I. Generality

Hemoglobin:
Protein that composes the hemoglobin (Hb).
Hemoglobin A (the dominant form in adults): molecular weight is 64400. It is composed of one α2β2 tetramer and 4 Heme molecules of a weight of 614 (X4).
There are different tetramers: α2β2 tetramers, mostly, in the adult; α2γ2 in the foetus most often, and other tetramers in the embryo. There is a wide range of hemoglobin genes. It brings out two fundamental notions:

- The notion of gene families (and the notion pseudogene, consequence of the family gene formation);
- The notion of sequential expression of genes from the same family through the development, in particular in the embryo development (See also the paragraph on the Hox gene family in Skeletal Development in Human).

Hemoglobin genetic anomalies can cause hemolytic anemias such as: sickle-cell anemia (Hbs), α thalassemias, β thalassemias (see details below), more or less severe diseases, depending on the mutation and/or the number of mutations (i.e. one α gene)
deletion is latent, but the deletion of 4 α genes cause hydrops foetalis and death in utero or during the neonatal period).

II. Hemoglobin genes
II.1. Gene Families
The hemoglobin genes (and the myoglobin genes of muscle) represent a family of gene. The common ancestor is more than 500 million years old. The ancestor gene duplicated (a number of times), and each duplicated copy mutated, so that the set of resulting genes brought a diversity of various functional genes, and non-functional genes (coding for non functional proteins, they are called pseudogenes).

Gene localization:
- Chromosome 11: localization in 11p15.5.
Gene coming from an ancient duplication (existence of homologous sequences) drifted by mutation and recombination.
The genes Gγ and Aγ are coding for the γ chain; 1 amino acid is different in position 136. Existence of a pseudogene ψβ akin to normal genes but mutated in a way that it is not coding for any protein.- Chromosome 16: localization in 16p13.3.
More recent duplication of the α1 and α2 genes; homology: they have close nucleotide sequences and an identical coding sequence. The θ gene is weakly express.
Each gene is made of 3 exons (coding sequences) separate by 2 introns (non-coding sequences).

II.2. Sequential gene expression through the development
The hemoglobin genes split the tasks: some are express by the embryo; others take over in foetus; and finally others in adult. Also, the sequential expression matches the physical distribution of the gene from 5’ to 3’. To be noted that a “foetal” gene can compensate a failing “adult” gene (hereditary persistence of the foetal hemoglobin):
- In the embryo, tetramers: α2ε2, ζ2ε2, ζ2γ2 and α2γ2;
- In the foetus: α2γ2 (and α2β2);
- In the adult, in majority, tetramers: α2β2 (but also α2δ2 and α2γ2).
III. Mutations (see example)

III.1. Definition
Most of the time silent mutation.
Deletion or insertion of a nucleotide: change in the reading frame: reading impossible; if the change takes place far from the end of the gene, there will be no protein synthesis.
Deletion or insertion of a triplet: 1 amino acid in more or less destabilizes the tertiary protein structure.
Extent deletion: frequent for the α gene: α thalassemia.
Fusion of 2 genes: unequal crossing over during meiosis: deletion at the end of the 1st gene and at the beginning of the 2nd gene; example Hb Lepore: fusion δβ.
Abnormal mRNA splicing: deletion at the beginning of an exon with, possibly, a change in the reading frame.
Mutation in one exon: 1 amino acid will be replaced by another one; variable consequences depending on the amino acid: most of the time a silent mutation; but the Sickle-cell anemia is due to a mutation at the 6th codon of the β gene (Glu→Val).
Nonsense mutation in an exon: cut the polypeptide chain; if the mutation takes place somewhere else that at the end of the gene, there will be no possible protein synthesis.
Mutation in the nonsense termination codon: the transcription does not stop; example Hb Constant Spring: α chain extends of 31 amino acids.
Mutation on the promoter.

III.2. Example

<table>
<thead>
<tr>
<th>Example of a platensical gene (philosophical gene, with a quadruplet codon, instead of our biological genes, having triplet codons) with duplication french/english in a common ancestor</th>
</tr>
</thead>
<tbody>
<tr>
<td>%... TRUE THEN NICE THEN GOOD STOP... VRAI DONC BEAU DONC BEIN STOP ...</td>
</tr>
<tr>
<td>quadruplets</td>
</tr>
<tr>
<td>%... TRUE THEN NICE THEN GOOD STOP...</td>
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<td>%... TRUE THEN NICE THEN GOOD STOP...</td>
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<td>%... TRUE STOP NICE THEN GOOD STOP</td>
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<td>%... TRUE STOP</td>
</tr>
<tr>
<td>%... TRUE THEN VRAI DONC BEAU DONC BEIN STOP</td>
</tr>
<tr>
<td>%... nice then good stop</td>
</tr>
<tr>
<td>%... true then nice then good girl made cake with nice ...</td>
</tr>
<tr>
<td>%... true then nice then good stop</td>
</tr>
</tbody>
</table>
**IV. Clinics - main syndromes**

- **Hemoglobinopathy**: Constitutional anomalies of the Hb structure (qualitative anomaly).
- **Thalassemia**: Constitutional anomalies of the Hb synthesis (quantitative anomaly).

**IV.1. Sickle-cell anemia**

- Hemoglobinopathy: Mutation at the 6th codon of the β gene (Glu→Val).
- Prevalent in Black populations (in some populations, up to 40% of the individuals are heterozygote); Mediterranean basin; ...
- Persistence of the gene frequency due to a positive selection of the heterozygote caused by the malaria (loss of the Hardy Weinberg equilibrium due to the selection effect).
- Tendency to polymerization of the mutated hemoglobin molecule (Hbs) --> red blood cells are deforms and rigid (sickle-cell anemia) --> hemolysis and thrombosis.
- Homozygote state
  - Starts in childhood:
    - Alteration of the general state, hemolytic disease, abdominal pain, feverish articular manifestation. In poor populations, the affected children (homozygotes) rarely live beyond the age of 2 years.
    - Hemolytic anemia with sickle-shaped red cells. Diagnosis by hemoglobin (Hb S) electrophoresis.
    - Evolution: hemolytic crises and thromboses (bone infarct, visceral infarct (in particular splenic), spleen atrophy, infectious complications). Frequent death in the childhood.
    - Symptomatic treatment (rehydration, transfusions).
    - Prenatal diagnosis: there is a restriction enzyme (ER) which normally recognises and cleaves the gene at the 6th codon, among other sites, producing a DNA fragment of 1,1 Kb. The mutation responsible of the disease eliminates this site at codon 6. Because the next site is farther on the gene, the fragment will be of 1,3 Kb. Then, by electrophoresis of the DNA, it is possible to discriminate the normal homozygotes (NN), the heterozygotes (NS) and the affected homozygotes (SS). See the figure below.
- Heterozygote state
  - Often asymptomatic.
  - Sometimes thrombosis.
- **Double heterozygote**: heterozygote for sickle-cell anemia associated with another mutation on the β chain for the other allele.
  - Often intermediate condition.

**IV.2. β Thalassemia**

Mediterranean basin, Southeast Asia,...

β chains synthesis in weak or nil quantity, depending of the anomaly.

Free α chains which precipitate --> Ineffective erythropoiesis.

β chains ± relieve by the synthesis of the α2γ2 tetramers chains: HbF (foetal) (if the HbF rate = 100% “PHHF” or hereditary persistence of the foetal hemoglobin: often asymptomatic).

- **Homozygote state** (or Cooley disease)
  - Starts in childhood:
    - Alteration of the general state, splenomegaly, deformed skull “turricephaly”.
    - Hypersideremic microcytic hypochromic anemia. Hb electrophoresis diagnosis: HbA (α2β2 tetramers), decreased: (β+ thalassemias), or absent: (β0 thalassemias), HbF increased.
    - Evolution: hepatomegaly, hepatic fibrosis, cardiac failure. Frequent death before 20 years.
    - Treatment: transfusions (→ hemochromatosis risk).
    - Prenatal diagnosis.
    - Heterozygote state
      - Often asymptomatic; microcythemia without anemia.
      - Related diseases
        - δβ Thalassemias: lack of δ and β genes; at the homozygote state intermediate condition.
        - Hb Lepore: mimicking β thalassemia condition.
IV.3. α Thalassemia
Southeast Asia, Africa, Mediterranean basin...
- 1, 2, 3 or 4 α genes affected: subnormal HbA synthesis, decreased, or impossible and absence or presence of Hb Bart (γ4) or d'HbH (β4) non functional.

Hydrops Foetalis:
- 4 genes affected. Non viable.

Hemoglobin H disease:
- 3 genes affected.

- Hemolytic microcytic hypochromic anemia from birth; splenomegaly.
One or two genes affected:
- Asymptomatic or discreet symptomatology.

This article should be referenced as such: