A Rare Case Diagnosed with Developmental and Epileptic Encephalopathy 49

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ICNC 2024 Footprints to the future
18TH INTERNATIONAL CHILD NEUROLOGY CONGRESS
Cape Town, South Africa I May 6-10, 2024

Introduction

The term "Developmental and Epileptic Encephalopathy" (DEE) describes epilepsy associated with developmental impairment that may be due to both the underlying etiology (Developmental Encephalopathy) and superimposed epileptic activity (Epileptic Encephalopathy)[1]. More than a hundred types of DEE have been described in the literature. Developmental and Epileptic Encephalopathy 49 (DEE49) (OMIM # 617281) is a severe autosomal recessive neurologic disorder. The clinical findings of DEE49 consist of the onset of seizures in the neonatal period, microcephaly, hypotonia, global developmental delay with intellectual disability and lack of speech, spasticity, and coarse facial features. Most patients of DEE49 have brain calcifications on brain imaging. DEE49 is caused by a homozygous or compound heterozygous mutation in the *DENND5A* gene (OMIM * 617278) on chromosome 11p15[2]. *DENND5A* encodes a DENN-domain-containing protein that functions as a RAB-activating guanine nucleotide exchange factor (GEF). This protein catalyzes the conversion of GDP to GTP and thereby converts inactive GDP-bound Rab proteins into their active GTP-bound form. DENND5A binds RAB6, a protein that regulates membrane trafficking and localizes to the transGolgi network.

In this case study, the Whole Exome Sequencing (WES) of the patient found a likely pathogenic homozygous de novo SNV within the *DENND5A* gene, associated with DEE49 which is a rare autosomal recessive disease. This variant was predicted to be important for the genotype phenotype correlation of DEE49.

Case Background

The patient was a 3-months-old female. Both had clinical features compatible with DEE49: Microcephaly, coarse facies, developmental delay, intracranial calcifications on brain imaging, hypotonia, abnormal EEG, epileptic encephalopathy, and myoclonus.

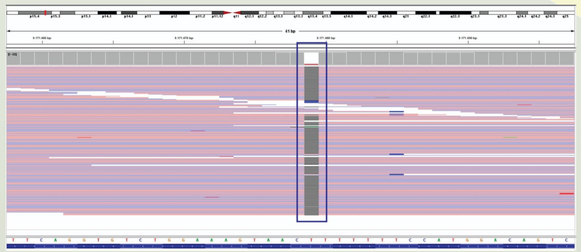
Methods

WES: Approximately 51 Mb of the human exome (targeting >99% of regions in the CCDS, RefSeq, and Gencode databases) was enriched from fragmented genomic DNA with the xGen™ DNA Lib Prep EZ (IDT) and other IDT hybridization Kit. The created library was sequenced on the Illumina platform with an average coverage depth of 70x-100x. The raw data obtained by the Next Generation Sequencing (NGS) method were analyzed using bioinformatics software according to the reference genome of GRCh37 (h19). Pathogenicity scoring of the variants was performed using the relevant guidelines[3,4].

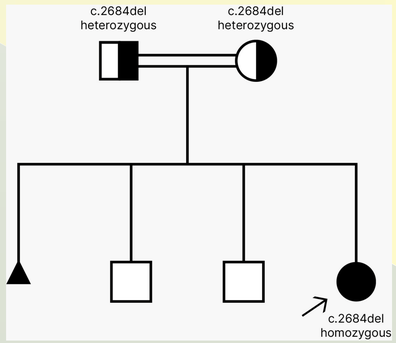
Result

All covered exons, especially the genes' exons associated with epileptic encephalopathies were analyzed using the WES test. A homozygous missense variant was detected in the *DENND5A* gene [NM_015213.4: chr11-9171678 CT>C; c.2684del; p.Lys895SerfsTer7]. This variant is a 1-base deletion, causing a frame shift and the formation of a stop codon 7 codons later. This variant, which is not found in the healthy population (0 heterozygous, 0 homozygous in gnomAD), is not associated with disease in the literature. In a segregation of *DENN5A* gene study, the parents were found to be heterozygous carriers. Considering the points mentioned above, the detected variant is classified as "Likely Pathogenic" according to guidelines[3,4] (PVS1, PM2).

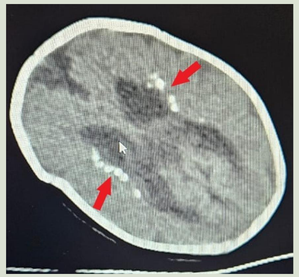
1)



2)



3a)



3b)

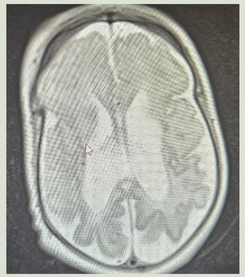


Figure 1. Integrative Genomics Viewer (IGV) image for the chr11-9171678 CT>C variant in *DENND5A* gene. Blue bar showed the homozygous deletion in the patient. **Figure 2.** Pedigree of patient family. **Figure 3. a)** Three months old female patient. Millimetric calcifications shows in bilateral periventricular white matter on CT image. **b)** Axial T2-weighted brain MR image is shows a simplified gyral pattern.

Conclusion

In our study, WES analysis detected homozygous likely pathogenic variants within the *DENND5A* gene. The homozygous mutations in the *DENND5A* gene caused the DEE49. The mutations were predicted to result in a loss of function. The loss of function mutations in *DENND5A* cause the disturbing of controls membrane trafficking pathways which is critical for normal neuronal development. According to the studies, researchers suggested that, the mutations of *DENND5A* may cause inappropriate synaptic connections and possibly neuronal death, contributing to neurologic dysfunction.

Brain imaging reveals abnormal calcium deposits accumulating in deep brain regions, including the thalamus, dentate nuclei, cerebellum, and occasionally other parts of the brain and spinal cord. Patients with *DENND5A* gene mutation are usually found to have calcifications on brain imaging. In addition to main responsible brain calcifications genes, *DENND5A* gene mutations and DEE49 should be considered in the differential diagnosis in patients with brain calcifications.

There are only five patients and four mutations in the literature about *DENND5A* gene and DEE[2,5]. When our patient is presented to the literature, we anticipate that it will be the 5th mutation reported case.

In conclusion, there are very few patients with DEE49 reported in the literature. As far as we know, the variant we identified is reported for the first time with DEE49 clinic. We predicted that the clinical findings and the variant detected in our patient will contribute to phenotype-genotype correlation. In addition, *DENND5A* gene mutations and DEE49 should be considered in the differential diagnosis in patients with brain calcifications.

References

1) PMID: 28276062
2) PMID: 27866705
3) PMID: 25741868
4) PMID: 30192042
5) PMID: 27431290