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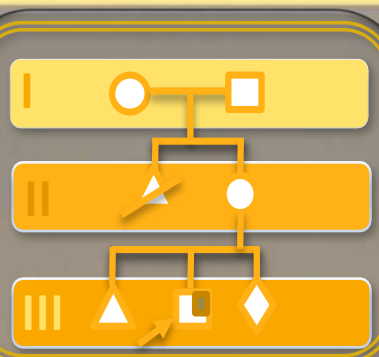
All India Institute of Medical Science Rishikesh

AIIMSR
Department of Pediatrics
Genetic -division

H1 H2A H2B H3 H4

Volume 5
Issue 49, June 2024



From the desk of Editor

The genetic division of the Pediatric Department publishes a monthly newsletter for all Medical Professionals. The newsletter is related to genealogical parlance and is a deliberate attempt to enhance awareness of genetic disorders with recent updates.

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DOI: 10.13140/RG.2.2.13188.74888

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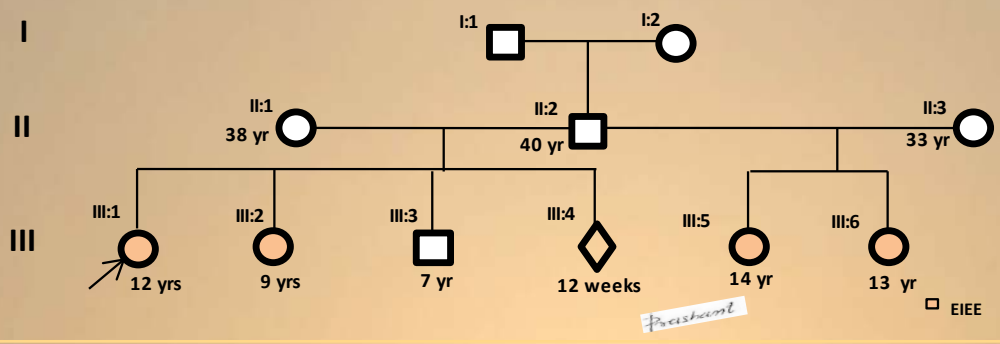
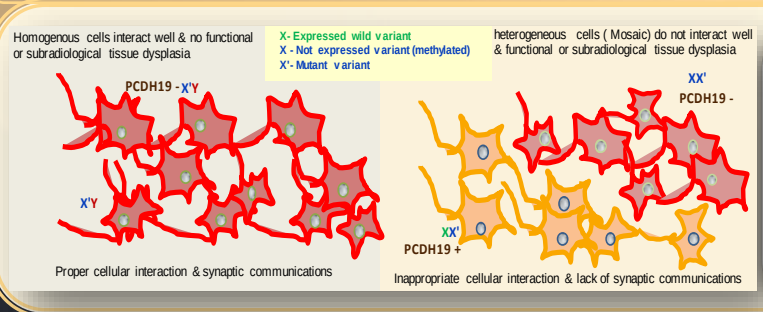
Neurogenetics: XVI: Intellectual Disability/X-Linked/ Developmental and Epileptic Encephalopathy 9 (Juberg-Hellman Syndrome) (Epileptic Encephalopathy, Early Infantile, 9)



Female-restricted, with mental retardation: cellular interference



- Lack of functional protein is compensated by alternative salvage gene*, and maintains cellular role without interfering with inter-cellular interactions in similar cell populations.
- Female's X inactivation process makes mosaic cell populations, which leads to loss of function at the cellular level but altered function at the tissue level.
- Mosaic cells have abnormal cellular interference, which leads to the progression of clinical features.
- ***That is why heterozygous females and males with mosaic mutations have only clinical features; mutations carrying male cases do not.***

* Non-paralogous Y-chromosome protocadherin gene, PCDH11Y

Insight:

1. What is the possible mechanism for **female-restricted expression** in Juberg-Hellman syndrome?
2. What are the protocadherins (Pcdhs) and the **protocadherinopathies**?
3. Is there any strategy for the sex selection in **Case III: 4**?
4. What is the clinical presentation of Epileptic Encephalopathy, Early Infantile, 9?
5. What are the symptoms and phenotypes of male carriers?

Plausible tenets:

Gene: PCDH19 (Xq22.1) Genomic coordinates (GRCh38:CM000685.2) **X: 100,291,644-100,410,273 (from NCBI)**

- **A delta-2 protocadherin; Pcdhs** are recognized by the cadherin motif, are a member of superfamily of cell adhesion molecules, highly regulate the synaptogenesis process, especially at the later stage
- **A calcium-dependent cell adhesion protein, which is expressed exclusively in the brain;** having five splice variants; 194 orthologues, and 61 paralogues.
- **Transcript: exons 6, coding exons: 6**; length of **9,756 bps**; 58 domains; and features. Protein has 1148 amino acids & a molecular weight of 126253 Da.
- **ClinVar variants: https://gnomad.broadinstitute.org/gene/ENSG00000165194?dataset=gnomad_r4**

Clinical phenotypes: developmental and epileptic encephalopathy 9; XL disorder

- In 1971, Juberg and Hellman described female-limited seizure disorders initiated by febrile illness.
- Also known as epilepsy and mental retardation restricted to females **(EFMR)**.
- Clinical features: Infantile onset seizure(any type but less severe than Dravet syndrome, associated 50–60 % with fever, usually self-terminate in the first decade), variable intellectual differences (mild to severe deficiency, even regression) with psychiatric and behavioral problems(autistic more common), ***normal motor system in examination.***
- **Male carriers** might have variable behavioral & personalities issues.

Approach: detail clinical evaluation, base line data analysis, ECG, MRI, panel test for developmental and epileptic encephalopathy (PS308350) (118 entries) or whole exome sequencing

Protocadherinopathies

The Protocadherins (Pcdhs), discovered in 1993, resemble the primordial (Proto) cadherin sequence (similar to Drosophila cell-adhesion protein Fat), but have significant structural differences from cadherin (Sano et al., 1993). In OMIM, there are fifty-eight entries for Protocadherin (PCDH), and even so, there are six clinical entries for human phenotypes

Protocadherinopathies besides DEE9

Disease	OMIM No.	Gene	MOI	Clinical features
Usher syndrome Type 1F (USH1F)	#602083	PCDH15	AR	Hearing loss (neurosensory) and progressive pigmentary retinopathy
Deafness, autosomal recessive 23 (DFNB23)	#609533	PCDH15	AR	Isolated SN hearing loss
Diencephalic-mesencephalic junction dysplasia syndrome 1 (DMJDS1)	#251280	PCDH12	AR	Developmental malformation of Mid brain Profound ID, progressive microcephaly, dystonia, and spasticity
Cone-rod dystrophy 15 (CORD15)	#613660	PCDH21/ CDHR1	AR	Progressive loss of visual acuity in the 3rd to 4th decades
Neurodevelopmental disorder with poor growth and skeletal anomalies (NEDGS)	#619880	PCDHGC4	AR	ID, hypotonia, progressive microcephaly, philtrum anomalies, dysplastic ear, craniosynostosis, joint contractures (scoliosis, swan neck deformity)
Usher syndrome, type 1D/F digenic	#601067	CDH23, & PCDH15	AR, DR	Congenital deafness, early retinitis pigmentosa

Sex selection guidelines for Case III: 4- Indian laws do not allow sex selection in any circumstances, even in the preimplantation stage, in view of the very high obsession for male babies, ritual compulsion, and statistically high female infanticide rate. Usually, due to a lack of these social issues, Western counties provide freedom for the couple for sex selection.

Thought Riveting:

- ***What is the alternative salvage pathway protein for mutant PCDH19?***
- ***Does the metabolic interference theory relate to DEE9 phenotypic variability at the cellular level?***
- ***Are protocadherinopathies one of the new emerging genetic diseases related to nervous system?***
- ***How does the refractory infantile seizure self-terminate at the particular age in DEE9?***
- ***Is there any role for adjuvant therapy, such as a ketogenic diet, for a carrier male with behavioral problems?***
- ***Is it ethical to recognize fetal sex before prenatal counseling for sex-linked genetic disorders?***