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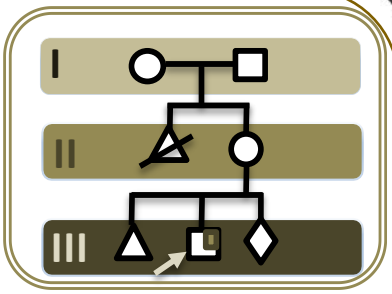
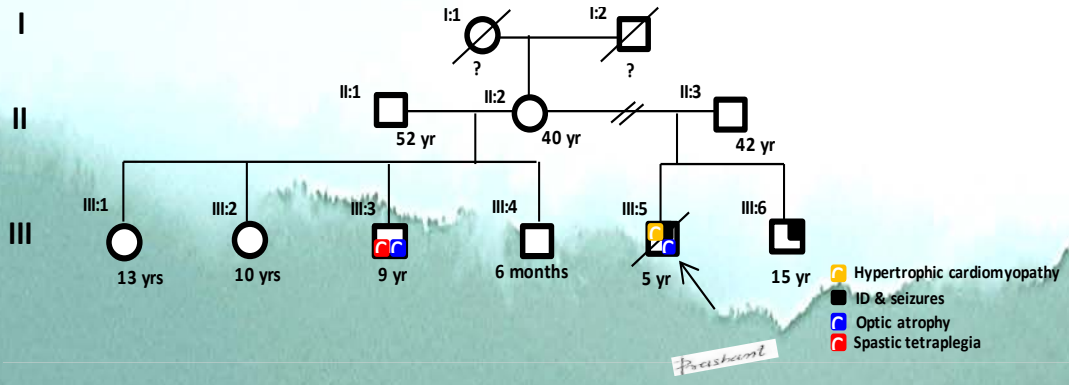


From the desk of Editor

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

Neurometabolic/Intellectual Disability/ X-Linked

HSD10 mitochondrial disease (HSD10MD)



Mitochondrial with HSD10MD

Electron microscopy picture

- Changes in shape- circular or elongated
- Membrane – Irregular and variable thick
- Cristae- enlarged, decreased or depleted
- Mitochondria several times increased in number

Insight:

1. What is the peak age of presentation for HSD10MD?
2. Can HSD10MD clinically present as spastic cerebral palsy?
3. How does electron microscopy help in the diagnosis of X-linked mitochondrial disease?
4. What is the mode of inheritance for the X-linked mitochondrial disorders?
5. How would you like to assess the cases II:1 & II:2 clinically? What is the clinical relevance?

Protein sequence

MAAACRSV
KGLVAVIT
GGASGLGL
ATAERLVG
QGASAVLL
DLPNSGGE
AQAKKLGN
NCVFAPAD
VTSEKDVQ
TALALAKG
KFGRVDVA
VNCAGIAV
ASKTYNLK
KGQTHTLE
DFQRVLDV
NLMGTFNV
IRLVAGEM
GQNEPDQG
GQRGVIIN
TASVAAFE
GQVGQAAY
SASKGGIV
GMTLPIAR
DLAPIGIR
VMTIAPGL
FGTPLLTS
LPEKVCNF
LASQVPFP
SRLGDPAE
YAHLVQAI
IENPFLNG
EVIRLDGA
IRMQP

- **Each Exon in different colours (Residue overlaps splice site)**

Plausible tenets:

Gene: HSD17B10 (Xp11.22): Location on X: **53,431,261-53,434,370**

- **Belong to the short-chain dehydrogenase/reductase superfamily; Protein product- 17-beta-hydroxysteroid dehydrogenase X,** having 9 splice variants, 214 orthologues, 25 paralogues
- Transcript: **Exons: 6**, **954 bps**; Protein has 261 amino acids, with a molecular weight of 26923 Da.
- Crucial for mitochondrial functioning including its DNA transcription. Indirectly It protects cell from post stress apoptosis & deposition of amyloid-beta.
- Mitochondrial dehydrogenase is involved in pathways of fatty acid, branched-chain amino acid (isoleucine degradation pathway) and steroid metabolism (hydroxysteroid dehydrogenase activity toward steroid hormones and bile acids) also help in processing of activation of gamma-aminobutyric acid receptors (**GABAARs**), **neurosteroid and cardiolipin** metabolism.
- HSD17B10 & TRMT10C/MRPP1, form a subcomplex of the mitochondrial ribonuclease (RNase) P, a complex that helps in tRNA maturation (most likely mechanism for .
- Being part of the Parkin/ PINK1 pathway, also help in the control of structure, activity and life cycle (*ineffective **mitophagy** leads to excess accumulation of mitochondria*).

Clinical phenotypes:

- **HSD10 mitochondrial disease (XLD)** highly variable age of onset and severity, a multisystemic disease (nuclear mitochondriopathy). **Onset**: infantile form (**cardiomyopathy -lethal**), juvenile form- (**late onset**), & atypical form (**without neurologic involvement**).
- **Classically** present like neurodegenerative disorder with or without **complex neurological features** such as hypotonia, seizures, abnormal movements and cerebral palsy (**CP**), & progressive ophthalmic involvement (visual loss due to optic atrophy or retinopathy).
- **Heterozygous females- may be intellectually normal to variable deficiency**
- **Rx: Symptomatic, surveillance & supportive**

Phenotypic series (PS): No specific available for **"X-linked mitochondrial disorders"** but more than twenty well recognized disorders have been discussed in the literature which have quite overlapping clinical, and biochemical features with some private(familial) phenotype, which need to recognize before planning molecular testing.

Biochemical marker: increased "2-methyl-3 hydroxybutyrate and tiglylglycine" in urine sample as by product of leucine metabolism. No acute crisis in neonatal period & urine levels do not match with phenotypic severity

Mitophagy: A complex process of catabolism of aged, non-functional mitochondria by mitophagy receptor pathways is essential for normal cytosolic activity & mitochondrial homeostasis. Role in various diseases and exact mechanisms or pathways needs evaluation.

Counsel the family for clinical assessment case II:1 & II:2- Clinical assessment of apparently asymptomatic cases needs expertise and it is a well-known ethical dilemma. Steps for assessment: 1. **Never do it in one setting,** 2. Explain the disease in proband and discuss the surveillance test and their role, 3. Understand **psychological status** in follow up, 4. Give serious consideration for cultural, social & national guidelines before further discussion, 4. Explain the term "apparently asymptomatic" and **discuss about advantages or disadvantages(psychological stress)** after knowing the disease status, 5. Need **written consent** from both (in few states), 6. **Clinical evaluate** before testing in details

Thought Riveting:

- ***What is/are mitophagy pathway/s involved with the diferuloylmethane (curcumin) action for its anticancer properties?***
- ***What are the rescue pathways for neurological normal HSD10MD cases?***
- ***Is there any early clinical marker for future prediction of neurocognitive status of HSD10MD case, like "ABCD ambulatory charts for CP"?***
- ***Will it be useful to do mitochondrial phenotyping for an undiagnosed intellectual deficiency case with inconclusive NGS reports as VUS in unmatched genomic areas?***

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