All India Institute of Medical Sciences Rishikesh (AIIMSR)
Department of Paediatrics

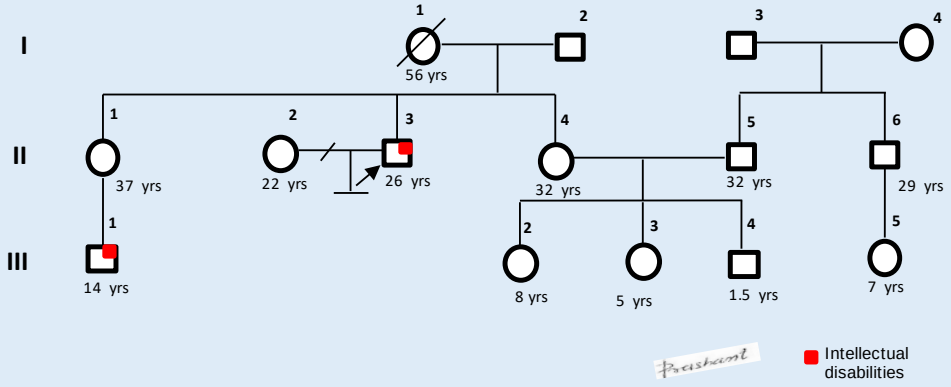
Rishi Vansh

Volume 2, Issue 16, September 2021

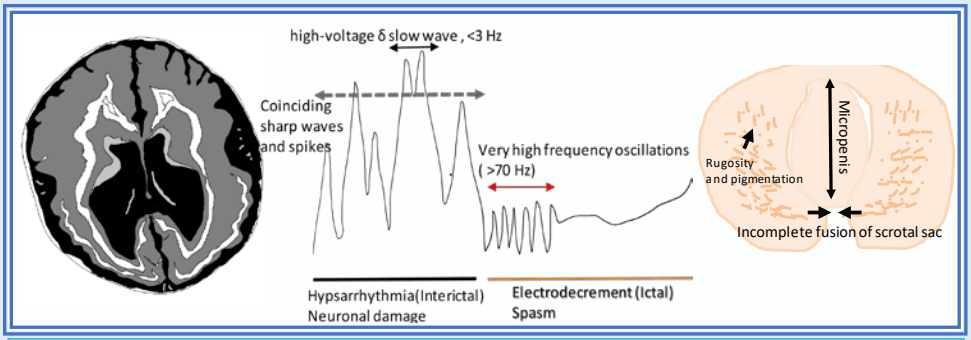
From the desk of Editor

The Department of Paediatrics is publishing a monthly newsletter for faculty and residents. The newsletter is related to genealogical parlance and deliberate attempt to enhance awareness for genetic disorders with recent updates.

Neurogenetics -IV: Intellectual Disability/ ***X-Linked***/ARX related disorders



Lissencephaly + Hypsarrhythmia EEG changes + Undervirilization



ARX (Aristaless-related homeobox- X linked) related disorders involving three overlapping phenotypic findings: Intellectual disability (ID), cortical dysplasia, epilepsy syndrome and undervirilization

Insight:

1. What is the prevalence of ARX gene associated learning disability in the community?
2. When would you suspect ARX spectrum disorders?
3. Is there any genotype and phenotype correlation with particular pathological variant?
4. What will be the counseling plan for case III (4)?
5. Why, all ARX associated phenotypes are not inherited as XLR?
6. What is the impact of ARX gene on pancreatic development?

Plausible tenets:

ARX Gene (Cytogenetic location: Xp21.3, Genomic location: X:25,003,693-25,015,964)

- **12.5 kb, 5 exons, two domains- a C-peptide (or aristaless domain)&** the **prd-like class homeobox**
- Inheritance is by XL & XLR mode: based on the severity of protein truncation & involvement of critical domains which are reliant on protein function in dosage-dependent manner
- A member of the group-II aristaless-related protein family **(homeobox-containing gene) →** expressed in the nervous system during development **→ Proprer cell differentiation & migration**
- **Overall 10 % cases of ID - X linked ID** in males **(33 % FXS + 7.5% ARX +** others X linked ID genes**-** online resources:http://www. ggc.org/xlmr.htm & http://xlmr. interfree.it/home.htm

Tissue/s	Regulatory Function
Pancreas, testes, & skeletal muscles	Cellular differentiation
Brain	Migration & communication of nerve cells by interneurons

Disease phenotypes:

Phenotypes	Characteristic features beside intellectual disability (Constant)	Phenotypic Series
DEE1/ Early infantile EE -1/ XL-West syndrome	Infantile onset progressive refractory seizures with specific EEG (hypsarrhythmia)	PS308350** - 98 Entries for DEE*
Hydranencephaly with abnormal genitalia	X-linked lissencephaly with abnormal genitalia as ambiguous genitalia, lethal in males	
Lissencephaly, X-linked 2		PS607432 - 16 Entries
Mental retardation, X-linked 29 & others (non-Syndromic)	With or without seizures, normal behavior, course facial features, obesity	PS309530 - 49 Entries
Partington syndrome	**Diverse types of movement disorders**	
Proud syndrome	Corpus callosum agenesis, abnormal genitalia	

- XLR others are XL, *DEE- Developmental and epileptic encephalopathy [Included - early infantile epileptic encephalopathies (EIEE) & different phenotypes as 'early myoclonic epilepsy' (EME), West & Drave syndromes and so on].

****Phenotypic Series Code:** Having the data of different genetic loci for a characteristic phenotype (genetic heterogeneity)

Genotype and phenotype correlation

Mutation/ Phenotype	Premature termination or nonsense mutations	Expansion of the polyalanine tract
Impact on CNS	Brain malformation syndromes	Mental retardation without brain malformations or epileptic encephalopathy
Syndromes	XLAG & Proud syndrome	DEE1/ Early infantile EE -1/ XL-West syndrome

- **Inter & intra-familiar phenotypic variation in severity even with same mutations**
- **Severity of phenotypes α loss of function in highly conserved regions**

Genetic counselling for case III (2,3,4):

Step 1: Pedigree analysis- Non-syndromic, X linked learning disabilities – maternal could be carrier up to 50 % (only male affected & no male to female transmission)
Step 2: Confirm the diagnosis in affected case II (3) & case III (1) – hospital data analysis
Step 3: Examination of case III (2,3,4), & case II (4), especially detailed examination for male case III (4) check genitals, neurodevelopment assessment & need to follow up six monthly for Neurodevelopment
Step 4: Confirm the disease in symptomatic case, but in asymptomatic case need to confirm carrier status first with proper counselling & psychological evaluation or consultation as per criterion

Effect of pancreas: maintenance of α-cell identity and quantity, truncated ARX leads to deletion and reduction of α-cells

Homeobox: [*homeo-* (hō'mē-ō). The same, alike & box - Genes families (have quite similar DNA sequence) in the genome. Transcript the DNA binding proteins those assist early developmental period & regulating morphogenesis by cellular patterning & differentiation mostly through concentration gradients inside the embryonic tissue.

In 1983, William McGinnis noticed this sequence & was named by Walter J. Gehring

Other homeobox genes are also reported for brain malformations:
PAX6- polymicrogyria with aniridia
SIX3- holoprosencephaly
EMX2-schizencephaly
HEXS1- septo-optic dysplasia

Thought Riveting:

- ***What could be the possible explanation for abnormal Morphogenesis of the Urogenital Primordia (Malformative DSD) in ARX related disorders?***
- ***What is the exact biomolecular explanation for hypsarrhythmia pattern in EEG?***
- ***Is there any molecular interaction between MAPK signaling and ARX gene?***
- ***What are the environmental factors modulating the plasticity of interneuron?***
- ***Could it be possible to isolate DSD with ARX mutation?***

Author: Dr Prashant Kumar Verma
Reviewer: Dr. Raksha Ranjan