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Hemoglobinopathies

David Ginsburg, MD

Reading:
Principles of Medical Genetics 2E
Chapter 6
Relationships with Industry

UMMS faculty often interact with pharmaceutical, device, and biotechnology companies to improve patient care, and develop new therapies. UMMS faculty disclose these relationships in order to promote an ethical & transparent culture in research, clinical care, and teaching.

• I am a member of the Board of Directors for Shire plc.
• I am a member of the Scientific Advisory Boards for Portola Pharmaceuticals and Catalyst Biosciences.
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Learning Objectives

• Understand how the basic *anatomy of a gene* has a direct bearing on the occurrence of genetic disease.
• Know the normal and abnormal *expression patterns* of the hemoglobin genes.
• Understand the mutations that cause *quantitative* abnormalities in globin.
  – Unequal crossing over, and every other possible type of mutation
• Recognize mutations that cause *qualitative* abnormalities in globin.
• Understand the *molecular basis of sickle cell anemia*. 
Figure 5.2 from Gelehrter, Collins and Ginsburg's Principles of Medical Genetics 2E.
Other specific promoter elements, e.g. CACCC in β-globin.

“CAP SITE” Transcription start site

“CCAAT” Box

“TATA” Box

ATG Initiation Codon

GT

AG

GT

AG

5’ untranslated region

INTRON 1

INTRON 2

3’ untranslated region

TAA, TGA, or TAG stop codon

AATAAAA Polyadenylation signal

Site for addition of (A)n

Gene

Enhancer

Tissue Specific elements

mRNA PECURSOR

CAP

GU

AG

GU

AG

3’ AAAAAA

5’

SPLICING

MATURE mRNA

CAP

AAAAAA

TRANSCRIPTION

Gelehrter, Collins and Ginsburg: Principles of Medical Genetics 2E; Figure 5.1
Gelehrter, Collins and Ginsburg: *Principles of Medical Genetics 2E;* Figure 6.3
NF Olivieri, NEJM 341:99, 1999. (or Principles of Medical Genetics: Figure 6.2)
Quantitative Abnormalities of Hemoglobin

• **α Thalassemia**
  - deficiency of α globin chains

• **β Thalassemia**
  - deficiency of β globin chains

• **HPFH**
  - Hereditary persistence of fetal hemoglobin
Gelehrter, Collins and Ginsburg: *Principles of Medical Genetics 2E*; Figure 6.14

**TETRAMERS**

**NORMAL**

\[
\begin{align*}
\alpha\beta & \quad \alpha\beta \\
\beta\alpha & \quad \beta\alpha \\
\alpha\beta & \quad \alpha\beta \\
\beta\alpha & \quad \beta\alpha
\end{align*}
\]

**α-THAL**

\[
\begin{align*}
\alpha\beta & \quad \beta \\
\beta\alpha & \quad \beta \beta \\
\alpha\beta & \quad \beta \beta \\
\beta\alpha & \quad \beta
\end{align*}
\]

**β-THAL**

\[
\begin{align*}
\alpha & \quad \alpha\beta \quad \alpha\alpha \\
\alpha\alpha & \quad \beta\alpha \\
\alpha\alpha & \quad \alpha\alpha
\end{align*}
\]

**RBCs**

**INCLUSION BODIES OF β₄ (HbH)**

**PRECIPITATION OF α₄ (VERY INSOLUBLE)**

**DESTRUCTION OF RBCs IN MARROW, SPLEEN**
Figure 6.16
Table 1. Point Mutations in α-Thalassemia

<table>
<thead>
<tr>
<th>Mutant Class</th>
<th>Origin</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Nonfunctional mRNA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. Nonsense mutants:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1) codon 116 (G-T)</td>
<td>Black</td>
<td>86</td>
</tr>
<tr>
<td>b. Frameshift mutants:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1) codon 30/31 (-4nts)</td>
<td>Black</td>
<td>65</td>
</tr>
<tr>
<td>c. Initiator codon mutants:</td>
<td>Mediterranean 110</td>
<td></td>
</tr>
<tr>
<td>2) ATG-ACG</td>
<td>Mediterranean</td>
<td>90a</td>
</tr>
<tr>
<td>3) CCCACCAG-CCCCATG</td>
<td>Mediterranean, Black 90, 96</td>
<td></td>
</tr>
<tr>
<td>4) ATG-GTG</td>
<td>Mediterranean, Black</td>
<td>90, 96</td>
</tr>
<tr>
<td>d. Terminator codon mutants</td>
<td>Mediterranean 8</td>
<td></td>
</tr>
<tr>
<td>5) αCs of HB Constant</td>
<td>Black</td>
<td>30</td>
</tr>
<tr>
<td>Spring (TAA-CAA)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6) αCd of Koya Dora</td>
<td>Indian</td>
<td>34</td>
</tr>
<tr>
<td>(TAA-TCA)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7) αEc of Hb Icaria</td>
<td>Mediterranean 29</td>
<td></td>
</tr>
<tr>
<td>(TAA-AAA)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8) αEm of Hb Seal</td>
<td>Black</td>
<td>15</td>
</tr>
<tr>
<td>Rock (TAA-GAA)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II. RNA Processing mutants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. Splice junction changes:</td>
<td>Mediterranean 100a</td>
<td></td>
</tr>
<tr>
<td>1) IVS-1 donor site (GGTGAGGCT-GGCT)</td>
<td>Mediterranean</td>
<td>100a</td>
</tr>
<tr>
<td>b. RNA cleavage and polyadenylation site</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1) AATAAA-AATAAG</td>
<td>Arab</td>
<td>64</td>
</tr>
<tr>
<td>III. Unstable globins</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1) αQiong Sze (codon 125 Leu-Pro)</td>
<td>SE Asian 59</td>
<td></td>
</tr>
<tr>
<td>2) αRao Doo (codon 209, Leu-Arg)</td>
<td>SE Asian 129</td>
<td></td>
</tr>
<tr>
<td>3) αPanck Tussoh (codon 110, Ala-Asp)</td>
<td>Middle East 65</td>
<td></td>
</tr>
<tr>
<td>4) αTanseen (codon 14, Trp-Arg)</td>
<td>Black 68</td>
<td></td>
</tr>
</tbody>
</table>

Note. Total number = 15; November, 1989.
<table>
<thead>
<tr>
<th>PHENOTYPE</th>
<th>GENOTYPE</th>
<th>DIAGRAM</th>
<th>SHORTHAND</th>
</tr>
</thead>
<tbody>
<tr>
<td>NORMAL</td>
<td>α α</td>
<td></td>
<td>αα/αα</td>
</tr>
<tr>
<td>HETEROZYGOUS α-THALASSEMIA 2</td>
<td>α α</td>
<td></td>
<td>αα/αα</td>
</tr>
<tr>
<td>&quot;SILENT CARRIER&quot;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HETEROZYGOUS α-THALASSEMIA 1</td>
<td>α α</td>
<td></td>
<td>αα/αα</td>
</tr>
<tr>
<td>&quot; α-THAL TRAIT&quot;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>α-THALASSEMIA 1 PHENOTYPE IN BLACKS</td>
<td>α α</td>
<td></td>
<td>αα/αα</td>
</tr>
<tr>
<td>HOMOZYGOUS α-THALASSEMIA 2</td>
<td>α α</td>
<td></td>
<td>αα/αα</td>
</tr>
<tr>
<td>&quot; α-THAL TRAIT&quot;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbH DISEASE (HbH = β₄)</td>
<td>α α</td>
<td></td>
<td>αα/αα</td>
</tr>
<tr>
<td>HYDROPS FETALIS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>with Hb BART'S (= γ₄)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Principles of Medical Genetics*: : Fig. 6.15
Normal peripheral blood smear

Hgb H disease
Image removed. See
Miller LH. *Nature*,
Figure 6.16

**Phenotype**

- **β-Gene Genotype**
  - **Thalassemia Minor**
    - Asymptomatic Heterozygote
    - \( β^0 \) Heterozygote
    - \( β^+ \) Heterozygote
  - **Thalassemia Intermedia**
    - Symptomatic, but not requiring transfusion
    - Two mild alleles
    - One very mild allele
    - Concurrent \( α-thal \) or HPFH
  - **Thalassemia Major**
    - Transfusion dependent
    - \( β^0 \)-Thalassemia
    - \( β^+ \)-Thalassemia
<table>
<thead>
<tr>
<th>EXON 1</th>
<th>INTRON 1</th>
<th>PHENOTYPE</th>
</tr>
</thead>
<tbody>
<tr>
<td>NORMAL</td>
<td>GCCAG</td>
<td>GT TG GTAT...</td>
</tr>
<tr>
<td>IVS - pos. 1</td>
<td>GCCAG</td>
<td>A TTG GTAT...</td>
</tr>
<tr>
<td>IVS - pos. 1</td>
<td>GCCAG</td>
<td>T TTG GTAT...</td>
</tr>
<tr>
<td>IVS - pos. 5</td>
<td>GCCAG</td>
<td>G TTG TAT...</td>
</tr>
<tr>
<td>IVS - pos. 5</td>
<td>GCCAG</td>
<td>G TTG C TAT...</td>
</tr>
<tr>
<td>IVS - pos. 6</td>
<td>GCCAG</td>
<td>G TTGG CAT...</td>
</tr>
<tr>
<td>CONSENSUS DONOR</td>
<td>CAG</td>
<td>GT A AGT</td>
</tr>
<tr>
<td></td>
<td>A</td>
<td>G T G</td>
</tr>
</tbody>
</table>
Figure 6.21: Schematic diagram of the normal and abnormal splicing pathways for the \( \beta \)-globin chain. The normal splicing pathway is shown at the bottom, while the abnormal alternative splicing pathway is depicted at the top. The consensus acceptor site is indicated by \( AG \).
Gelehrter, Collins and Ginsburg: *Principles of Medical Genetics 2E*; Figure 6.22
Gelehrter, Collins and Ginsburg: *Principles of Medical Genetics 2E*; Figure 6.18
Normal peripheral blood smear

β-Thalassemia (homozygous)
**Fig 3.** Fall in the birth rate of β-thalassemia homozygotes in Sardinia.

**Fig 8.** Change in birth rate of thalassemic children in four countries after the introduction of preventive programs. Adapted with permission.⁵⁵,⁶⁸
Qualitative Abnormalities of Hemoglobin

- Silent Variants
- Unstable hemoglobins
  - Heinz body hemolytic anemia
- Methemoglobinemia
- High affinity hemoglobins
  - Polycythemia (↑hematocrit and hemoglobin)
- Low affinity hemoglobins
  - Mild anemia (↓hematocrit and hemoglobin)
- Hemoglobin S
- Hemoglobin C
Gelehrter, Collins and Ginsburg: Principles of Medical Genetics 2E; Figure 6.7

DNA
- codon 5: GAG
- codon 6: GAG
- codon 7: GAG

Protein
- codon 5: Glu
- codon 6: Val
- codon 7: Lys
Gelehrter, Collins and Ginsburg: *Principles of Medical Genetics* 2E; Figure 6.9
Hemoglobin SS Disease
Complications of Sickle Cell Anemia

- autosplenectomy
- hyposthenuria
- Infections
  - encapsulated organisms-- pneumococcus
  - salmonella, staph
- Painful crises
- Bone infarcts, aseptic necrosis
- Stroke
- Acute chest syndrome
- Hand-foot syndrome
- Chronic organ damage
**Table 10–11. FREQUENCY OF HEMOGLOBIN GENOTYPES AMONG BLACK AMERICANS**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Percentage of Population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>*</td>
</tr>
<tr>
<td>AS</td>
<td>8.6</td>
</tr>
<tr>
<td>SS</td>
<td>0.14</td>
</tr>
<tr>
<td>AC</td>
<td>2.4</td>
</tr>
<tr>
<td>CC</td>
<td>0.02</td>
</tr>
<tr>
<td>SC</td>
<td>0.13</td>
</tr>
</tbody>
</table>

*Survey of 250,000 black Americans*\(^{556}\)

**Review of literature*\(^{557}\)
Hb S only occurs on 4 haplotypes...only occurred 4 times in history
Hb S is a balanced polymorphism
  * homozygotes (1 in 500) are selected against
  * heterozygotes (1 in 12) are selected for
Sickle Cell Anemia: Treatment

- IV fluids
- Analgesia
- Infection
  - penicillin prophylaxis
  - vaccines
- Oxygen
- Transfusion
- Erythropoietin
- Hydroxyurea
- Bone Marrow Transplantation
Learning Objectives

• Understand how the basic anatomy of a gene has a direct bearing on the occurrence of genetic disease.
• Know the normal and abnormal expression patterns of the hemoglobin genes.
• Understand the mutations that cause quantitative abnormalities in globin.
  – Unequal crossing over, and every other possible type of mutation
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