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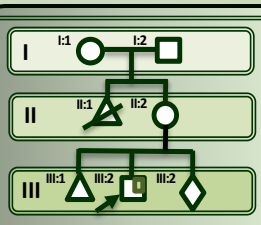
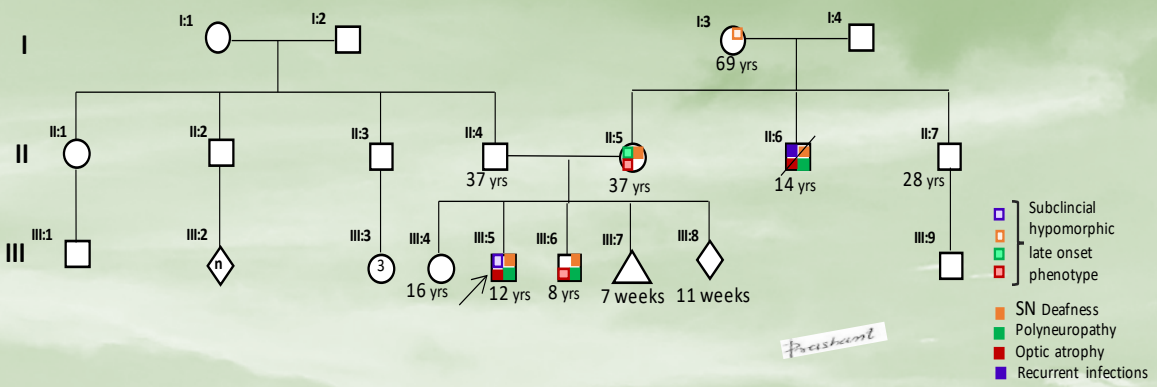
Neurogenetics -XX - Neurometabolic /Intellectual deficiency / Phosphoribosylpyrophosphate synthetase 1 (PRPS 1) related disorders

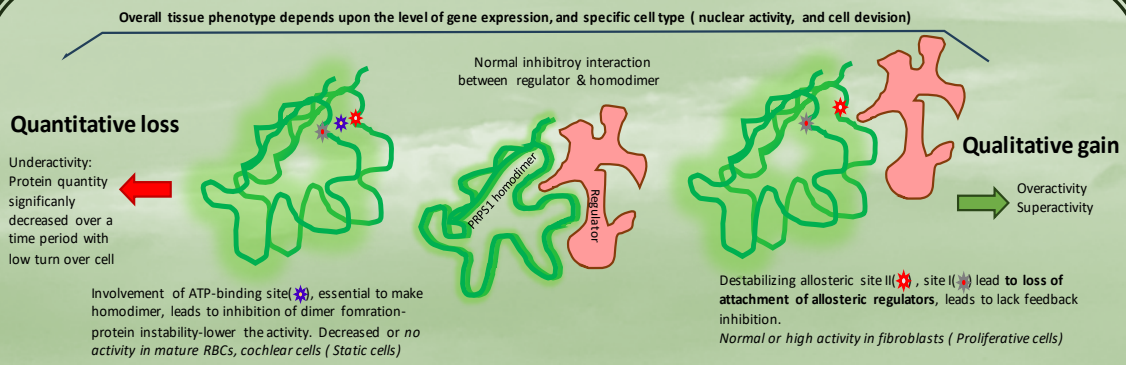
From the desk of Editor

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.





Molecular mechanism of V142L/ c.424G>C (p. Val142Leu) mutation phenotypes



- Molecular modeling is a used technique for predicting the possible changes with protein interaction.

Moran R, Kuilenburg AB, Duley J, Nabuurs SB, Retno-Fitri A, Christodoulou J, Roelofsen J, Yntema HG, Friedman NR, van Bokhoven H, de Brouwer AP. Phosphoribosylpyrophosphate synthetase superactivity and recurrent infections is caused by a p.Val142Leu mutation in PRS-I. Am J Med Genet A. 2012 Feb;158A(2):455-60. doi: 10.1002/ajmg.a.34428. Epub 2012 Jan 13. PMID: 22246954.

Insight:

1. How would you counsel **Case III: 8**?
2. What is the clinical spectrum of PRPS 1-related disorders?
3. What is the possible explanation of mixed phenotype for V142L variant?
4. What is the phosphoribosylpyrophosphate synthetase (PRPS) complex?
5. What is the Goss-Harris method?

Phosphoribosyl transferase domain ***https://www.ebi.ac.uk/interpro/entry/pfam/PF00156/***
Sequence Ontology: 0000417
This domain family enzymes: phosphoribosyl transferase enzymes: Adenine phosphoribosyl-transferase, Hypoxanthine-guanine-xanthine phosphoribosyl-transferase, Hypoxanthine phosphoribosyl-transferase, Ribose-phosphate pyrophosphokinase Amidophosphoribosyltransferase, Orotate phosphoribosyl-transferase, Uracil phosphoribosyl-transferase, Xanthine-guanine phosphoribosyl-transferase.
There is proximity of functionally related genes in few genomic landscapes as On Xq: **G6PD --HPRT1--PRPS1--alpha-GAL--PGK1--centromere.**

Goss-Harris method was used for mapping genes in human chromosomes.

Plausible tenets:

Gene: PRPS1 (Phosphoribosylpyrophosphate synthetase) Xq22.3, genomic coordinates (GRCh38): X:107,628,510-107,651,026

- Protein related to the pentose phosphate pathway. It is an enzyme that catalyzes the phosphoribosylation of ribose 5-phosphate to 5-phosphoribosyl-1-pyrophosphate. Magnesium (as a cofactor) and inorganic phosphate are needed for its activation. Ubiquitous expression in all tissues. It might have some role in inner ear development.
- **Unusually**, translation of this gene starts at a non-AUG (ACG) codon in vitro study, and transcription starts on +/ forward or sense strand.
- Gene : 30 Kb in size; 320 orthologues, 4 paralogues , and 25 splice variants.
- Transcript: 7 exons; 144 domains and features; transcript length 2,079 bps.
- Protein: 318 AA with 34834 Da molecular mass. Ubiquitination & glycosylation are major post-translation modification.
- **Gene tree** (**a pedigree of gene**) (ENSGT00950000182803)- ***Number of***: genes -1076, speciation nodes- 882, duplication-130, ambiguous- 61, gene split events- 2
  https://asia.ensembl.org/Homo_sapiens/Gene/Compara_Tree?db=core;g=ENSG00000147224;r=X:107628428-107651993;t=ENST00000372435

Phenotype: All phenotypic features are progressive in nature, inherited in an XL manner (females mostly have subclinical features), and inter/intrafamilial variability of phenotypes for both sexes.

Phenotype	MOI	Characteristic features
*Arts syndrome	XL	A neurodegenerative disease, floppy infant with gross developmental delay, late-onset abnormal movement (ataxia) with polyneuropathy (CN II, **CN VIII**, spinal & peripheral), and early death due to recurrent infections.
*Charcot-Marie-Tooth disease, X-linked recessive, 5	XL	Classical triad of deafness (early infantile), polyneuropathy (axonal sensorimotor neuropathy), & optic atrophy (1st to 2nd decade); **PS**– without optic atrophy, or with intellectually different (overlapping **mild** features of Arts syndrome)
*Deafness, X-linked 1	XL	In male (1st to 2nd decade) and female (5th decade); **PS**- subclinical presentations as changes in lab reports (electrophysiological and MRI brain) mild form of arts syndrome
#Gout, PRPS-related	XL	Urolithiasis, Hyperuricemia and Hyperuricosuria; PS- early onset sensorineural deafness; and in a few cases, like Arts syndrome with the **V142L variant**
#Phosphoribosyl pyrophosphate synthetase superactivity (gain of function)		

PS- phenotypic spectrum, * - loss-of-function mutation, #- gain of function mutation

- Need recommended surveillance, need an Individualized Education Program (**IEP**), & symptomatic management; no standard clincial treatment guideliens. Addition of PS-adenosylmethionine (SAM) & nicotinamide riboside have been reported to have some clinical benefits.

Lenherr N, Christodoulou J, Duley J, Dobritzsch D, Fairbanks L, Datta AN, Filges I, Gürtler N, Roelofsen J, van Kuilenburg ABP, Kemper C, West EE, Szinnai G, Huemer M. Co-therapy with S-adenosylmethionine and nicotinamide riboside improves t-cell survival and function in Arts Syndrome (PRPS1 deficiency). Mol Genet Metab Rep. 2021 Jan 20;26:100709. doi: 10.1016/j.ymgmr.2021.100709. PMID: 33532242; PMCID: PMC7823043.
Mittal R, Patel K, Mittal J, Chan B, Yan D, Grati M, Liu XZ. Association of PRPS1 Mutations with Disease Phenotypes. Dis Markers. 2015;2015:127013. doi: 10.1155/2015/127013. Epub 2015 May 24. PMID: 26089585; PMCID: PMC4458296.

Phosphoribosylpyrophosphate synthetase (PRPS) complex related entries in OMIM

PRPS	Genomic location	Function	Genetic disease association	Miscellaneous
PRPS1	Xq22.3	Nucleotide synthesis	PRPS1 related disorders	Wide phenotype spectrum
PRPS2	Xp22.2	Nucleotide synthesis	? SLE	Target gene for cancer therapy
like 1 (PRPS1L1) or PRPS3	7p21.1	Nucleotide synthesis	?? imperfect spermatogenesis	Expressed in testis only
PRPS1Pseudogene 1 (P1)	2q24.3	-	-	Regulatory roles, A processed pseudogene
PRPS1pseudogene 2 (P2)	9q33.3	-	-	Regulatory roles, Retrotransposition or gene duplication
PRPS Associated Protein 1; PRPSAP1 (PAP39)	17q25.1	A subunit of PRS complex (non-catalytic associated)	Hepatocellular Carcinoma	Negative regulatory role
PRPS Associated Protein 2; PRPSAP2 (PAP41)	17p11.2	A subunit of PRS complex (non-catalytic associated)	-	Negative regulatory role
PRPS: phosphoribosyl pyrophosphate synthetase, PRS1 & PRS2 are catalytic subunits of PRS complex				

Counsel the family for Case III: 8 – Recurrence risk is 50% in each pregnancy, & usually males will be affected more severely than females. First, the variant must be detected in the proband; the same variant could be used for antenatal testing in case III:8.

Thought Riveting:

- ***What are the investigation strategies for Pseudogene-Related Disorders (PRD)?***
- ***What is the dose of S-adenosylmethionine (SAM) supplementation for a child having a PRPS1-related disorder?***
- ***What could be the additional mechanism for hypo/dysmyelination with PRPS1 dysfunction besides reducing the purine nucleotides?***
- ***What is the role of miR-376 in tissue-dependent expression and disease progression?***
- ***Why do cochlear cells have a low threshold for protein truncation as compared to other tissue?***