Rishi Vansh

All India Institute of Medical Sciences, Rishikesh

Department of Paediatrics

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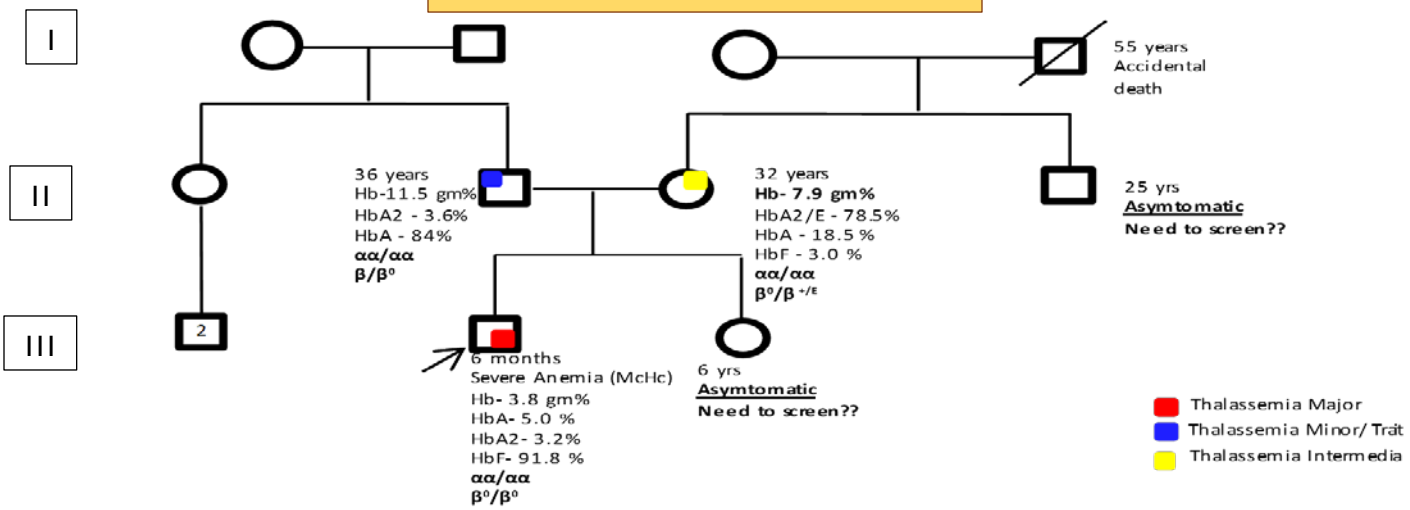
From the desk of Editor

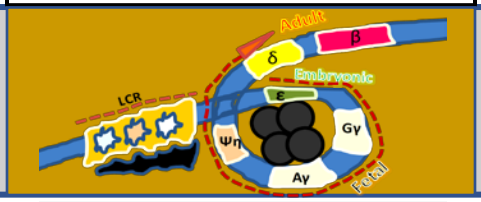
The Department of Paediatrics is publishing a monthly newsletter for faculty and residents. The newsletter is related to genealogical parlance and deliberate attempt to enhance awareness for genetic disorders with recent updates.

Hb(hemoglobin) Genetic Facts - I

HBB Gene



Genes in Beta-globin cluster



McHc- Microcytic hypochromic

ε-epsilon , γ-gamma
ψ psi (pseudogene/β-like globin)
β-beta, δ-delta

Insight:

1. What is the proportion of consanguinity in beta-thalassemia major?
2. What is the importance of HBB gene in malaria?
3. What is the role of Luspatercept in thalassemia?
4. Is it possible to prevent inheritance of beta thalassemia in the community completely?
5. What are the complexities in genetic counselling for asymptomatic case of thalassemia?

Plausible tenets:

Hb A1 (α2β2) a globin tetramer: 97 % of Adult hemoglobin

- The alpha **(HBA)** and beta **(HBB)** loci determine the structure of the 2 types of polypeptide chains
- Hemoglobinopathies are **the most common** monogenic diseases in the world.
- Fall into two main groups**: Thalassemia syndromes** and **structural hemoglobin variants** (abnormal hemoglobins like HbS, HbE,HbC)
- Neonatal screening for hemoglobinopathies strarted in early 1970s in USA.

HBB Gene/ECYT6/CD113t-C/Hemoglobin subunit beta;

- **Cytogenetic band**:11p15.4 in Beta-globin cluster(5'-epsilon-gamma-G-gamma-A-delta-beta-3'in60kb span), here arrangement of the genes directly reflects the temporal differentiation of their expression during development.
- Transcriptional switching lead to synthesis of all type of Hbs(HbA,HbA2,HbF,etc.) **except** Gower I (ζ2ε2), Portland I (ζ2γ2) as there is alpha switiching also
- Major Regulatory molecules of Transcription factor binding sites**(TFBS)** at HBB gene promoter: C/EBP beta, FOXD1, FOXO3b GATA-1 IRF-1, STAT3, TBP, USF-1, USF1
- **Allelic heterogeneity** (***One gene many phenotypes***) **First described** in HBB as methemoglobinemia, beta thalassemia & Sickle cell anemia
- Molecular function: Oxygen transport, **LVV-hemorphin-7** (atypical endogenous opioid peptides produced by the cleavage of hemoglobin beta chain) potentiates the activity of bradykinin, causing a decrease in blood pressure
- Hemoglobin E β thalassemia, is by far **the most common** severe form of β thalassemia (50%) globally

- **Resistance to Malaria**: 3 coding SNP (single nucleotide polymorphism) in the HBB gene confer resistance to malaria in different populations: HbS, HbC and HbE (***Polymorphism -one of two or more variants of a particular DNA sequence*).**
- **Neonates possess resistance** for malaria by dual process:
  - Selective invasion of F cells by malaria parasite (fetal RBCs with HbF)
  - Paucity of amplification of malarial parasite in F cells because of more stable HbF tetramers

Luspatercept: a recombinant fusion protein, enhance late-stage erythropoiesis or differentiation of red blood cells by binding TGF-β and diminishing Smad2 / 3 signaling and prevent ineffective erythropoiesis.

A strong government initiative and determination with a combined guideline for awareness, education and population-based screening, periconceptional, preimplantational and antenatal testing of thalassemia disorders will facilitate its complete prevention.

Genetic testing in apparently asymptomatic individual is indicated because of

- Around 2/3 cases are reported with consanguinity and remaining 1/3rd cases are non-consanguineous
- The carrier rates range from 2-19% in the different populations
- Wide cultural, social and religious structures in the countries
- More than 200 β-thalassemia mutations have been described wide range of phenotypic severity
- Ameliorating factors as co-inheritance of α-thalassemia & increase the HbF production by modifier genes

Hence advisable only if the result is expected to alter the disease course and individual understands the social and personal repercussions

Thought Riveting:

- *What is the current purview of modification of the molecular defect of HBB by different strategies?*
- *Is there any role of **minihepcidins** in transfusion dependent anemia?*
- *Are **TFBS at HBB gene promotor** the new drug target sites for thalassemia treatment?*
- *Unrelated cord blood transplantation-is it the ideal policy at present?*

Author: Dr Prashant Kumar Verma and Dr. Raksha Ranjan
Reviewers: Dr. Vyas K Rathaur