Clinical Genetics

WILEY

CLINICAL GENETICS

RESEARCH LETTER

Homozygous ASTN1 Nonsense Variant Linked to Epileptic Encephalopathy: A Detailed Report With Unique Clinical Presentation

Akif Ayaz[1] | Safiye Güneş Sager[2] | Ahmet Sercan Gökşen[3] | Kıvanç Kök[4] | Emine Caliskan[5] | Omar Alomari[3]

[1]Genetic Diseases Assessment Center, Memorial Health Group, Şişli Hospital, Turkey | [2]Department of Pediatric Neurology, University of Health Sciences, Kartal Dr.Lütfi Kırdar City Hospital, Turkey | [3]Hamidiye International School of Medicine, University of Health Sciences, Turkey | [4]Department of Biostatistics and Medical Informatics, International School of Medicine, Istanbul Medipol University | [5]Department of Pediatric Radiology, University of Health Sciences, Kartal Dr.Lutfi Kirdar City Hospital, Turkey

Correspondence: Omar Alomari (dromari2001@gmail.com)

Received: 22 October 2024 | **Revised:** 2 December 2024 | **Accepted:** 3 December 2024

Funding: The authors received no specific funding for this work.

Keywords: ASTN1 gene | epileptic encephalopathy | neurodevelopmental disorders | whole exome sequencing

The development of the mammalian brain and cerebellar cortex is a highly orchestrated process. A variety of genetic factors influence neuronal migration, with astrotactin being a key player [1]. Astrotactin, a neuronal adhesion molecule, is essential for the glial-guided migration of neuroblasts within the cortical regions of the cerebrum and cerebellum. To date, only four cases involving ASTN1 variants have been reported in the literature, and none has provided conclusive evidence of a direct link between these variants and specific clinical phenotypes [2, 3]. This underscores the necessity for further research and comprehensive documentation. Herein, we present a case involving a homozygous pathogenic variant in the *ASTN1* gene. This variant has not yet been assigned an Online Mendelian Inheritance in Man phenotype number, making this case particularly noteworthy.

A 7-month-old girl born to consanguineous parents, was referred to our center for comprehensive genetic testing due to concerns about motor development retardation and epileptic encephalopathy, which began at 2.5 months of age. The prenatal period was unremarkable, with no abnormalities detected on fetal ultrasound. Delivered via cesarean section at 38 weeks and 4 days, she had a birth weight of 3.5 kg (50–75th), a length of 51 cm (75–90th), and a head circumference of 35 cm (50–75th). By 7 months, the patient exhibited significant developmental delays. The patient could hold her head up but not sit unsupported. She had increased reflexes, axial hypotonia, and extremity hypertonia. Eye contact was absent without ophthalmoparesis. Cerebellar and cranial nerve exams were normal.

At 2.5 years old, the patient experienced further neurological decline with severe spasticity and clonus in the lower extremities. Despite a normal cerebellar exam, she could not make eye contact or speak. Focal motor seizures began at 2.5 months, slowing motor development. By 6 months, she had tonic seizures, controlled with Levetiracetam, Clobazam, and Lacosamide.

Cranial MRI showed diffuse cerebral atrophy, deepened sulci, increased cerebrospinal fluid spaces, and a thinned corpus callosum. The EEG showed background activity slowing and multifocal epileptic potentials. These findings, along with epileptic tonic seizures and developmental delays coinciding with seizure onset, supported a preliminary diagnosis of developmental and epileptic encephalopathy (DEE). A candidate variant (p.R517X) was detected in the patient by Sanger sequence analysis and a family study was conducted for this variant (Figure 1). Importantly, the wild-type protein consists of 1294 amino acids, but the truncated protein is significantly smaller, missing four out of five domains.

The genetic pathophysiology of DEE remains not fully understood. Recently, a new gene has been linked to this condition.

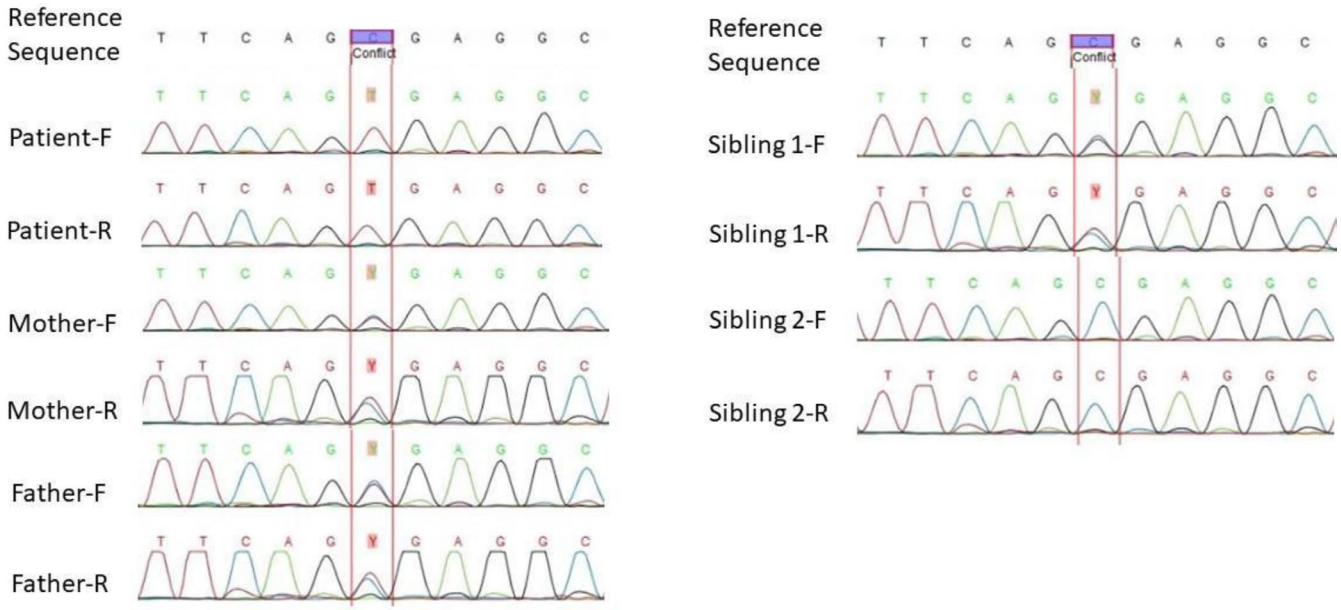

FIGURE 1 | Electropherogram image of the c.1549C>T variant detected as homozygous in the ASTN1 gene in the case. The variant is heterozygous in her mother, father, and one of her healthy siblings, and normal in the other sibling. [Colour figure can be viewed at wileyonlinelibrary.com]

Their study highlighted a novel compound heterozygous variation in the *P4HTM* gene in a Turkish female patient [4]. Their case underscores the importance of genetic testing and reanalysis in undiagnosed DEE and emphasizes the need for continuous genetic exploration to better understand and manage these complex disorders.

This report presents a case suggesting that biallelic *ASTN1* loss-of-function pathogenic variants may be associated with epileptic encephalopathy. Therefore, ASTN1 variants may be considered in the differential diagnosis of developmental and epileptic encephalopathy. However, further studies and functional data on the specific mechanisms and molecular interactions of the *ASTN1* protein may enhance our understanding of the nervous system development and lead to new diagnostic and therapeutic approaches for neurological diseases.

Author Contributions

Conceptualization: Safiye Güneş Sager. Methodology: Akif Ayaz, Omar Alomari, Emine Caliskan. Software: Omar Alomari. Formal analysis: Akif Ayaz. Investigation: Ahmet Sercan Gökşen. Writing: Omar Alomari. Writing – review and editing: Omar Alomari. Supervision: Omar Alomari. Project administration: Akif Ayaz.

Ethics Statement

The ethical approval was waived for case reports by the polices of Kartal Dr. Lutfi Kırdar Training and Research Hospital.

Consent

Informed consent was obtained from the participants to participate in the current study.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Peer Review

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/cge.14674.

References

1. J. M. Fink, B. Hirsch, C. Zheng, G. Deitz, M. E. Hatten, and M. E. Ross, "The CNS Neuronal Migration Gene, Astrotactin, Is Mapped to Human Chromosome Band 1q25 by Fluorescence In Situ Hybridization (FISH) (Abstract)," *American Journal of Human Genetics* 57 (1995): A133.

2. W. Wiszniewski, P. Gawlinski, T. Gambin, et al., "Comprehensive Genomic Analysis of Patients With Disorders of Cerebral Cortical Development," *European Journal of Human Genetics* 26, no. 8 (2018): 1121–1131.

3. S. Anazi, S. Maddirevula, E. Faqeih, et al., "Clinical Genomics Expands the Morbid Genome of Intellectual Disability and Offers a High Diagnostic Yield," *Molecular Psychiatry* 22, no. 4 (2017): 615–624.

4. O. Alomarı, O. Bebek, A. Turkyilmaz, and S. G. Sager, "Novel Compound Heterozygous P4HTM Variants in a Girl With Developmental and Epileptic Encephalopathy: First Case Report of P4HTM Variant-Associated Epileptic Encephalopathy," *Seizure: European Journal of Epilepsy* 124 (2024): 1059–1311.