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Abstract Title:- DENND5A related DEE49: a clinical mimic of Aicardi Goutieres syndrome.

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Aims:-Developmental and epileptic encephalopathy-49 (DEE49) is an ultra-rare autosomal recessive developmental disorder with early onset encephalopathy and variation in the DENND5A gene. Affected individuals exhibit global developmental delay, and seizures during the neonatal period along with hypotonia/spasticity, coarse facial features, and microcephaly. Patients are reported to have brain calcifications in the periventricular and basal ganglia, indicating phenotypic overlap with Aicardi-Goutieres syndrome. Till date, only six patients from four unrelated consanguineous families with DEE49 are reported. A sib pair from a consanguineous family with molecularly confirmed DEE49 is the subject of our description.

Methods:- Neuroimaging of the sibs to assess effects on the brain. Exome sequencing to identify a variant and its novelty in DENND5A. Sanger sequencing to confirm the state of the variant. Cell-based assays to predict possible pathophysiological conditions.

Results:- Neuroimaging of the sibs detected basal ganglia calcification. Exome sequencing in the girl child returned a novel homozygous frameshift variant, c.2215dup in DENND5A. Sanger sequencing confirmed the presence of the same variant in a homozygous state in the similarly affected elder brother and both parents were heterozygous carriers. The elder brother presented with the typical phenotype of DEE49 which are- no head holding, no cooing, inability to recognize mother, no dystonia, Brisk reflexes, upturned lobule, tonic seizure, and cortical blindness. The NCCT report of the elder sibling confirmed the clinical symptoms of the disease namely- moderate dilation of the bilateral ventricle, periventricular and basal ganglia calcification.

Conclusions:- DENND5A functions as a guanine nucleotide exchange factor and activates RAB GTPases that regulate membrane trafficking events. Defective DENND5A has been hypothesized to cause improper synaptic connection leading to neuronal death on the basis of cell-based assays. However, the detailed molecular pathophysiology of this disorder has not been elucidated.

Keywords:- Aicardi-Goutieres syndrome, spasticity, upturned lobule, basal ganglia calcification, seizures.