements).

Speech delay, especially in the presence of other neurological findings such as microcephaly, developmental delay or intellectual disability, may be a clue to an underlying neurogenetic disease, therefore, patients presenting with speech delay should be evaluated carefully. And with the development of modern genetic diagnosis methods, the number of patients diagnosed with genetic neurodevelopmental delay is increasing day by day.

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