BIO0119 - Genética e Evolução Humana

Aula 3 – Padrão dominante e padrões não clássicos de herança

Prof. Dr. Michel Naslavsky

Tópicos

- Resolução do exercício de fibrose cística
- Herança autossômica dominante
- Mutações novas: acondroplasia
- Expansões, mutações dinâmicas e antecipação: Doença de Huntington
- Padrões monogênicos não clássicos: Mosaicismo germinativo, somático e herança mitocondrial

Atividade individual para a próxima aula

Revisão de conceitos e aplicação

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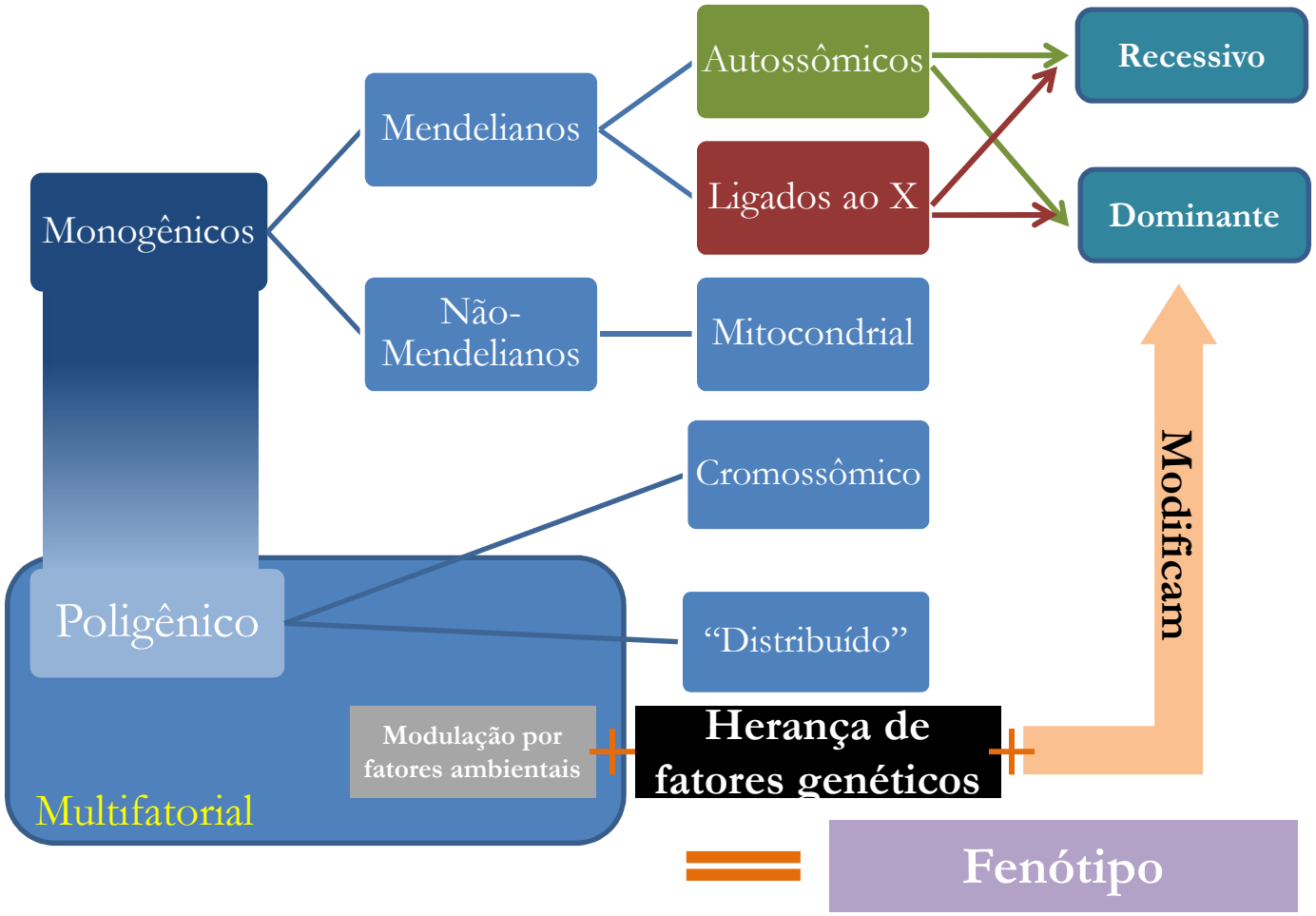
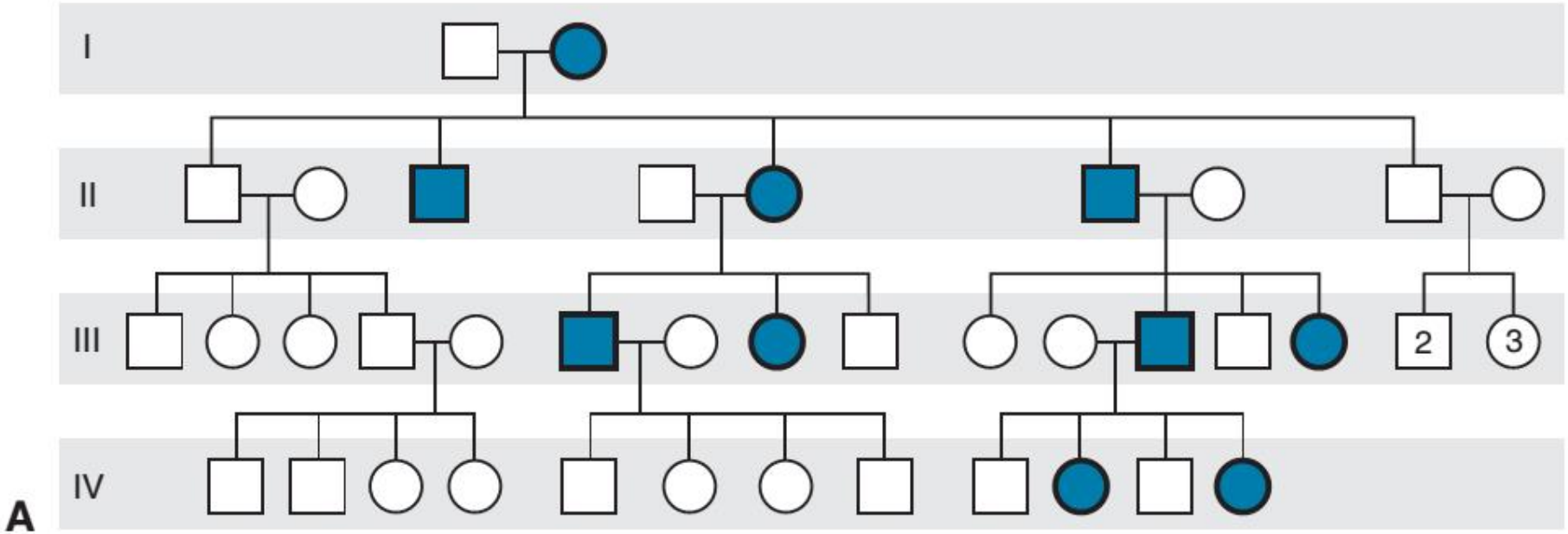

Monogênicos
Mendelianos
Autossômicos
Ligados ao X
Recessivo
Dominante
Não-Mendelianos
Mitocondrial
Cromossômico
Poligênico
"Distribuído"
Modificam
Modulação por fatores ambientais
Herança de fatores genéticos
Multifatorial
Fenótipo

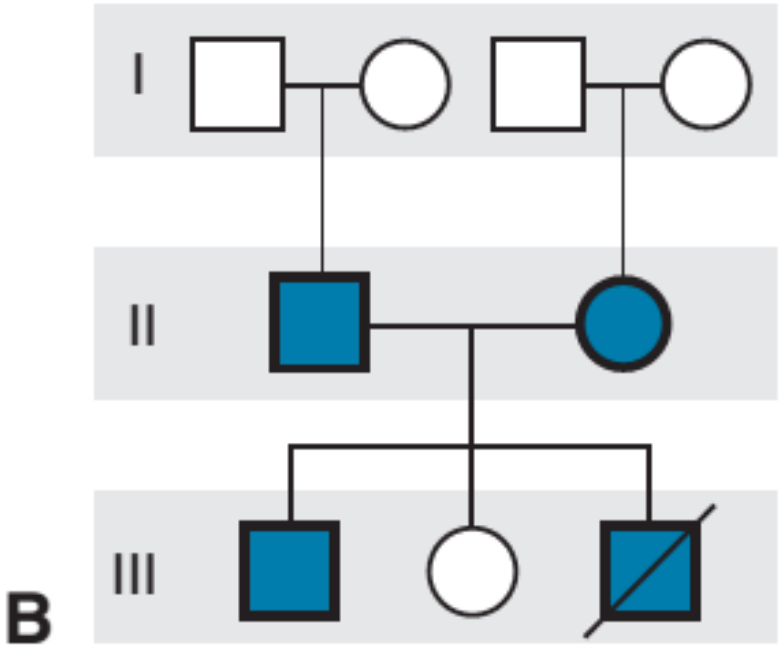
Análise de heredogramas



Análise de heredogramas

Uma hipótese sobre o heredograma: homozigose do alelo patogênico associado à doença de herança dominante.

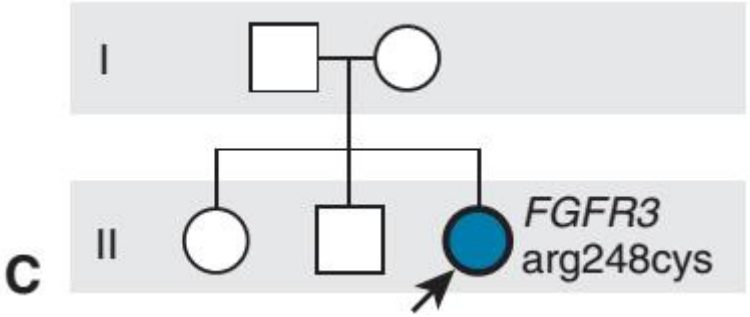
Dominância "incompleta", pois o fenótipo se manifesta mais gravemente no homoziogoto



Análise de heredogramas

Mutação nova (ou *de novo*) não herdada dos pais.

Se a mutação é deletéria e afete o sucesso reprodutivo do portador, a doença é considerada geneticamente letal. Portanto, todos os portadores são decorrência de mutação nova.



Características da herança dominante

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

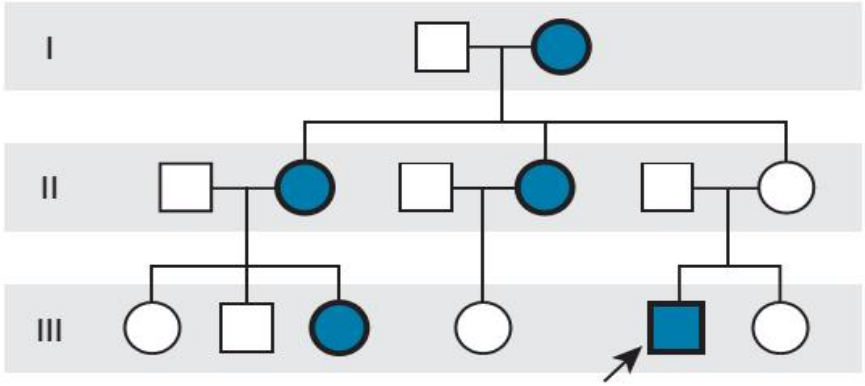
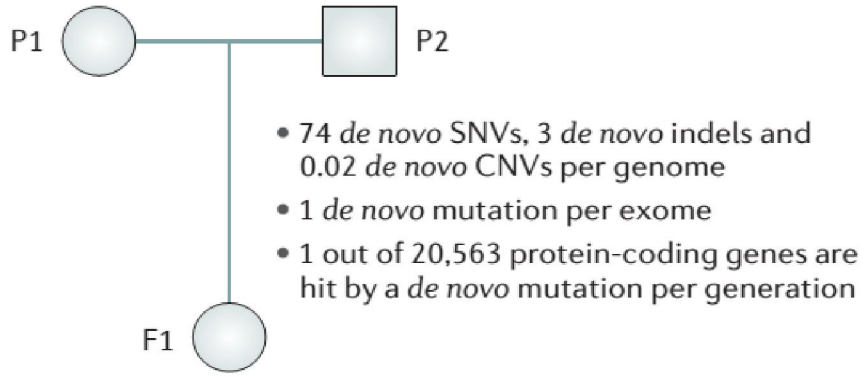


Figure 7-10 Pedigree of split-hand deformity demonstrating failure of penetrance in the mother of the proband *(arrow)* and his sister, the consultand. Reduced penetrance must be taken into account in genetic counseling.

Características da herança dominante

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

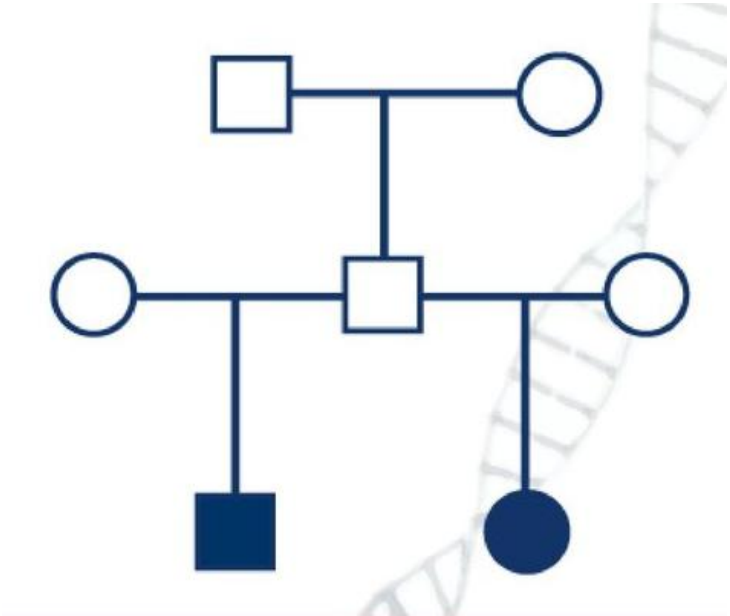


De novo mutations in human genetic disease

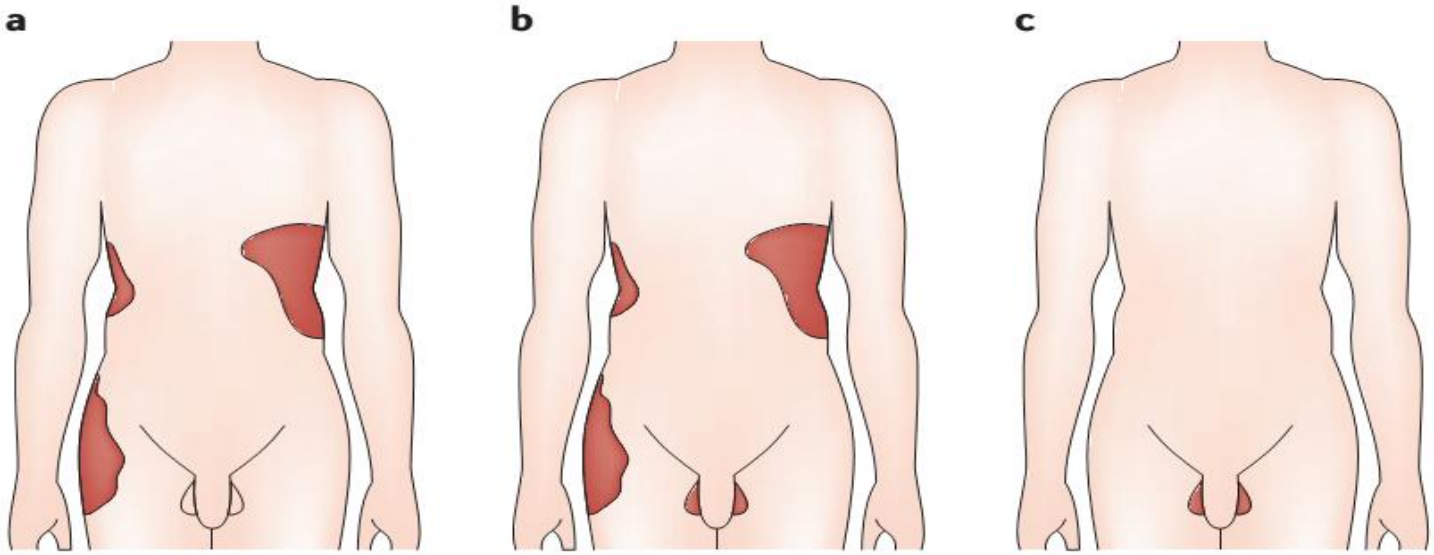
Joris A. Veltman and Han G. Brunner

Características da herança dominante

- Como explicar?

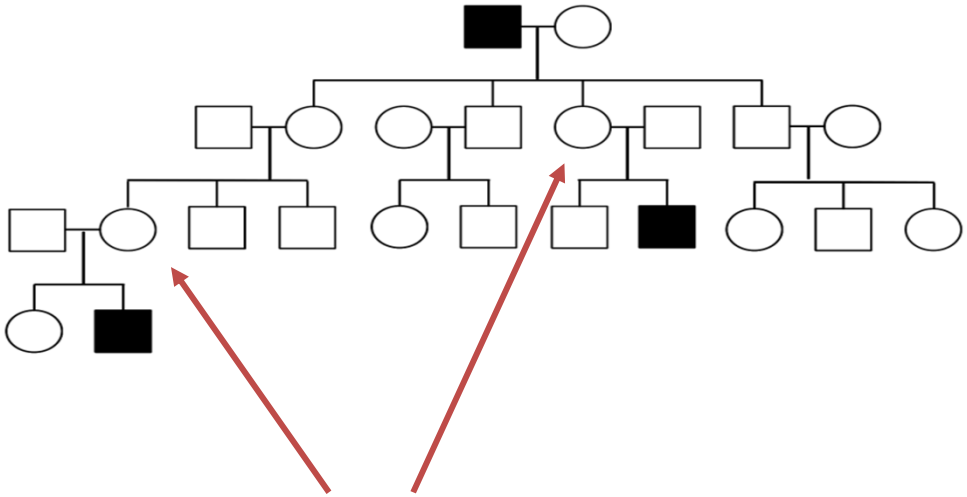


Características da herança dominante



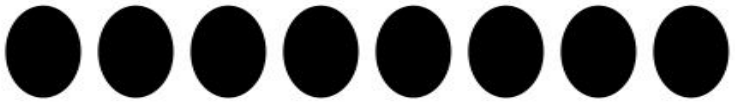
Somático Gonadosomático Gonadal

Penetrância e expressividade

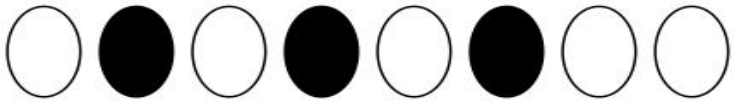


Penetrância incompleta

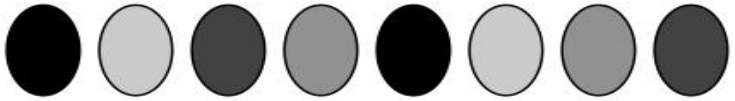
Penetrância e expressividade



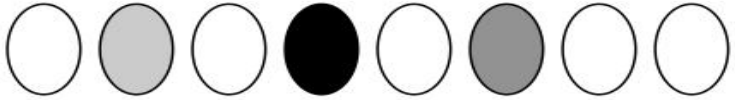
Penetrância completa
Expressividade pouco variável



Penetrância incompleta
Expressividade pouco variável



Penetrância completa
Expressividade variável



Penetrância incompleta
Expressividade variável

Penetrância e padrões de herança

Portanto, os padrões de herança dependem da **interação entre si dos alelos** de um locus sobre a função daquele gene, da interação deles **com outros alelos** e como estas **combinações se manifestam** em fenótipos

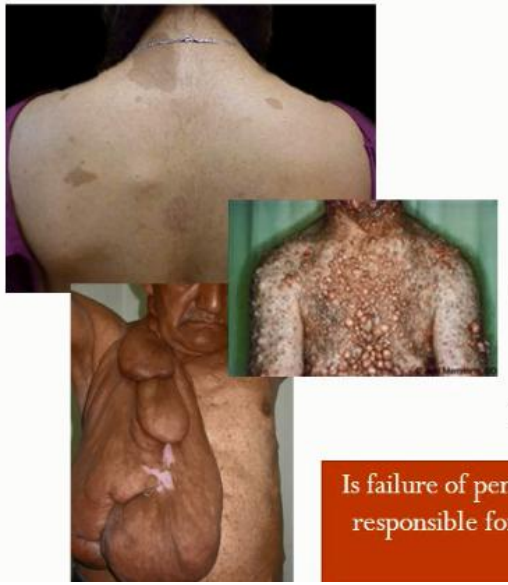
Exercício Heredogramas

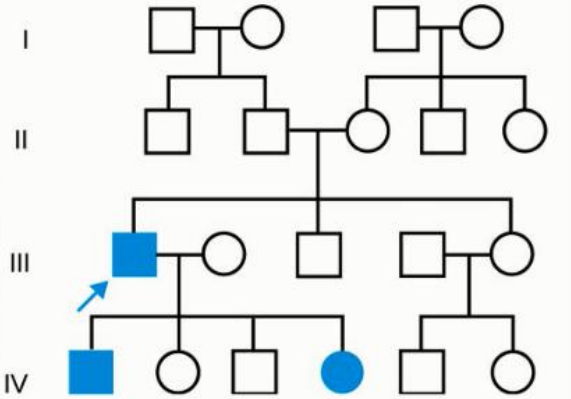
https://forms.gle/bWNsCaZ7tW7cqZ5L9

Neurofibromatose tipo 1

- Expressividade variável intrafamiliar, penetrância idade-dependente

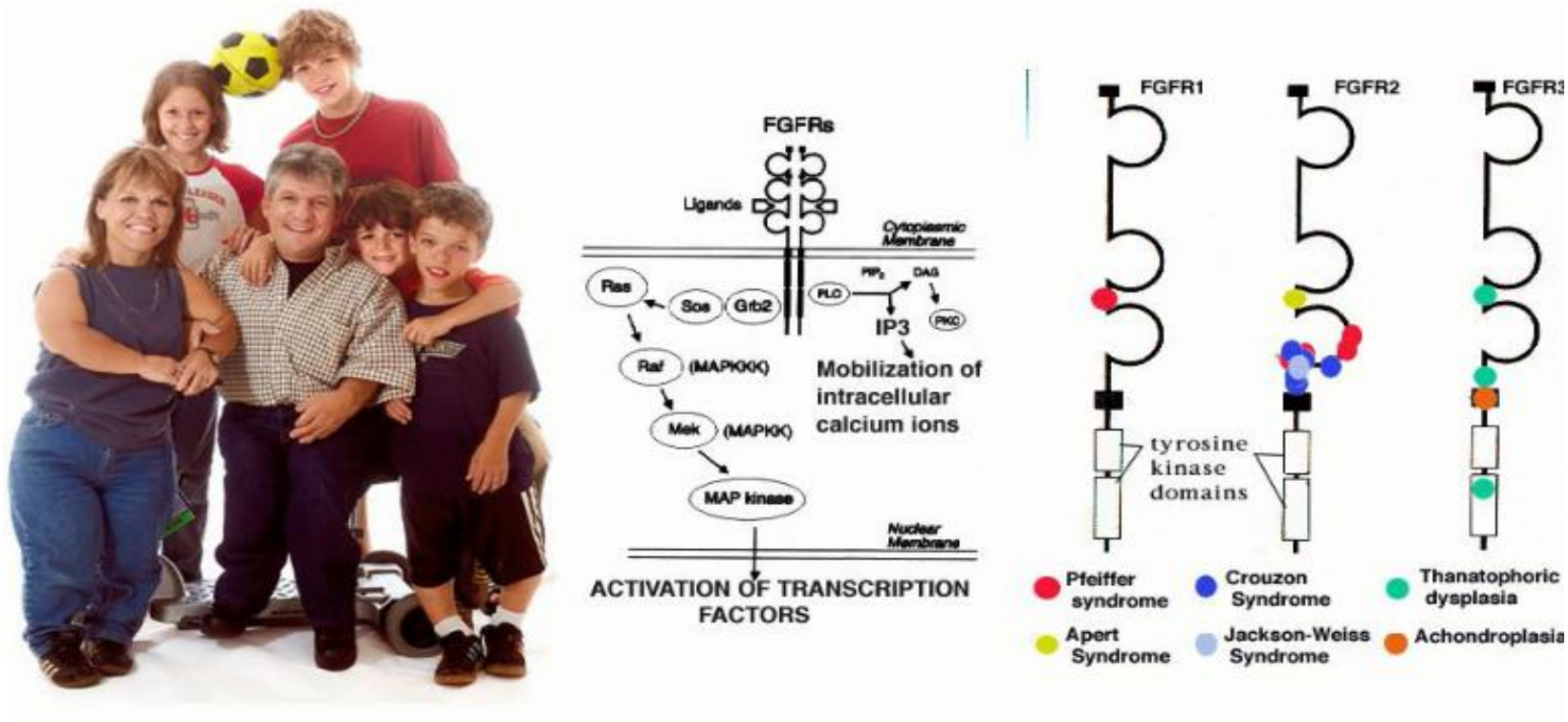
Neurofibromin is a tumor suppressor protein encoded by the *Nf1* gene on human chromosome 17. Neurofibromin helps protect cells against cancer by suppressing Ras, a potent activator of cell growth and proliferation. People with mutations in the Nf1 gene develop neurofibromatosis type I (NF1), a neurological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

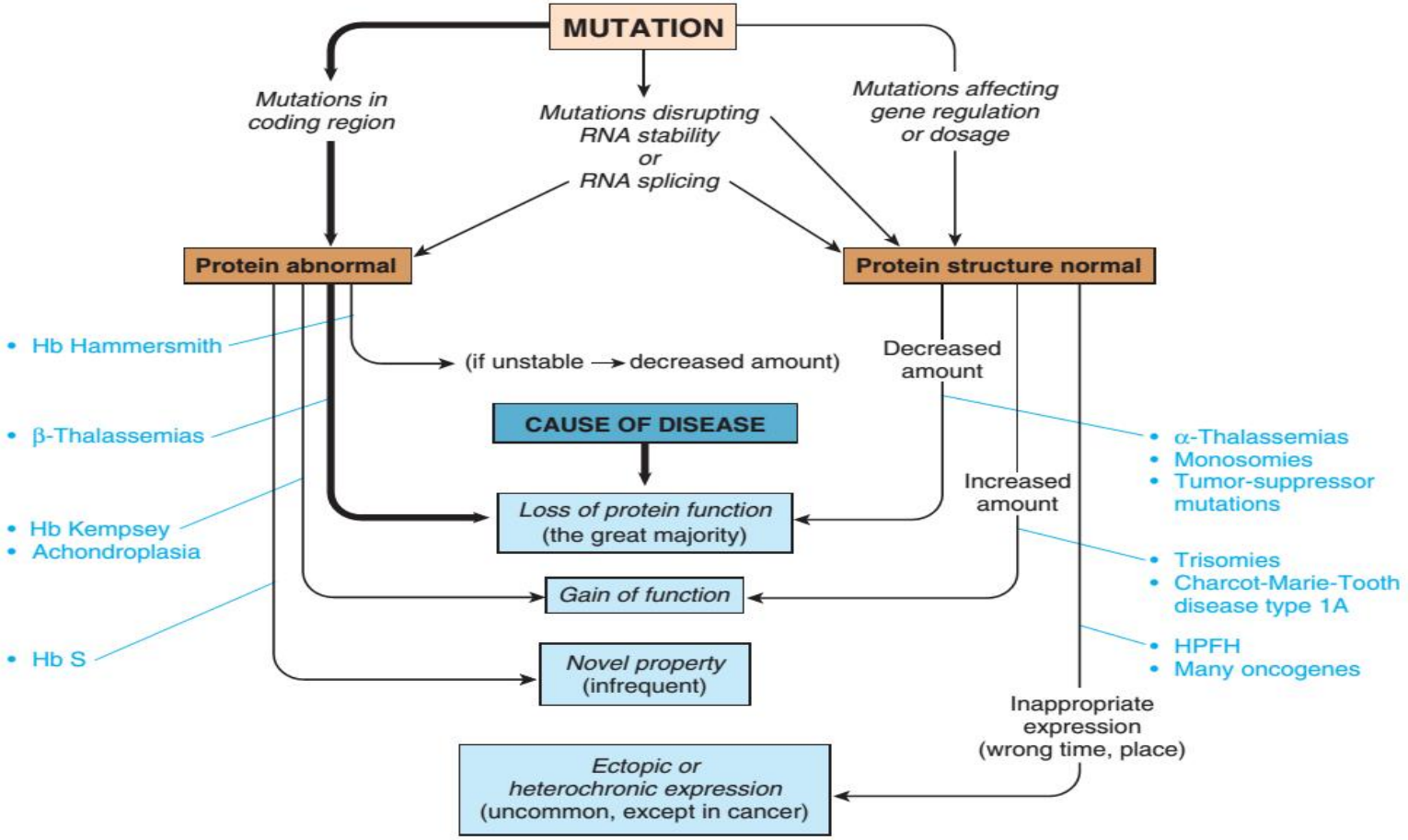




Is failure of penetrance or new mutation or variable expressivity responsible for the proband's phenotype (all susceptible adults display a phenotype)?

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
• α-Thalassemias
• Monosomies
• Tumor-suppressor mutations
• β-Thalassemias
CAUSE OF DISEASE
Increased amount
• Hb Kempsey
• Achondroplasia
Loss of protein function (the great majority)
• Trisomies
• Charcot-Marie-Tooth disease type 1A
Gain of function
• Hb S
Novel property (infrequent)
• HPFH
• Many oncogenes
Inappropriate expression (wrong time, place)
Ectopic or heterochronic expression (uncommon, except in cancer)

Categorias funcionais

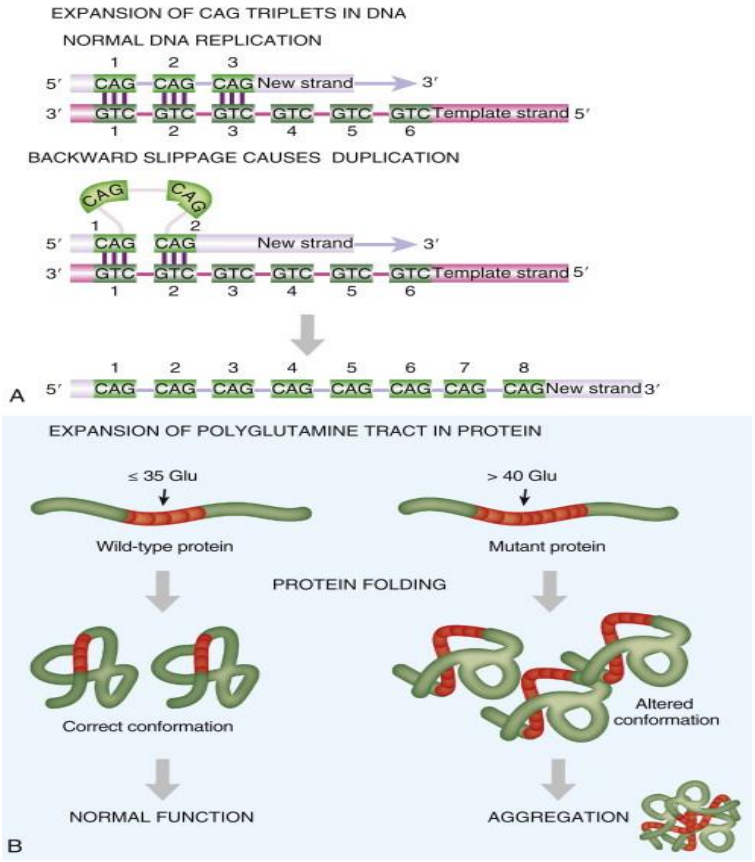
- **Perda de função:** um alelo perde sua função normal e o outro é insuficiente para manter a função normal (haploinsuficiência);
- **Ganho de função:** o alelo passa a ser mais ativo e isso é de alguma forma deletério. Por exemplo, ativação exarcebada de alguma via;
- **Dominante negativo:** o alelo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

Atividade Retinoblastoma

https://goo.gl/qNNQew

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3119181/

Mutações dinâmicas



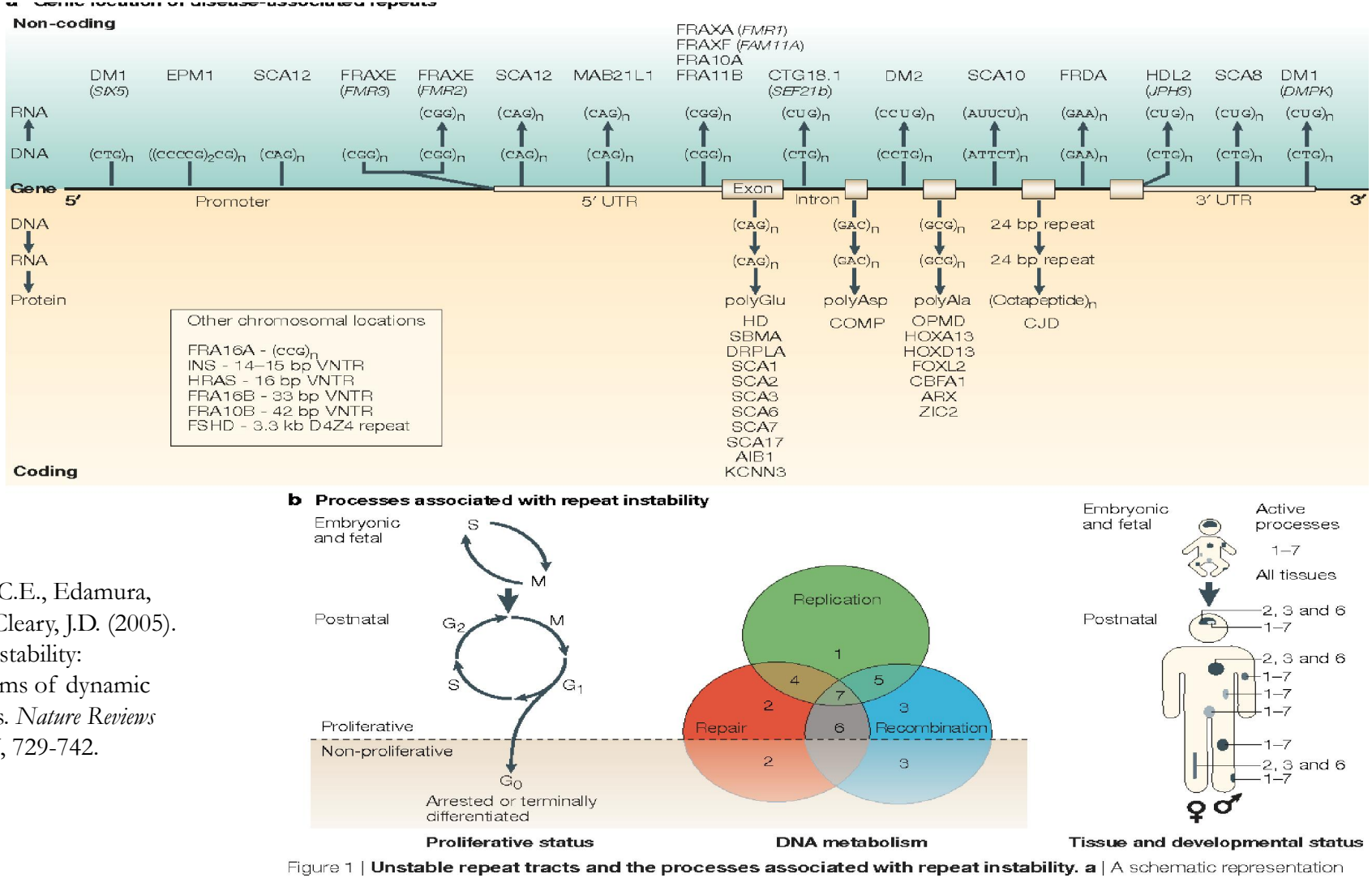


Figure 1 | **Unstable repeat tracts and the processes associated with repeat instability. a** | A schematic representation

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

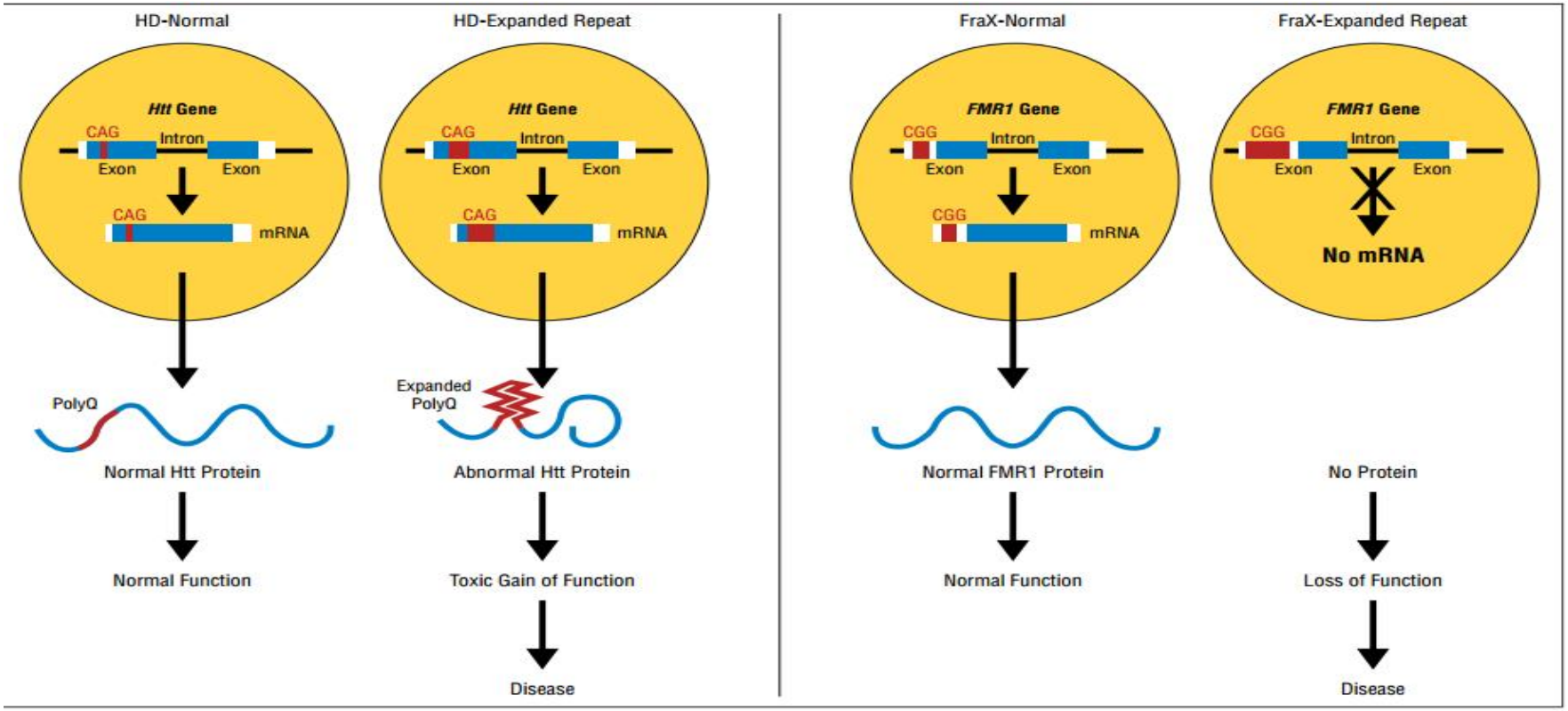
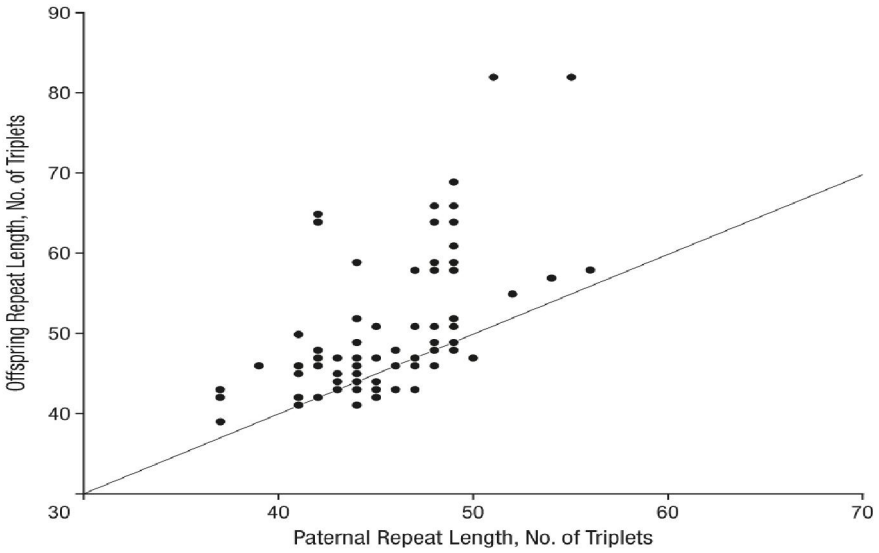
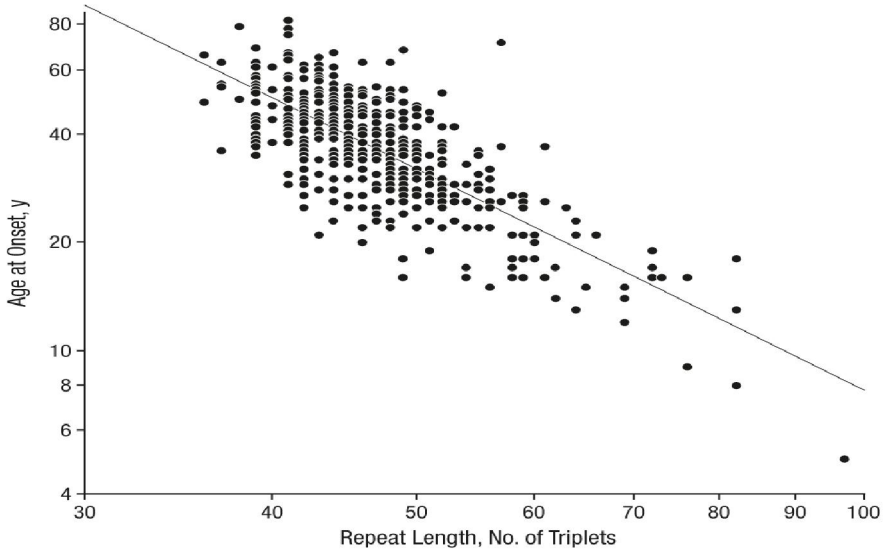


Figure 1. *Molecular pathogenesis of Huntington disease (HD) and the fragile X (FraX) syndrome. Left, The effect of a CAG repeat expansion in the* Htt *gene. Within the nucleus (yellow), genes with either a normal CAG repeat or an expanded CAG repeat are transcribed into messenger RNA (mRNA), with normal 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

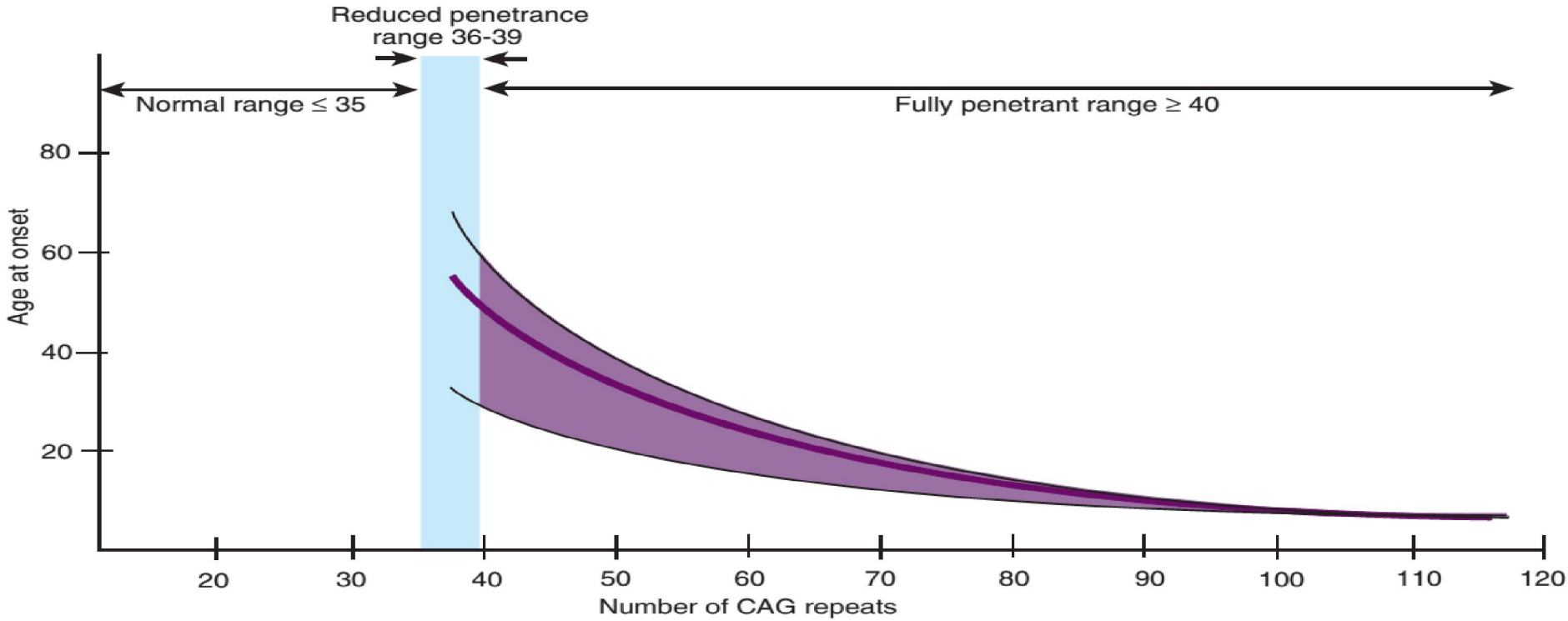
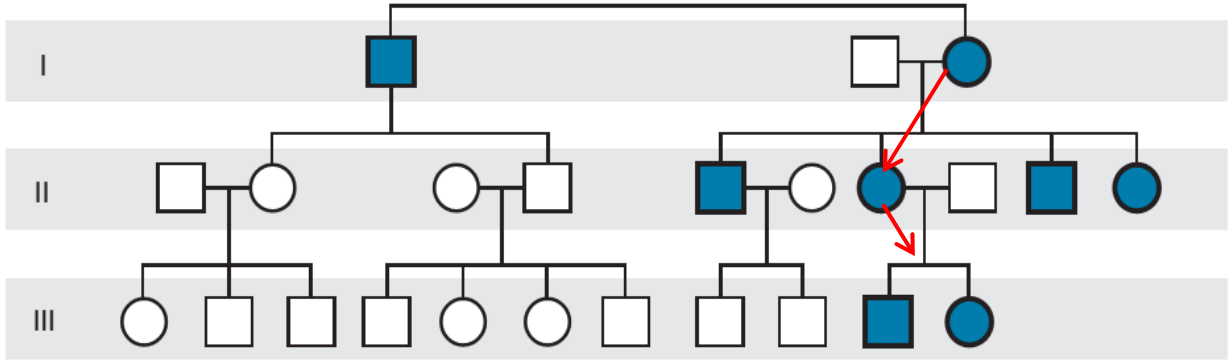


Figure 7-20 **Graph correlating approximate age of onset of Huntington disease with the number of CAG repeats found in the *HD* gene.** The *solid line* is the average age of onset, and the *shaded area* shows the range of age of onset for any given number of repeats. *See Sources & Acknowledgments.*

Neuropatia ótica hereditária de Leber



Homoplasmia e heteroplasmia

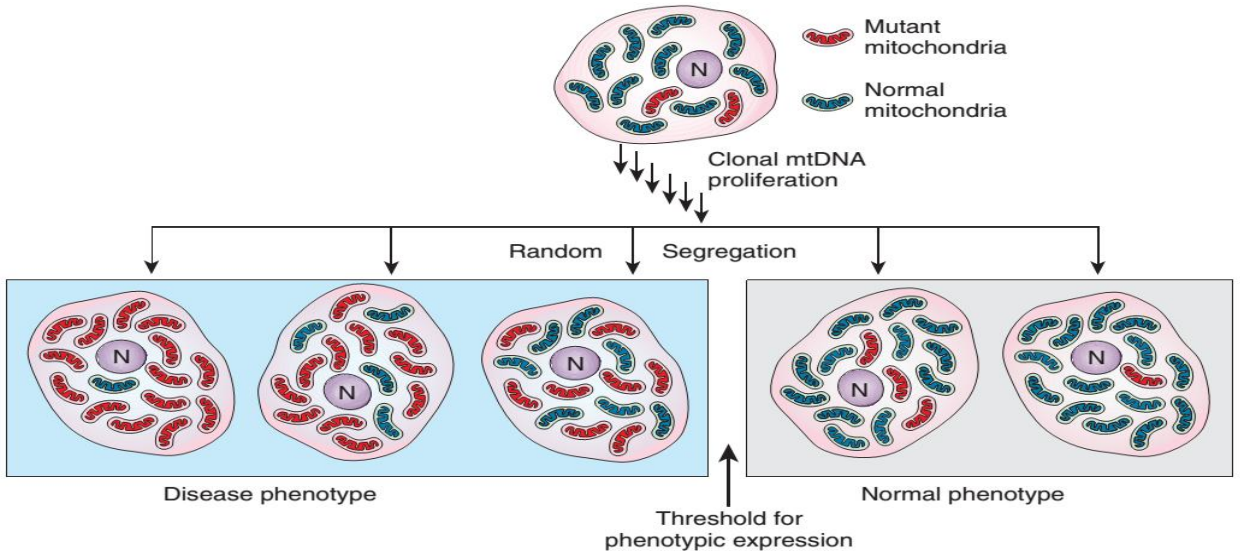


Figure 7-25 **Replicative segregation of a heteroplasmic mitochondrial mutation.** Random partitioning of mutant and wild-type mitochondria through multiple rounds of mitosis produces a collection of daughter cells with wide variation in the proportion of mutant and wild-type mitochondria carried by 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.