DENN Domain-Containing Protein 5A

Alternative Names
DENND5A
RAB6-Interacting Protein 1
RAB6IP1
KIAA1091

Record Category
Gene locus

WHO-ICD
N/A to gene loci

Incidence per 100,000 Live Births
N/A to gene loci

OMIM Number
617278

Mode of Inheritance
N/A to gene loci

Gene Map Locus
11p15.4

Description
DENND5A encodes a protein that functions as a guanine nucleotide exchanger factor (GEF). These GEF proteins activate RAB GTPases by promoting the replacement of GDP by GTP in association with the GTPase. The DENND5A protein specifically functions as a guanine nucleotide exchange factor for the activation of RAB39. The protein is also a component of the trans-Golgi network; it is involved in calcium ion transmembrane transport and has been found to interact with RAB6 and SNX1 to regulate Golgi traffic.

The gene is associated with Epileptic Encephalopathy, Early Infantile, 49 (EIEE49), a severe autosomal recessive disorder characterized by neonatal-onset seizures, intellectual disability, global developmental delay, microcephaly, hypotonia, spasticity and facial dysmorphia.

Molecular Genetics
The DENND5A gene is located on chromosome 11 at the position 11p15.4. The gene spans a length of 126 kb and consists of 26 exons. The protein encoded by DENND5A has a molecular mass of 147 kDa and is made up of 1287 amino acids. Alternative splicing results in an additional isoform made up of 1241 amino acids. While the gene is widely expressed in the body, overexpression is seen in the heart, spinal cord and adult brain. Mutations in the gene associated with EIEE49 are generally homozygous missense mutations or frameshift and premature truncations.

Epidemiology in the Arab World
Saudi Arabia
Anazi et al. (2016) studied 337 Intellectual Disability (ID) patients and found genomic tools to have a higher diagnostic yield than standard clinical evaluations. Exome sequencing helped identify DENND5A gene mutations in two patients: a homozygous loss-of-function mutation c.3811del (p.Gln1271Argfs*67) in a 26 month old female and a homozygous missense mutation c.1622A>G (p.Asp541Gly) in a 21 month old female. Both mutations had a minor allele frequency <0.001 based on 1500 Saudi exomes, fully segregated with the phenotype and there were no other candidate variants. The DENND5A gene was considered a candidate gene as it is a regulator of neurite outgrowth during neuronal differentiation. Further, the missense mutation was located in the dDENN domain and was predicted to affect the binding and functional efficiency between DENND5A and Rab GTPases. Both children were born to consanguineous parents and shared the phenotype of severe early infantile encephalopathy, progressive microcephaly, seizures, global developmental delay, central hypotonia and peripheral hypertonia.

References
Anazi S, Maddirevula S, Faqeih E, Alsedairy H, Alzahrani F, Shamseldin HE, Patel N, Hashem M, Ibrahim N, Abdulwahab F, Ewida N, Alsaif HS, Al Sharif H, Alamoudi W, Kentab A, Bashiri FA, Alnaser M, AlWadei AH, Alfadhel M, Eyaid W, Hashem A, Al Asmari A, Saleh MM, AlSaman A, Alhasan KA, Alsughayir M, Al Shammari M, Mahmoud A, Al-Hassnan ZN, Al-Husain M,

Osama Khalil R, Abd El Meguid N, Masri A, Ali R, Ben-Omran T, El Fishway P, Hashish A, Ercan Sencicek A, State M, Alazami AM, Salih MA, Altassan N, Arold ST, Abouelhoda M, Wakil SM, Monies D, Shaheen R, Alkuraya FS. Clinical genomics expands the morbid genome of intellectual disability and offers a high diagnostic yield. Mol Psychiatry. 2016 Jul 19. PMID: 27431290.

Related CTGA Records

Epileptic Encephalopathy, Early Infantile, 49 (EIEE49)??

External Links

http://www.genecards.org/cgi-bin/carddisp.pl?gene=DENND5A

Contributors

Sayeeda Hana
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