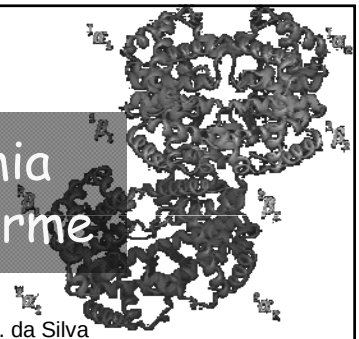
Anemia Falciforme



Felipe R. da Silva

Embrapa Recursos Genéticos e Biotecnologia

Distúrbios Genéticos

- monogênicos (*Mendelianos*)
- cromossômicos
- complexos

Herança Mendeliana no Homem

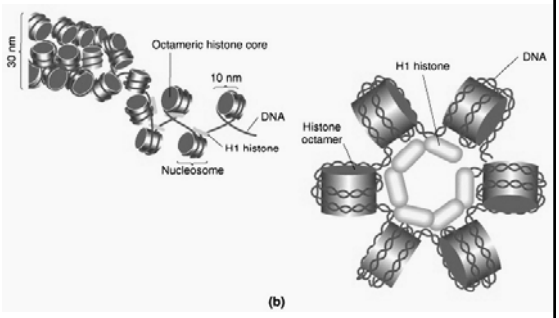
- Referência clássica (12ª ed. 1998) de Victor A McKusic
- Versão *on-line*:
  - OMIM
  - (www.ncbi.nlm.nih.gov/sites/entrez?db=OMIM)

O*n-line* **M***endelian* **I***nheritance in* **M***an*

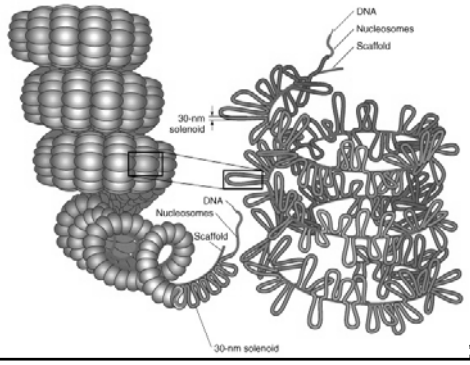
Distúrbios Monogênicos

- Primariamente pediátricos
  - 10% após a puberdade
  - <1% após o período reprodutivo
- Individualmente raros
  - como um todo, significativos:
    - 1 em cada 300 pessoas apresenta distúrbio monogênico grave!

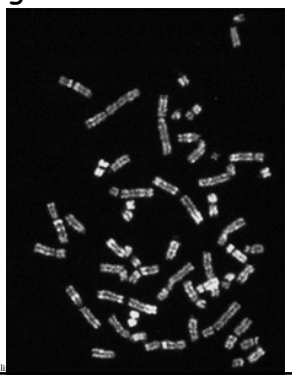
Estrutura do cromossomo



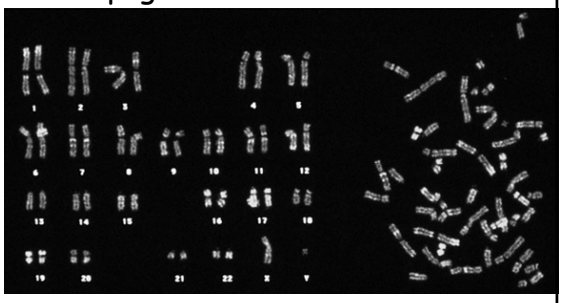
Estrutura do cromossomo



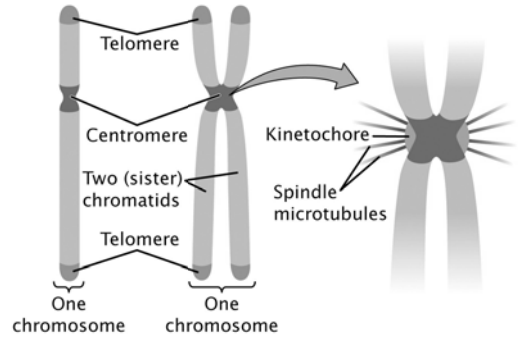
Topografia dos cromossomos



Topografia dos cromossomos



Conjunto de cromossomos humanos = 23 pares



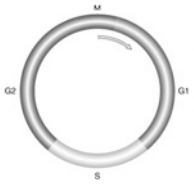
Mitose

- Forma de divisão celular pela qual uma **célula somática** eucariota se duplica.
- É reprodução **assexuada**.
- Divisão celular é a continuação da vida baseada na **reprodução das células**.

Mitose

têm o mesmo número de cromossomos que a original!

Célula Original → Células Filhas

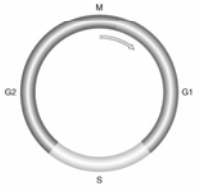


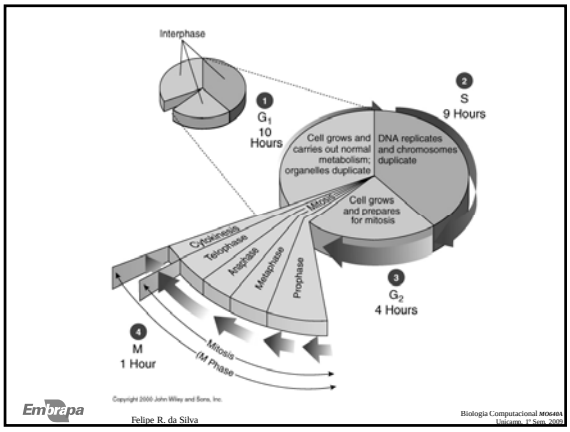
Estágios do ciclo celular:
M = mitose
S = Síntese de DNA
G = *Gap* (intervalo)

Ciclo Celular

- Intérfase — Crescimento e replicação do DNA
- Prófase
- Metáfase
- Anáfase
- Telófase

} Mitose!

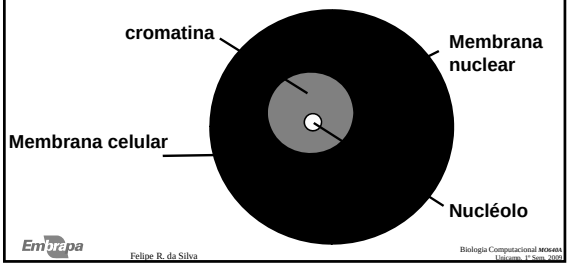




Embrapa

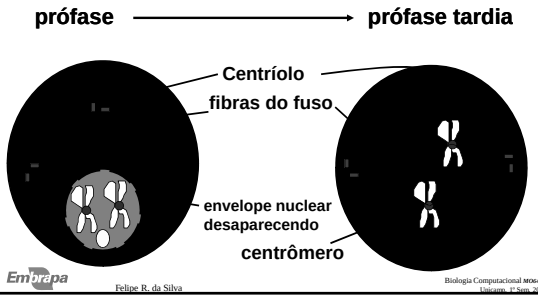
Intérfase

- Núcleo e núcleolo visíveis



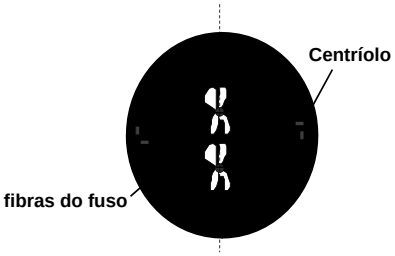
Embrapa

Prófase



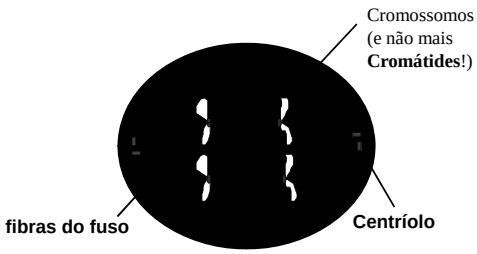
Embrapa

Metáfase



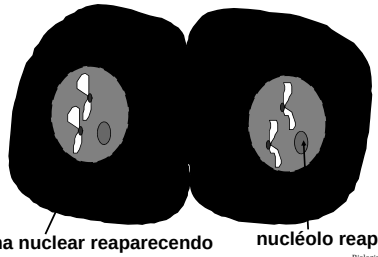
Embrapa

Anáfase



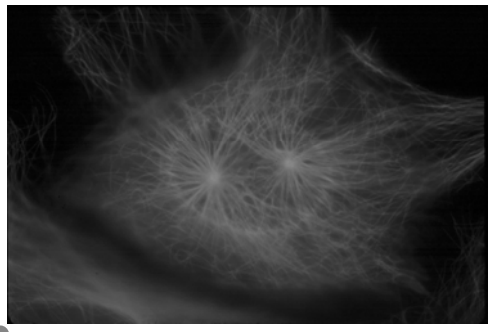
Embrapa

Telófase

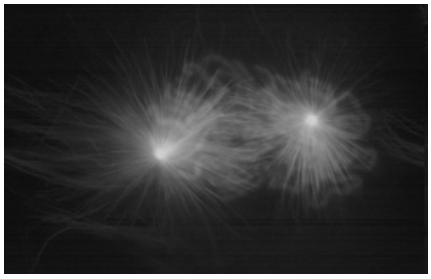


Embrapa

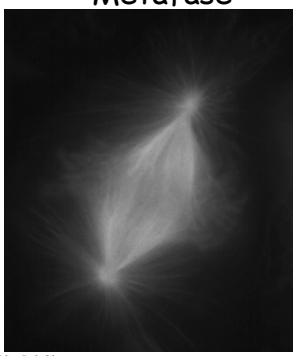
Intérfase



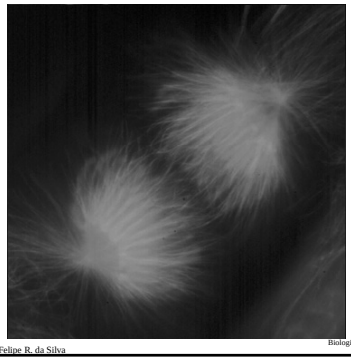
Prófase



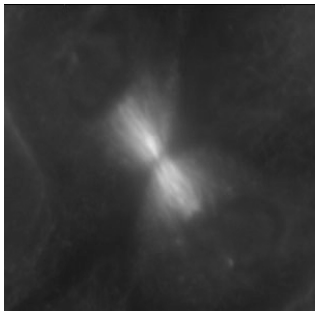
Metáfase

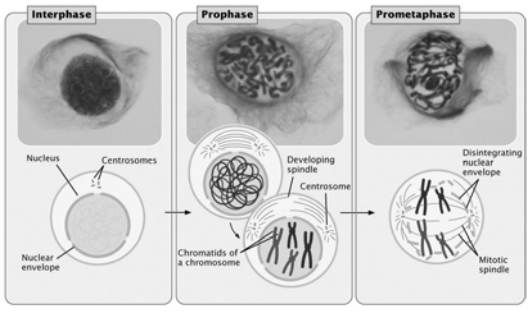


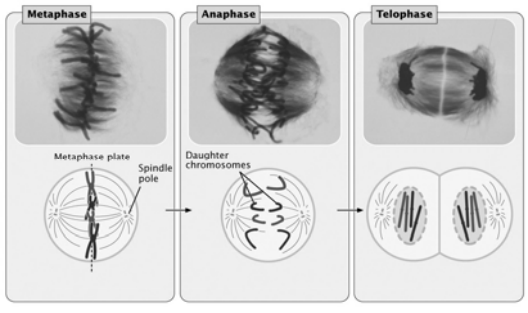
Anáfase



Telófase

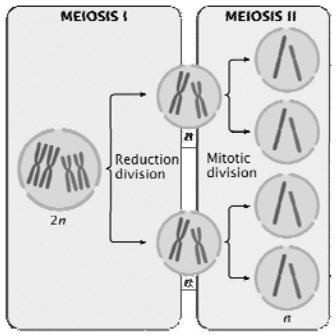




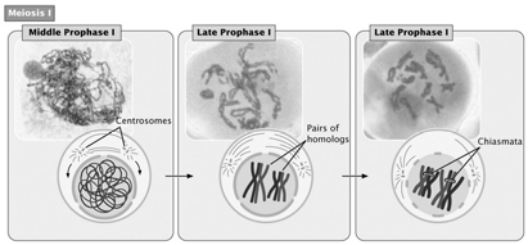


Meiose

Duas divisões celulares após uma única duplicação de DNA

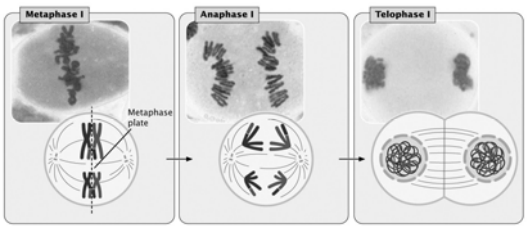


Meiose

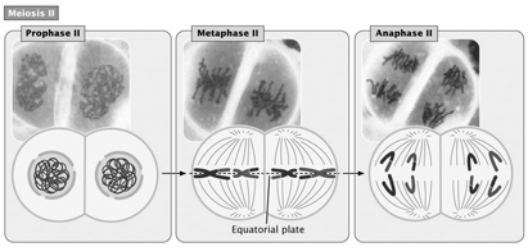


Prófase da 1ª divisão (Prófase I) tem 5 estágios

Meiose (cont.)

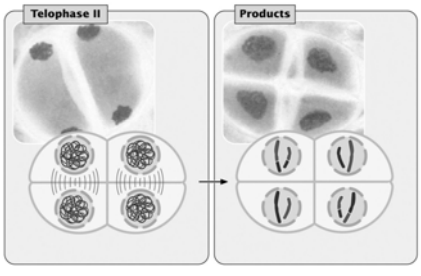


Meiose (cont.)

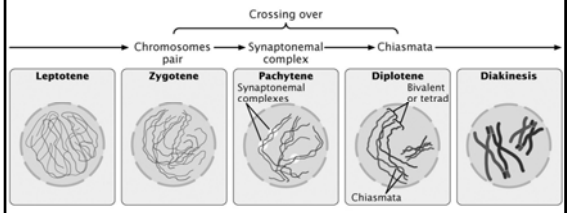


Meiose II

Meiose (cont.)

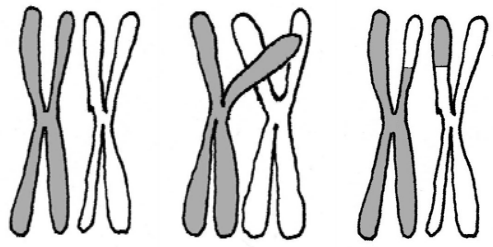


Crossing over

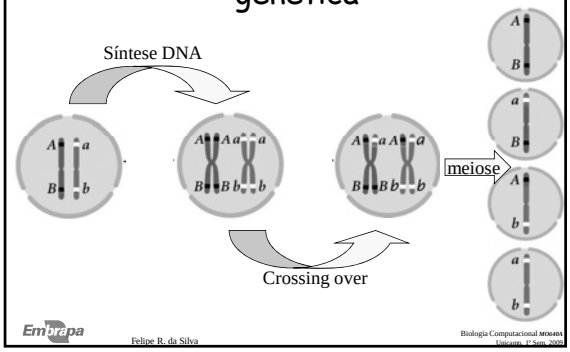


- Acontece na prófase I da meiose.
- É evidente em 3 dos 5 estágios

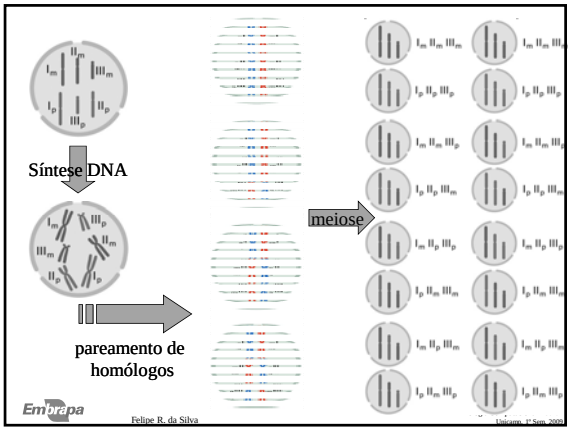
Crossing over

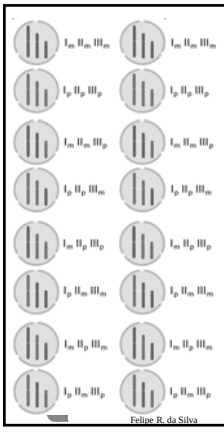


Crossing over produz variação genética



Só o crossing over produz variação genética?

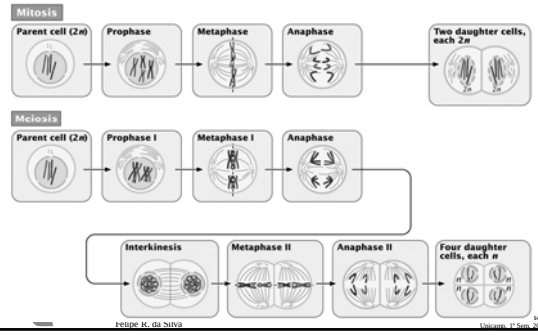




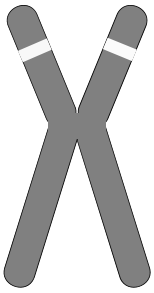
Neste exemplo específico, temos 2^3 combinações = 8 genótipos

No caso de humanos, são 2^{23} combinações ~8,4 milhões!

Comparação de Mitose e Meiose

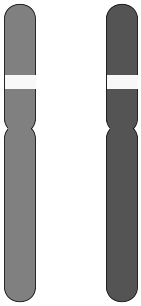


Alelo?



Nem pensar!

Alelo?



Cromossomo do pai

Cromossomo da mãe

Alelo dominante?

- Dominante X Recessivo

Longo silêncio na turma...

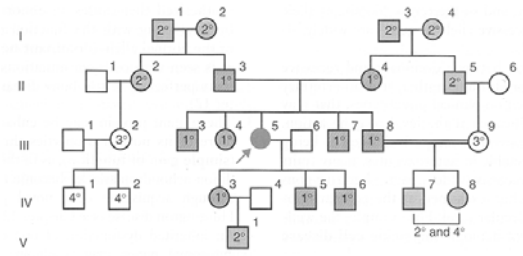
Alelo dominante?

- Dominante X Recessivo
- Co-dominante
- Nível
  - Clínico
  - Fisiológico
  - Protéico
- Fenótipo expresso no heterozigoto é o Dominante!

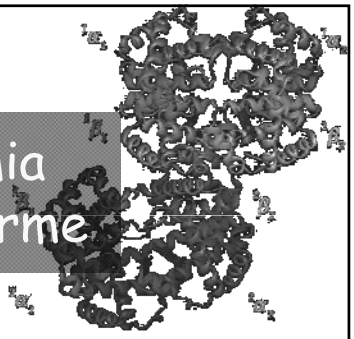
Padrões de Distúrbios Monogênicos

	Dominante	Recessivo
Autossômico	Autossômico Dominante	Autossômico Recessivo
Ligado ao X	Dominante Ligado ao X	Recessivo Ligado ao X

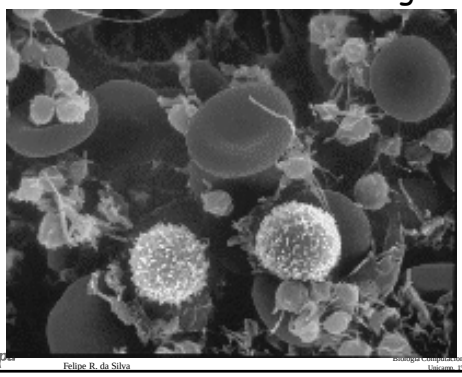
Heredograma



Anemia Falciforme

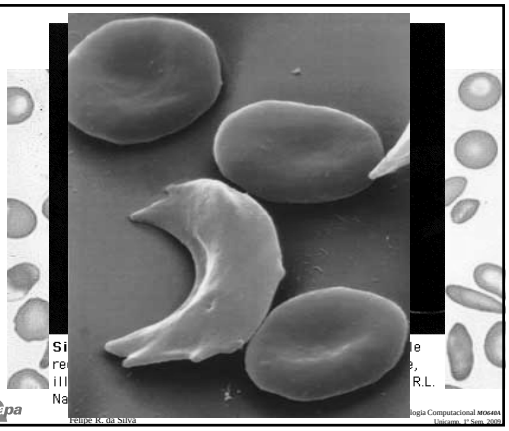


Elementos celulares do sangue

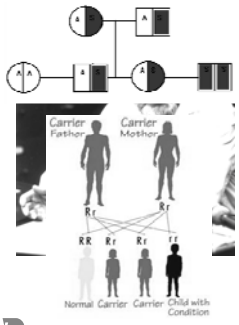


Anemia Falciforme

- Doença conhecida há séculos
  - oeste África
- Sintomas
  - Anemia
  - Dor
    - Ossos
    - Juntas
    - Abdome



1941: James Van Gundia Neel

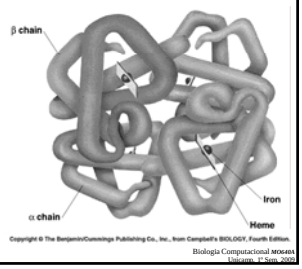


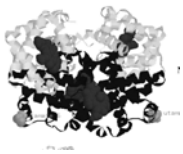
Observando o **padrão de herança** conclui que a doença podia ser explicada como resultado da **homozigose** de um **alelo mutante**.

1951: com dados mais completos de famílias confirma a hípotese de que a anemia falciforme é herdada como um caráter **recessivo** Mendeliano simples.

Hemoglobina

- Proteína formada por 4 cadeias peptídicas (tetrâmero)
  - 2 sub-unidades α
  - 2 sub-unidades β
- Grupo Heme
  - Um em cada cadeia





Hemoglobina normal

Hemoglobina mutante

mRNa da Hemoglobina normal

ACAUUUGCUUCUGACACAACUGUGUUCACUAGCAACCUCAAACAGACACCAUGGUGCACC
UGACUCCUG**A**GGAGAAGUCUGCCGUUACUGCCCUGUGGGGCAAGGUGAACGUGGAUGAAG
UUGGUGGUGAGGCCCUGGGCAGGCUGCUGGUGGUCUACCCUUGGACCCAGAGGUUCUUUG
AGUCCUUUGGGGAUCUGUCCACUCCUGAUGCUGUUAUGGGCAACCCUAAGGUGAAGGCUC
AUGGCAAGAAAGUGCUCGGUGCCUUUAGUGAUGGCCUGGCUCACCUGGACAACCUCAAGG
GCACCUUUGCCACACUGAGUGAGCUGCACUGUGACAAGCUGCACGUGGAUCCUGAGAACU
UCAGGCUCCUGGGCAACGUGCUGGUCUGUGUGCUGGCCCAUCACUUUGGCAAAGAAUUCA
CCCCACCAGUGCAGGCUGCCUAUCAGAAAGUGGUGGCUGGUGUGGCUAAUGCCCUGGCCC
ACAAGUAUCACUAAGCUCGCUUUCUUGCUGUCCAAUUUCUAUUAAAGGUUCCUUUGUUCC
CUAAGUCCAACUACUAAACUGGGGGAUAUUAUGAAGGGCCUUGAGCAUCUGGAUUCUGCC
UAAUAAAAAACAUUUAUUUUCAUUGC

mRNa da Hemoglobina falciforme

ACAUUUGCUUCUGACACAACUGUGUUCACUAGCAACCUCAAACAGACACCAUGGUGCACC
UGACUCCUG**U**GGAGAAGUCUGCCGUUACUGCCCCUGUGGGGCAAGGUGAACGUGGAUGAAG
UUGGUGGUGAGGCCCUGGGCAGGCUGCUGGUGGUCUACCCUUGGACCCAGAGGUUCUUUG
AGUCCUUUGGGGAUCUGUCCACUCCUGAUGCUGUUAUGGGCAACCCUAAGGUGAAGGCUC
AUGGCAAGAAAGUGCUCGGUGCCUUUAGUGAUGGCCUGGCUCACCUGGACAACCUCAAGG
GCACCUUUGCCACACUGAGUGAGCUGCACUGUGACAAGCUGCACGUGGAUCCUGAGAACU
UCAGGCUCCUGGGCAACGUGCUGGUCUGUGUGCUGGCCCAUCACUUUGGCAAAGAAUUCA
CCCCACCAGUGCAGGCUGCCUAUCAGAAAGUGGUGGCUGGUGUGGCUAAUGCCCUGGCCC
ACAAGUAUCACUAAGCUCGCUUUCUUGCUGUCCAAUUUCUAUUAAAGGUUCCUUUGUUCC
CUAAGUCCAACUACUAAACUGGGGGAUAUUAUGAAGGGCCUUGAGCAUCUGGAUUCUGCC
UAAUAAAAAACAUUUAUUUUCAUUGC

HbS

mRNA Normal

GUG CAC CUG ACU CCU GAG GAG AAG
val his leu thr pro **glu** glu lys
1 2 3 4 5 6 7 8

Proteína Normal

Mutação

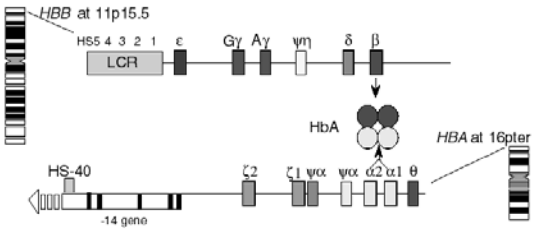
mRNA Mutante

GUG CAC CUG ACU CCU GUG GAG AAG
val his leu thr pro val glu lys
1 2 3 4 5 6 7 8

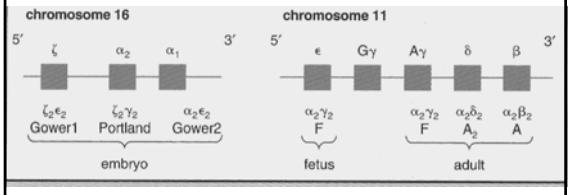
Proteína Mutante

Glutamato (glu), (aa negativamente carregado) é substituído por valina (val) (que não tem carga)

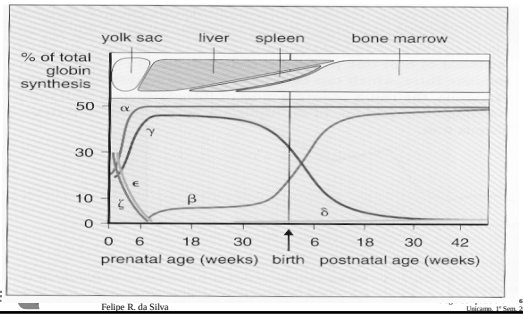
Genes de globinas



Síntese das globinas



Síntese das globinas/idade



Tipos de Hemoglobinas

- Adulto
  1. Hb A - $2\alpha2\beta$; 95%
  2. Hb A_2 - $2\alpha2\delta$; 3%
  3. Hb F - $2\alpha2\gamma$; 2%
- Feto
  1. Gowers 2 - $2\alpha2\varepsilon$ chains
  2. Gowers 1 - 4ε chains

Adulto normal

1. Hb A - $2\alpha2\beta$; 95%
2. Hb A_2 - $2\alpha2\delta$; 3%
3. Hb F - $2\alpha2\gamma$; 2%

Links interessantes

- Uma animação muito bem feita explicando as causas moleculares da anemia falciforme:
  - http://www.yourgenesyourhealth.org/sickle/cause.htm
  - ou http://www.yourgenesyourhealth.org/sickle/ para ver o material todo do site.
- Um site com tudo sobre estrutura de hemoglobina:
  - http://www.sicklecellinfo.net/index.htm