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

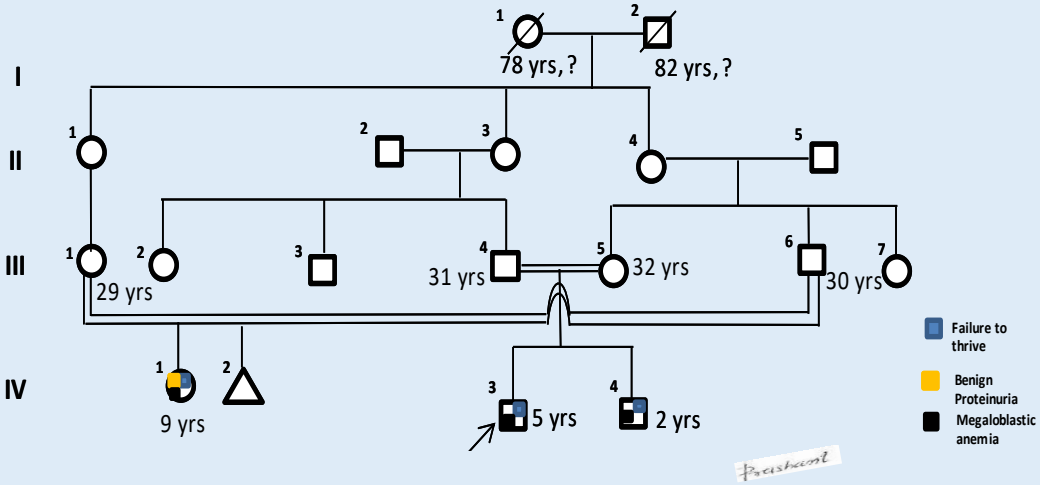
Rishi Vansh

Volume 2, Issue 9 February 2021

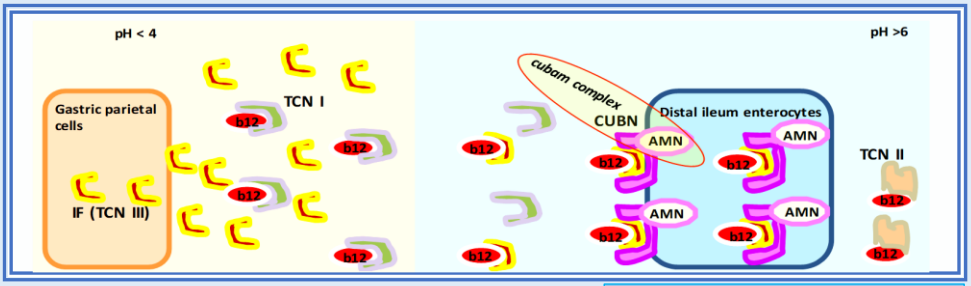
From the desk of Editor

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

Hereditary disorders of RBCs -III: **Pernicious Anemia (PA)**



Genes and their roles - Carriage & Absorption of cobalamin (Cbl)



IF – Intrinsic factor
TCN – Transcobalamin
Cbl/Vitamin B12- cobalamin

Insight:

1. What is the percentage of classical PA in the blood relative of a patient of PA?
2. What will be the possible non-hematological findings in case IV (1,3, and 4)?
3. Is antenatal diagnosis indicated in case IV (2)? What are the ethical concerns?
4. What is the cause of proteinuria in case IV (1)?
5. What will be the approach to an etiological diagnosis for case IV (3)?

Plausible tenets:

Genes related to carriage & absorption of cobalamin.

TCN genes: TCNI (haptocorrin), TCNII, and TCNIII (IF) {most likely emerged by gene duplication during evolution)

- **TCN I** (11q12.1): 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)

Intrinsic factor Recptor (IFR): AMN and CUBN [Cubam complex]*

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

Pernicious anemia:

-Clinical features**:**

- ***Classical PA*****:** commonest form, present in elderly and middle-aged adult, **20** % PA reported in patient's family, although complex genetic mechanism is not clear
  - Haematological: Fatigue, pallor, and reduced cognitive and physical functions
  - Neurological manifestation: Ataxia, psychosis, peripheral neuropathy, paraesthesia, bladder and bowel involvement secondary to spinal cord involvement[Subacute combined degeneration (SCD)] .
  - Ectodermal: Beefy-red tongue, and skin pigmentation
  - Organomegaly
- ***Congenital PA***: rare & presents <5 yrs, without gastric atrophy or antibodies, slow progression (neurological deficits may precede the haematological deficits); thought to be inherited as AR

-Diagnostic test: Peripheral smear, low cobalamin level (<100 ng/L), Serum Gastrin level and antibodies against IF, Schilling test (used in the past)

-Treatment: short course parenteral Vit B12 with folic acid or lifelong replacement in Congenital PA

* **CUBAM complex: Function as receptor for B12+ IF in ilium & a protein reabsorption complex in the proximal renal tubule**

Vitamin B12 Plasma Level Quantitative Trait Locus 1; B12qtl1: Sporadic reports, FUT2 gene regulator for various cellular process

Autoimmune disorders reported with PA		
DISORDER (OMIM No.)	**GENE**	**INHERITANCE**
Autoimmune Polyendocrine Syndrome, Type I, With or Without Reversible Metaphyseal Dysplasia (240300)	Aps1, AIRE	AR, AD
Stiff-Person Syndrome; SPS (184850)	??locus	Sporadic cases
Autoimmune Disease (High Titer Autoantibody) (109100)	?? locus	Sporadic cases
Vitiligo-Associated Multiple Autoimmune Disease Susceptibility 1; VAMAS1(606579)	NALP1 gene	Sporadic cases, AD
Autoimmune Disease, Susceptibility To, 2 & 3; AIS2 & 3(608391 & 608392)	Chr. 7 & 8	Sporadic cases
Thymoma (274230)		Somatic mutation, Familial
Pernicious Anemia: Autoimmune (170900)	?? locus	AD, sporadic

Genetic Counselling for case IV (2) for antenatal diagnosis: positive for homozygous CUBN genes deletion

- **PROCHOB* and B12 deficiency can be well managed clinically.**
- **Not a life-threatening disease and guideline for therapy is well-established.**
- **25 % chance in each pregnancy**
- **IVF and embryo selection can help (success rate still low)**
- **National law and society regulations help decision making and genetic counselling.**

***Chronic benign nonprogressive proteinuria (PROCHOB): AR, isolated proteinuria in the first 10yrs without altered renal function reported with CUBN gene mutation.**

Thought Riveting:

- ***Why autoimmunity specifically and selectively develops for few proteins? Is Self-tolerance protein specific or cell specific?***
- ***Are there any other physiological roles of TCN I, II and III?***
- ***Is there any need for establishing the guidelines for B12 testing in autoimmune disorders?***
- ***Should prophylactic B12 therapy be a recommendation in all chronic cases of GERD?***
- ***Is there any biomarker or diagnostic tool to predict classical PA in pre symptomatic stage?***

Author: Dr Prashant Kumar Verma, Dr Vinod Kumar
Reviewer: Dr. Raksha Ranjan, Dr Swathi Chacham