Rishi Vansh

All India Institute of Medical Sciences, Rishikesh

Department of Paediatrics

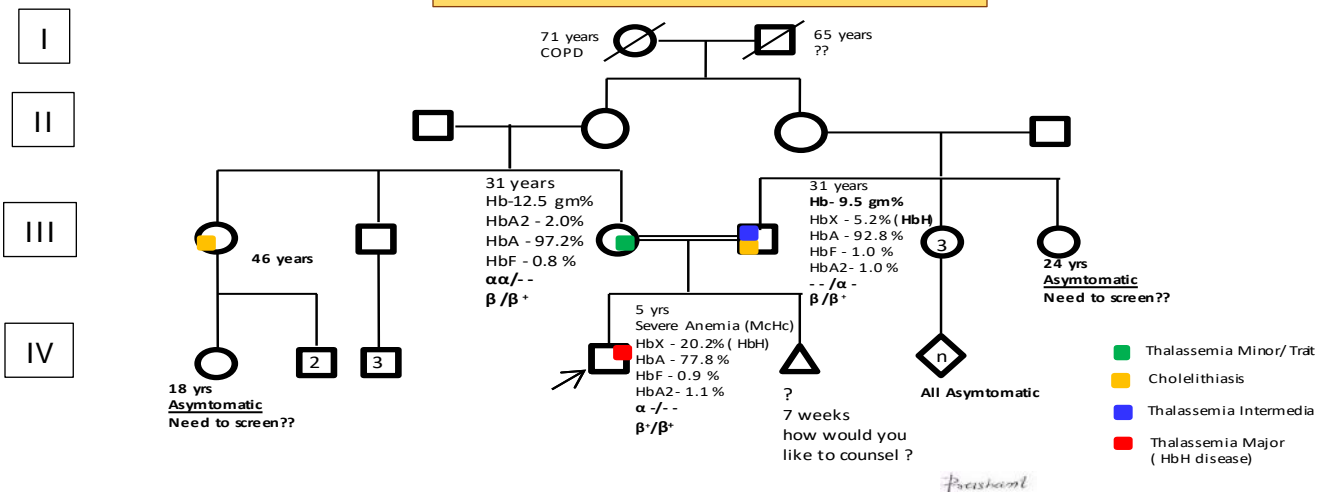
Volume 1, Issue 4 **September 2020**

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.

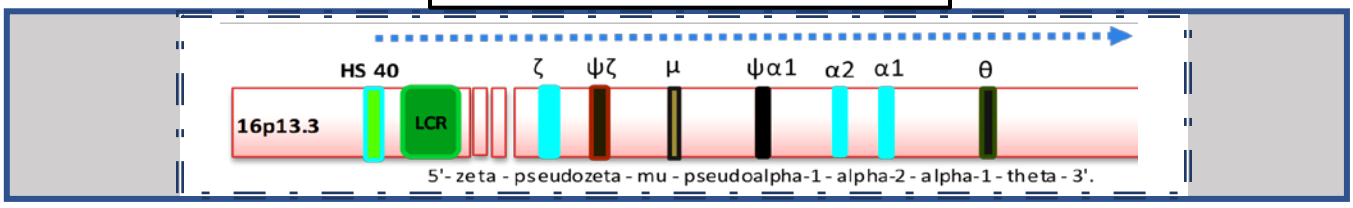
Hb(hemoglobin) Genetic Facts - II

HBA (1&2) Genes



McHc- Microcytic hypochromic
COPD - chronic obstructive pulmonary disease

Seven Loci in Alpha-globin cluster



Insight:

1. What is the proportion of α -thalassemia in different populations?
2. What are HbH and Hb-Q diseases?
3. Does α thalassemia has any association with intellectual disabilities?
4. What is the association between α -globin genotype and malaria?
5. What are the key aspects of Genetic counselling in α thalassemia?

Plausible tenets

HBA Genes {Two tandem alleles HBA1 (α subunit 1) and HBA2 (α subunit 2)} located on Chr. 16p

- HBA1/A2 are **paralogs**** and both encode identical 141-amino acid proteins
- α-globin synthesis occurs in both copies of the α-globin gene at an α2: α1 ratio of 3:1

Phenotype

- HBA1: Methemoglobinemia- α phenotype
- HBA1& A2: Erythrocytosis 7, Heinz body anemias type α, Hemoglobin H disease-nondeletional, α- thalassemia

α-Thalassemia

- ***Probably* the most common** monogenic gene disorder in the world
- More than 120 mutations have been reported (deletion- 85-90% & point mutation- 10-15%) in any (α2 α1/ α2 α1) locus
- Seven most common α-thalassemia deletions ***Two*** α^{+} thalassemia deletions -α3.7 and α4.2 and ***Five*** α^{0}-thalassemia deletions -(α)20.5, - -SEA, - - Med I, - - Thai and - - Fil
- Deletions of the **upstream enhancer elements** (multispecies conserved sequences **(MCS)-R1-4**)) also cause α-thalassemia despite having normal α -globin genes (denoted as [αα] T)
- **Carrier frequency***of α-thalassemia may be as high as 80-90% in tropical & subtropical populations, almost at **fixation#**
- Ratio of α/β is < 0.8 indicative of α-thalassemia was first described in 1965 by Weatherall and Clegg.

*****Paralogs***: are gene copies created by a duplication event within the same genome.* ****carrier frequency** *relative frequency of an allele (variant of a gene) at a particular locus in a population* # **Fixation:** *only gene variant present in any member in the population after random genetic drift or positive selection*

HbQ disease - Common in north and west India (Sindhi community)

- α -chain structural Hb variant, due to point mutation of HBA1 gene at position 223 of the coding region of exon 64.
- Is usually clinically silent in heterozygous state unless coexisting with β-thalassemia, α-thalassemia, HbE disease, etc.

HbH disease

- HbH inclusions in erythrocytes (β-4 tetramers of excess β-globin chains) due to three abnormal α-genes inheritance
- The syndrome of HbH disease is usually mild (thalassemia intermedia) but there is considerable variability in the severity which is by no means certain (due to non-deletional allele)

ATRS16 (α- Thalassemia intellectual diability syndrome): deletion type, **Autosomal dominant** inheritance

- Contiguous gene (SOX8,HBA1,HBA2) deletion syndrome of chromosome 16
- Male:female=1:1

ATRX (α- Thalassemia X-linked Intellectual Disability syndrome): non deletion type, **X-linked dominant** inheritance

- Distinctive craniofacial features, urogenital anomalies, hypotonia, developemental delays/intellectual disabilities.
- Affected gene ATRX or XH2 is responsible for chromatin remodelling and transcription regulation

Malaria and alpha-thalassemia:

- In malaria endemic regions of the world, α^{+}Thalassemia is mostly caused by 1 of 4 deletions-α3.7I, α3.7II, α3.7III or α4.2 which is the result of selective forces imposed on human genome by malaria

Genetic counselling

- To prevent pregnancies with the Hb Bart's hydrops fetalis and obstetric complications and the necessity for long-term transfusion therapy (amidst the quandary of ethical issues)

Father - Genotype	Mother- Genotype	% Offspring in each pregnancy- Phenotype
--/αα	-α/αα	25% - HbH
αα/--	--/αα	25% - Hb Bart
αα/--	-α/-α	50% - HbH
-α/αα	-α/-α	50% - α Thalassemia Trait (in trans)

Thought Riveting:

- *What are the current best possible **transfusion guidelines for Hb Bart syndrome**?*
- *Is there any direct role of **hemoglobin genes products** with **mental disorders**?*
- *How does **ATRX gene alters the HBA gene expression at molecular level?***
- *What will be probable causes for **HbH (<1%, Acquired α-thalassemia)** in some myeloid disorders?*

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