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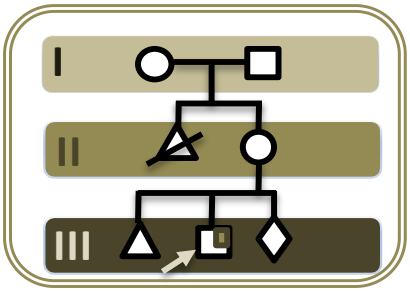

From the desk of Editor

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.

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Neurogenetics-(XIII)/Intellectual Disability/ X-Linked/(IDXL)/ Multiple Congenital Anomalies-Hypotonia-Seizures Syndrome-2 (MCAHS2); PIGA related disorders

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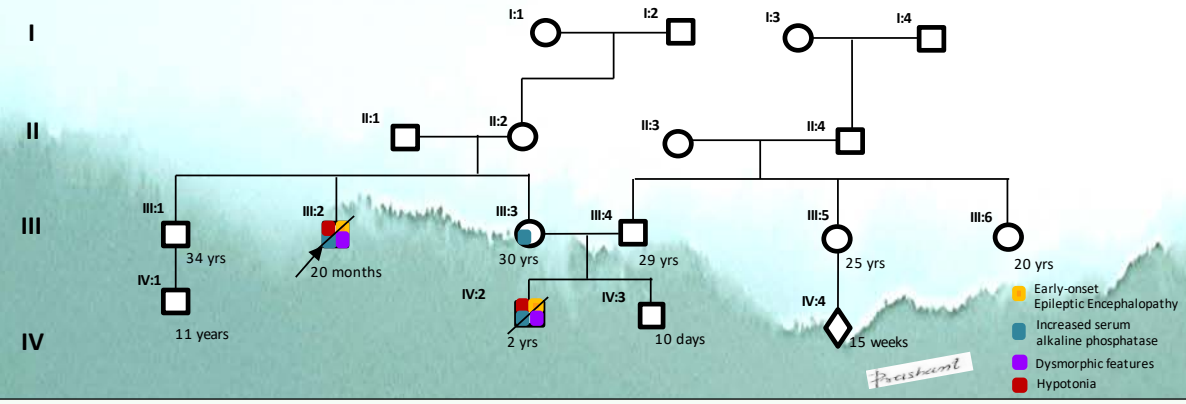
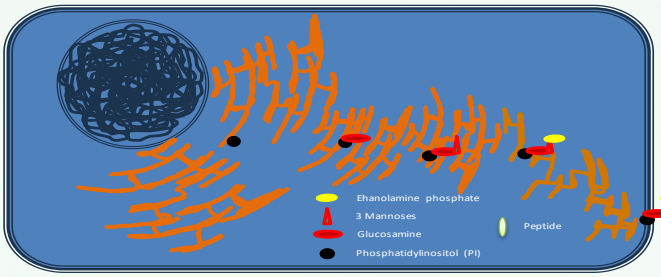


Glycosylphosphatidylinositols (GPIs)



- A cell membrane anchor for attachment of >150 proteins
- Synthesis by a multistep complex process in the endoplasmic reticulum (ER) by > 20 different proteins
- Consists of a molecule of phosphatidylinositol (PI) and a glycan core that contains glucosamine, three mannoses, and an ethanolamine phosphate

Insight:

1. How do you clinically differentiate MCAHS with other syndromic hypotonia?
2. What are the types of MCAHS?
3. What does the PIGA (Phosphatidylinositol glycan class A) protein do at cellular level?
4. What are glycosylphosphatidylinositols (GPIs)?
5. How would you counsel case IV:3?

Protein sequence:

MACRGGAGNGHRASATLSR
VSPGSLYTCRTRTHNICMVS
DFFYPNMGGVESHIYQLSQC
LIERGHKVIIVTHAYGNRKGI
RYLTSGLKVYYLPLKVMYNQ
STATTLFHSLPLLRYIFVRE
RVTIIHSHSSFSAMAHDALF
HAKTMGLQTVFTDHSLFGF
ADVSSVLTNKLLTVSLCDTN
HIICVSYTSKENTVLRAALNP
EIVSVIPNAVDPTDFTPDPFR
RHDSITIVVVSRLVYRKGI
DLLSGIIPELCQKYPDLNFIIG
GEGPKRIILEEVRERYQLHD
RVRLLGALEHKDVRNVLV
QGHIFLNTSLTEAFCMAIVE
AASCGLQZVVSTRVGGIPEVL
PENLIILCEPSVKSLCEGLE
KAIFQLKSGTLPAPENIHNIV
KTFYTWRNVAERTEKVYDR
VSVEAVLPMDKRLDRLISHC
GPVTGYIFALLAVFNFLFLIF
LRWMTPDSIIDVAIDATGPR
GAWTNNYSHSKRGGENNEI
SETR

Plausible tenets:

Gene: PIGA (Xp22): Belong to the **PIG family**, a **Catalytic Subunit of a complex protein "glycosylphosphatidylinositol-N-acetylglucosaminyltransferase (GPI-GnT)' c – consider as biosynthesis class A,**

- Genomic coordinates (GRCh38) **X:15,319,451-15,335,554,** a related pseudogene is located on chromosome 12.
- Exons: 6, coding exon: 5, **Size: 16,104 bases,** 10 domains and features, 212 orthologues, 19 splice variants or transcripts, 3 paralogues.
- Transcript length: **3590** bps. Translation length: **484** amino acids, with a molecular weight of 54127 Da
- **Initiator catalytic subunit for a cellular anchor protein "Glycosylphosphatidylinositol (GPI)"**
- Presumed to be associated with apoptosis regulation
- Important for normal embryonal development, especially the central nervous system

Clinical phenotypes: X-linked recessive inheritance - *100% skewed X inactivation in carrier females*

- A syndrome with neurodevelopmental disorder with truncal hypotonia and multiple congenital anomalies.
- **Neurological findings**: Epileptic encephalopathy (Hypsarrhythmia & Burst-suppression pattern), neuroregression, spastic limbs, corpus callosum, pons, & olfactory tracts dysplasia, delayed myelination, deaf & cortical blindness
- **Head and neck anomalies**: coarse facies, micrognathia, small, triangular & downturned corners of the mouth, dental dysplasia, short & anteverted nose, upslanting palpebral fissure & hypertelorism
- **Trunk & limbs:** joint contractures, cardiac defects, hepatomegaly, vesicoureteral reflux & nail dysplasia

Other Pathological Phenotypes of PIGA-

- **Neurodevelopmental disorder with epilepsy and hemochromatosis-** (with less lethal protein truncated variations)– clinically has mild to moderate features, & cumulative iron deposition in the body, which primarily targets the liver, & leads to juvenile-onset hemochromatosis.
- **Paroxysmal nocturnal hemoglobinuria (PNH1)- somatic mutations in hematopoietic stem cells** produce RBCs without the GPI, so dysregulation of various anchoring proteins, including the regulating complement proteins (i.e**., CD55 & CD59, etc.)** that why leads to recurrent intravascular hemolysis. Cell-free hemoglobin (**CFHb**) binds with nitrous oxide (**Hb iron nitrosyl**), and rapid low nitrous oxide leads to acute endothelial dysfunction sequences (**AEDS**) (vascular spasm, thrombosis, visceral pain, erectile dysfunction, etc.).

Phenotypic Series -PS614080- Multiple congenital anomalies-hypotonia-seizures syndrome - 4 Entries

OMIM No.	MCAHS Type	Location/ Gene/ MOI	Gene function
614080	1	18q21.33/ PIGN/AR	GPI ethanolamine phosphate transferase-1(class N Protein)
300868	**2**	**Xp22.2/PIGA/XLR**	**Catalytic subunit in the first step of GPI biosynthesis**
615398	3	20q13.12/PIGT/AR	Phosphatidylinositol-glycan biosynthesis class T
618548	4	16p13.3/PIGQ/AR	Catalytic subunit in the first step of GPI biosynthesis

Pretest counselling for case IV:3- Ask first for antenatal testing if done, then analysis of the report. A detailed clinical evaluation of the newborn is mandatory and followed up with the vaccination schedule for an undetermined report as a variant of unknown sequence (VUS) or even in a negative report for a pathological variant. **An asymptomatic high-risk neonate** needs to be tested before planning the discharge as this is an early onset lethal untreatable disorder because it helps the family's **prognostication, psychosocial support, supportive management & financial planning in advance**

Thought Riveting:

- ***Can selectively targeting the GPI anchoring be utilized for better macromolecule replacement therapy for rare diseases?***
- ***What could be the possible biochemical markers for the 'GPI biosynthesis defects' (GPIBD)?***
- ***What is the impact of environmental factors on GPI turnover (epigenetic regulation)?***
- ***Does the Somatic mutation of GPI proteins associate with, late-onset metabolic disease or the complex autoimmune mechanism?***
- ***Does the PIGA interact differently with proteins of the developmental pathway during embryonic development?***

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