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

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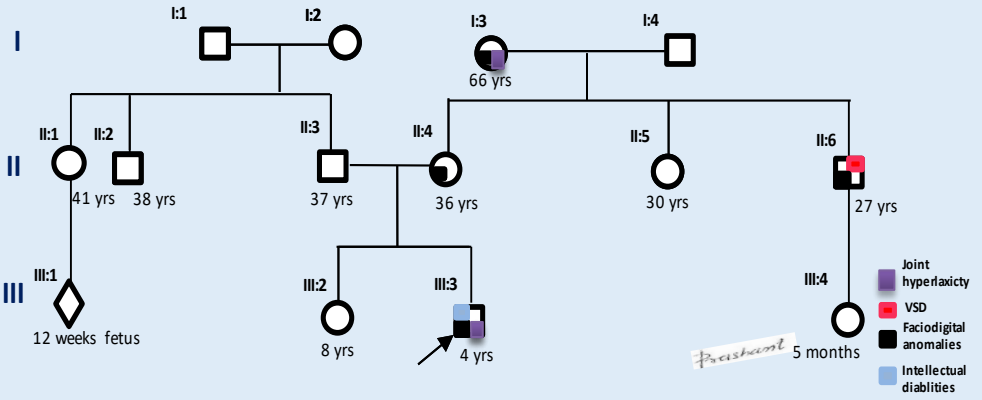
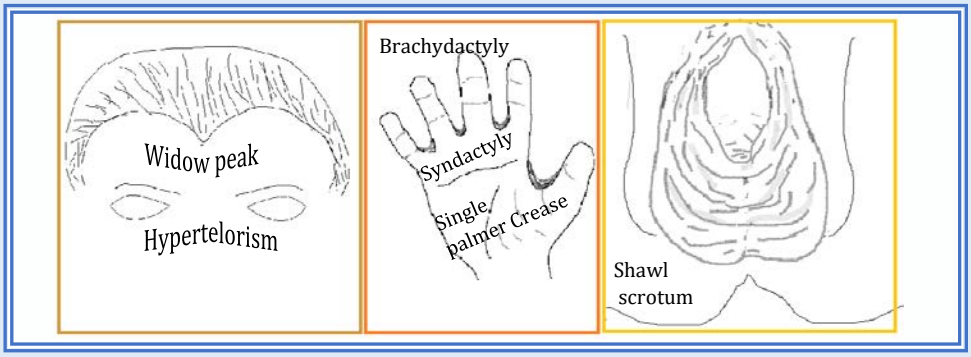
From the desk of Editor

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***/ MRXS16/Aarskog-Scott Syndrome (**ASS**)



Characteristics clinical features



Syndrome with F- facial, D- Digital & G- Genital -anomalies
Isolated F/D/G are reported with various syndromes but constellation of FGD is characteristic feature of Faciodigitogenital syndrome (FDG syndrome)

Insight:

1. What percentage of cases have been reported to have intellectual disabilities with ASS?
2. Is there any variation of phenotype with age in ASS?
3. What will be the counselling plan for case II:1, III:1 & III:2?
4. Do the clinical features overlap with Noonan syndrome?
5. What is the shawl scrotum?

Plausible tenets:

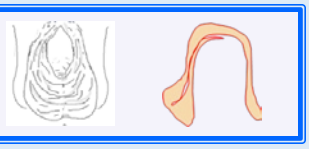
Gene: FYVE, RhoGEF, & PH DOMAIN-CONTAINING PROTEIN 1; FGD1 (Xp11.22)

- **Transcript has 18 exons** & annotated with **44 domains & features**
- A member of the **Ras-like family** of Rho- & Rac proteins
- **Binds to GTPase Cdc42Hs →** Stimulate the **GDP-GTP →** Activated protein **kinase→ SAPK/JNK1 activation**
- Regulating the **actin cytoskeleton & cell shape & signal transduction &** mammalian **morphogenesis**
- FGD1 protein has 961 amino acids, 2 potential SH3-binding sites & a cysteine-rich zinc finger-like region
- Few families follow XL semi- dominant or AD mode of inheritance although not elucidated genetically

ASS phenotypes:

- Triad of facial, digital & genetial anomalies
- *Phenotypic overlap with **Noonan Syndrome*** **[**Short stature, mild to moderate failure to thrive, downslanting palpebral fissures, short neck with or without webbing, dental & auricular dysplasia, pectus excavatum, cryptorchidism, vertebral abnormalities, brachydactyly & learning disabilities
- **Other Ocular findings:** optic nerve hypoplasia, hypertelorism, retinal vessel tortuosity, ophthalmoplegia retinal vessel, hyperopia, deficient ocular elevation & anisometropia
- **Rare findings:** Hirschsprung malformation, **ASD & PS,** polymicrogyria, craniosynostosis, hypospadias
- **Fertility is not affected & neurobehavioral disorders are more common than learning disabilities** (1/3 cases)
- Facial features show **age dependent penetration** & normalize with age
- Few cases were reported with lumbar ribs (also present with Hox10 mutations)

Ventral scrotal folds or Shawl scrotum : Superior margin of the scrotum superior to the base of the penis. Other names- 'saddle-bag scrotum', transposition of the scrotum. Reported with around twenty six syndromes.



The penetrance (for a genetic disorder) is the probability based on different literature resources to know how frequently a specific phenotype is expressed for a particular genotype or vice versa
Modifiers for expression of phenotype: when modified by age it is entitled "age-related penetrance". Penetrance is more commonly directly proportional to increasing age. Other modifiers are age, sex (as with X linked disease), epigenetic, epistasis & modifier genes. Variable penetrance is a feature of dominant disorders.
For example:
Retinoblastoma Penetrance - 90% penetrance, means only *10 % probability for not developing a disease in spite of carrying mutant allele or gene & the* **other way around for 10 %** penetrance means, 90 % probability for not having the disease with mutant gene or allele
TBX5's penetrance is 100% & it's called "full penetrate"

Dagfinn Aarskog (Norway), (1970) & Charles I. Scott, Jr. (USA), (1971)- independently described the syndrome

Pasteris et al.

- In 1994, isolated YAC clones spanning the t(X;8) breakpoint associated with Aarskog-Scott syndrome.
- In 1995, isolated the mouse Fgd1 homolog with human FGD1 94.7% identity (96.3% similarity)
- In 1995, suggested that mouse will serve as a useful model for research

Genetic counselling for case II:1 & III:1:
Step 1: Confirm the Phenotype of proband case III:3 & confirm the molecular diagnosis
Step 2: FGD would be less likely in the fetus because disease is not inherited in this family **but** need counselling for advanced age & beta thalassemia

Genetic counselling for case III:2
Step 1: Asymptomatic case can be offered genetic testing only if it fulfilled the medical ethics (Justice, Autonomy, Beneficence & Non-injurious) So, testing is deferred even after clinical diagnosis is suspected till adulthood
Step 2: In X linked disorders, diagnosing a carrier female without her mature understanding is often associated with negative impact on her life like mild to severe psychological disorders and various social & community issues

Thought Riveting:

- ***Can the recombinant FGD1 antibodies be used as anticancer therapy even at late stages of selected carcinomas?***
- ***Does the Shawl scrotum result from early developmental defect of pelvic floor inlet?***
- ***What is the exact role of FGD1 after birth?***
- ***How should be management of the neurobehavioral disorders manage at early ages for better outcome?***
- ***What could be the epistatic genes for modification of FGD1 phenotypes in the family?***
- ***Should every case with joint laxity be examined for other subtle dysmorphology of ASS?***

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