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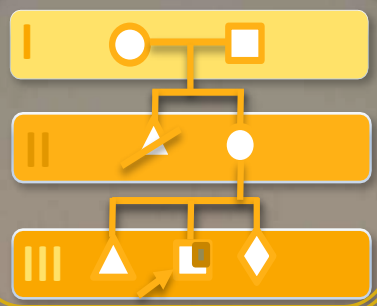
All India Institute of Medical Science Rishikesh

AIIMSR
Department of Pediatrics
Genetic -division

H1 H2A H2B H3 H4

Volume 5
Issue 45, March 2024



From the desk of Editor

The genetic division of the Pediatric Department publishes a monthly newsletter for all Medical Professionals. The newsletter is related to genealogical parlance and is a deliberate attempt to enhance awareness of genetic disorders with recent updates.

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DOI: 10.13140/RG.2.2.22894.18246

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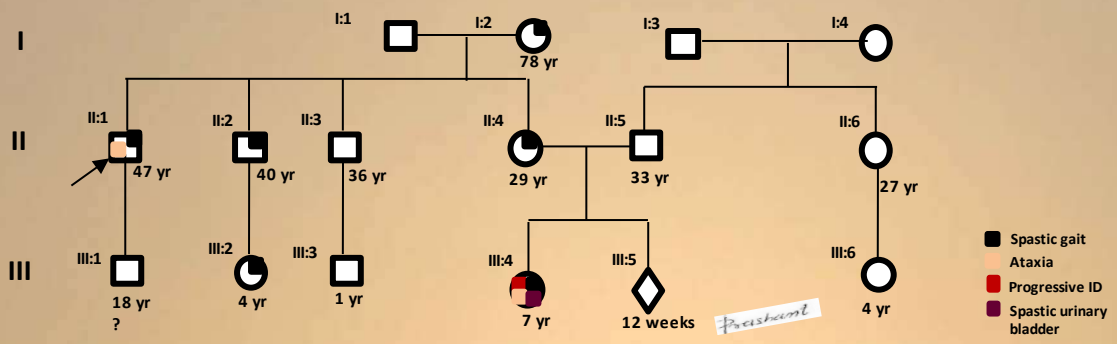
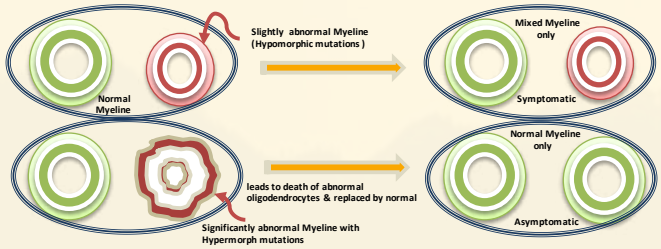
Neurogenetics -XV- Neurometabolic/ Intellectual Disability/ X-Linked/ PLP1 related Disorders,

included Pelizaeus-Merzbacher disease (PMD) & spastic paraplegia 2 (SPG2)



Paradoxical Phenomenon in Carrier Female with Severe Versus Mild mutations



- Hypomorphic mutations do not cause apoptosis of oligodendrocytes.
- In heterozygous females, abnormal oligodendrocytes persist and can cause neurologic signs
- Hypermorph mutations lead to degenerating oligodendrocytes, which are replaced by those expressing the normal PLP1 allele. So normal heterozygous females without any neurological signs
- ***That is why, carrier females have some clinical features with a mildly affected case, while asymptomatic with severe disease in the male***

Insight:

1. What are the clinical phenotypes of PLP1 related disorders?
2. What are the functions of the PLP1 protein?
3. How would you counsel the family for **Case III: 5**?
4. What are the differential diagnoses of Leukodystrophy, hypomyelinating (**HLD**)?
5. What is the mechanism for paradoxical phenomenon in carrier female with severe versus mild mutations?

Plausible tenets:

Gene: PLP1 (Xq22.2) Genomic coordinates (GRCh38) **X:103,776,506-103,792,619 (from NCBI)**

- **Lipophilin (Transmembrane proteolipid protein)** makes up a large proportion of myelin **[up to fifty percent myelin protein] in two isoform, PLP1 (central) and DM20 (peripheral)].** In the human prefrontal cortex, It **increases** from very early age to adulthood **(up to 46 years),** having 23 splice variants; 274 orthologues; 2 paralogues.
- Transcript: **Coding exons: 7**; length of **3,011 bps**, 18 domains, and features, Protein has 277 amino acids, with a molecular weight of 30077 Da.

Clinical phenotypes: PMD and SPG2 have been observed in **different males within the same family** [Hodes et al 1993, Sistermans et al 1998].

Age of onset	Distinct syndromes	Neurological features						
		Nystagmus	Spastic paraparesis	Initial Hypotonia	cognitive impairment	Ambulation	Speech	others
1st 5 yrs	Classic PMD	After birth	+++	+	+++	Early childhood Loss	+	Ataxia, Extrapyramidal movements
	PLP1 null syndrome	-	++	-	++	+	+	Peripheral neuropathy
	Complicated SPG (SPG2) & HEMS*	+	+	-	+	+	+	Ataxia, autonomic dysfunction
	Uncomplicated SPG (SPG2)	-	+	-	-	+	+	Autonomic dysfunction, maybe late onset in 3rd decade
Neonatal period	Severe "connatal" PMD	At birth	++++	++	++++	-	-	± seizures

*HEMS = hypomyelination of early myelinating structures

The risk of disease in females:**(Highest)**Nonsense/indel leads to a PLP1 null syndrome **> (moderate)** Missense mutations **> The lowest risk** with duplications **(favorably skewed X-chromosome inactivation).**

Testing strategies:

Cytogenetic method: FISH, MLPA 60-70 % (deletion & duplication mutations), & 1 % X chromosome inversion 70 kbp upstream of PLP1

Molecular: qPCR, Sanger sequencing, NGS based (Clinical, Exome or genome) sequencing - 30-40 % (point mutation)

OMIM Phenotypic Series - PS312080 Leukodystrophy, hypomyelinating - PS312080 (HLD)- 27 Entries, PLP1 only has X linked MOI (**HLD1**)

Key facts related to Population Genetics, Genotype and Phenotype

- **Severe forms** of PMD have **missense mutations in exons 2 and 4. SPG** was reported with splice site mutations **(leaky mutations),** and **truncating mutations** result in a relatively **mild phenotype.**
- **A PLP gene duplication** can manifest in females as an **early-onset neurologic phenotype; later, they** show clinical improvement by increased expression of a favourable X-inactivation pattern **(plasticity of oligodendrocytes).**
- **Around two-thirds carrier rate** was reported in mothers with **point mutation cases, while 91%** were in **duplicated cases. A significant male mutational imbalance** was observed only **for the duplications.**
- **k value of PLP1** was estimated from **9 to 11. The mutant fraction** or **frequency (k)** is the proportion of mutant people in a population.
- **The mutation rate (μ)** is an accumulation of mutations, 10−4 to 10−6 per gene per generation**. The point mutation rate is 1 in 10^8 per generation,** which leads to **approximately thirty point mutations in each gamete.**

Counsel the family for Case III: 5- Mutation testing of proband Case II:1, followed by testing of Case II:4, including her karyotype. Antenatal testing can be offered. Thalassemia screening and testing and routine genetic testing (for instance, the trisomies) could be planned in the same setting. In cases of positive results for the variant, the family has to be counselled for the complexity of interfamilial phenotype variability in a few cases.

Thought Riveting:

- ***What are other genomic regions associated with microhomology-mediated break-induced replication (MMBIR)?***
- ***Why is the duplication of the PLP1 gene the most common type of mutation? What can be the possible loci for an exact similar type of mutation spectrum in the human genome?***
- ***What are the proteins related to the unfolded protein response (UPR) pathway and their role in PLP1 related disorders?***
- ***Is there any role of hydroxyurea and prednisolone in the early stages of HLD?***
- ***Will it be possible to regulate the PLP1 gene overexpression within a physiological range with pharmacological agents?***