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

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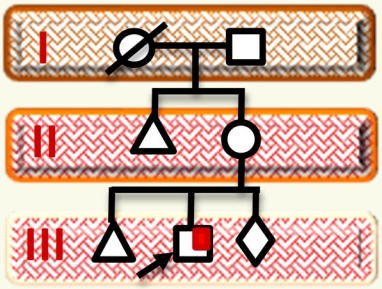
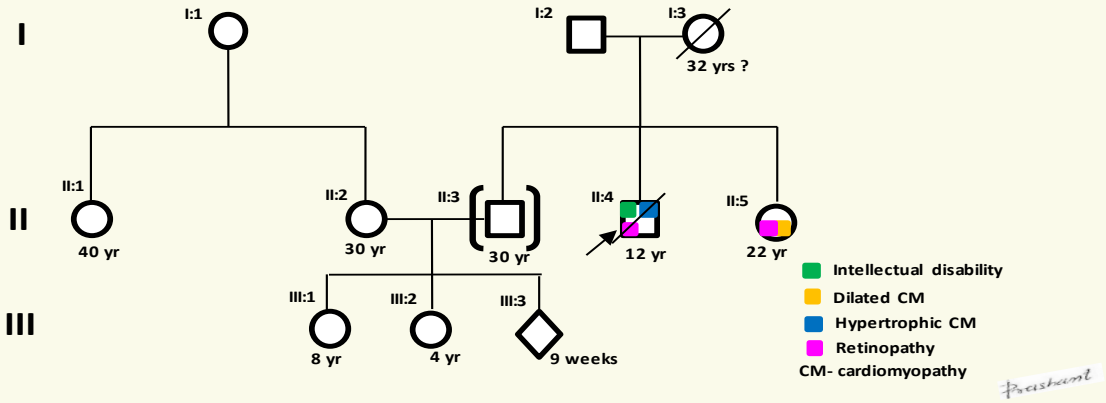
From the desk of Editor

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.

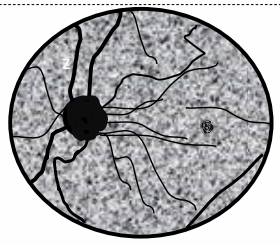


Inherited Metabolic Diseases

Neurometabolic/Intellectual Disability/ X-Linked/ Danon disease (Pseudoglycogenosis II)



Rod-cone dystrophy



A mosaic pattern of hypopigmentation

- The progressive degeneration of rod-cone (Usually Rods followed by cons)
- Alternative names: retinitis pigmentosa (most common form), Pigmentary retinopathy, Tapetoretinal degeneration
- Rod-cone dystrophy types: non-syndromic (common) & syndromic forms

Insight:

1. What are the differences in the life span between male and female patients?
2. What is the most common "cardiac preexcitation" finding with Danon disease?
3. What are sex-dependent phenotypic differences in Danon disease?
4. What do # & the first digit indicate in the OMIM database?
5. How would you counsel the family for case III:3?
6. How to approach a male child with retinitis pigmentosa with intellectual disability?

Plausible tenets:

- **Gene: LAMP2 (Xq24): Lysosome associated membrane proteins; a member of membrane glycoproteins' family**
- **Exons: 9, 43.218 kb, 22 domains and features, 199 orthologues, 4 splice variants or transcripts, 3 paralogues. Transcript length: 6,535 bps. Protein has 410 amino acids, with molecular weight 44961 Da.**
- Compose the lysosome boundary to protect & maintain it, & also help in adhesion, besides fusion of autophagosomes & chaperone-mediated autophagy. Required for efficient MHCII-mediated presentation of exogenous antigens but inversely suppressing the expression of the endogenous antigen.

Clinical phenotype:

- No formal diagnostic criteria; need to suspect in any school-age male **(Age dependent penetrance)** having chest pain and palpitations (cardiomyopathy), gradually progressive proximal muscle weakness with raised CPK level and +/- night blindness (**retinopathy, ≈11%**). **EKG changes** of Wolff-Parkinson-White syndrome (48 %) are the most commonly reported cardiac Pre-excitation.
- Neurological features: Developmental delay and mild learning disability (lack of strong evidence for direct causation).
- **Phenotype differences in females(XLD):** variable presentation, 10-15 years later than males, average life span – male 2nd decade and female 3rd decade, 88% males have hypertrophic while 50% females have dilated cardiomyopathy, and female IQ usually ≥70%
- **Management:** No consensus management guidelines, need expert consultation, follow surveillance guidelines (https://www.ncbi.nlm.nih.gov/books/NBK554742/#danon.Management), & cardiac transplantation. (D'Souza **et al [2014] PMC4169002)**

X linked intellectual disability Syndromes with retinitis pigmentosa

OMIM No.	Disease, Gene and MOI	Key findings
#300578	CHROMOSOME Xp11.3 DELETION SYNDROME	severe, early-onset retinitis pigmentosa, mental retardation, mild to moderate Normal intelligence in carrier females
#302800	CHARCOT-MARIE-TOOTH DISEASE, X-LINKED DOMINANT, 1; CMTX1 **(XLD)**	Central nervous system involvement (in some patients)
#300998	INTELLECTUAL DEVELOPMENTAL DISORDER, X-LINKED, SYNDROMIC, 35; MRXS35 (XLR)	Progressive microcephaly (up to -9.6 SD)
#300804	JOUBERT SYNDROME 10; JBTS10 (XLR)	Molar tooth sign, dysregulated breathing patterns
308200	ICHTHYOSIS AND MALE HYPOGONADISM (RUD syndrome, included)	epilepsy, mental retardation, infantilism, congenital ichthyosis, and retinitis pigmentosa.
#309900	MUCOPOLYSACCHARIDOSIS, TYPE II; MPS2 (AR)	MPS phenotype & progressive mental disorder
#310600	NORRIE DISEASE; NDP (XLR)	Sensorineural deafness, complex psychobehavioral phenotype
#300653	PHOSPHOGLYCERATE KINASE 1 DEFICIENCY; PGK1 (XLR)	hemolytic anemia, myopathy, and neurologic involvement
#300896	CONGENITAL DISORDER OF GLYCOSYLATION, TYPE IIm; CDG2M **(SMo, XLD)**	
251240	MICROCEPHALY WITH CHEMOTACTIC DEFECT AND TRANSIENT HYPOGAMMAGLOBULINEMIA	severe microcephaly, mental retardation, short stature, and recurrent infections.

Minor Xp21 deletion associated with Duchenne muscular dystrophy, chronic granulomatous disease, retinitis pigmentosa, & McLeod syndrome

#- Phenotype description, known molecular basis, SMo- Somatic mosaicism.
OMIM entry is given a unique six-digit number and first digit indicates location of the gene:
1----- (100000-) 2----- (200000-) Autosomal loci or phenotypes (entries created before May 15, 1994), 3----- (300000-) X-linked loci or phenotypes, 4----- (400000-) Y-linked loci or phenotypes, 5----- (500000-) Mitochondrial loci or phenotypes, 6----- (600000-) Autosomal loci or phenotypes (entries created after May 15, 1994)

Counsel the family for case III:3- Husband II:2 is an adopted child, so his risk carrying the pathological genes is not more than the general population. There is no need to test for carrier status without additional risk and lack of national guidelines for particular disease. So, case III:3 will be less likely to have any other risk than the general population to have a specific genetic disease. So, case III:3 do not have any indication for molecular testing and has a risk for a genetic disorder like general population.

Thought Riveting:

- ***How valuable can biochemical markers be for carrier detection of genes related to intellectual deficiency?***
- ***Can Anti-LAMP proteins help in preventing tumor cell metastasis?***
- ***What could be the possible role of LAMP1 for tissue-specific pleiotropy of LAMP2 mutations?***
- ***Can screening for RP as a standard protocol help in the clinical diagnosis for all intellectual disabilities?***
- ***What are the issues of gene therapy for genetic disorders having age depended-penetration?***

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