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

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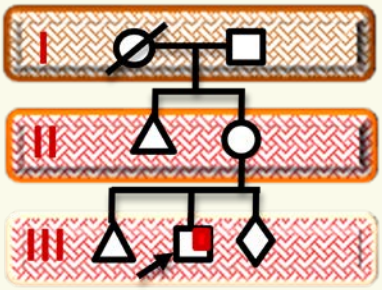
Volume 3, Issue 23, April 2022

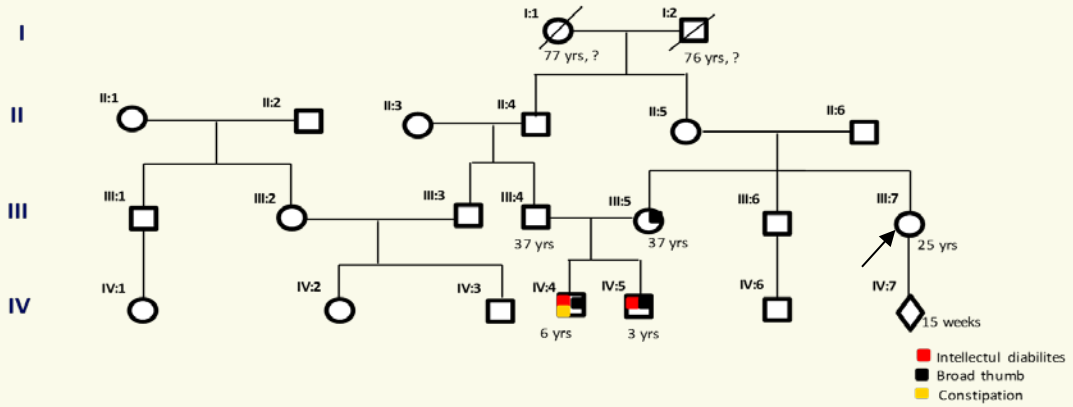
From the desk of Editor

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.

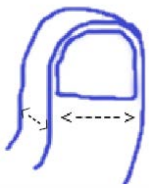


Neurogenetics -VI

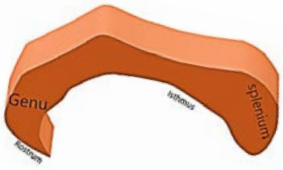
Intellectual Disability/ *X-Linked*/(IDXL)/ MED12-Related Disorders



Characteristic clinical features



Broad Thumb, (Subjective): *Increased thumb width without increased dorso-ventral dimension*



Corpus callosum: thick layer of *connecting nerve fibers between two halves of the brain, dysgenesis has variable clinical phenotype*

Insight:

1. What are the modes of inheritance of MED12 related disorders?
2. How does the MED12 protein dysfunction lead to intellectual disabilities(ID)?
3. Is there any role of antenatal MRI in case IV:7 in genetic counselling?
4. How to approach a case of IDXL with the broad thumb?
5. What is the non-syndromic clinical relevance of MED12 gene?

Plausible tenets:

Gene: MED12 (Xq13.1); 25.561 kb & 45 Exons

- **Belong to family of Mediator complex**
- 35 domains, 54 transcripts (splice variants), 192 orthologues & 1 paralogues
- Protein (**2177 AA**) subunit of a complex protein structure called mediator complex, having around 25 protein subunits, works as a transcriptional regulator in all genes, especially SHH & Wnt signaling pathways so having a critical role in early embryonic development like cell migration& differentiation.
- Smoothen the communicattion between different transcritional factors including regulatory proteins & RNA polymerase II transcription machinery.

Clinical phenotypes:

- Can be divided in three categories on the basis of inheritance pattern

A. Phenotype affected male only			
FG syndrome type 1 (**FGS1**) **or** Opitz-Kaveggia Syndrome; OKS	**XR**	Intellectual disability (**ID**), Hypotonia, malformations of corpus callosum, proportionate large head & simple ear	**Broad thumb & halluces**, constipation or anal anomalies & behavioral disorders
Lujan-Fryans syndrome (**MRXSLF**)	**XR**		**Marfanoid habitus**
X-linked Ohdo syndrome (**XLOS**)	**XR**	Course facies & **blepharophimosis**	
B. Phenotype affected both sexes but female without ID			
Hardikar syndrome (**HS**)	**XD**	**Coarctation of the aorta, hepatobiliary & GIT malformations(malrotations), oral cleft, pigmentary retinopathy**	
C. Variable phenotype in both sexes & female with ID			
Nonspecific ID (**NSID**)	**XL**	ID without specific dysmorphology	

1868- DMD: First clinical reported IDXL

1917- MPS II: First metabolic disorder diagnosed as IDXL

1926-Incontinentia pigmenti: First reported dominant IDXL

IDXL with Broad Thumb: Differential diagnosis

Syndrome	Key finding
Keipert syndrome	Cupid's bow upper lip
Tonne-Kalscheuer syndrome	Stiff gait & autism
X-linked intellectual developmental disorder-99	Excess aggression & joint hyperlaxity
Craniofrontonasal syndrome	Frontonasal dysplasia
Simpson-Golabi-Behmel syndrome type 1	Pre- and postnatal overgrowth
Simpson-Golabi-Behmel syndrome type 2	Macrocephaly & ciliary dyskinesia

Role of MRI in counselling with case IV:7

- Beside Corpus callosum dysgenesis, reveals other brain anomalies
- Normal MRI do not exclude the MED12 pathological mutations
- Poor prognostication in case of additional findings in MRI which could be missed in sonography

Non syndromic role of MED12:

1. Dysregulation of transcription with somatic mutation of MED12 leads to tumor & also opposition to chemotherapy agents.
2. Up to 80 % of somatic mutations have been reported with hormone-dependent tumors such as uterine leiomyomas, phyllodes tumors of the breast, prostate cancer, ovarian cancer & fibroadenomas.
3. Role in hematopoietic stem cell (HSC) homeostasis - Inactivation of MED12 in the laboratory leads to bone-marrow aplasia.
4. Role in apoptosis with chemotherapy- loss of MED12 prevented apoptosis of cells in Jurkat leukemia.
5. Alteration of cellular growth factors such as TGF βR2 by cytoplasmic MED12 -affects drug response.
6. MED12 Somatic mutations are cell line-specific & detailed mechanisms not precise.

Thought Riveting:

- ***Why "inherited as X-Linked manner" is not used for all X chromosome related genes disorders?***
- ***What are the issues for using a large protein MED12 as an anticancer medicine?***
- ***What is the exact spatial relationship of different proteins in the mediator complex?***
- ***What are the high-risk polymorphic markers of other mediator complex subunit genes in case of NSID?***
- ***Is there any role of cyclopamine in management of intellectual disabilities for FGS1 & MRXSLF?***
- ***Does first trimester Zinc prophylaxis have any preventive role in complex congenital malformations in fetus?***

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Reviewer: Dr Rakshat Ranjan