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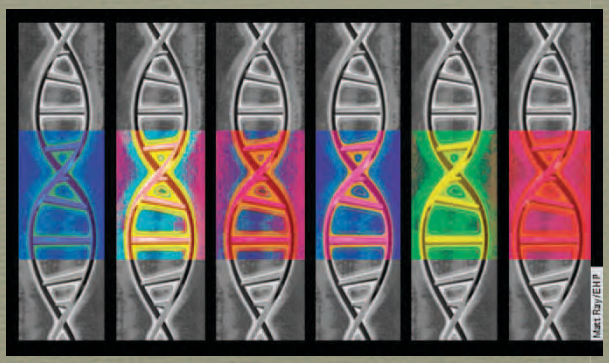
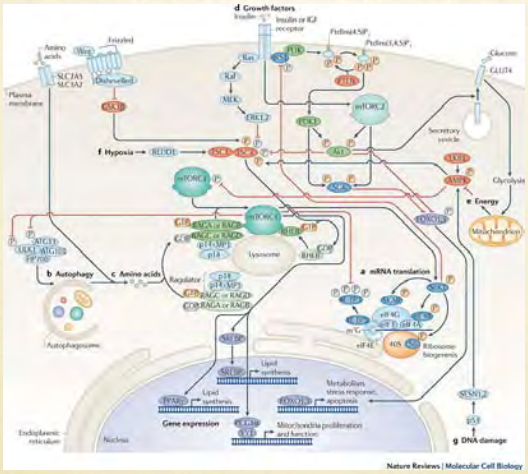


NÃO MENDELIANA

HEREDITARIEDADE MENDELIANA

HEREDITARIEDADE NÃO MENDELIANA



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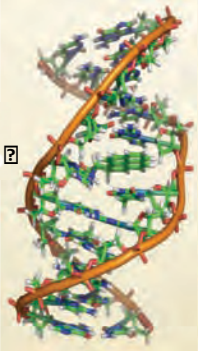

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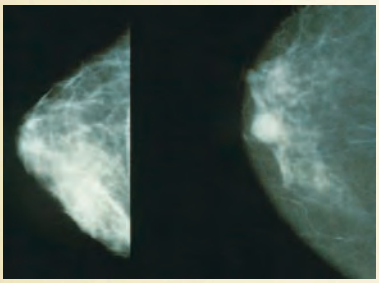
Hereditariedade

Influenciada pelo sexo

HEREDITARIEDADE INFLUENCIADA PELO SEXO



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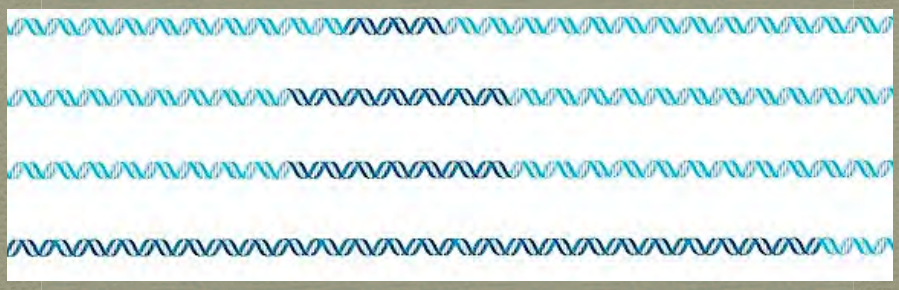
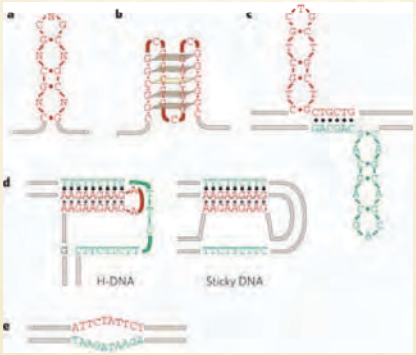


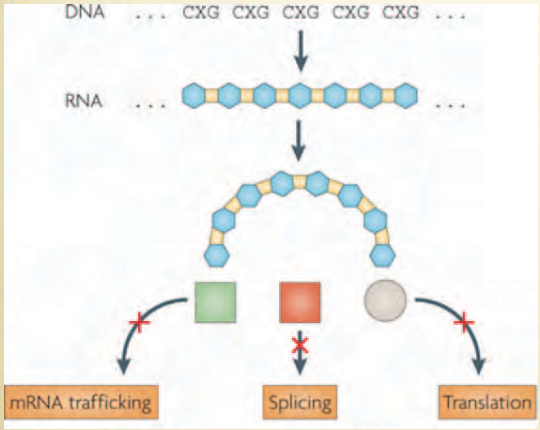
DINÂMICAS

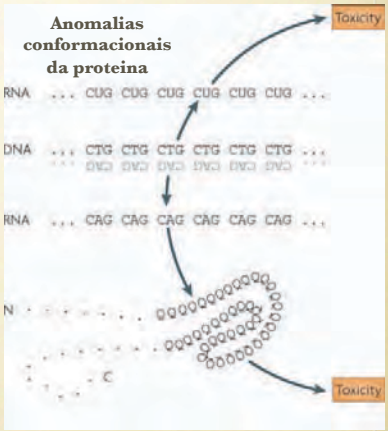
MUTAÇÕES DINÂMICAS



- ✓ **Ocorrem em regiões repetitivas do DNA (repetição em *tandem* de número variável)**
- ✓ **As repetição em *tandem* constituem uma fração considerável do genoma de muitos organismos eucarióticos**
- ✓ **A expansão número de repetições pode ocorrer devido a instabilidade mitótica**
- ✓ **A expansão não afecta o fenótipo, até um certo número de unidades repetitivas, denominando-se esta fase de pré-mutação. A partir de um certo tamanho, observa-se um efeito patogénico.**
- ✓ **O nº de unidades repetitivas não se mantém constante transgeneracionalmente, podendo diminuir ou aumentar.**

MUTAÇÕES DINÂMICAS





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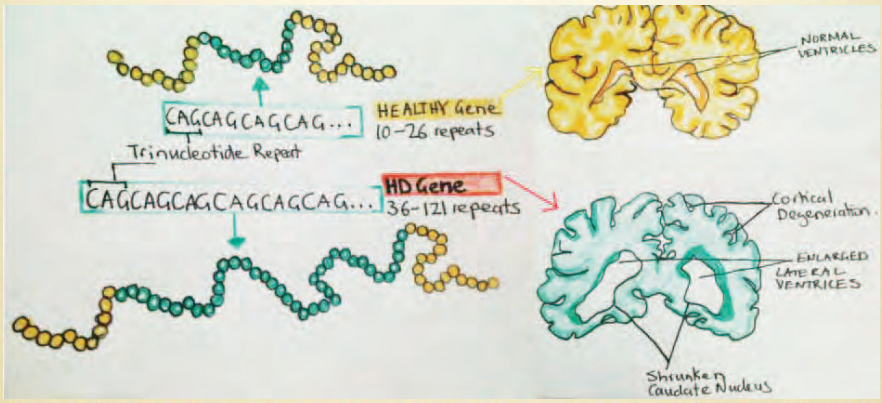
DOENÇA DE HUNTINGTON-*HTT*



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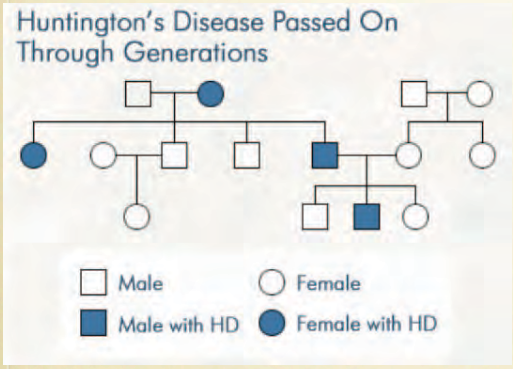
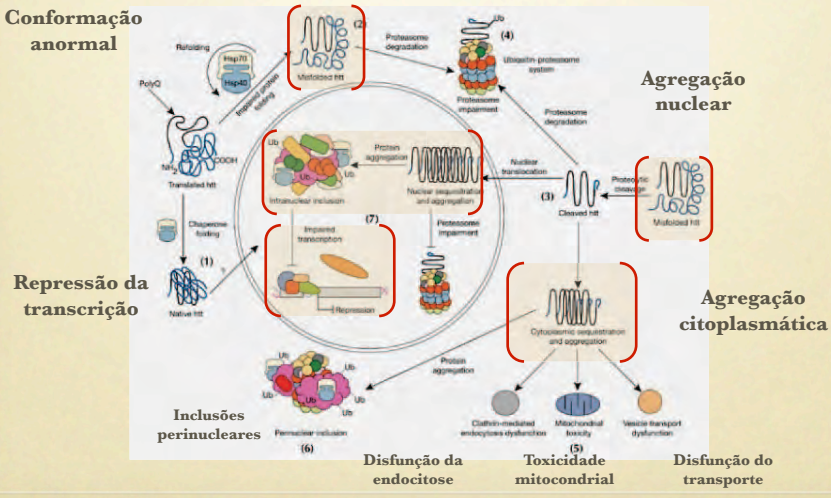


Repeat Ranges for Huntington Disease	
Description	**CAG Repeat Size**
Normal	10 to 26
Premutation	27 to 41
Affected	36 to 121

Quanto maior a expansão, mais graves e precoces serão os sintomas

MUTAÇÕES DINÂMICAS

FISIOPATOLOGIA NA DOENÇA DE HUNTINGTON



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DISTROFIA MIOTÓNICA – *DMPK*

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ANTECIPAÇÃO

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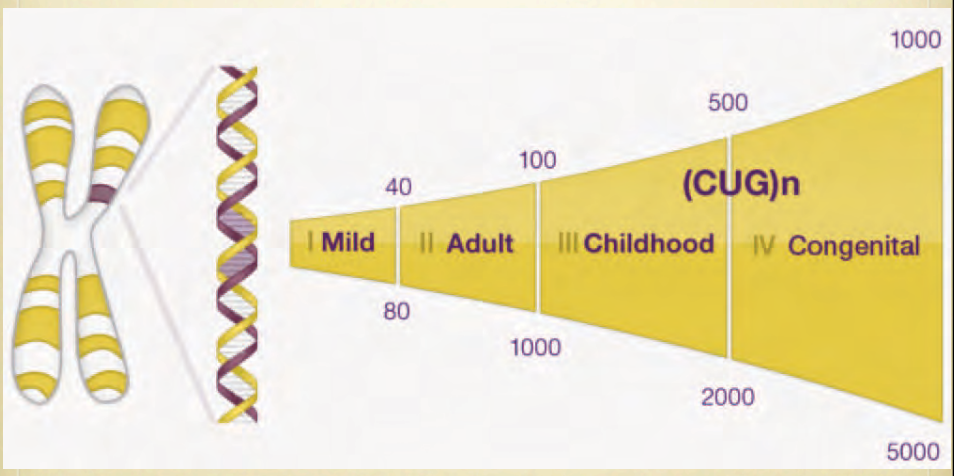

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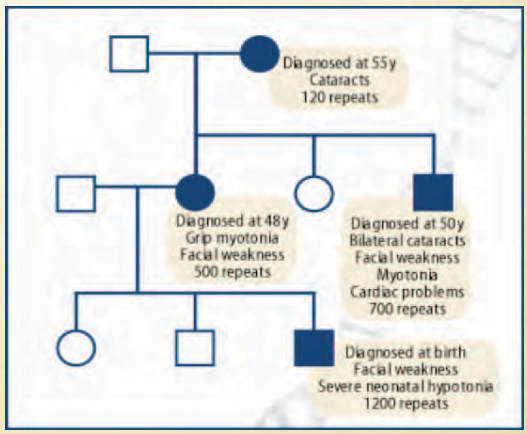

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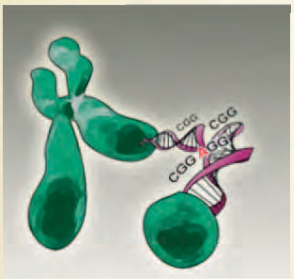
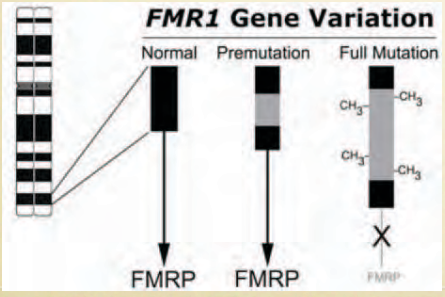
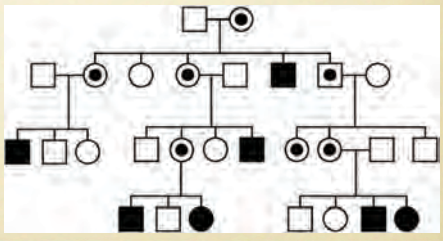


X- FRÁGIL

FRAXA





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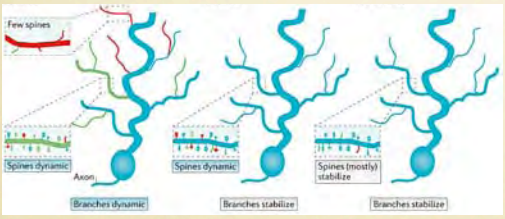

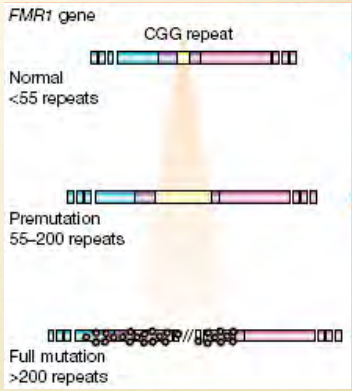

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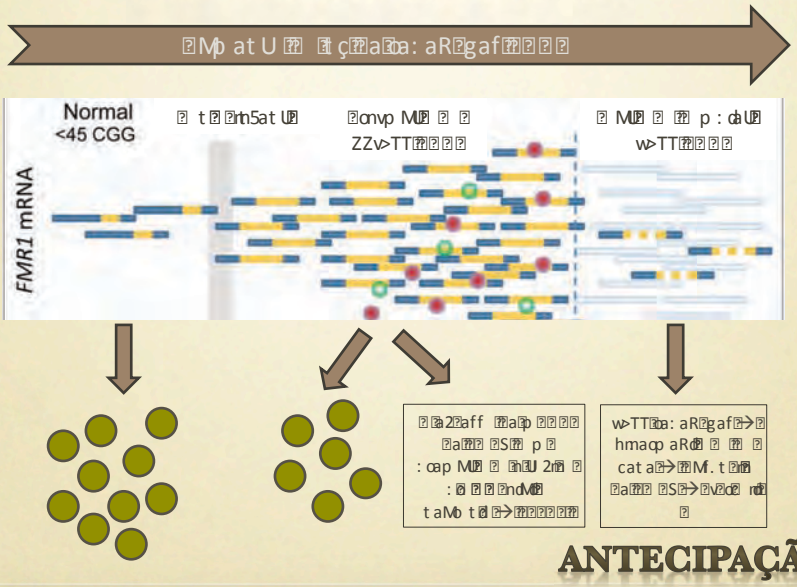

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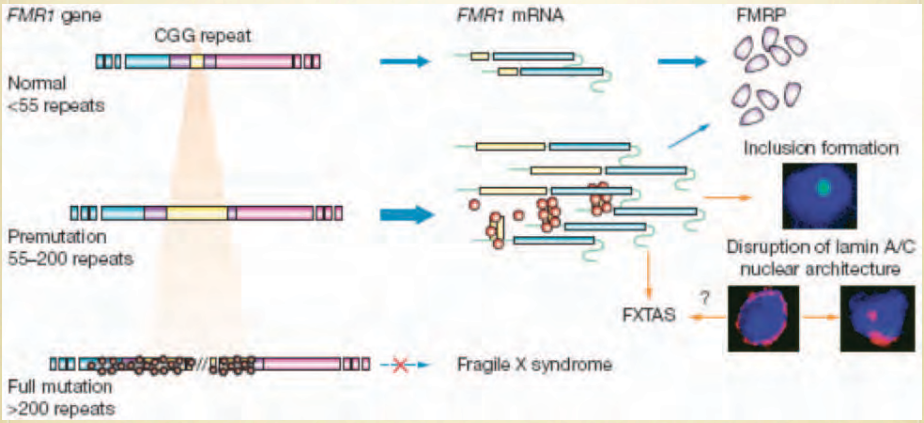
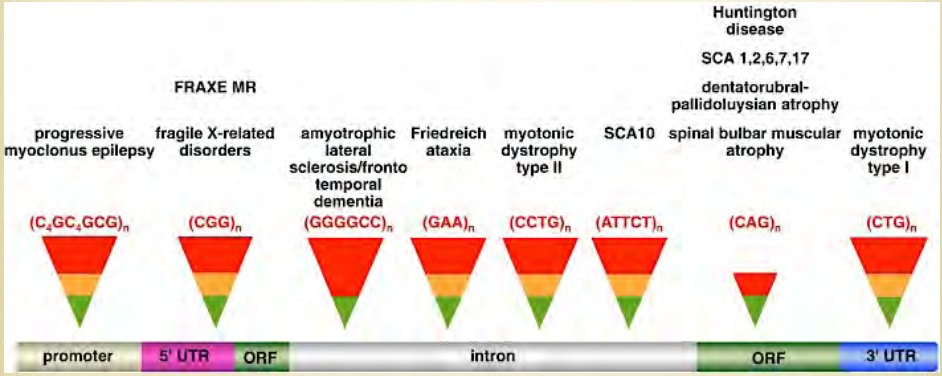
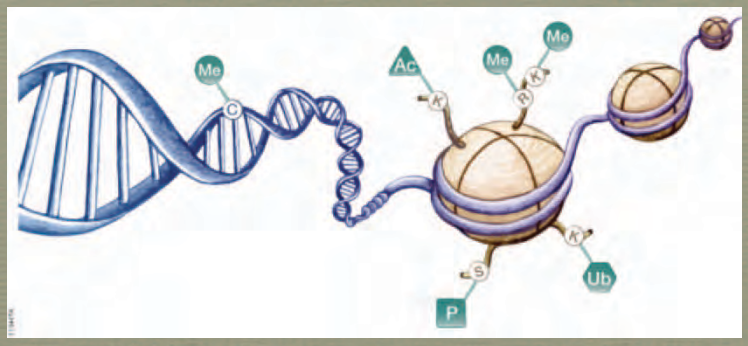


OUTRAS MUTAÇÕES DINÂMICAS



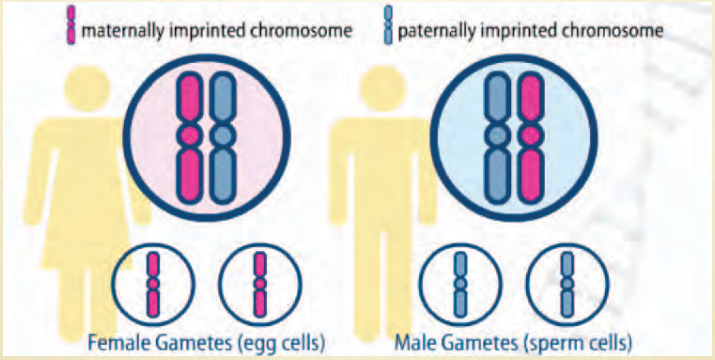
DOENÇAS EM REGIÕES



SUJEITAS A IMPRINTING

DOENÇAS EM REGIÕES SUJEITAS A IMPRINTING

IMPRINTING



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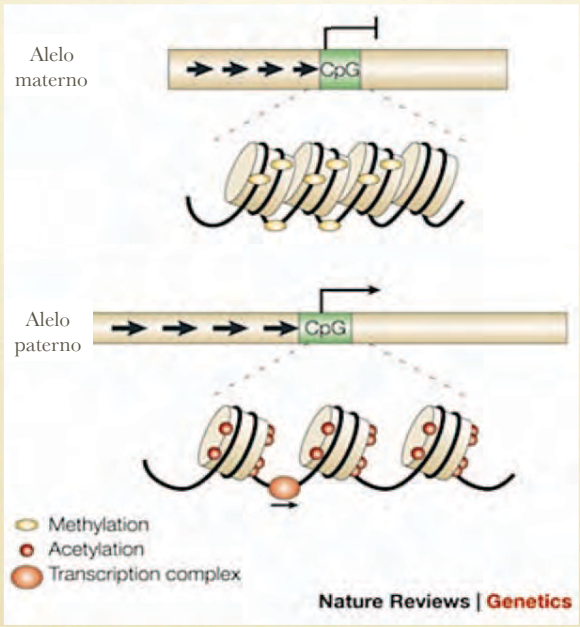

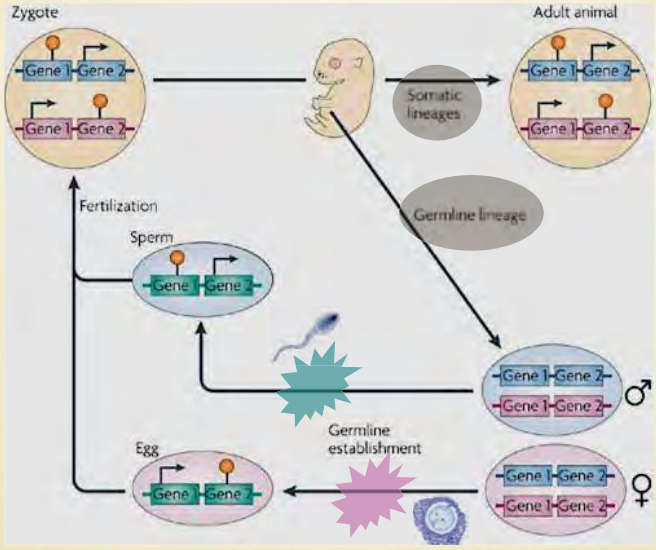

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DISSOMIA UNIPARENTAL

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Am J Hum Genet. 1988 Feb;42(2):217-26.

Uniparental disomy as a mechanism for human genetic disease.

Spence JE, Perciaccante RG, Greig GM, Willard HF, Ledbetter DH, Hejtmancik JF, Pollack MS, O'Brien WE, Beaudet AL.

Institute for Molecular Genetics, Baylor College of Medicine, Houston, TX 77030.

Abstract

A female with cystic fibrosis and short stature was investigated for molecular or cytogenetic abnormalities that might explain the combined phenotype. Analysis with polymorphic DNA markers indicated that the father did not contribute alleles to the propositus for markers near the CF locus or for centromeric markers on chromosome 7. High-resolution cytogenetic analysis was normal, and the result could not be explained on the basis of nonpaternity or a submicroscopic deletion. All of the data indicate that the propositus inherited two identical copies of maternal sequences for much or all of chromosome 7. The occurrence of uniparental disomy could be explained by models postulating postfertilization error, gamete complementation, monosomic conception with subsequent chromosome gain, or trisomic conception followed by chromosome loss. Uniparental disomy in an individual with a normal chromosome analysis is a novel mechanism for the occurrence of human genetic disease.

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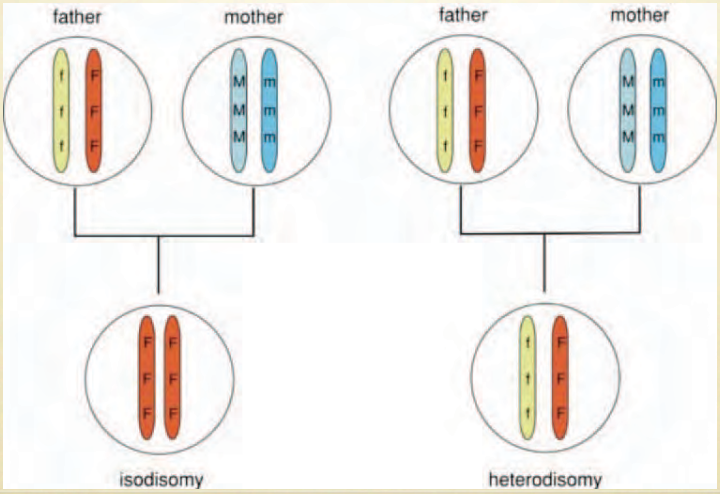

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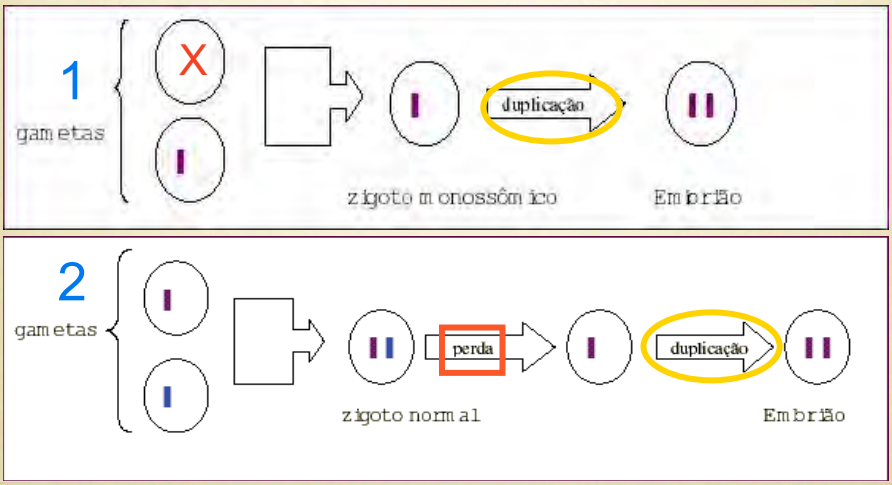

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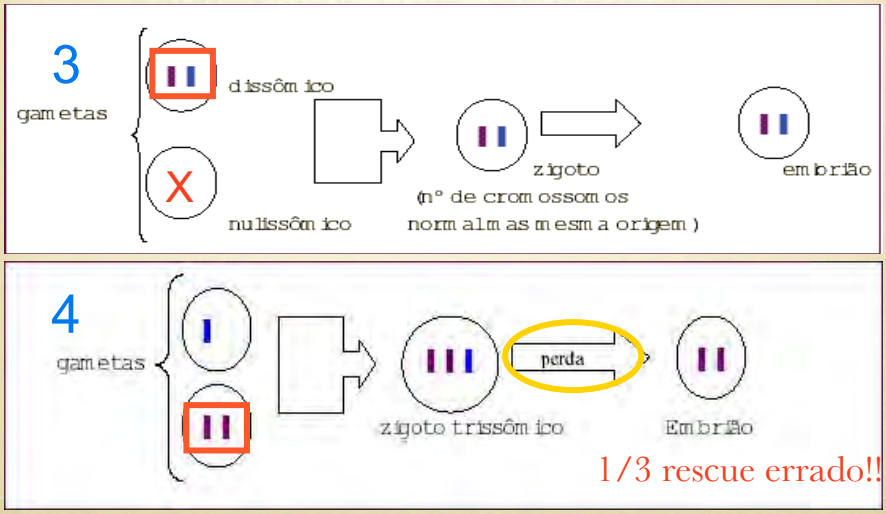

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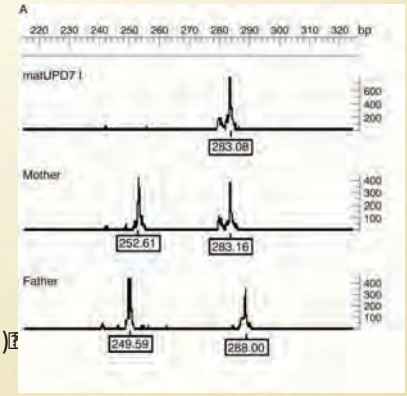

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Phenotype – Syndromes involving imprinted genes	Chromosomal location

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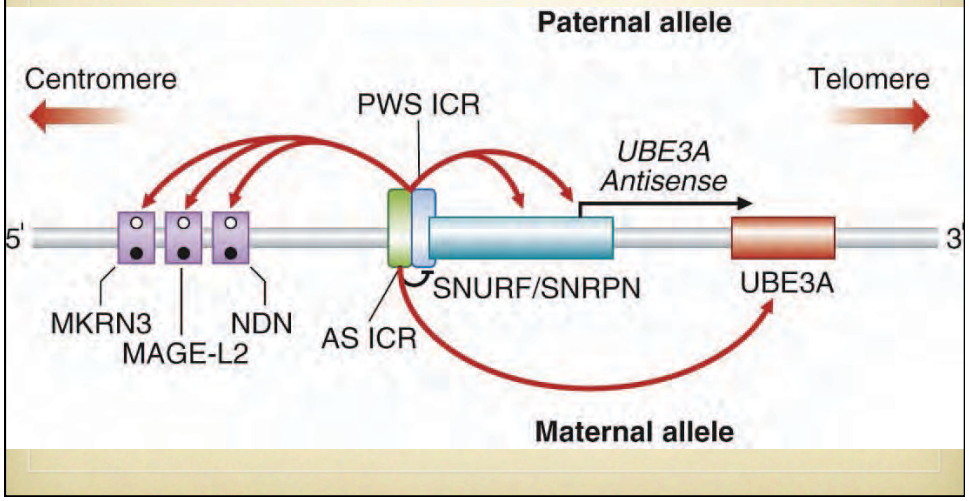
ANGELMAN/ PRADER-WILLI



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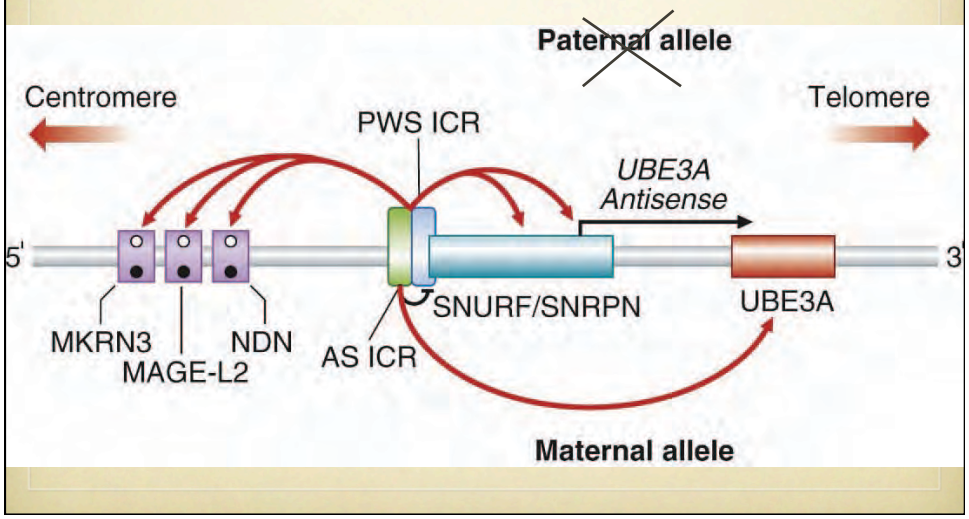
SÍNDROME PRADER-WILLI



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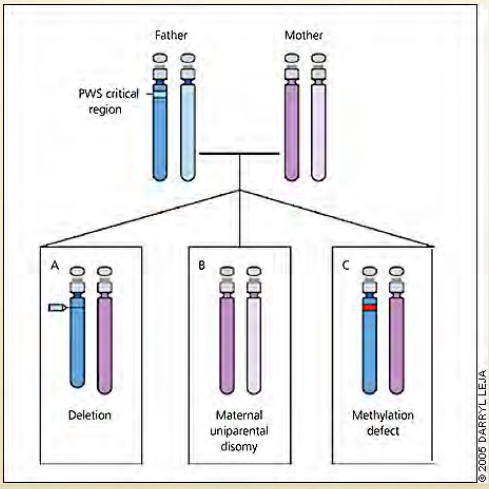

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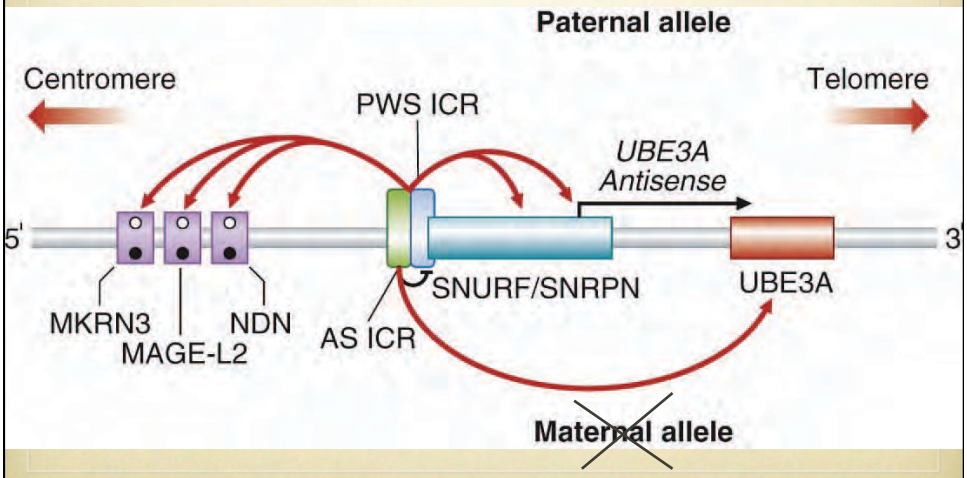

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SÍNDROME ANGELMAN

DOENÇAS EM REGIÕES SUJEITAS A IMPRINTING

SÍNDROME ANGELMAN

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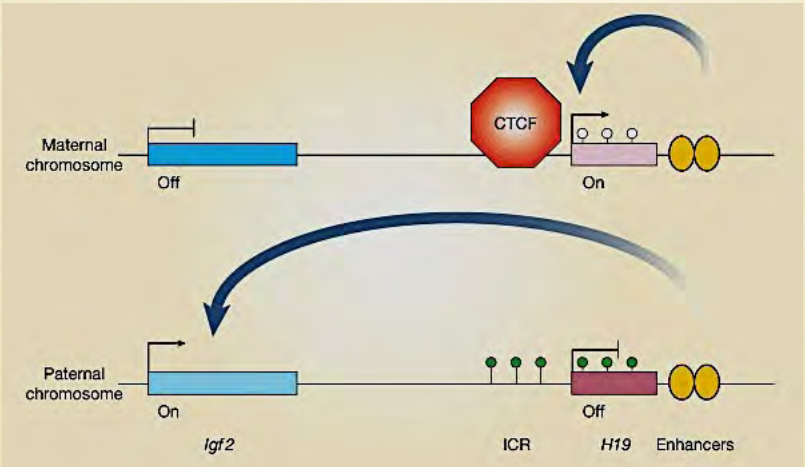
BECKWITH-WIEDEMANN/ SILVER-RUSSELL



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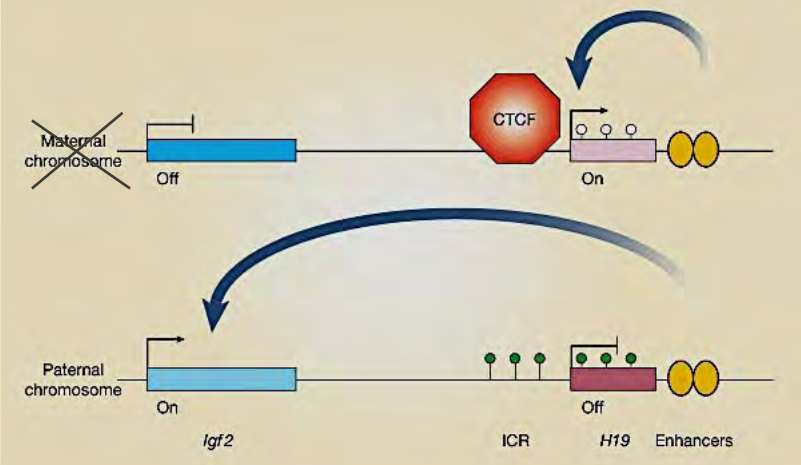
SÍNDROME DE BECKWITH-WIEDEMANN



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SÍNDROME BECKWITH-WIEDEMANN

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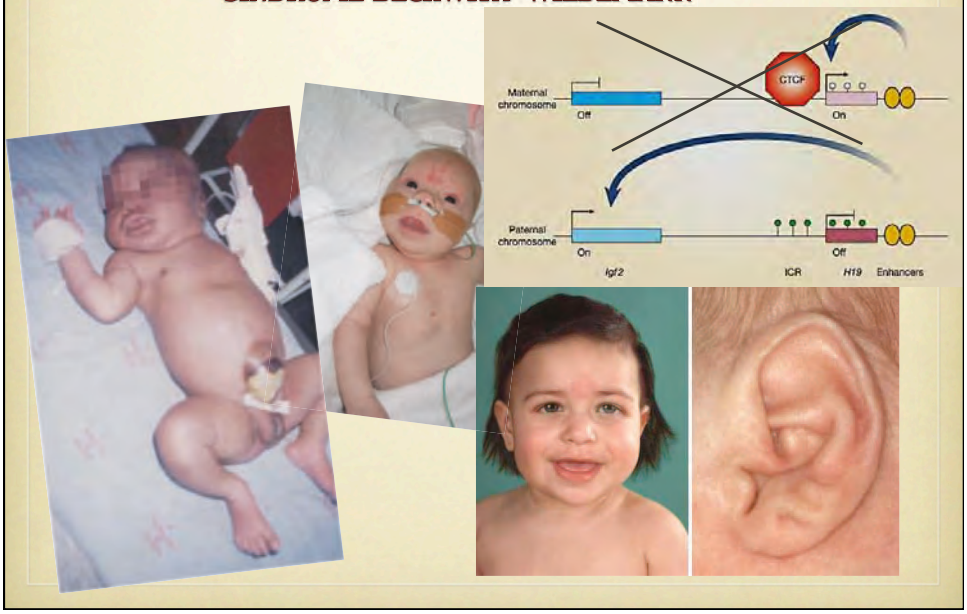
SÍNDROME BECKWITH-WIEDEMANN



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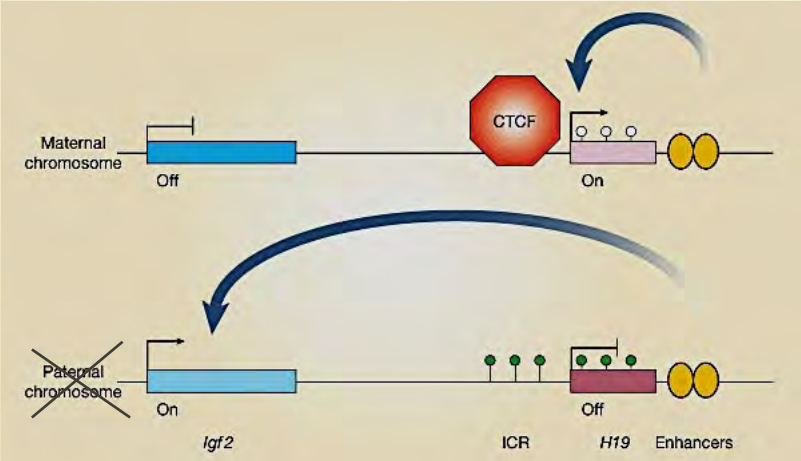
SÍNDROME DE SILVER-RUSSEL



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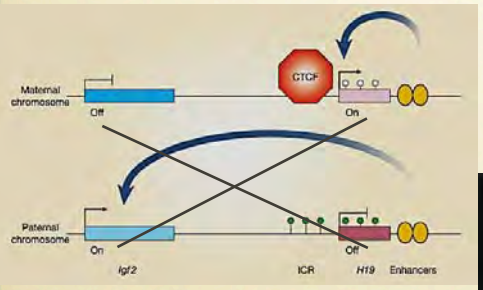
SÍNDROME SILVER-RUSSEL



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SÍNDROME SILVER-RUSSELL

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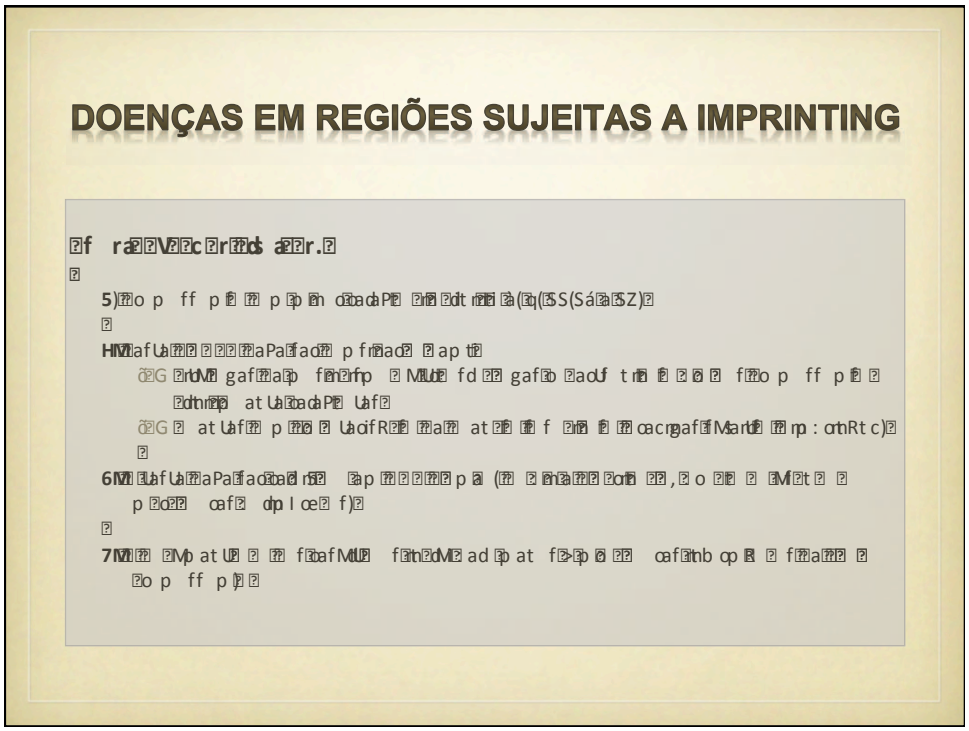

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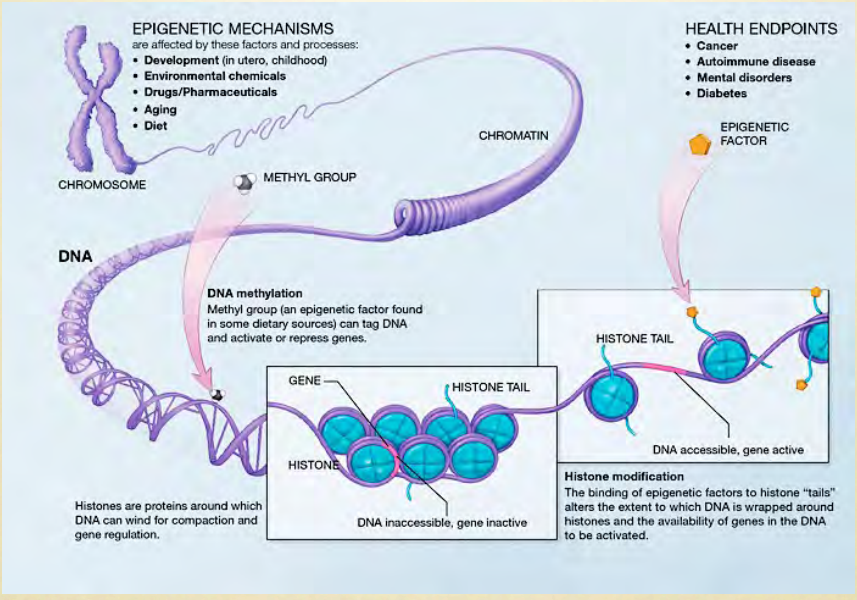

HEREDITARIEDADE

MITOCONDRIAL

DOENÇAS COM HEREDITARIEDADE MITOCONDRIAL

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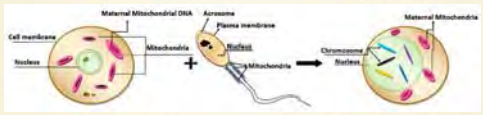

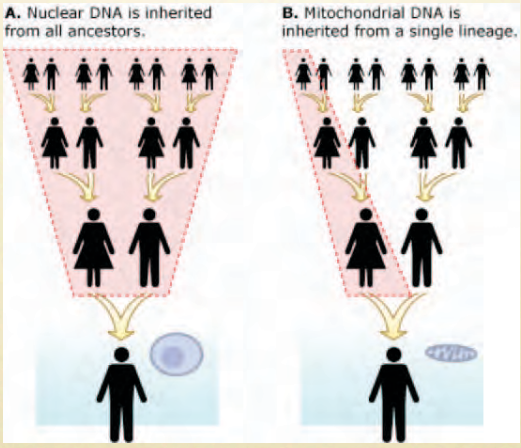

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A MITOCONDRIA

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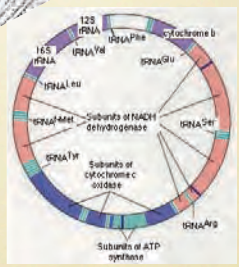
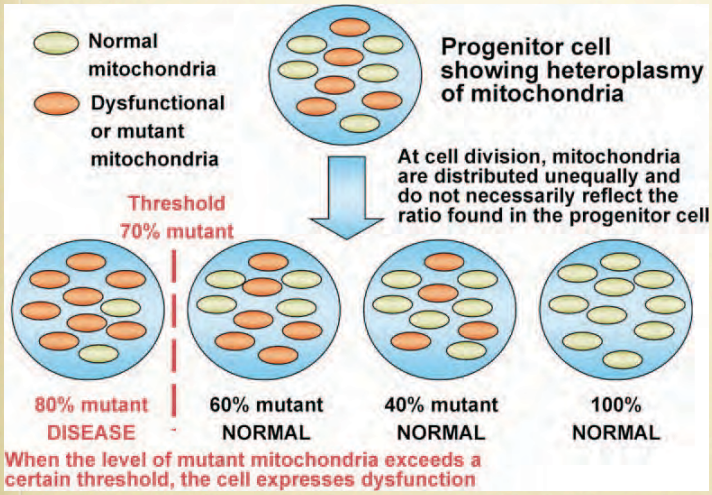


DOENÇAS COM HEREDITARIEDADE MITOCONDRIAL

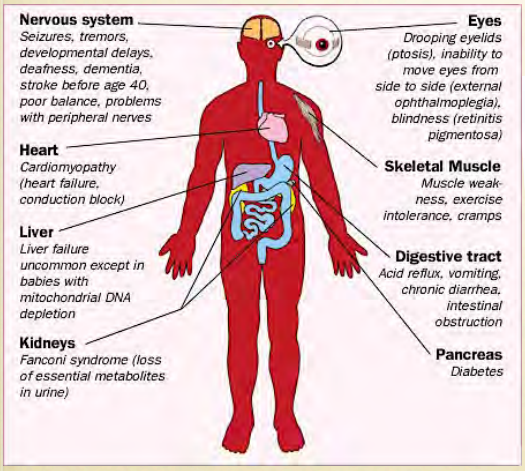


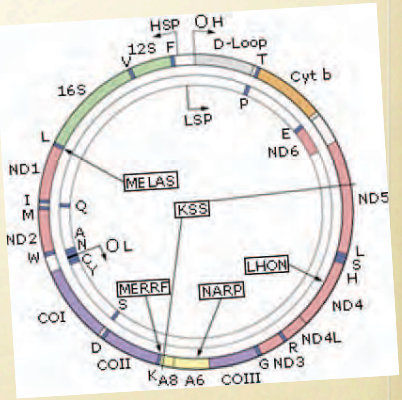
Bottle-neck

Heteroplasmia vs Homoplasmia

Mosaicismo somático

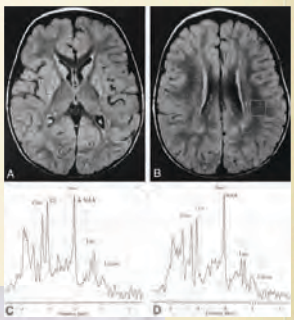
DOENÇAS COM HEREDITARIEDADE MITOCONDRIAL





DOENÇAS COM HEREDITARIEDADE MITOCONDRIAL

Síndrome de Leigh



DOENÇAS COM HEREDITARIEDADE MITOCONDRIAL

Síndrome de Kearns-Sayre

DOENÇAS COM HEREDITARIEDADE MITOCONDRIAL

MELAS

- ✓ m: R p rb t orl (
- ✓ at abl : R (
- ✓ m fa R a
- ✓ a: rfl mf "fUo uavoha"

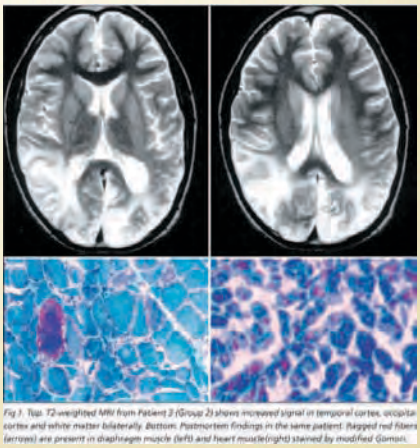
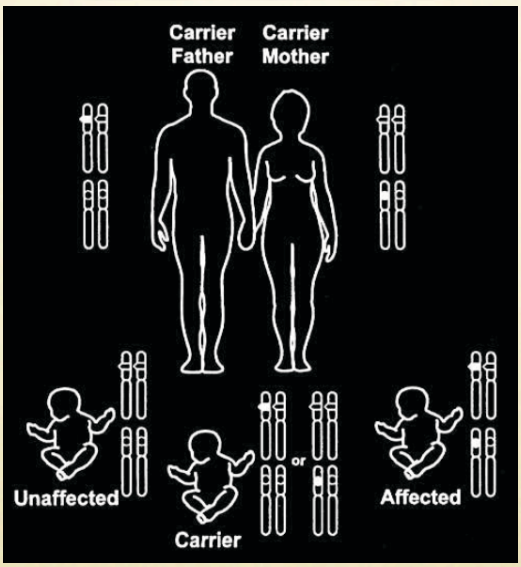


Fig 1. Top. T2-weighted MRI from Patient 3 (Group 2) shows increased signal in temporal cortex, occipital cortex and white matter bilaterally. Bottom. Postmortem findings in the same patient. Ragged red fibers (arrows) are present in diaphragm muscle (left) and heart muscle(right) stained by modified Gomori.

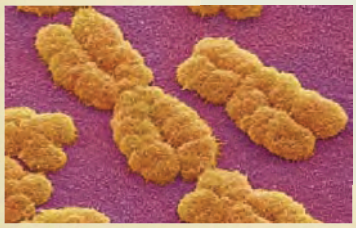
DOENÇAS

DIGÉNICAS

DOENÇAS DIGÉNICAS

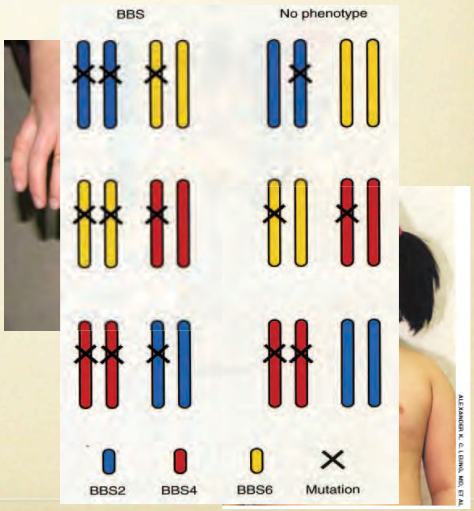


DOENÇAS DIGÉNICAS



DOENÇAS DIGÉNICAS

SÍNDROME DE BARDET-BIEDL



DOENÇAS DIGÉNICAS

THROMBOCYTOPENIA-ABSENT RADIUS (TAR)

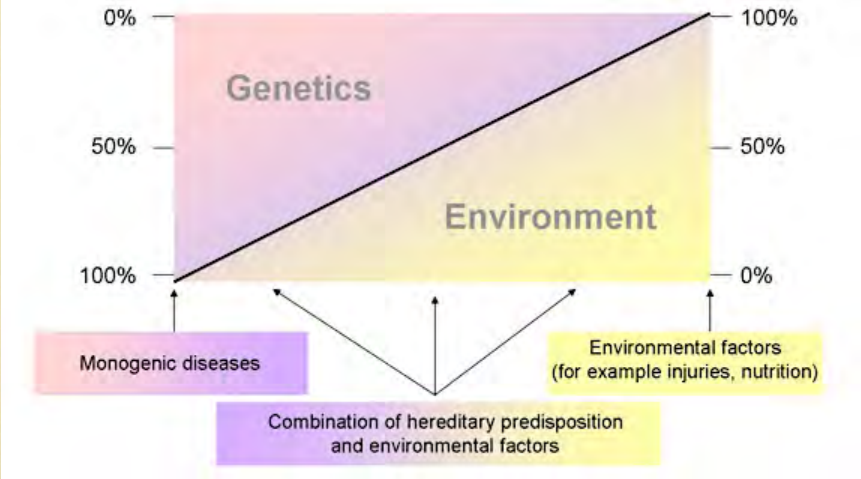
DOENÇAS

GENÉTICAS COMPLEXAS

DOENÇAS GENÉTICAS COMPLEXAS

- [illegible]
- [illegible]

DOENÇAS GENÉTICAS COMPLEXAS



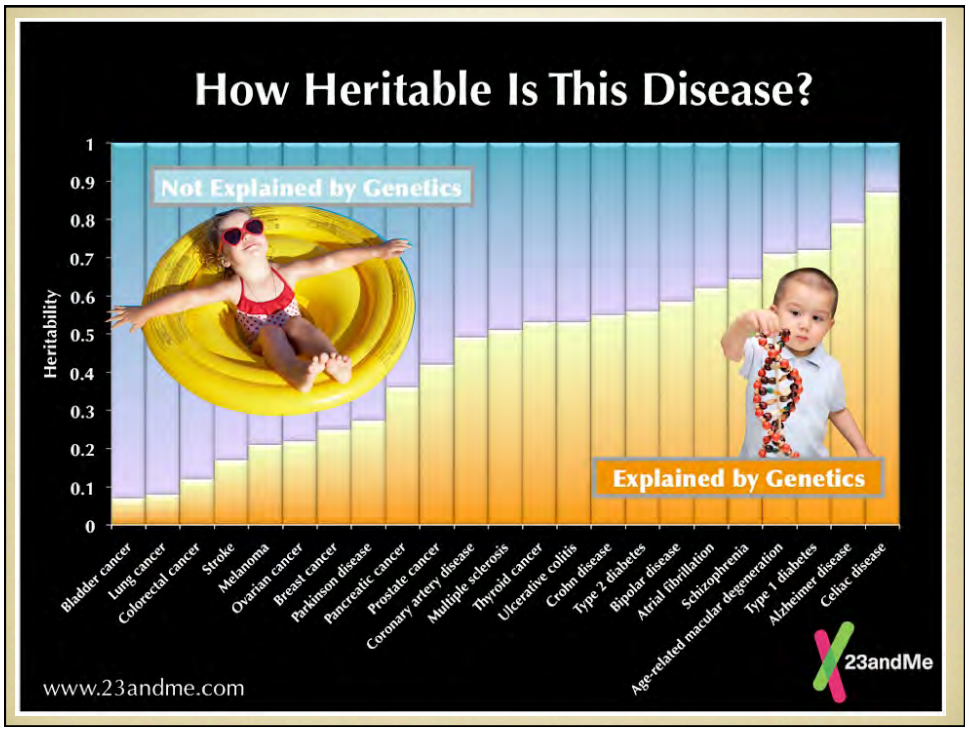
DOENÇAS GENÉTICAS COMPLEXAS

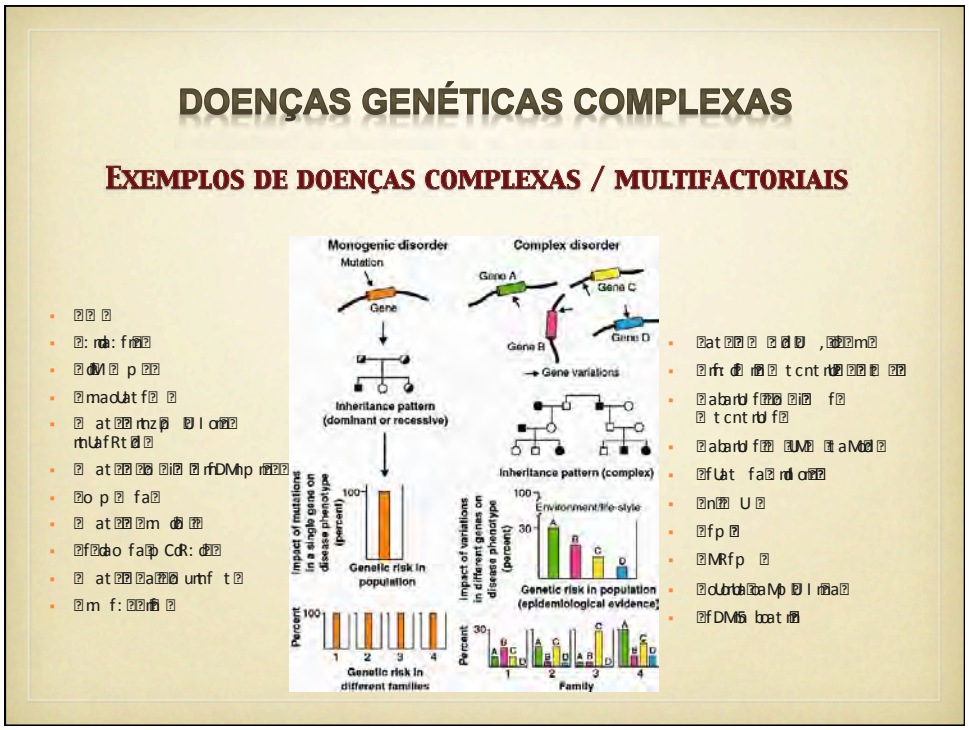
HERITABILIDADE

- [illegible]

- [illegible]

$$H^2 = \frac{Var(G)}{Var(P)}$$


How Heritable Is This Disease?
Heritability
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Not Explained by Genetics
Explained by Genetics
Bladder cancer
Lung cancer
Colorectal cancer
Stroke
Melanoma
Ovarian cancer
Breast cancer
Parkinson disease
Pancreatic cancer
Prostate cancer
Coronary artery disease
Multiple sclerosis
Thyroid cancer
Ulcerative colitis
Crohn disease
Type 2 diabetes
Bipolar disease
Atrial fibrillation
Schizophrenia
Age-related macular degeneration
Type 1 diabetes
Alzheimer disease
Celiac disease
www.23andme.com
23andMe


DOENÇAS GENÉTICAS COMPLEXAS
EXEMPLOS DE DOENÇAS COMPLEXAS / MULTIFACTORIAIS
Monogenic disorder
Mutation
Gene
Inheritance pattern (dominant or recessive)
Impact of mutations in a single gene on disease phenotype (percent)
100
Genetic risk in population
Percent
100
1 2 3 4
Genetic risk in different families
Complex disorder
Gene A
Gene C
Gene B
Gene D
Gene variations
Inheritance pattern (complex)
Impact of variations in different genes on disease phenotype (percent)
100
Environment/life-style
30
A B C D
Genetic risk in population (epidemiological evidence)
Percent
30
A B C D
1 2 3 4
Family

DOENÇAS GENÉTICAS COMPLEXAS

CARACTERÍSTICAS DA "HEREDITARIEDADE COMPLEXA"

5M [illegible]

HM [illegible]

6M [illegible]

[illegible]

[illegible]

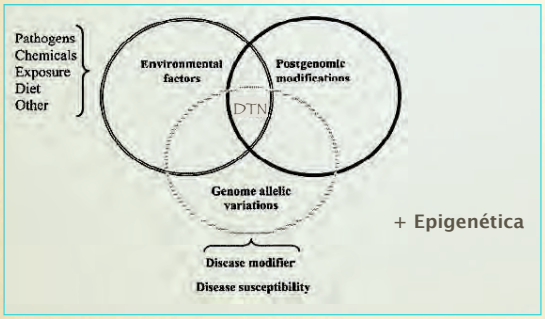
[illegible]

5M [illegible]

HM [illegible]

DOENÇAS GENÉTICAS COMPLEXAS

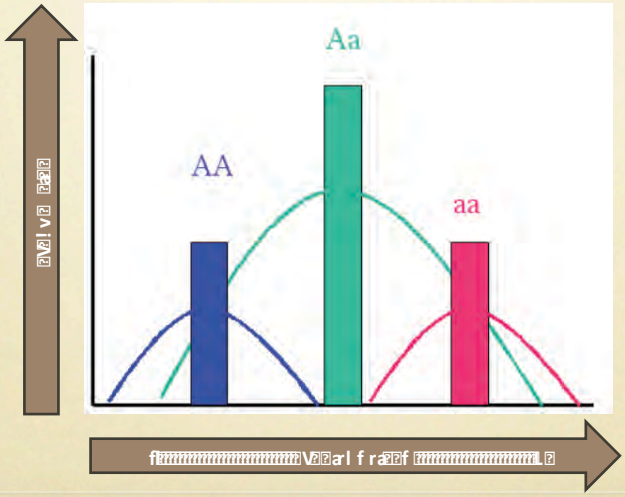
O EXEMPLO DO DTN



Individual affected	Population incidence		
	1/200	1/500	1/1000
One sib	5	3	2
Two sibs	12	10	10
One second-degree relative (uncle/aunt or half-sib)	2	1	1
One third-degree relative	1	0.5–1	0.5
One parent	4	4	4

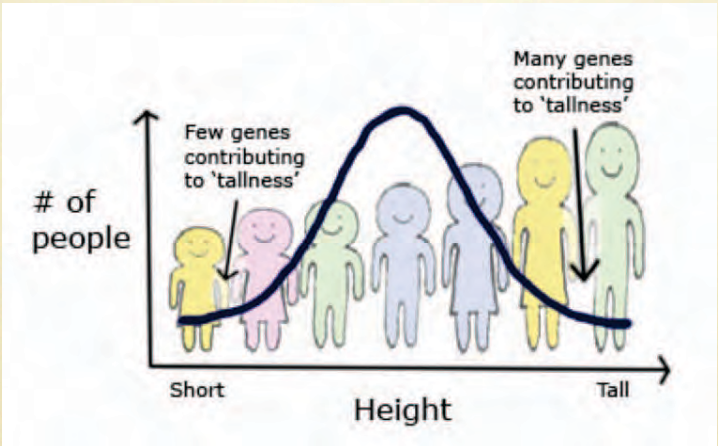
DOENÇAS GENÉTICAS COMPLEXAS

PARA CADA VARIANTE QUE CONFERE PREDISPOSIÇÃO:



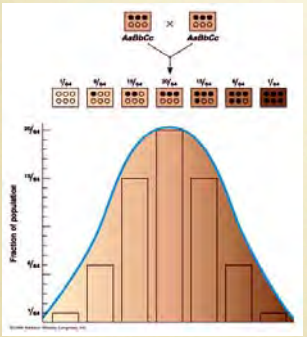
DOENÇAS GENÉTICAS COMPLEXAS

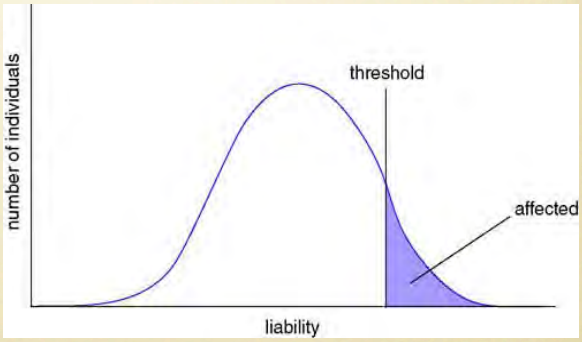
EXEMPLO:



DOENÇAS GENÉTICAS COMPLEXAS

- ✓ [illegible]
- ✓ [illegible]





DOENÇAS GENÉTICAS COMPLEXAS

CÁLCULO DE RISCO

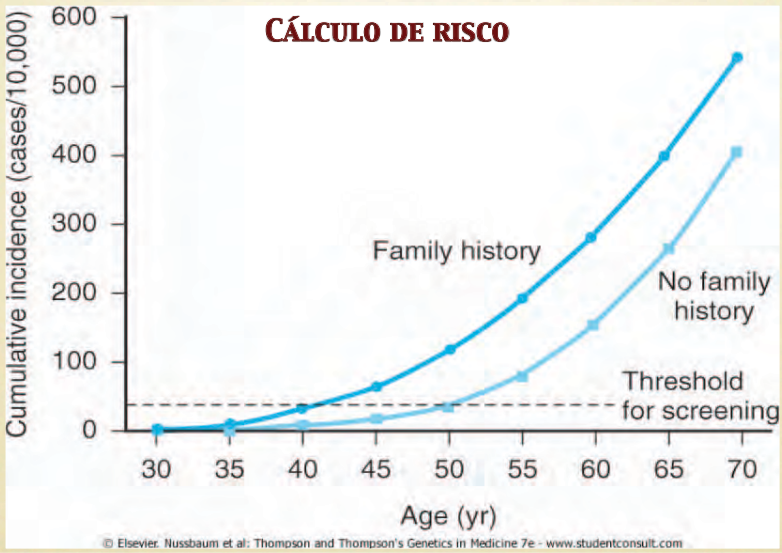
- ✓ [illegible]
- ✓ [illegible]

[illegible]

- ✓ [illegible]
- ✓ [illegible]
  - [illegible]
  - [illegible]
  - [illegible]

DOENÇAS GENÉTICAS COMPLEXAS

CÁLCULO DE RISCO



DOENÇAS GENÉTICAS COMPLEXAS

CÁLCULO DE RISCO

Factores que afectam o RR:

- Relação familiar com o probando
- Gravidade da doença
- O nº de afectados na família
- O sexo do probando
- Consanguínidade

LOST
CONFUSED
UNSURE
UNCLEAR
PERPLEXED
DISORIENTED
BEWILDERED