Novel homozygous AP3B2 mutations in four individuals with developmental and epileptic encephalopathy: A rare clinical entity

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- Homozygous AP3B2 pathogenic variant is rare
- p.Ala149Serfs*34 and p.Pro993Argfs*5 variants as homozygous have never been reported before.
- Frameshift AP3B2 gene variants are thought to cause disruption of neuron-specific neurotransmitter release.
- The variants of the AP3B2 genotype are considered to be related to clinical severity.
- Four individuals with developmental and epileptic encephalopathy related homozygous AP3B2 gene mutations in the present article reveal intrafamilial and interfamilial phenotypic variation.

OBJECTIVES

Adaptor-related protein complex 3 beta-2 subunit (AP3B2) gene, also known as neuronal adaptin-like protein, encodes a neuron-specific subunit of adapter protein complex 3 [1]. Autosomal recessive variants of AP3B2 have been shown to be associated with developmental and epileptic encephalopathy-48 (DEE48; MIM 617276) [2,3]. Mutations in AP3B2 are thought to cause disruption of neurotransmitter release [4]. To date, only 14 cases of AP3B2 mutations have been reported in the literature.

The findings of this study, which featured a long-term follow-up of four affected children with DEE48 who were from two unrelated families and had two previously unreported mutations in the AP3B2 gene, allowed the expansion of the specific clinical and molecular spectrum of the mutations in the AP3B2 .

MATERİALS & METHODS

In this study, whole exome sequencing (WES) was performed on two of the four pediatric patients who came from two unrelated families and were affected by DEE. As a result of WES, previously unreported variants, that is, p.Ala149Serfs*34 and p.Pro993Argfs*5, were detected in the AP3B2 gene. These variants were studied using the Sanger sequencing in the siblings affected by DEE of the said pediatric patients and in their healthy parents. The childrens had inherited the variants from the unaffected mothers and fathers, both in heterozygous state (Figure 1).

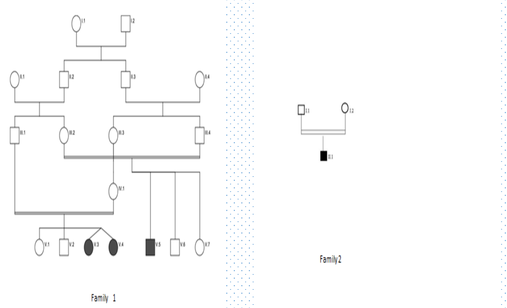

Figure 1. Pedigrees of two families affected by AP3B2 mutations

RESULTS

In our study, we detected the c.445_448delGCTA (p.Ala149Serfs*34) and c.2978_2979delAT (p.Pro993Argfs*5) variants as homozygous in the AP3B2 gene according to the NM_004644 transcript. To our knowledge, these variants are novel. The variants of the AP3B2 genotype are considered to be related to clinical severity. This study features four pediatric patients who had DEE phenotype involving severe global developmental delay emerged, which is characterized by early-onset infantile epileptic encephalopathy, severe hypotonia, postnatal microcephaly, poor eye contact, speech retardation, abnormal involuntary movements, stereotypical hand movements, progressive intellectual disability, and behavioral and neuropsychiatric findings.

Table 1. Genetic description of the AP3B2 variations

Family	Genomic Change (hg19)	Coding Change (GenBank:)	Protein Change	Inheritance	Impact on Transcript
I	Chr15:83350245 delTAGC	NM_004644 c.445_448delGCTA	p.Ala149Serfs*34	Homozygous	Frameshift
II	Chr15:8330614 delAG	NM_001278512 c.2978_2979delAT	p.Pro993Argfs*5	Homozygous	Frameshift

CONCULSIONS

- Given the limited number of patients reported in the literature, detailed studies of the specific clinical and molecular features of AP3B2 gene variants, will shed light on the genotype-phenotype correlation.
- The findings of this study suggest that detailed determination of clinical features in individuals with autosomal recessive variants in AP3B2 and with early-onset DEE may bring a new perspective in phenotyping.

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