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

Rishi Vansh

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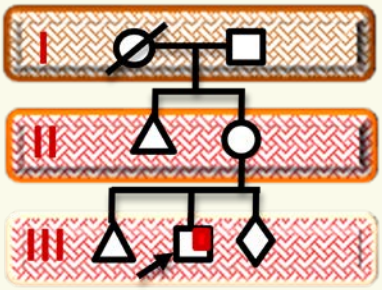
From the desk of Editor

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.



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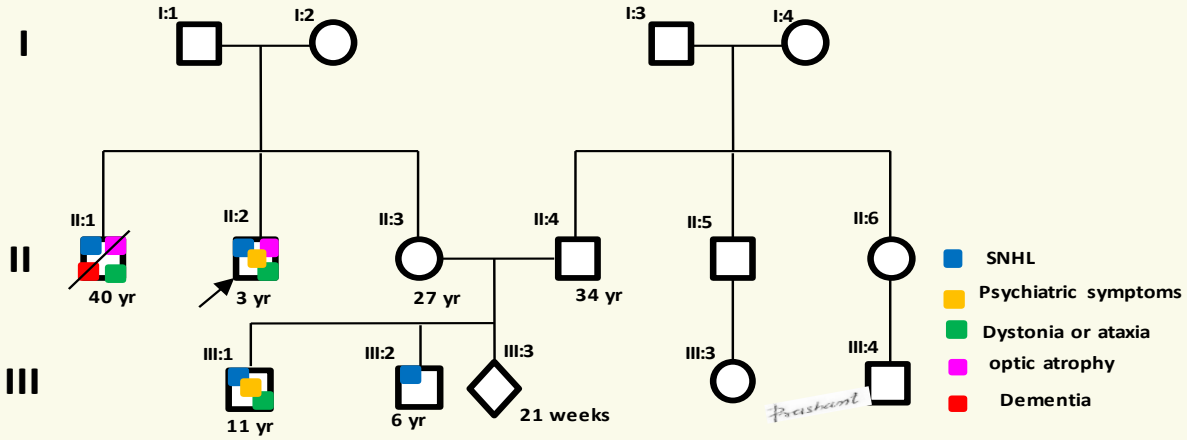
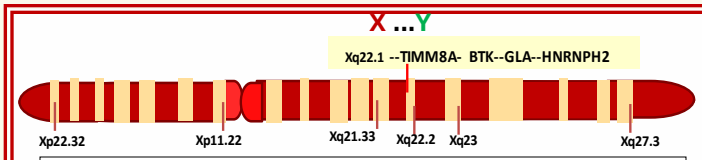
Neurogenetics -VII

Intellectual Disability/ ***X-Linked***/(IDXL)/ **Deafness-Dystonia-Optic Neuronopathy Syndrome (DDON), Mohr-Tranebjaerg syndrome (MTS)**



Xq22.1 contiguous genes' locations



X...Y two **location** are very close, coinheritance mostly

X:101,345,660	TIMM8A(DDON)
X:101,349,449	BTK (Agammaglobulinemia, X-linked 1)
X:101,397,802	GLA (Fabry disease)
X:101,408,221	HNRNPH2 (Intellectual developmental disorder, X-linked, syndromic, Bain type)

Insight:

1. Is DDON a mitochondrial disease?
2. How does DDON progress clinically with time?
3. Does DDON categorize as a neurodegenerative disorder?
4. Does clinical or lab-findings guide for selecting molecular testing in DDON?
5. How can the proband's genotyping help in genetic counseling of case III:3?

Plausible tenets:

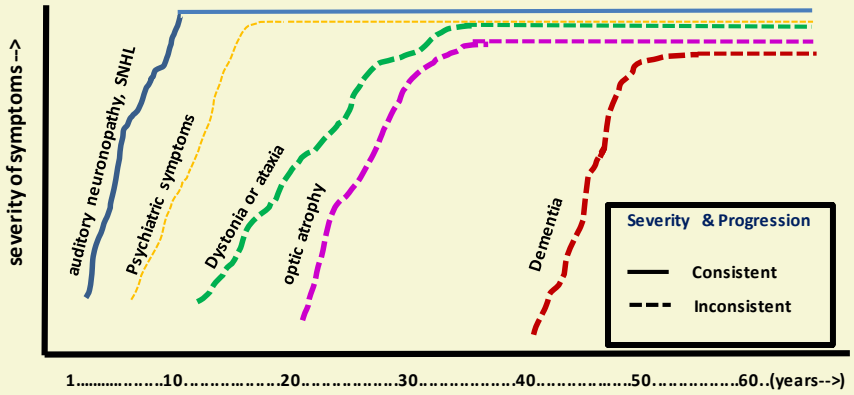
Gene: TIMM8A (Translocase Of Inner Mitochondrial Membrane 8A) (Xq22.1); 3,536 bps & 2 Exons

- **Belongs to the family of translocase & chaperone, present between the mitochondrial membranes**
- Transcript length: 1201 bps, Seven domains and features, four splice variants, 213 orthologues, one paralogue
- Chaperon Protein [(97 AA), Molecular mass: 10998 Da] introduces and incorporation of hydrophobic membrane proteins from the cytoplasm into the mitochondrial inner membrane.
- Directly essential for the normal mitochondrial function that leads to overlapping phenotypic spectrum of Mitochondrial disease as ganglia degeneration, progressive disease, myopathy & so on

--- Clinical phenotypes ---

- **X Linked inheritance** pattern
- Isolated hearing loss is not Reported & phenotypes have age related penetration
- **No clincial diagnositic criteria**
- Female might have Dystonia (focal) and hearing loss

- A contagious gene deletion case has additional findings
- Management -supportive



The first time, Mohr(M) and Mageroy named it DFN-1, **the first XL** nonsyndromic hearing loss disorder. in 1960

While in **1995, Tranebjaerg(T)** defined other phenotypes so, which are presently called MT syndrome.

Molecular Testing strategies

Clinical feature/s	Molecular testing
SNHL with immunodeficiency (X-linked agammaglobulinemia (XLA)	A contiguous gene deletion - Microarray
SNHL due to auditory neuropathy	*1st NGS based Gene Panel testing (having TIMM8A)* 2nd deletion and duplication test

Linkage analysis is a statistical technique that indirectly estimates the closeness between the two sequences based on the possibility of moving these sequences together in DNA replication.

So, if you know location 'X' and present it only in the selected phenotype. There would be a strong possibility that having a nearby located 'Y' sequence might cause that particular phenotype.

LOD (logarithm of the odds): is a statistical tool to calculate the possibility of co-inheritance of two loci in the genome (indirect proximity to each other). **Score ≥3**, usually coinheritance (very close loci).

Role of Genotyping in counselling with case III:3

- Confirming the diagnosis WITH genotyping is very essential **but no exact** database for helping genotype and phenotype correlation
- **Essential Prerequisite before doing any molecular test: Family should well understand its overall utilities, limitations & psychological impacts**

Thought Riveting:

- ***What is the constellation of clinical findings with malfunctioning of "sorting and assembly machinery" (SAM) complex?***
- ***Why does the TIMM8A deficiency predominantly involve the nervous system?***
- ***What is the non-Mito function of TIMM8A?***
- ***Is there any role of neuroimaging in estimating the disease progression in the first decade of life?***
- ***What is the scope of use of cochlear implant in DDON?***

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