Lectures 12 - 13

Genetics of Human Disease: Hemoglobinopathies

November 7 - 8, 2002

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.
  – Missense mutations primarily
Textbook Figure 5.2
Textbook Figure 6.3

Textbook Figure 6.2
Textbook Figure 6.4

Textbook Figure 6.5
Quantitative Abnormalities of Hemoglobin

- **α Thalassemia**
  - deficiency of α globin chains
- **β Thalassemia**
  - deficiency of β globin chains
- **HPFH**
  - Hereditary persistance of fetal hemoglobin
### Textbook Figure 6.15

<table>
<thead>
<tr>
<th>PHENOTYPE</th>
<th>GENOTYPE</th>
</tr>
</thead>
<tbody>
<tr>
<td>NORMAL</td>
<td>α α</td>
</tr>
<tr>
<td>HETEROZYGOS α-THALASSEMA 1: &quot;SILENT CARRIER&quot;</td>
<td>α α</td>
</tr>
<tr>
<td>HETEROZYGOS α-THALASSEMA 1: &quot;α-THAL TRAIT&quot;</td>
<td>α α</td>
</tr>
<tr>
<td>α-THALASSEMA 1 PHENOTYPE IN BLACKS</td>
<td>α α</td>
</tr>
<tr>
<td>HOMOZYGOS α-THALASSEMA 2: &quot;α-THAL TRAIT&quot;</td>
<td>α α</td>
</tr>
<tr>
<td>ß HEMOLYTIC DISEASE (HbH = ß δ )</td>
<td>α α</td>
</tr>
<tr>
<td>HYDROPS FETALIS WITH Hb BART'S (ß δ )</td>
<td>α α</td>
</tr>
</tbody>
</table>

### Textbook Figure 6.16

[Diagram showing genetic markers and phenotypes]
_thal is almost always related to unequal crossing over or deletions.

Rarely, loss of function of an _-globin gene arises from point mutations, but in contrast to _thal, these mutations are in the minority.
Textbook Figure 6.15

The percentage gene frequencies (numbers on map) of α-thalassaemia in Melanesia parallels the intensity of malaria transmission (endemicity). The malaria transmission intensity goes from most intense (holoendemic) to least intense (hyperendemic). A, Australia; PNG, Papua New Guinea; SI, Solomon Islands; NC, New Caledonia; V, Vanuatu; ES, Espiritu Santo — an island in Vanuatu where the study by Williams et al. was performed. Figure adapted from the data in Flint et al.
Example of unequal crossing over as a mechanism of inactivating the _-globin gene.

Textbook Figure 6.12
Unequal crossing over between _ and _ genes…clinically leads to a combined quantitative and qualitative abnormality (Lepore).

Notice that individuals with an anti-Lepore chromosome make normal amounts of _ and _, but also make the novel anti-Lepore hemoglobin.

Textbook Figure 6.13

Loss of the normal termination codon near the end of _-globin gene

Loss of the normal termination codon near the end of α-globin gene

Textbook Figure 6.11
Mutations in the _globin promoter can give rise to _+ thalassemia

Textbook Figure 6.19
Splicing abnormalities lead to predictable phenotypes

Textbook Figure 6.20

Most common cause of _+ thalassemia in Mediterranean is related to an abnormal splice acceptor site.

Textbook Figure 6.21
Hgb E – this mutation gives rise to a quantitative abnormality (activation of a cryptic splice donor site) and a qualitative abnormality (missense mutation at codon 26)

Textbook Figure 6.22

Textbook Figure 6.18
Untreated thalassemia

Treatment of thalassemia major
Textbook Figure 6.24

Textbook Figure 6.25
Fig 6. Change in birth rate of thalassemic children in four countries after the introduction of preventive programs. Adapted with permission.\textsuperscript{85,90}

Textbook Figure 6.26
10 large Pakistani families with hemoglobinopathies
5 large Pakistani families without hemoglobin disorders
All carriers & married couples with 2 carriers ➔ genetic counseling

Half-solid symbols represent those who are heterozygous for _-thalassemia
Solid symbols represent those with _-thalassemia major
• Average cost of Fe chelation therapy is $4,400, or 10 times the average annual income.
• Treatment costs for 1 year – currently 4% of government health-expenditures.
• 183 / 591 (31%) of persons in families with an index case tested were carriers
• All carriers reported using the information provided in counseling
• “Testing of extended families is a feasible way of deploying DNA-based genetic screening in communities in which consanguineous marriage is common.”

Screening for _-thalassemia in Sardinia

Cao & Galanello, NEJM 347: 1202, 2002
Summary

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