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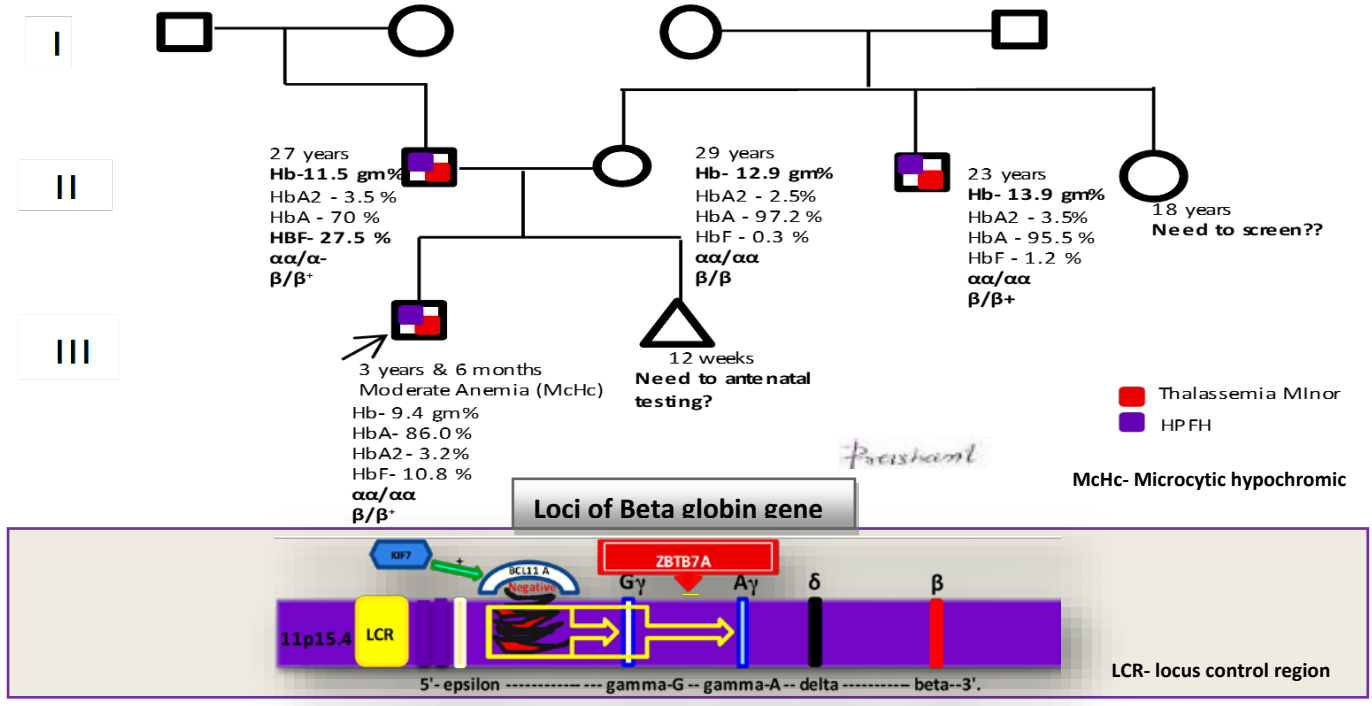
From the desk of Editor

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 - III

HBG (1&2) Genes



Insight:

1. What is the proportion of Hereditary persistence of fetal hemoglobin (HPFH) in the population?
2. What are the known genetic loci for alternation of HBG1/2 genes expression?
3. Does ectopic SIRT1 expression enhance HBG 1/2?
4. What is the X-linked beta thalassemia?
5. Why is it essential to do further research for inducers of HBG1/2 genes?

Plausible tenets

HBG Genes {Two tandem alleles HBG2 (Gγ) and HBG1 (Aγ)} found on Chr. 11p15.4

- Differ at residue 136 where glycine is found in HBG2 and alanine is found in the **HBG1** (HBG1 **predominant at birth**)
- SIRT1 promotes the looping of the LCR to HBG promoter & inhibit the **HBG suppressors** BCL11A, KLF1, HDAC1/ C2
- Among **First Vertebrate globin genes** show the **negative relationship** with cytosine methylation and transcription

Phenotype

- HBG2: Cyanosis, transient neonatal (AD)
- HBG1 & G2: Fetal hemoglobin quantitative trait locus 1 (AD)

Hereditary persistence of fetal hemoglobin

- **Define**: A multifactorial trait with increased HbF in ≥ 2nd year of life
- **F cells:** A subset of RBCs distributed unevenly among red cells
  - **Pancellular:** Higher expression of HbF (up to 40 %)
  - **Heterocellular:** Lower expression of HbF although these stand for a spectrum, HbF range from ≈ 0.8% to 5%, present in 10 to 15% of individuals
- Biochemical studies showed that most of the HbF had gamma-A (HBG1), with a small (10%) amount of the gamma-G (HBG2)
- High fetal hemoglobin (HbF, α2γ2) levels **improve** the **clinical manifestations** of sickle cell disease and β thalassemia

Multiple genetic loci influenced HBG1/2 expression		
*Fetal **Hemoglobin Quantitative Trait Locus** 1; **HBFQTL**1/ HPFH, Delta-beta thalassemia*	**AD**	**HBG1/G2**
Fetal Hemoglobin Quantitative Trait Locus 2; HBFQTL2	**AD**	**6q22.3-q23.1**
Fetal Hemoglobin Quantitative Trait Locus 3; HBFQTL3	**XL D?**	**Xp22.2 (FCPX locus)**
Fetal Hemoglobin Quantitative Trait Locus 4; HBFQTL4	**?**	**8q**
Fetal Hemoglobin Quantitative Trait Locus 5; HBFQTL5	**AD**	**2p16.1**
Fetal Hemoglobin Quantitative Trait Locus 6; HBFQTL6	**?**	**KLF1**
Chromosome 2p16.1-P15 Deletion Syndrome	**Isolated case**	**2p16.1-p15 Deletion**
??? not reported in human	**?**	**LRF/ZBTB7A**
Cyanosis, Transient Neonatal; TNCY	**AD**	**HBG2**
Intellectual Developmental Disorder with Persistence of Fetal Hemoglobin,	**AD**	**BCL11A**
Diamond-Blackfan Anemia 1; DBA1	**AD**	**RPS19**
Diamond-Blackfan Anemia 3; DBA3	**AD**	**RPS24**
Thrombocytopenia with Beta-Thalassemia, XLTT	**XLR**	**GATA1**
Anemia, Congenital Dyserythropoietic, Type IV; CDAN4,	**AD**	**KLF1**

Many epigenetics changes have been studied in vitro to enhance HBG genes expression.

- **GATA1**: binds at sequence 5'-[AT]GATA[AG]-3' within regulatory regions of globin genes and possibly alters globin genes switching
- **RPS19 & 24**: Required for pre-rRNA processing and maturation of 40S ribosomal subunits. Involved in many protein synthesis
- **BCL11A (2p16.1)**: BAF Chromatin Remodeling Complex Subunit.
- **LRF/ZBTB7A**: keeps the nucleosome density necessary for gamma-globin gene silencing in adults. Knockout of LRF in immortalized adult human erythroid cells resulted in HbF levels of greater than 60%
- **KLF1**: A transcriptional activator, high-level expression of the adult beta-globin promoter by binding to its CACCC element. Need for proper expression of BCL11A

Hydroxyurea effect on HbF - **highly variable**, from 2% to greater than 30% (**Pharmacogenetic**) and *still exact* mechanism elusive.

Pharmacogenetic: **Concerning to genes deciding drug metabolism while pharmacogenomics includes all genes in the genome that may decide drug effect**

Epigenetic Mechanism: All molecular mechanism which alter DNA transcription without changing the DNA sequence
Types: Epigenetic changes for long term adapted and short term adapted

- **Long term adapted mechanism:** chromatin remodeling and reorganization, nucleosome remodeling/repositioning, histone modifications, DNA methylation and hydroxymethylation and other epigenetic techniques
- **Short term adapted mechanism:** noncoding RNA regulation; and RNA editing. regulation of gene transcription, depending on the targeting site in the promoter—Mostly used for therapeutic purposes

Thought Riveting:

- *What will be the effects on other genes expression in **BCL11A knock down stem cells**?*
- *Is there any **specific and selective molecule** for enhancing HBG 1/2 genes transcription?*
- *Would amendment of epigenetic mechanism be the newer therapy for beta thalassemia in future?*
- *What will be probable molecular mechanism for diverse types of **HBFQTL**?*

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