Rishi Vansh

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Department of Paediatrics

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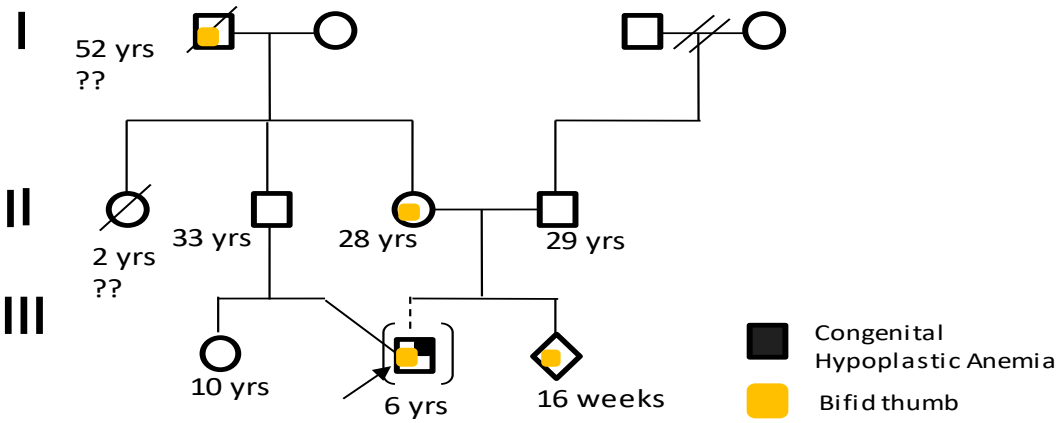
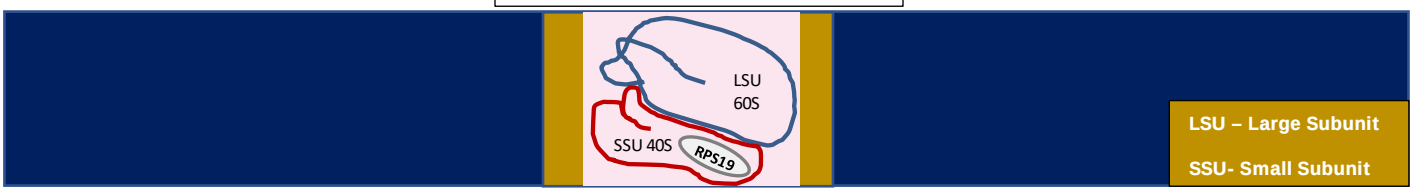
From the desk of Editor

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

Hereditary disorders of RBCs -II: **Diamond–Blackfan Anemia (DBA)**



RPS 19 location in Ribosome



Insight:

1. What is specific in genetic counselling for DBA in early gestation?
2. What feature differentiates DBA from Fanconi anemia?
3. Is there any role of karyotype in DBA?
4. What are the various phenotypic features associated with DBA?
5. What is the clinical usefulness of erythroid adenosine deaminase activity (**eADA**)?

Plausible tenets:

Ribosomopathies (qualitative or quantitative defect in *Ribosomes)*

- Possible hypothetical molecular mechanism: reduction in **tissue specific** mRNA translation
- **The most common diseases:** 5q-syndrome, Schwachman-Diamond syndrome (SDS), Dyskeratosis congenita (DC), Cartilage hair hypoplasia (CHH) & Treacher Collins syndrome (TCS)

Diamond-Blackfan Anemia(DBA)

- Described as a specific clincial disease by **Louis Diamond and Kenneth Blackfan in 1938**
- Mostly a sporadic disorder, **18 types defined at molecularl level(Genetic Heterogeneity),** No gene has been found for DBA 2
- Inherited as **AD**, **except** type 14 DBA with mandibulofacial dysostosis which is **XLR** (TSR2 is a negative regulator of NF-kappa-B help in RP processing)

RPS19 gene (Small Ribosomal Subunit Protein ES19) **(**Cytogenetic location**: 19q13.2)**

- Responsible for Type 1 DBA and accounts for approx **25%** of total DBA cases,

DBA clincial presentation

- Congenital hypoplastic (normochromic,macrocytic) anemia.
- Onset in early infancy, inter and intrafamilial variable expressivity
- Associated phenotype - **short stature, thumb abnormalities** as preaxial polydactyly & hypoplastic thumbs, webbed neck, cleft palate**, high-arched palate**, congenital heart disease, hypertelorism, **strabismus,** and structural abnormalities of the kidney- in **35% to 40% cases**
- **Chromosome fragility test**: Negative in DBA and differentiate it from **Fanconi anemia**

* **Genetic Heterogeneity**: similar phenotypes by different mutations in two or more genes

Erythrocyte adenosine deaminase (eADA)

- Key enzyme in the purine retrieve pathway, **first time** reported to be raised in DBA in 1983
- Elevated eADA is a valuable biomarker to differentiate DBA from other inherited bone marrow failure syndromes **(IBMFSs)**, with a specificity of 95%, sensitivity of 84%, negative & positive predictive values of 91%. (*16% of patients have normal eADA*)

Erythrocyte reduced glutathione (GSH) (biomarker): raised GSH with eADA more effectively rule out other IBMFSs

Genotype and phenotype correlation

- **Birth defects** most reported with **RPL5**(**craniofacial malformations**) and least with **RPS19**
- **Hand malformations** associated with **RPL11**
- **RPS19** – needs **chronic therapy** but not chronic blood transfusion

5q- syndrome (Belgian disease or **'anemie refractaire de type belge'**):

- **Van den Berghe et al. (1974) first described** it as refractory macrocytic anemia
- Acquired somatic deletion of chromosome 5q and consequent loss of **RPS14**
- A subtype of low-risk myelodysplastic syndrome (**MDS**)
- Primarily affects aged females and found in 10 % of all MDS cases
- Clinically present as **transfusion depended anemia** (TDA)

Antenatal Genetic Counselling

- **Expound**: Disease/ Molecular test/ Mosaicism/Population genetics
- **First confirm the disease in Proband –** molecular genetic testing
- ***Standard Genetic Care &*** **Parents genotype -** Rule out silent carrier status
- **Scenario 1-** positive silent carrier status - need antenatal diagnosis
- **Scenario 2-** negative for silent carrier status – Less likely to have a disease
- **Possibility of inheritance of two traits -** AD preaxial polydactyly
- **Newborn examination and follow-up in early infancy with CBC & RC**

Standard genetic care

Pedigree analysis (PA) & *screening for* -

- Beta thalassemia
- Trisomies
- Malformation scan
- Personalized based on Pedigree

Thought Riveting:

- ***Why does ribosomal defects express in selected tissues and not all?***
- ***What is the molecular mechanism of raised eADA level in DBA?***
- ***Which molecular pathway is altered and cause dysplastic changes in DBA?***
- ***Is the chaperone therapy a future milestone in the management of Ribosomopathies?***

Author: Dr Prashant Kumar Verma

Reviewer: Raksha Ranjan