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

Rishi Vansh

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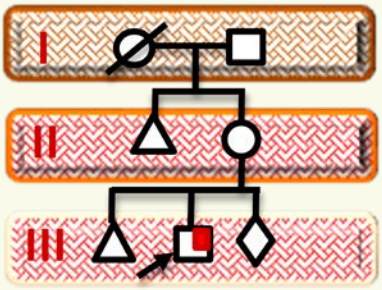
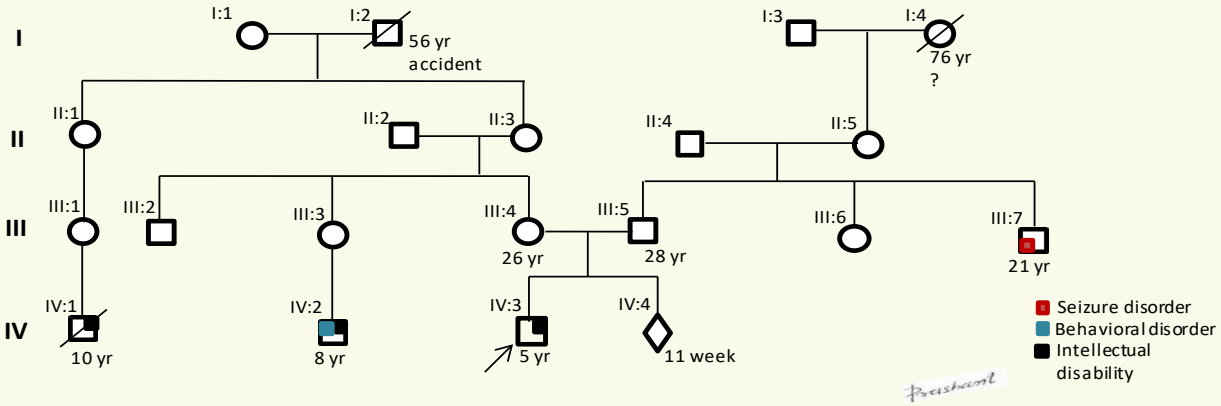
From the desk of Editor

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.

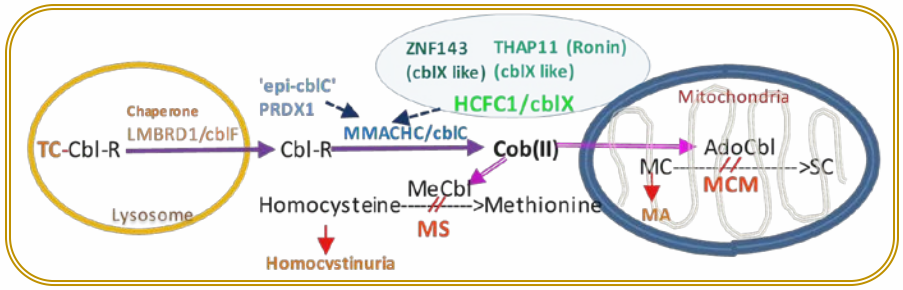


Inherited Metabolic Diseases

Neurometabolic/Intellectual Disability/ **X-Linked**/ Methylmalonic Aciduria and Homocystinuria, cblX TYPE;
MAHCX / X linked Disorders of Intracellular Cobalamin Metabolism



Intracellular B12 role & genes interaction with cblX



MS: Methionine synthase or methyltetrahydrofolate homocysteine methyl transferase,
MCM: methylmalonyl-CoA mutase,
AdoCbl: adenosylcobalamin,
MeCbl: methylcobalamin,
SC: Succinyl-CoA,
MA: Methylmalonic aciduria
'--->': Transcription regulator

Insight:

1. What are the specific clinical characteristics of intracellular cobalamin metabolism disorders?
2. Can B12-related disease and its severity be diagnosed alone with laboratory tests without mutation testing?
3. Which NGS-based test will be ordered in the first place for case IV:3?
4. What are the genes related to extracellular B12 metabolism?
5. Is there any biomarker existing for disorders of Intracellular Cobalamin Metabolism?

Plausible tenets:

Gene: HCFC1 (Xq28); 24,805 bp & 26 Exons

- **A member of the host cell factor family, a multiprotein-DNA complex as a global transcriptional coregulator**
- Transcript (**8,876 bps)**, 4 transcripts (splice variants), 157 orthologues & 10 paralogues; 69 domains and features
- Protein HCF-1 **(2035 AA, 208732 D**): a fibronectin-like motif, five *Kelch* repeats, & six *HCF* repeats (Cleavage sites)
- Help in the formation of cofactors for two cobalamin-dependent enzymes (MCM & MS) for whole animal kingdom
- A potent regulator of chromatin & embryonic neural development
- Cell cycle regulator (assists G1 to S phase shift), complex interact & moderate with various transcription factors as homeobox protein, FOXO3 & E2F1 (beta-cell growth) & chromatin modifier proteins (epigenetic regulation)

Clinical phenotypes: Simplified Genotype and Phenotype relationship (**MOI- X linked recessive**)

Phenotype	Genotype- HCF-1 activity/ HCFC1 Gene expression
Methylmalonic aciduria and homocystinemia	**Absent**
X-linked intellectual disability (variable severity)	**Partial**

- Other associated features: intractable epilepsy, hypotonia, microcephaly, choreoathetosis, & behavioral problems

Management:

- **Investigation:** Evaluation of the methylmalonic acid (MMA) level in urine and blood and total plasma homocysteine (tHcy) level are the mainstays of biochemical testing.
- **Complementation analysis - cblC type**, so need confirmatory testing by gene sequencing.
- **Acute** R: vital care, early intervention for thromboembolic & metabolic complications, retaining anabolic state
- **Long term** R: Decrease MMA, tHcy level & sustain normal concentrations of methionine in plasma & Injectable hydroxocobalamin (OHCbl) and betaine. Standard treatment for other symptoms as per protocol

Intracellular B12 pathway related disorder recognized by complementation analysis in pregenomic era. Eight complementation groups*- mut and cblA–cblG, have been reported with defective B12-dependent cofactors (MeCbl & AdoCbl).

*Technique based on study of biochemical reaction by autoradiography in multinucleate fibroblast (**heterokaryons** made by fusion of different patient's fibroblast) to know the gene expression indirectly. (Greek words "heteros," meaning "other than,")

-Initially, Rosenblatt's laboratory in the McGill University used that technique for diagnostic purposes

Roel of HCFC1 with herpes simplex virus (HSV) infection: facilitated the transcription through the formation of multiprotein-DNA complex with viral transactivator protein POU2F1& VP16

Hodgkin first deciphered the structure of cobalamin via x-ray crystallography.
The most chemically complex vitamin & also has a cobalt atom situated in the center.

Genes related to carriage & absorption of cobalamin Cbl with their role

TCN genes: TCN I (haptocrrin), TCNII , and TCN III (IF) { most likely arose by gene duplications)

- **TCN I**(11q12.1): haptocorrin, **R** ('rapid')binder protein, found in many secretions
- **TCN II** (22q12.2):Transcobalamin II deficiency(AR), plasma globin for b12 transportation
- **TCNIII** or **CBLIF** (IFD)(11q12.1) : Intrinsic factor deficiency(AR)

IFR: AMN and CUBN [Cubam complex]*:

- **CUBN** (10p13): Chronic benign proteinuria (PROCHOB)(AR), Imerslund-Grasbeck syndrome(**IGS**) 1(AR)
- **AMN** (14q32): **IGS 2** (AR), do TCN III glycosylation & trafficking to the cell surface with CUBN help

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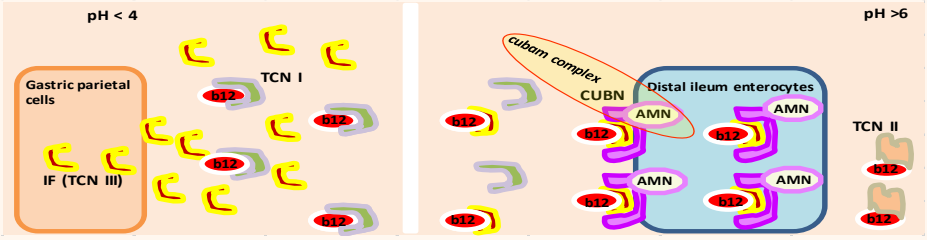

Genetic counselling test for IV:3- NGS based panel for pathological variants in any of the genes related to intracellular B12 processing of cofactors formation: HCFC1 (cblX), THAP11(cblX-like), ZNF143(cblX-like), MMACHC (cblC- *most common type*), MMADHC (cblD-combined and cblD-homocystinuria), MTRR (cblE), LMBRD1 (cblF), MTR (cblG), ABCD4 (cblJ)

Thought Riveting:

- ***Is there any role of B12 metabolism defects in hemolytic uremic syndrome (HUS)?***
- ***What are the genomic regulators for the universal CpG-island (CGI) promoters?***
- ***Can YY1 and GABP mutations present like intracellular B12 pathway-related disorders?***
- ***Does antenatal B12 supplementation have any protective role on congenital malformation and non-syndromic intellectual deficiency?***
- ***Can HCFC1 expression inhibition be a novel therapy for viral encephalitis, primarily due to the Herpesviridae family?***

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