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

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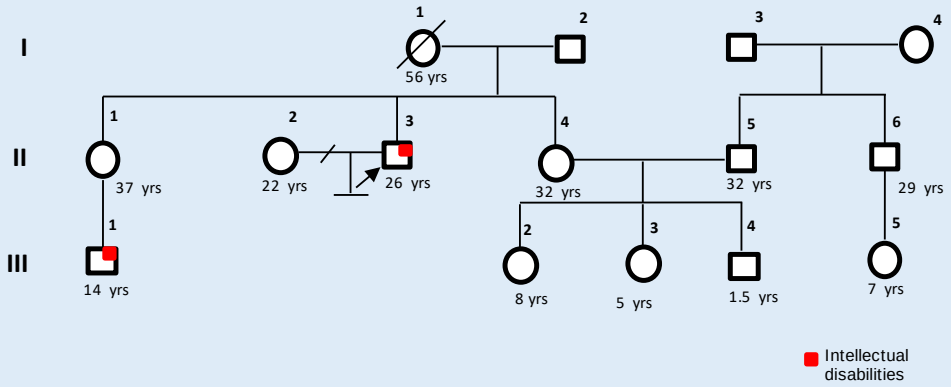
From the desk of Editor

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

Neurogenetics -IV: Intellectual Disability/ ***X-Linked***/ FMR1 disorders/Fragile X syndrome (**FXS**)



FMR1 & FMR2 Genes location of X chromosome

PAR1 and PAR2- Pseudo-autosomal region 1 and 2, Fra(X) (q27.3)- cytogenetic location of FMR1 gene, long arm of X chromosome, band segment 2, subsegment 7 & Sub subsegment 3

Insight:

1. What will be the counseling plan for case III (2,3,4)?
2. What would be the scientific modus operandi at the society level for the prevention of FXS?
3. What are the factors which predict high risk for autism spectrum disorder (ASD) in an infant with FXS?
4. What is the role of folic acid and cannabidiol (CBD) in FXS?
5. What are the roles of CGG & AGG repeats in influencing disease phenotype and subsequently for genetic counseling?

Plausible tenets:

Gene linked to fragile X with MR: (Folate sensitive fragile sites on X chromosomes)

1. **FMR1** (First localized by Lubs in 1969 as fragile site later sequenced by Verkerk et al. in 1991.
   - **The first** genetic disorder revealed to be due to mutation in "***Trinucleotide repeat expansions***".
   - **FMR1 associated with polyribosomes and transcript has 17 exons** & annotated with **52 domains**
   - **>99% cases have CGG expansion → Methylation** of FMR1 **promoter** region→ impede transcription
   - **mRNA regulating functions as alternative splicing, trafficking, stability, dendritic transportation & selective translation modulator**
   - **Role in neurotransmitter release & the modulation of presynaptic action potential (AP) by a translation-independent mechanism** & **Limit DNA damage response (DDR) mechanisms**
2. AF4/**FMR2** FAMILY, MEMBER 2; **AFF2** (FRAXE) (FMR1-mutation negative, *Second fragile site)*
   - Transcriptional activator, normal **GCC** repeats have 6 to 25 copies

Disease phenotypes: (Having charectersitic features of "Anticipation")

- **FMR1:** FXS is the **most common** inherited single gene intellectual disability disorder
  - **Dysmorphic features come at particular age (age dependent penetration) in male and unexplained autism spectrum disorder in both M/F**
  - Fragile X-associated tremor/ataxia syndrome (**FXTAS**): ataxia, parkinsonism, tremor & +/- dementia
  - Fragile X-associated primary ovarian insufficiency (**FXPOI**): < 40 yrs, hypergonadotropic hypogonadism
  - Fragile X-associated neuropsychiatric disorders (**FXAND**)
  - Cannabidiol gel might improve the behaviour & reduce anxiety & folic acid has no role
- **FMR2**: Intellectual developmental disorder, **X-linked 109**, a nonsyndromic X-linked intellectual disablities(**ID**), overlapping neuropsychiatric disorders with subtle dysmorphic features

AGG repeats present at every nine to ten CGG repeats; provides CGG stability during cell division (especially with repeats < 90). AGG genotyping by repeat-primed PCR is undervaluation.

Anticipation: appearance of the pathological phenotype not seen in previous generation and is more severe in the next generation

Fragile sites(FS): Two types on the basis of folate sensitivity. **Sites** on chromosomes which **fail to compact in presence of** restricted DNA replication

Phenotypes and investigation panel for CGG repeats of FMR1 gene.

Repeats	5-44	45-54 (Borderline)	55-200 (Premutation)	>200(Mutant)
Phenotypes	Normal	Normal	FXTAS, FXPOI, FXAND	FXS
Meiotic or mitotic instability	little or no	Unstable & in 14 % expand to < 200. Modifier: AGG repeats	Chance of Expansion to > 200, during oogenesis • <10 % at < 70 but • 50 % -70 -80 and • 100 % > 140 repeats	Average IQ ≈ 40 92% - developmental delay 60.7% have ASD (DSM-5) 45.4% - either ADHD, anxiety, or both
PCR testing	Yes	Modified PCR	Modified PCR	Modified PCR
Southern blot analysis	Yes	No	Only for larger-sized	Yes

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

Step 1: Confirm the diagnosis of proband case II (3)

Step 2: Detail maternal clinical evaluation (History and neurological)
Step 3: Asymptomatic case can be offered genetic testing only to help in antenatal diagnosis. If symptomatic, molecular testing is must.

Step 4: Cases III (2,3,4) need a follow up for developmental assessment and no need for genotyping.

- **Preventive modus operandi – increased awareness about the disease at community level; availability & affordability of genetic testing & medical resources.**
- **Population screening is not in practice for asymptomatic cases because:**
  - **Late onset disorder,**
  - **Lacking specific therapy,**
  - **Undesirable psychosocial consequences &**
  - **Paucity of scientific evidence.**

Asymptomatic case only be offered genetic testing *with pretest psychological counseling* if it helps in antenatal diagnosis & family planning.

Thought Riveting:

- ***How is post-transcriptional regulation severely altered in neurons with the loss of fragile X mental retardation protein (FMRP) as compared with non-neuronal cells? which is the most affected pathway?***
- ***What could be the possible hypothesis for the Nucleoporins (Nups) assembling around nuclear pore?***
- ***Is the augmentation of transcriptional decipher therapy new ray of light for triplet repeat disorders?***
- ***Can Aberrant Behavior Checklist-Community-FXS version (ABC-CFX) be used for prognosticating the FXS?***
- ***Can Fragile X-Related Epigenetic Element 2 DNA methylation (FREE2m) assessment be used as population screening tool?***
- ***Will the amending of "leak metabolism" prove to be the target pharmacotherapy for FXS in human?***

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