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

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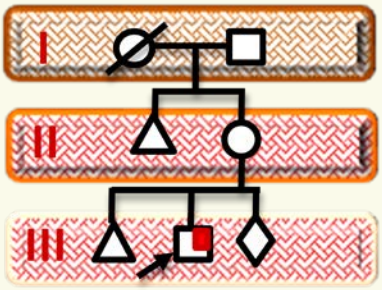
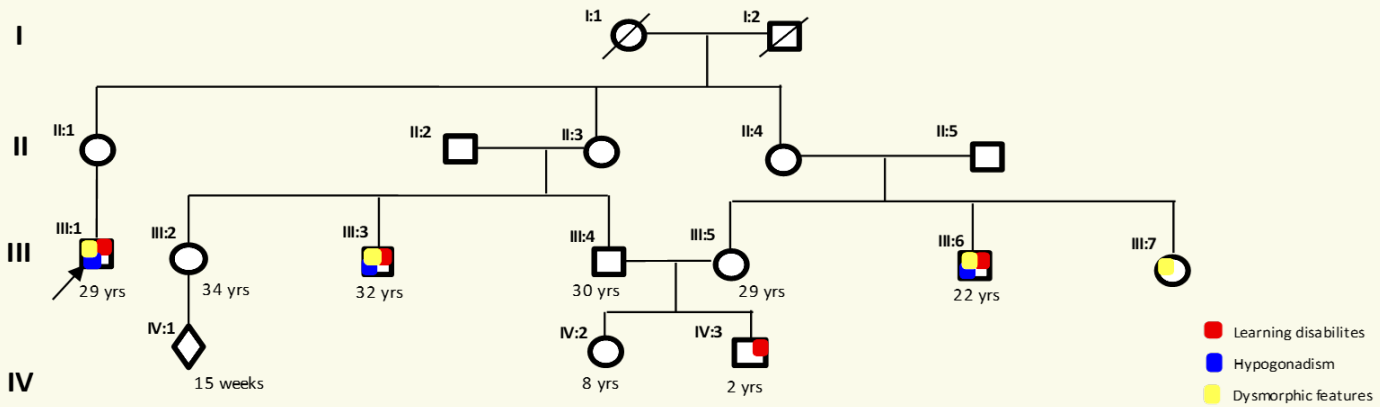
From the desk of Editor

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



Neurogenetics -V

Intellectual Disability/ ***X-Linked***/ Borjeson-Forssman-Lehmann Syndrome; **MRXBFLS**



Characteristics clinical features

Prominent Supraorbital Ridges, (Subjective): *Greater than average forward and/or lateral protrusion of the supraorbital portion of the frontal bones*

Eye, Deeply Set (Subjective): *An eye that is more deeply recessed into the plane of the face is typical*

Insight:

1. What is the reason for quite different clinical phenotype in male and female with BFLS?
2. Why does not the case IV:3 have the specific dysmorphic features?
3. What are the common inherited causes of hypogonadism with XLMR?
4. What is the state-of-the-art for counselling for the case III:2?
5. What should be the initial approach towards a male child with possible XLMR?

Plausible tenets:

Gene: PHF6 (Xq26.2); 19.905 kb, 11 Exons & 25 domains

- **Belong to family of the plant homeodomain (PHD)-like finger (PHF)**
- 1,095-bp open reading frame (ORF), 12 transcripts (splice variants), 198 orthologues & 3 paralogues
- Protein (**365 AA**) containing two zinc fingers domains express in all tissues with highest expression in nervous system during embryonic period
- Transcriptional regulator & also help in retrieval of DNA repair in G2 phase of cells through promoting end joining-mediated repair of DNA(classical non-homologous end joining)
- Symptomatic females reported as sporadic cases due to more truncated mutations or deletion while familial mutations have missense mutations with residual expression & only males have classical phenotypes
- Highly skewed X-inactivation of the chromosome which carries mutant PHF6 escort as X linked recessive inheritance

Clinical phenotypes:

- **Classically present** with **severe learning disabilities, hypogonadism, obesity, facial anomalies & seizures**
- **Facial dysmorphology:** More obvious with advancing age especially postpubertal; prominent bony part on face - supraorbital ridge and cheek bones, course facial features & large fleshy ears
- **Ophthalmic anomalies:** dense eyebrows, deep set eyes, ptosis, epicanthus, pale optic discs, nystagmus, blepharophimosis, hyperopia and predisposition to develop cataract & visual impairment
- **Neurological:** hypotonia, seizures, microcephaly, severe mental retardation & poor alpha rhythms
- **Endocrine:** short stature, obesity, hypogonadism(small atrophic testes), cryptorchidism & gynaecomastia
- **Musculoskeletal:** tapered fingers, hyperextensible joints, short wide & flexed toes, kyphosis

Management: symptomatic as antiepilectics, surviallnace for cataract, behaviour, speech and occupational therapy

First published by three scientists in 1962- **Borjeson M, Forssman H, Lehmann O**:

An X-linked recessively inherited syndrome characterized by grave mental defect, epilepsy and endocrine disorder.

Acta MedScand 171:13, 1962.

XLMR & hypogonadism: Differential diagnosis

Syndrome	Key finding
Aarskog syndrome	Shawl scrotum,
FG syndrome	Midline defects
Simpson-Golabi-Behmel syndrome	Overgrowth
Lowe syndrome	Congenital cataracts
Renpenning syndrome	Micro-orchidism
RUD syndrome	Both hypo & hypergonadotropic hypogonadism
Chudley- Lowry syndrome	Deafness
Norrie disease	Childhood blindness
Wilson-Turner syndrome	Heavy eyebrows
MRX2	Relative

Approach to a male child with possible XLMR:

1. Educational history and IQ status including of *the mother*
2. Examination for dysmorphic features and neurological signs *plus both parents*
3. Rule out *common treatable disorders*: Neonatal PKU and hypothyroidism
4. Consider free T3 thyroid function tests *if spastic paraplegia is present*
5. EEG to assist the definition of epilepsy phenotype *even in asymptomatic cases*
6. Microarray *(Better)*/ Karyotype analysis (550 banded resolution)
7. Fragile X study
8. Brain MRI *if abnormal neurological findings or head circumference*
9. Metabolic screen including Urine and plasma creatine/creatinine ratio *if clinically indicated*

State-of-the-art: Genetic counselling with case II:2

Step 1: Maintain privacy, assess financial assistance and psychological status
Step 2: Explain the risk for other genetic diseases like Trisomies
Step 3: Role of non-invasive prenatal testing **(NIPT);** (a screening test with more specificity than sensitivity, could be used for even single gene disorders)
Step 4: Talk on turn over time for NGS based test or invasive test and target gene testing with microarray of fetus amniocytes

Thought Riveting:

- ***How does the PHF6 operates with the nucleolar transcriptional regulator UBF, & NuRD chromatin remodeling complex?***
- ***Why does not the MRSBFLS patient develop cancer despite PHF6 having gene repair function and reported to be mutant in various somatic cancers?***
- ***Why does the majority of BFLS syndrome carrier females have extreme skewed X-inactivation?***
- ***What are the near and distant gene regulator for PHF6 gene in human genome?***
- ***Can PHF6 protein be used against cancer as adjuvant therapy?***

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