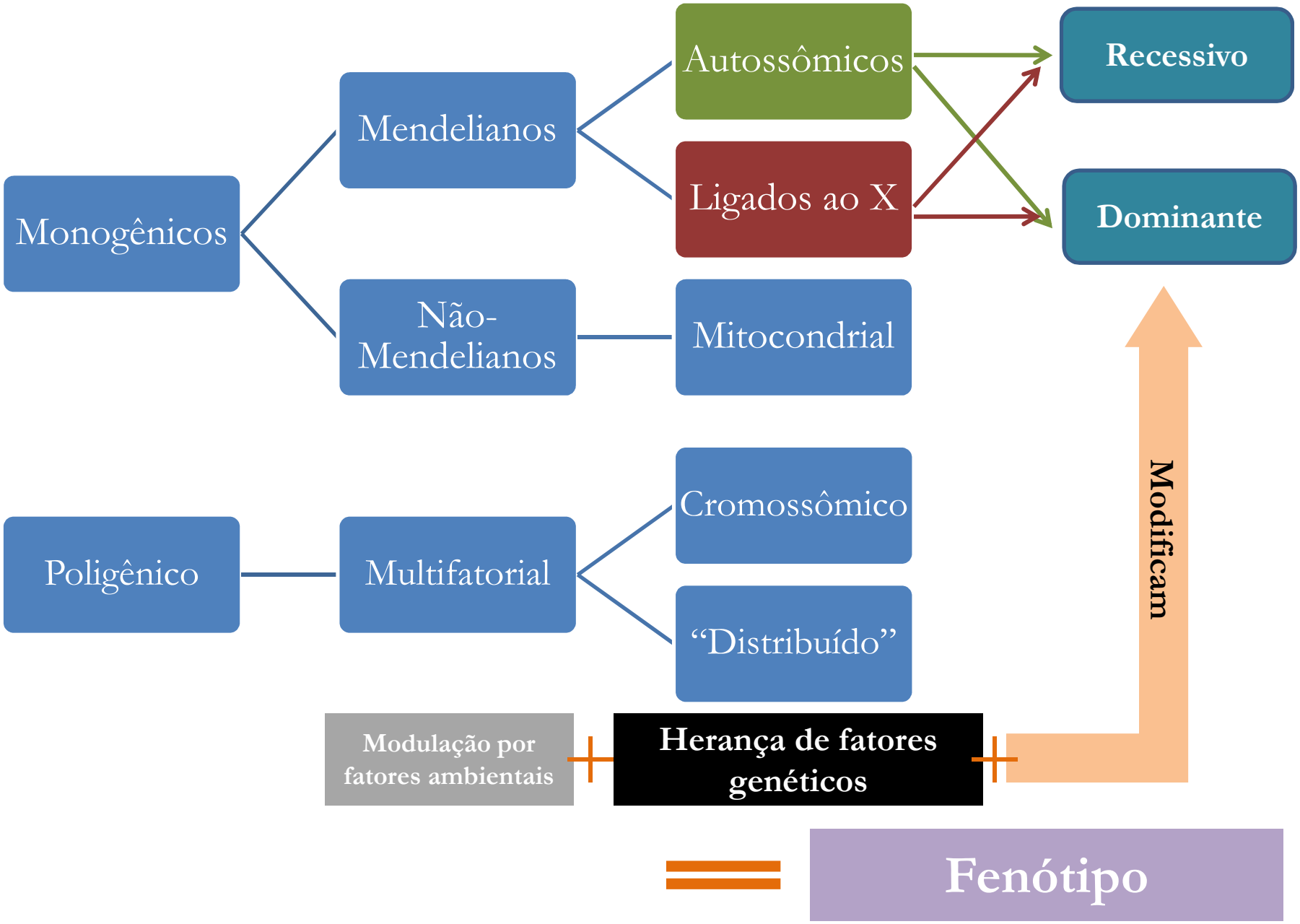
BIO0119 - Genética e Evolução Humana

Padrões monogênicos
Herança dominante

Prof. Dr. Michel Naslavsky

Padrões de herança



Padrões de herança

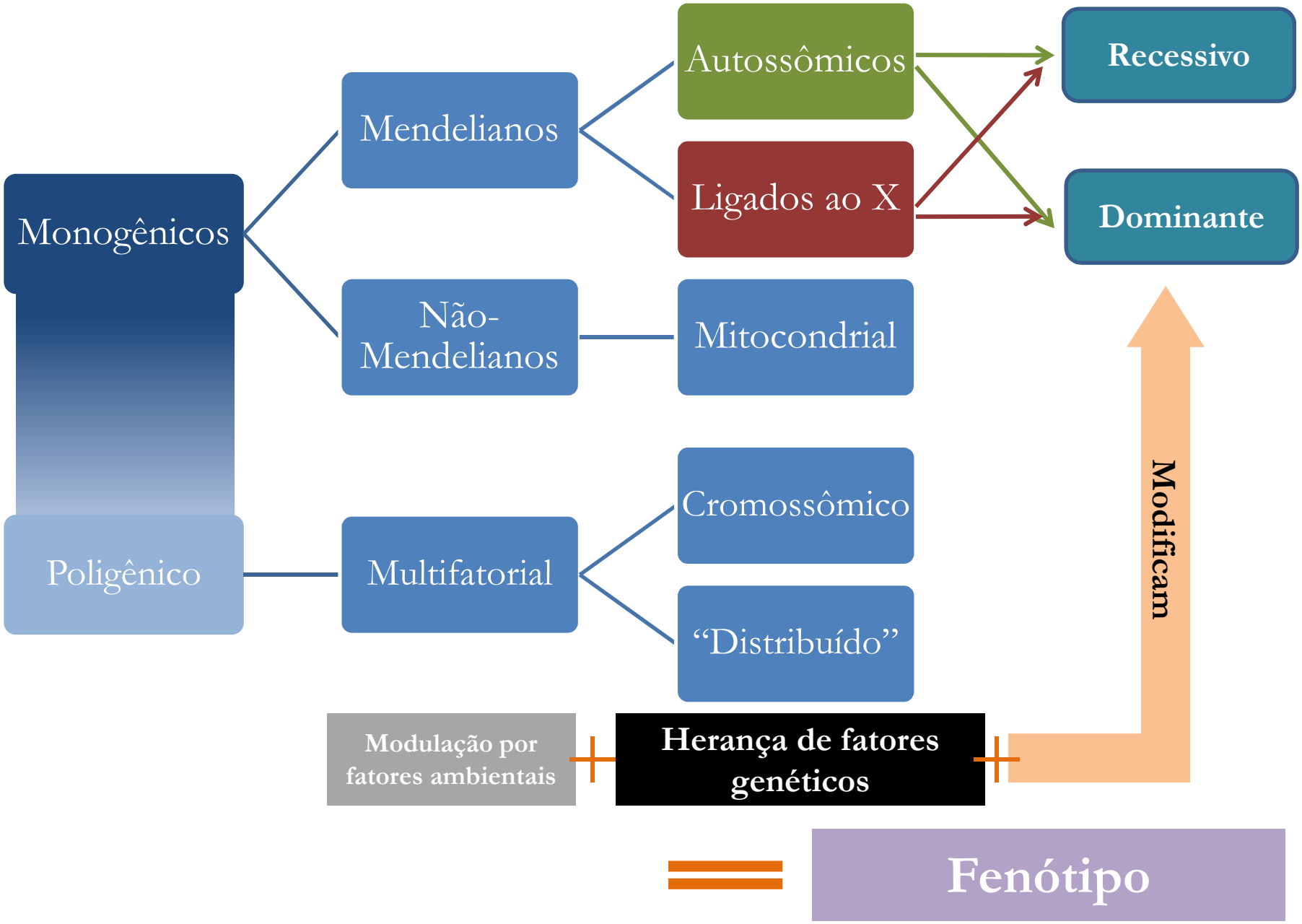
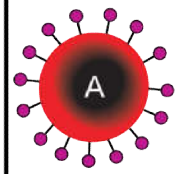
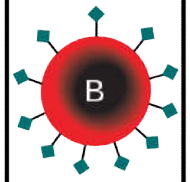
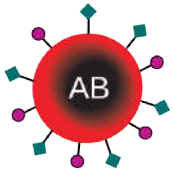
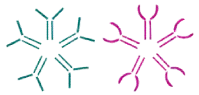


TABLE 7-1 ABO Genotypes and Serum Reactivity

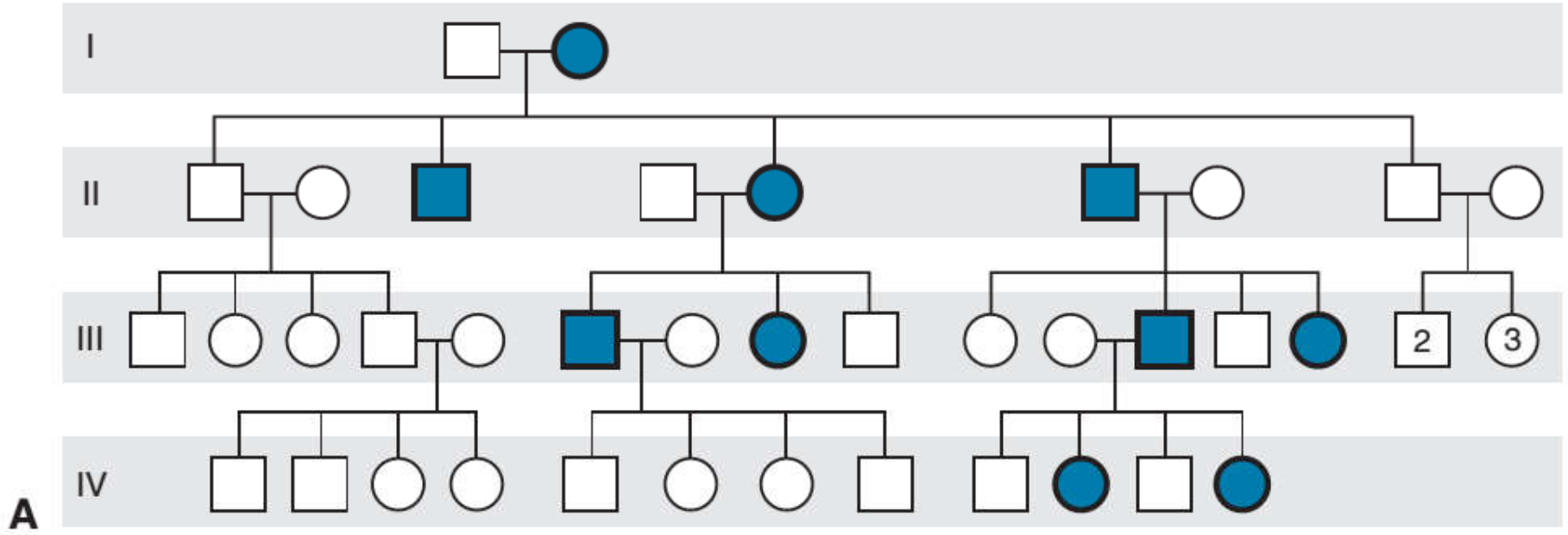
Genotype	Phenotype in RBCs	Reaction with Anti-A	Reaction with Anti-B	Antibodies in Serum
OO	O	−	−	Anti-A, anti-B
AA or *AO*	A	+	−	Anti-B
BB or *BO*	B	−	+	Anti-A
AB	AB	+	+	Neither

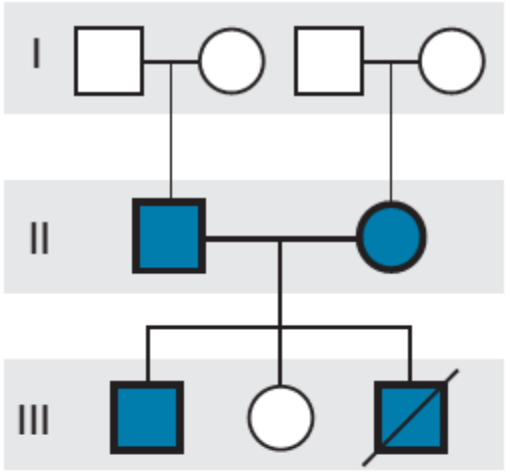
− Represents no reaction; + represents reaction. RBC, red blood cell.

	Group A	Group B	Group AB	Group O
Red blood cell type				
Antibodies in Plasma	 Anti-B	 Anti-A	None	 Anti-A and Anti-B
Antigens in Red Blood Cell	A antigen	B antigen	 A and B antigens	None

ABO genotype in the offspring		ABO alleles inherited from the mother		
		A	B	O
ABO alleles inherited from the father	A	A	AB	A
	B	AB	B	B
	O	A	B	O

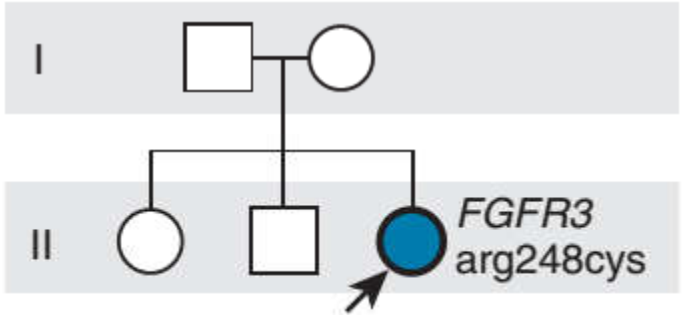
Análise de heredogramas





B

C



Características da herança dominante

- Fenótipo ocorre em todas as gerações, afetando indivíduos filhos de afetados. Exceções:

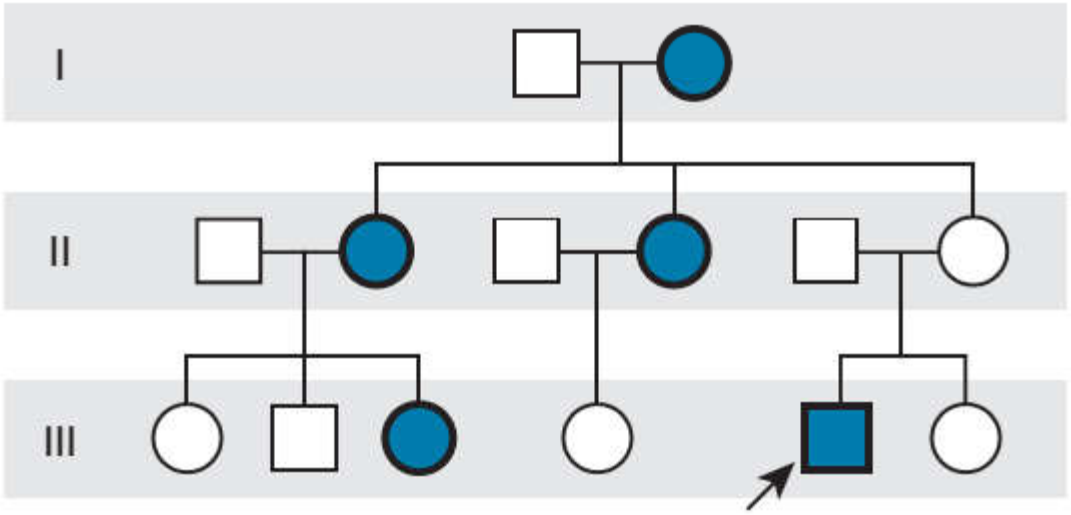
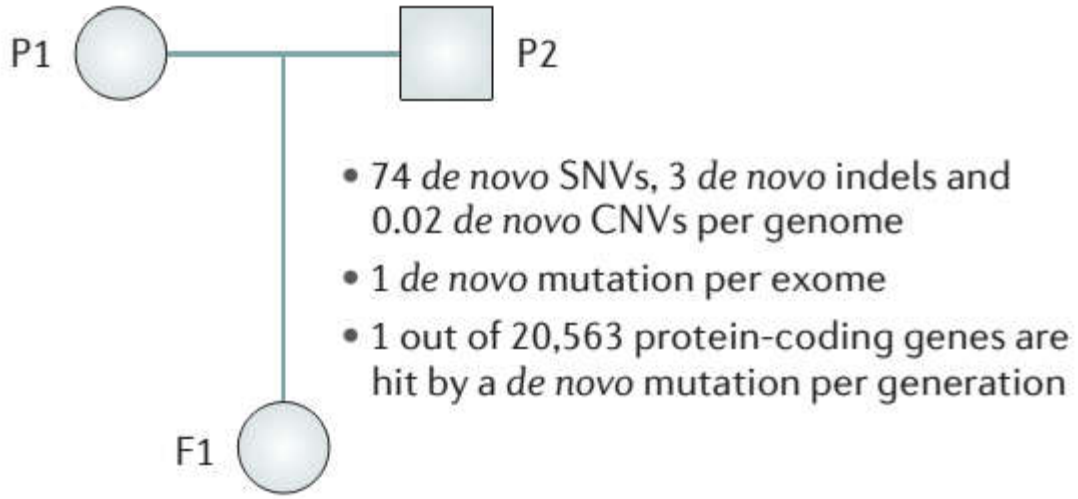


Figure 7-10 Pedigree of split-hand deformity demonstrating failure of penetrance in the mother of the proband *(arrow)* and his sister, the consultand. Reduced penetrance must be taken into account in genetic counseling.

Características da herança dominante

- Fenótipo ocorre em todas as gerações, afetando indivíduos filhos de afetados. Exceções:

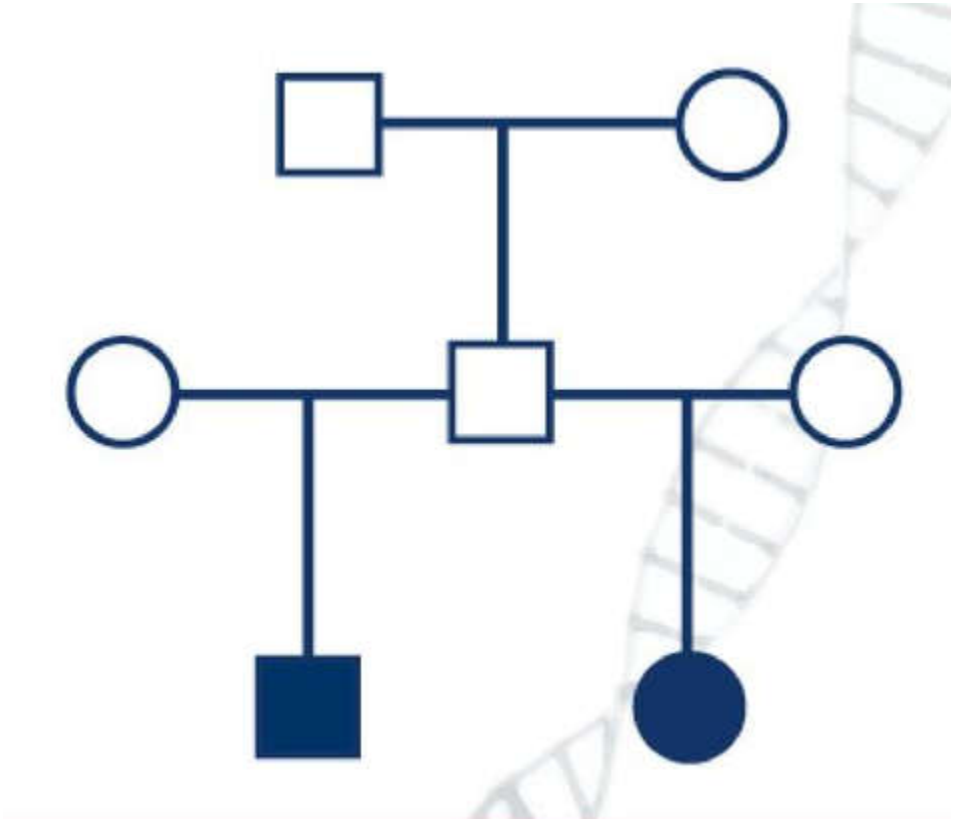


De novo mutations in human genetic disease

Joris A. Veltman and Han G. Brunner

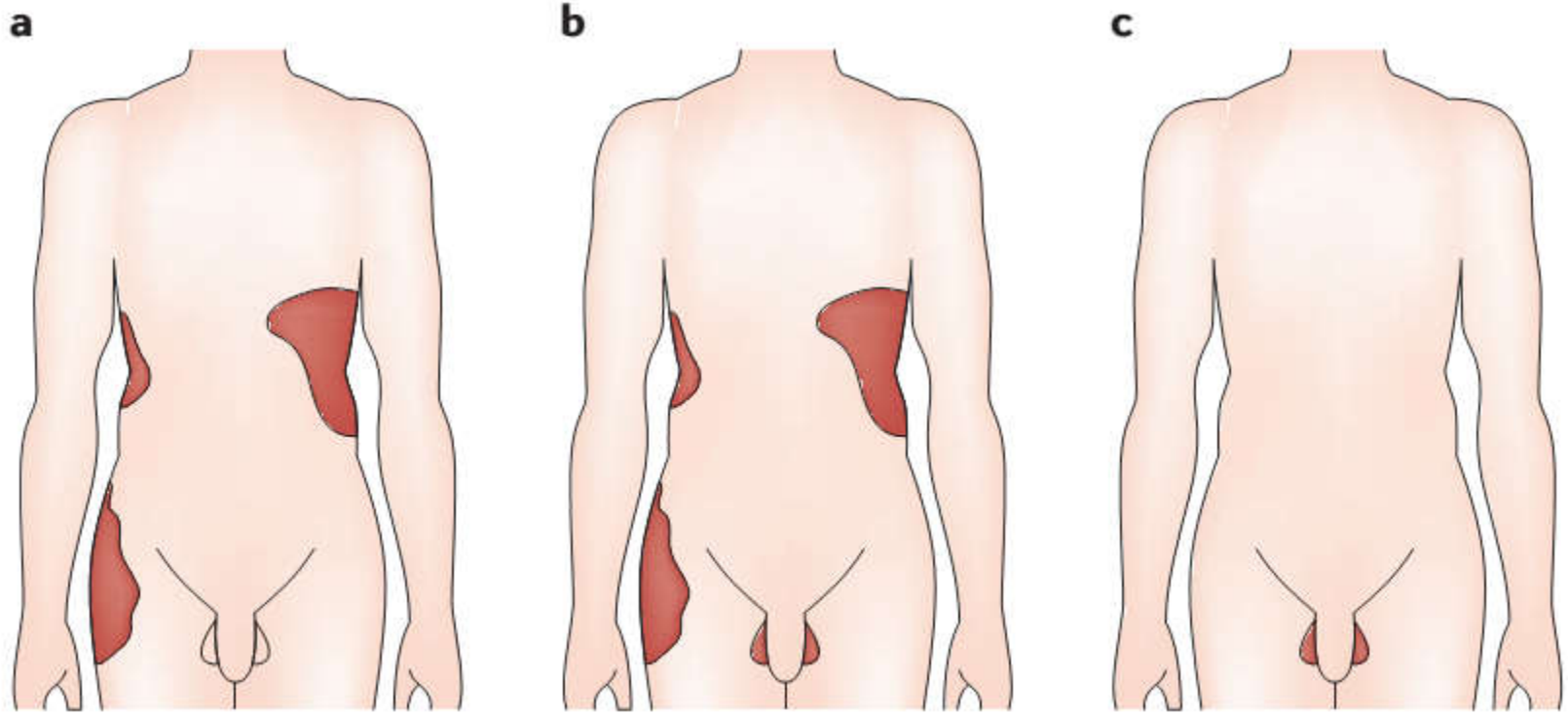
Características da herança dominante

- Como explicar?



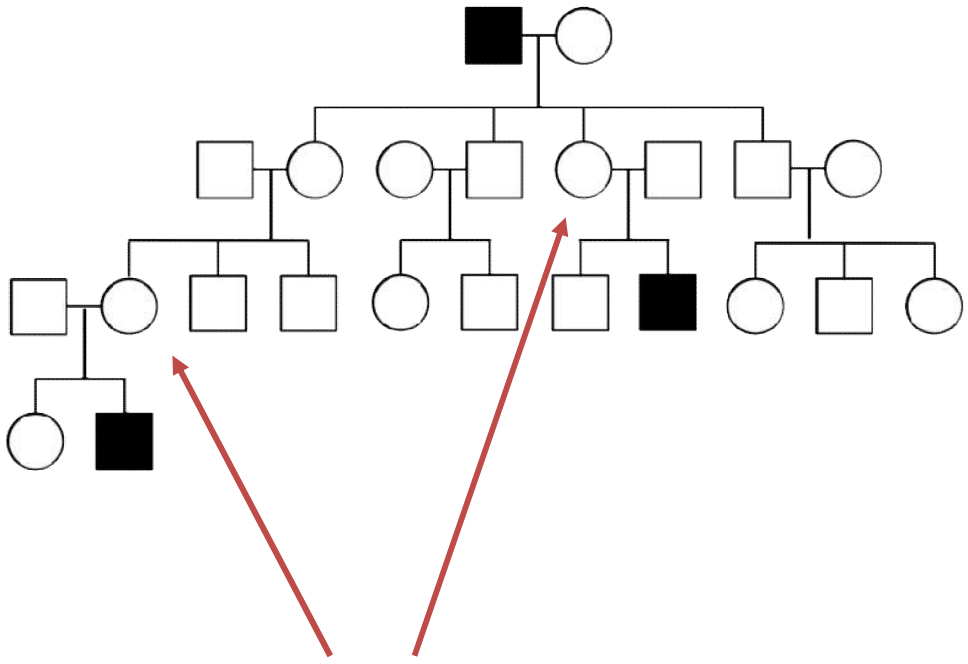
Características da herança dominante

- Como explicar?



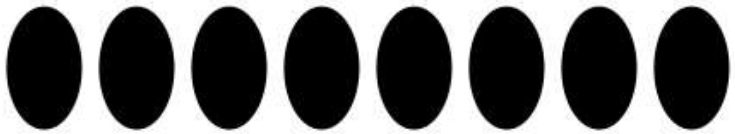
Somático Gonadosomático Gonadal

Penetrância e expressividade

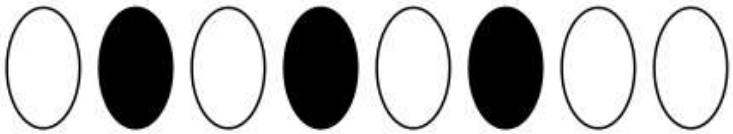


Penetrância incompleta

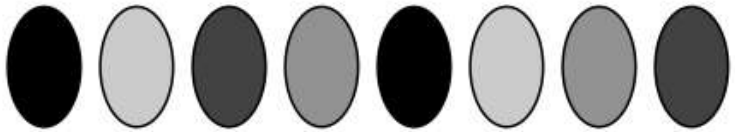
Penetrância e expressividade



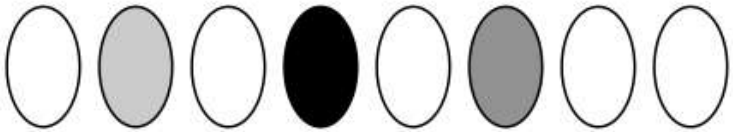
Penetrância completa
Expressividade pouco variável



Penetrância incompleta
Expressividade pouco variável



Penetrância completa
Expressividade variável

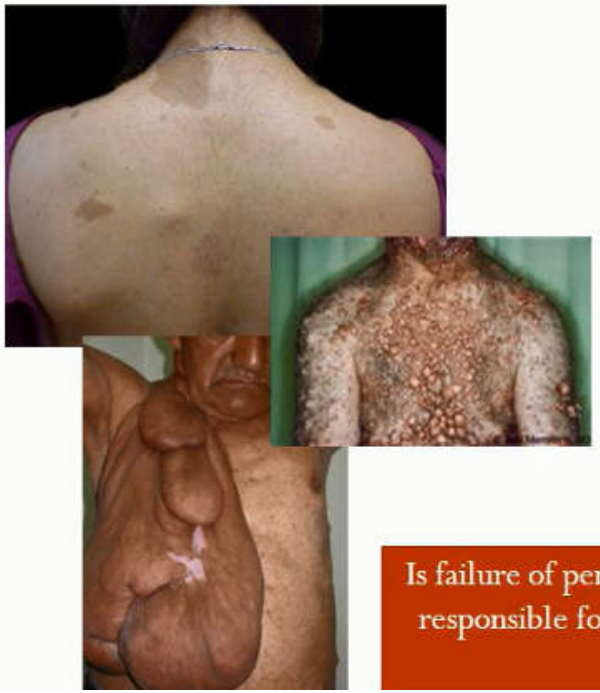


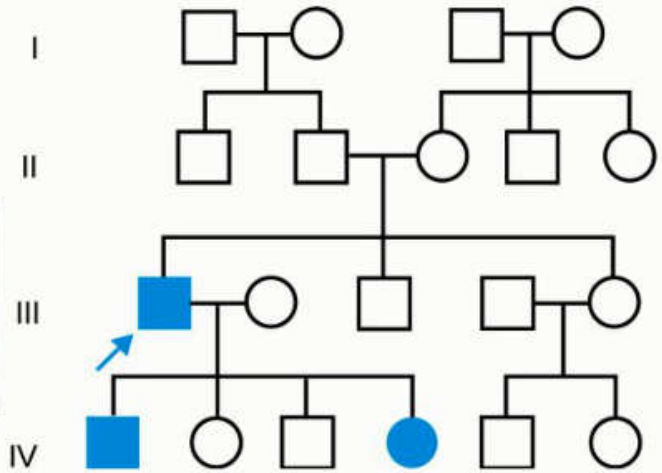
Penetrância incompleta
Expressividade variável

Neurofibromatose tipo 1

- Expressividade variável intrafamiliar, penetrância idade-dependente

Neurofibromin is a tumor suppressor protein encoded by the *Nf1* gene on human chromosome 17. Neurofibromin helps protect cells against cancer by suppressing Ras, a potent activator of cell growth and proliferation. People with mutations in the Nf1 gene develop neurofibromatosis type I (NF1), a neurological disorder that affects 1 in 3,500 people world-wide.



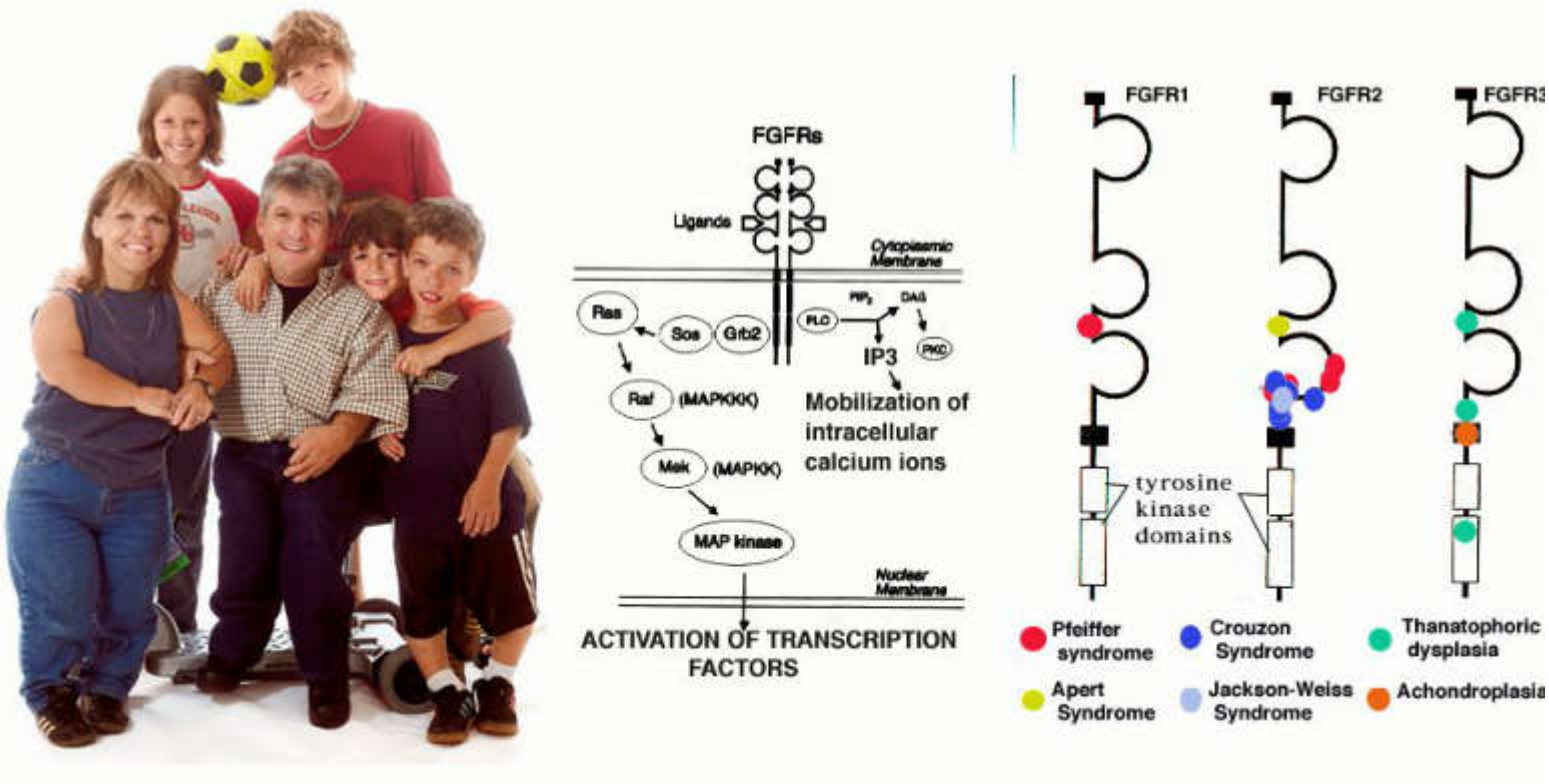


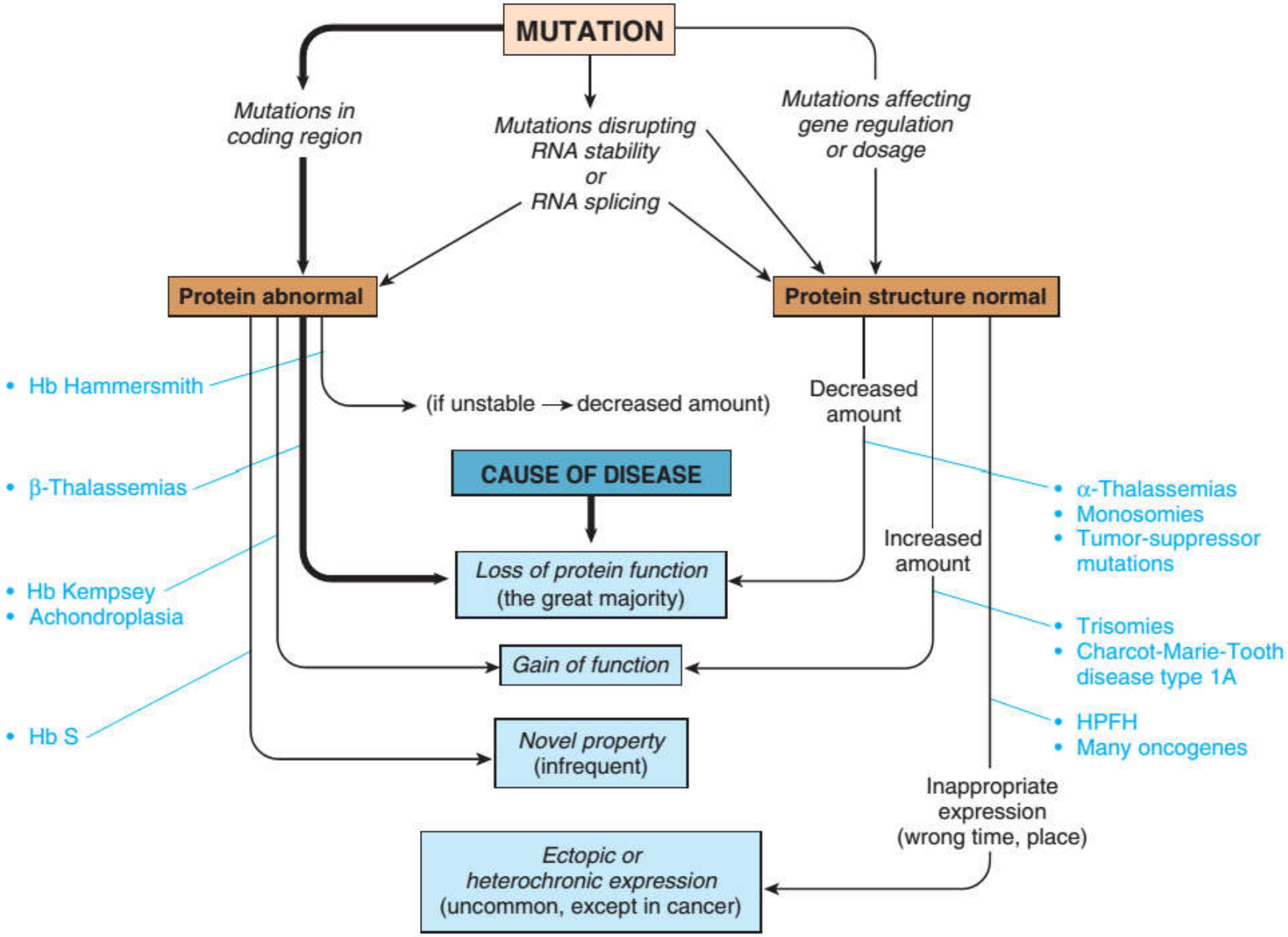
Is failure of penetrance or new mutation or variable expressivity responsible for the proband's phenotype (all susceptible adults display a phenotype)?

Atividade Retinoblastoma

https://goo.gl/qNNQew

Acondroplasia

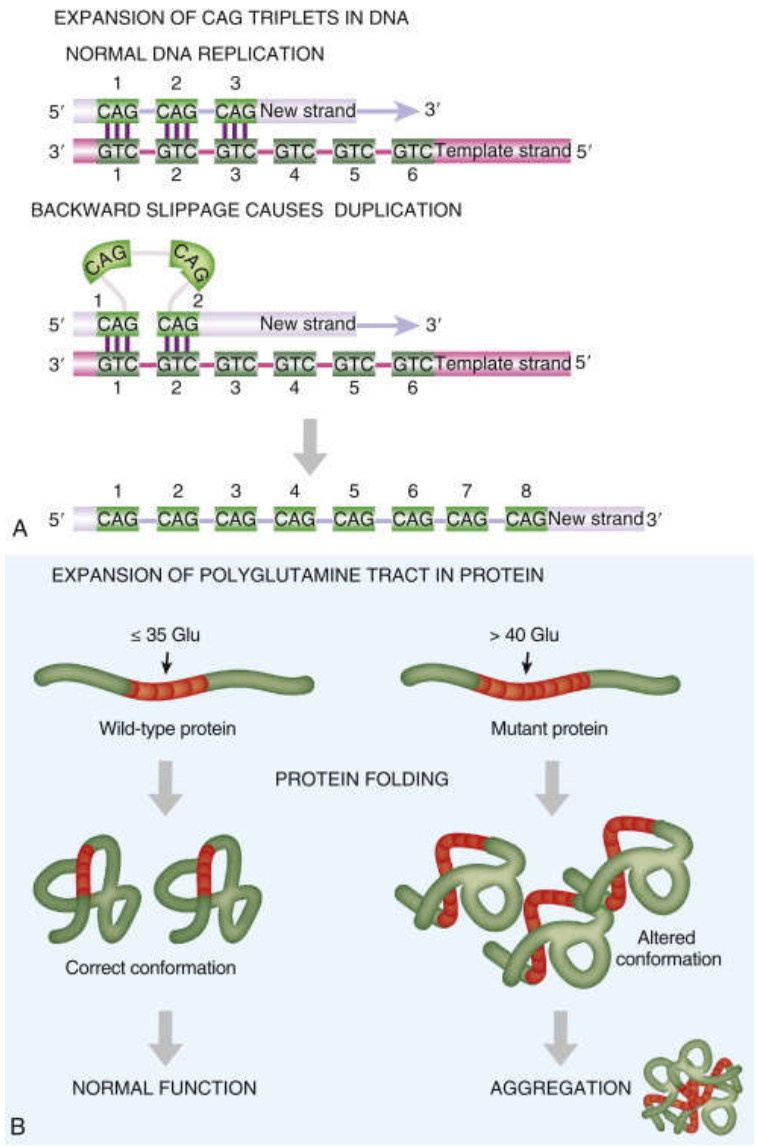



MUTATION
Mutations in coding region
Mutations disrupting RNA stability or RNA splicing
Mutations affecting gene regulation or dosage
Protein abnormal
Protein structure normal
• Hb Hammersmith
(if unstable → decreased amount)
Decreased amount
CAUSE OF DISEASE
• β-Thalassemias
• α-Thalassemias
• Monosomies
• Tumor-suppressor mutations
Increased amount
Loss of protein function (the great majority)
• Hb Kempsey
• Achondroplasia
• Trisomies
• Charcot-Marie-Tooth disease type 1A
Gain of function
• Hb S
• HPFH
• Many oncogenes
Novel property (infrequent)
Inappropriate expression (wrong time, place)
Ectopic or heterochronic expression (uncommon, except in cancer)

Categorias funcionais

- **Perda de função:** um alelo perde sua função normal e o outro é insuficiente para manter a função normal (haploinsuficiência);
- **Ganho de função:** o alelo passa a ser mais ativo e isso é de alguma forma deletério. Por exemplo, ativação exarcebada de alguma via;
- **Dominante negativo:** o alelo com a alteração passa a interferir na função do alelo normal.

Mutações dinâmicas



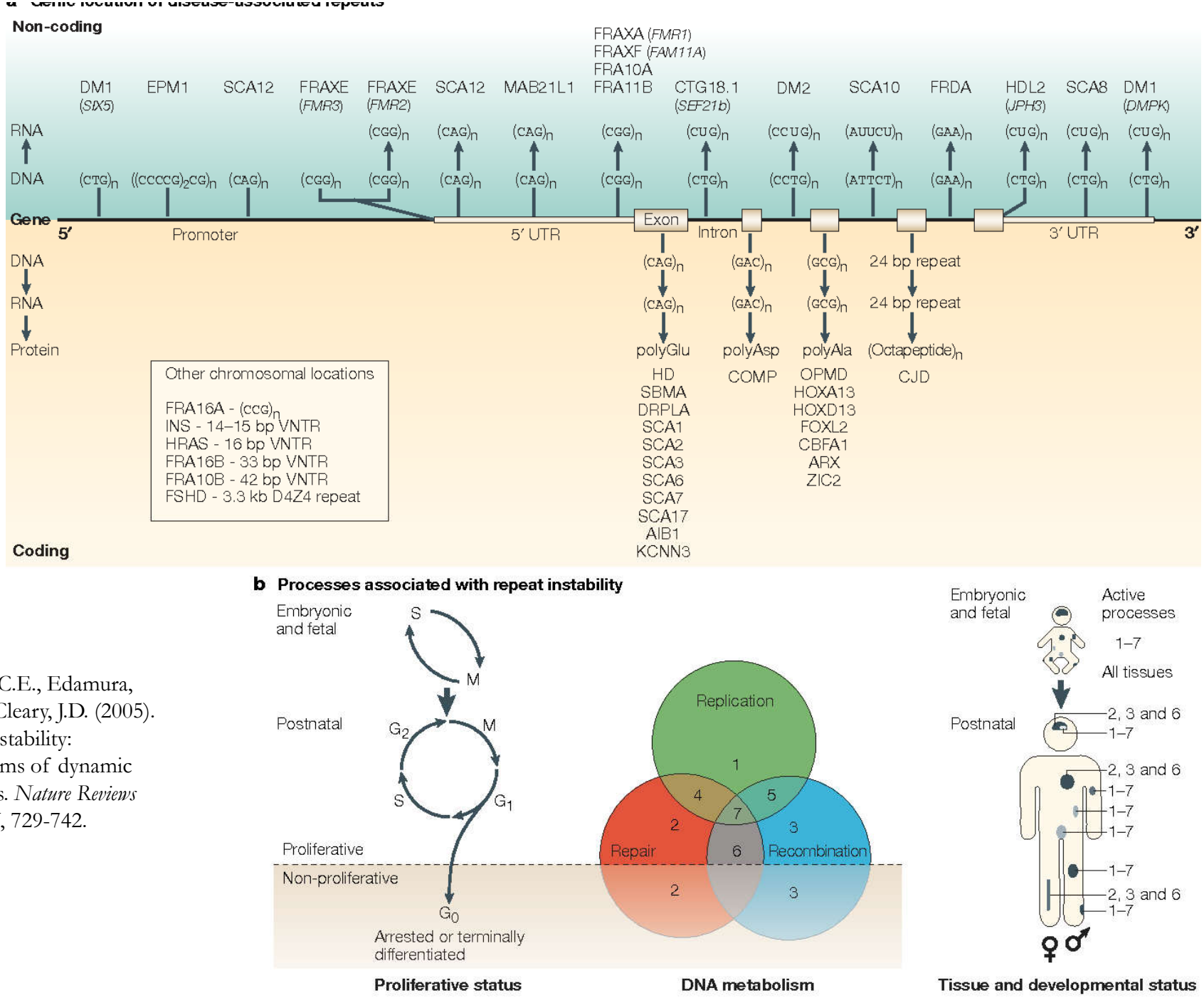


Figure 1 | **Unstable repeat tracts and the processes associated with repeat instability. a** | A schematic representation

Pearson, C.E., Edamura, K.N., & Cleary, J.D. (2005). Repeat instability: mechanisms of dynamic mutations. *Nature Reviews Genetics, 6*, 729-742.

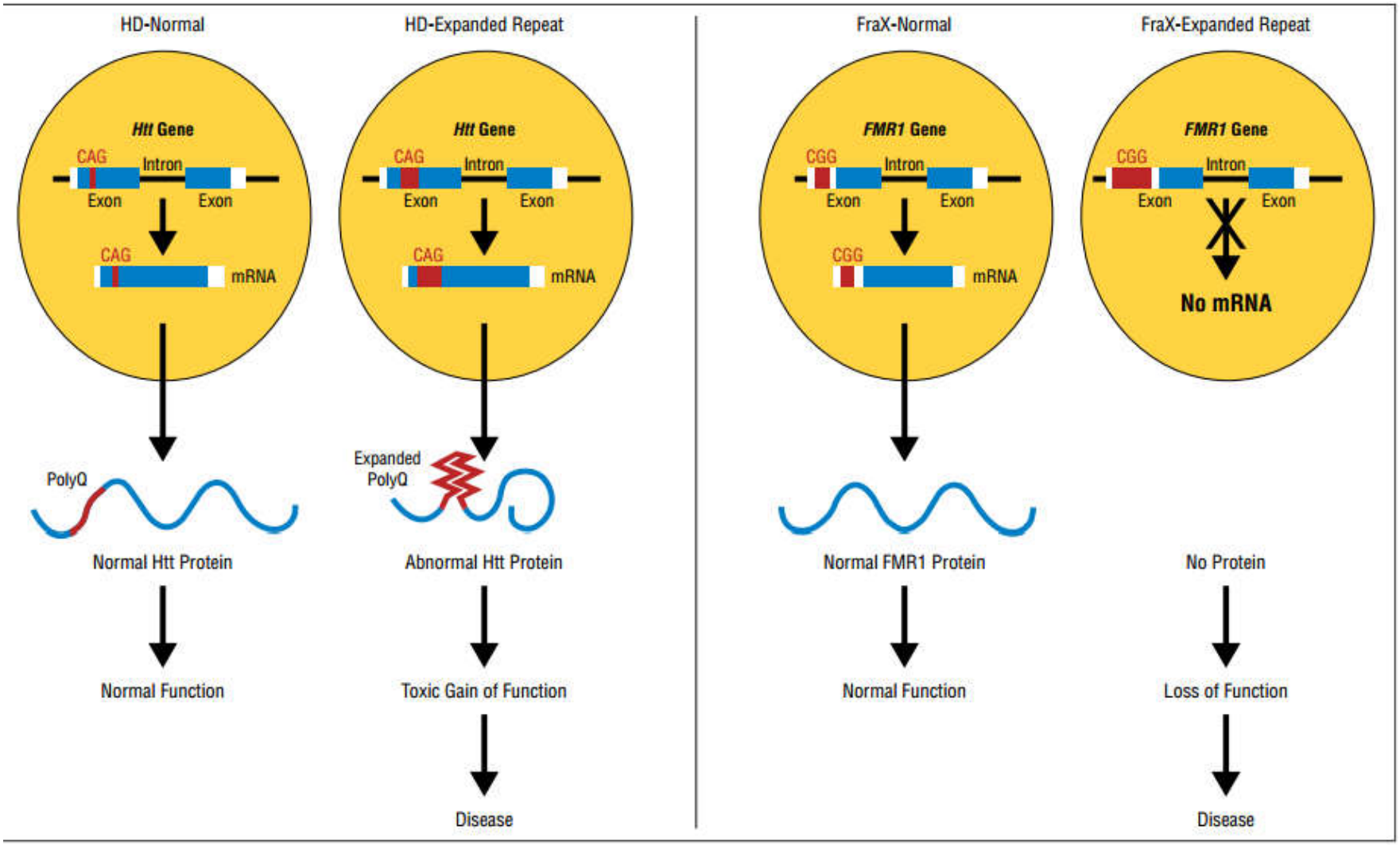
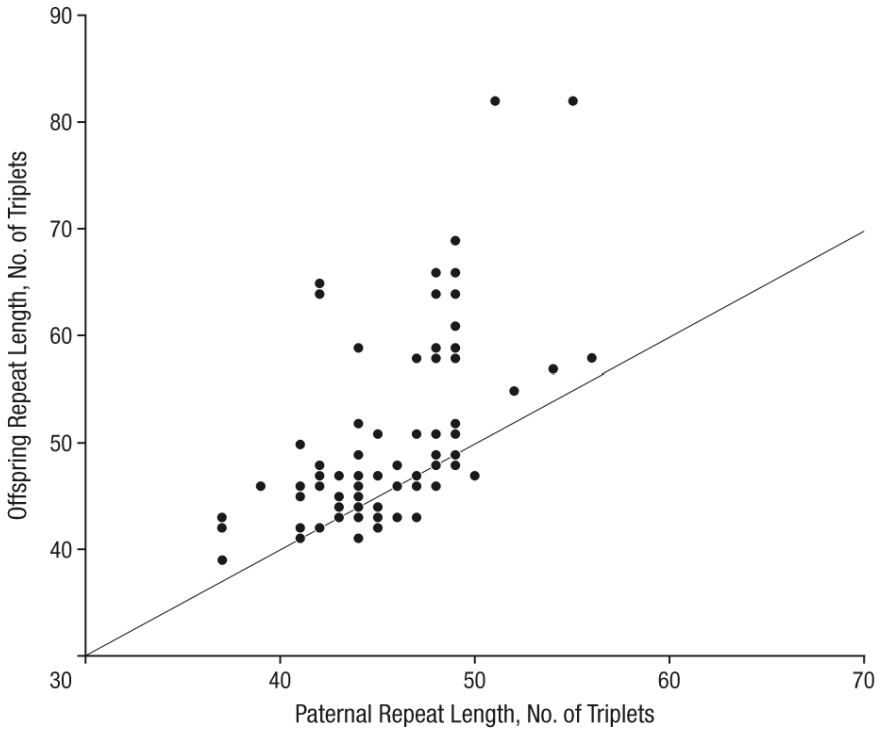
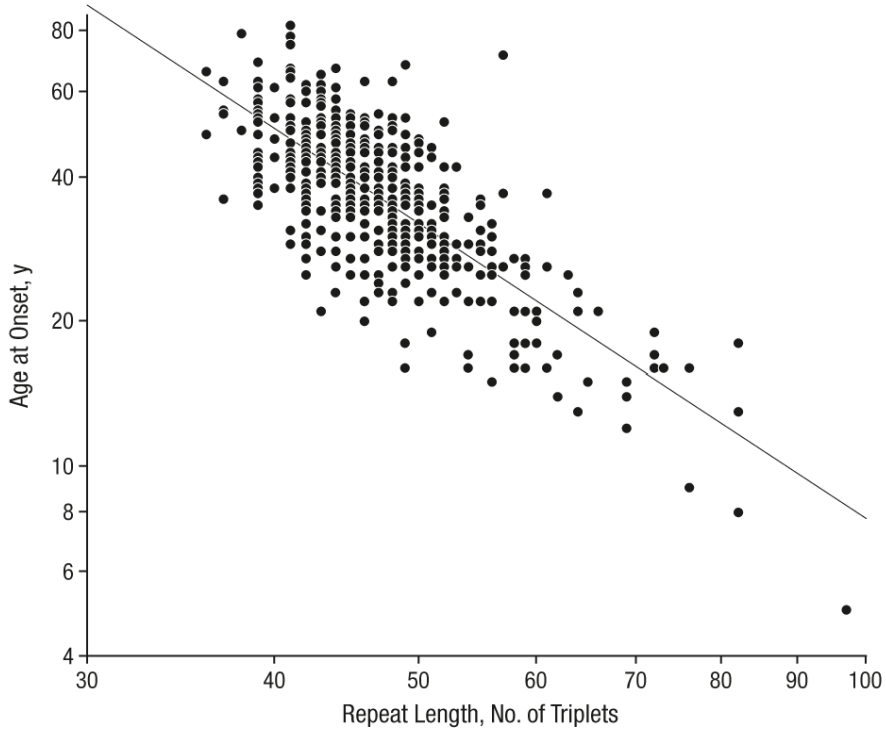


Figure 1. *Molecular pathogenesis of Huntington disease (HD) and the fragile X (FraX) syndrome. Left, The effect of a CAG repeat expansion in the* Htt *gene. Within the nucleus (yellow), genes with either a normal CAG repeat or an expanded CAG repeat are transcribed into messenger RNA (mRNA), with normal excision of introns and splicing together of exons. Outside the nucleus, mRNA with either a normal or a long CAG repeat is translated into protein. The CAG repeat itself, located within a protein coding region (blue), is translated into a stretch of the amino acid glutamine (Q). The mutant protein, containing an excessively long polyglutamine (polyQ) repeat, takes on an abnormal conformation that confers new and toxic properties to the protein. Right, The effect of an expansion of the CGG repeat in the FraX mental retardation type 1 (*FMR1*) gene. In* FMR1 *with a normal-length repeat, the gene is transcribed into mRNA, and the mRNA is translated into protein. The CGG repeat is located outside the protein coding region and, hence, is not translated into an amino acid repeat. In* FMR1 *with an expanded CGG repeat, the expansion prevents gene transcription into mRNA and therefore no protein is synthesized. Disease arises from a lack of the protein.*





Margolis RL, McInnis MG, Rosenblatt A, Ross CA. Trinucleotide Repeat Expansion and Neuropsychiatric Disease. *Arch Gen Psychiatry*. 1999;56(11):1019–1031. doi:10.1001/archpsyc.56.11.1019

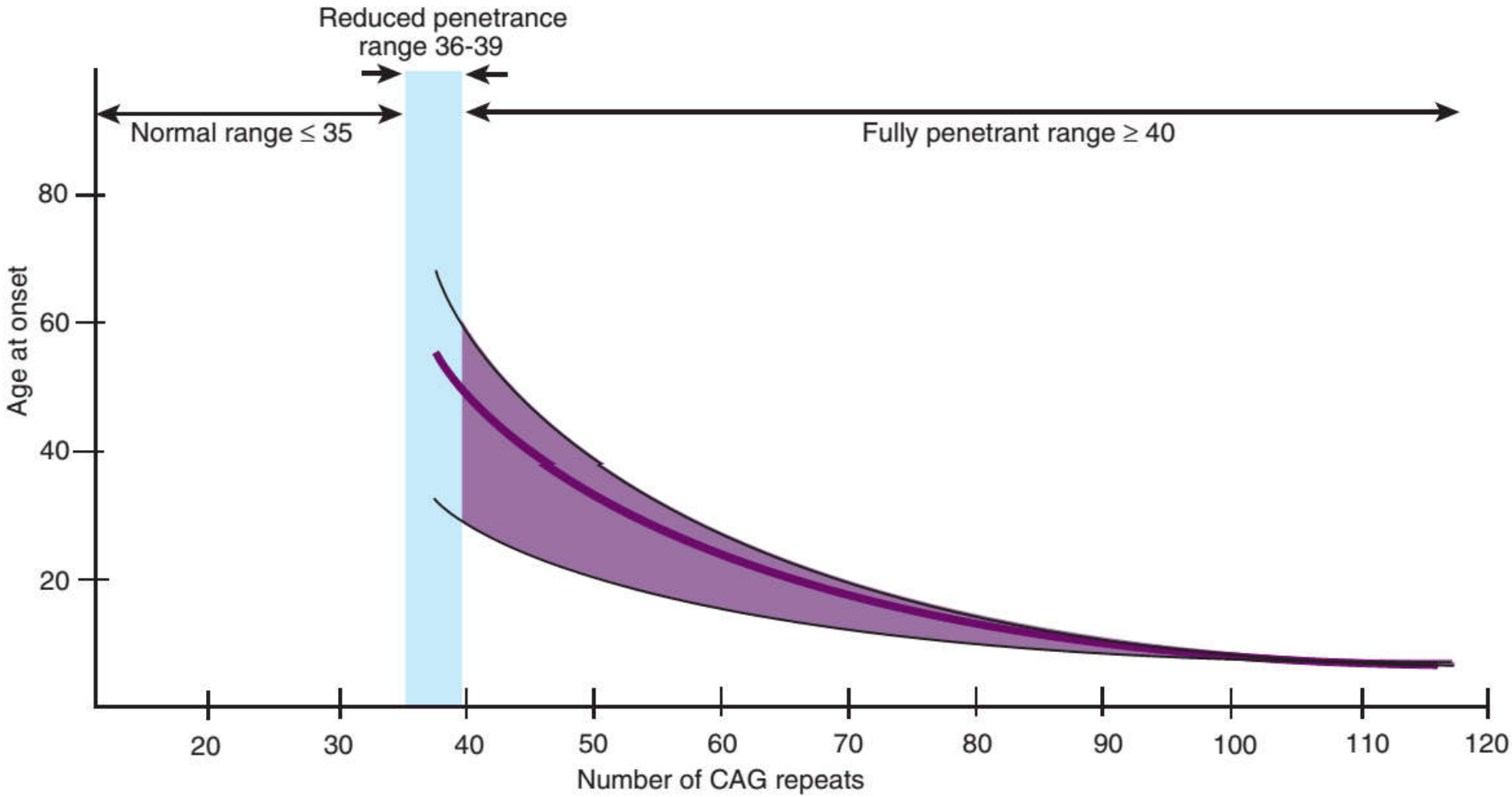
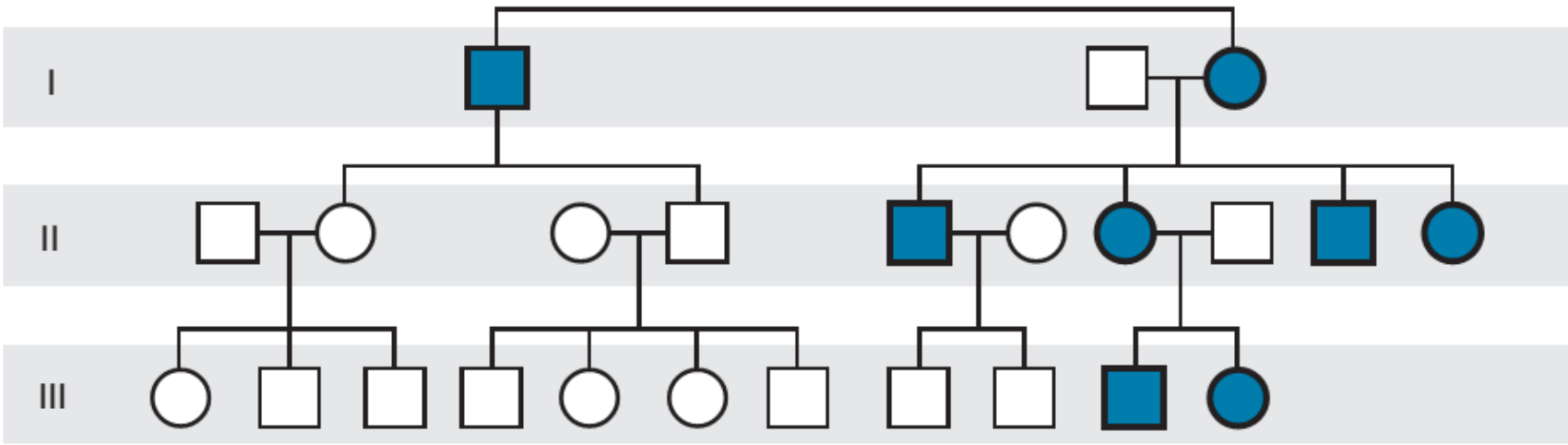


Figure 7-20 **Graph correlating approximate age of onset of Huntington disease with the number of CAG repeats found in the *HD* gene.** The *solid line* is the average age of onset, and the *shaded area* shows the range of age of onset for any given number of repeats. *See Sources & Acknowledgments.*


I
II
III

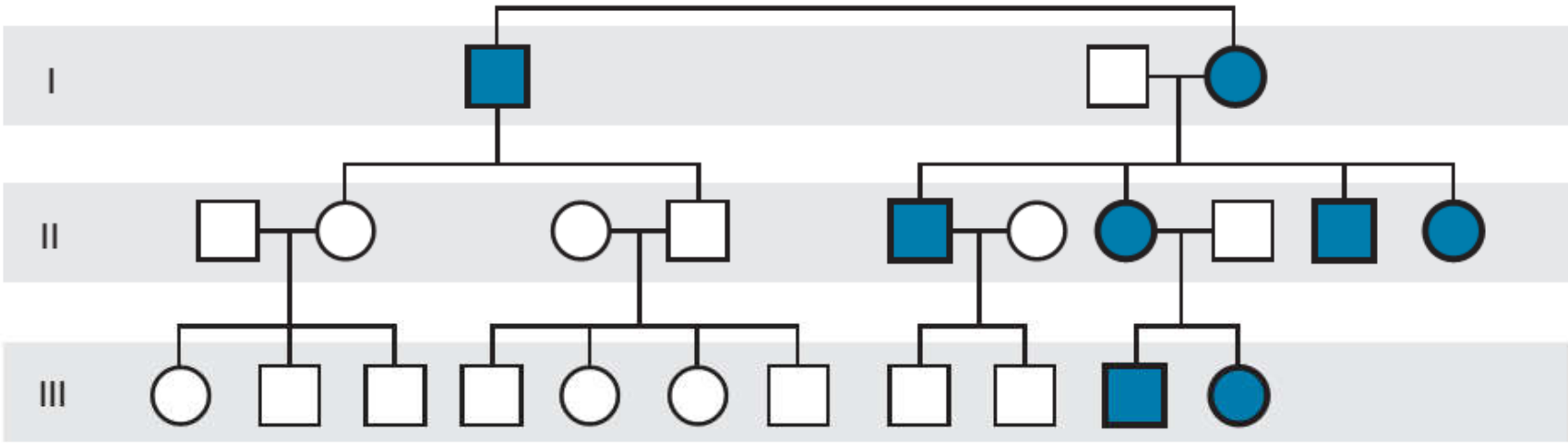


Figure 7-24 Pedigree of Leber hereditary optic neuropathy, a form of adult-onset blindness caused by a defect in mitochondrial DNA. Inheritance is only through the maternal lineage, in agreement with the known maternal inheritance of mitochondrial DNA. Note that no affected male transmits the disease.

Homoplasmia e heteroplasmia

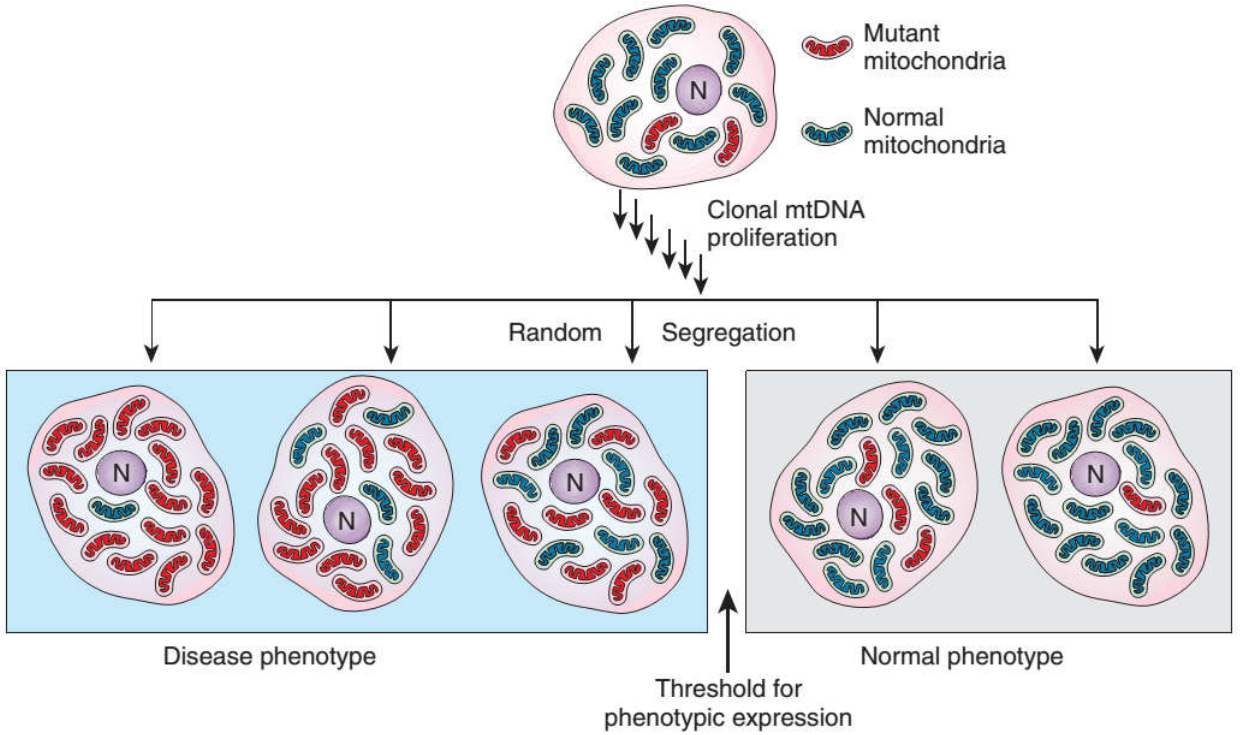


Figure 7-25 **Replicative segregation of a heteroplasmic mitochondrial mutation.** Random partitioning of mutant and wild-type mitochondria through multiple rounds of mitosis produces a collection of daughter cells with wide variation in the proportion of mutant and wild-type mitochondria carried by each cell. Cell and tissue dysfunction results when the fraction of mitochondria that are carrying a mutation exceeds a threshold level. mtDNA, Mitochondrial DNA; N, nucleus.

Phenotypes at Different Levels of Analysis	Normal $Hb\beta^A Hb\beta^A$	Carrier $Hb\beta^A Hb\beta^S$	Diseased $Hb\beta^S Hb\beta^S$	Dominance Relations at Each Level of Analysis
β-globin polypeptide production				$Hb\beta^A$ and $Hb\beta^S$ are codominant
Red blood cell shape at sea level	Normal	Normal	Sickled cells present	$Hb\beta^A$ is dominant $Hb\beta^S$ is recessive
Red blood cell concentration at sea level	Normal	Normal	Lower	
Red blood cell shape at high altitudes	Normal	Sickled cells present	Severe sickling	$Hb\beta^A$ and $Hb\beta^S$ show incomplete dominance
Red blood cell concentration at high altitudes	Normal	Lower	Very low, anemia	
Susceptibility to malaria	Normal susceptibility	Resistant	Resistant	$Hb\beta^S$ is dominant $Hb\beta^A$ is recessive

Discutiremos na próxima aula

- Hipercolesterolemia **familial** vs. **esporádica**;
- Doença de Alzheimer de **início precoce** vs. **tardio**;

Fontes de estudo:
Thompson e Thompson
OMIM
GeneReviews