

ORGANIZAÇÃO DO GENOMA HUMANO



Departamento de Genética

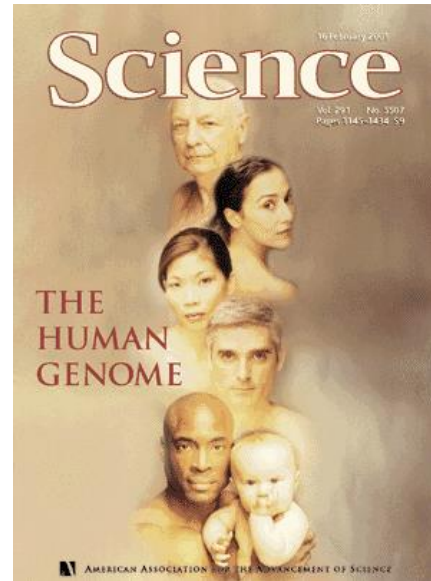
Nilce M. Martinez Rossi

Fenótipo = GENÓTIPO
+
AMBIENTE



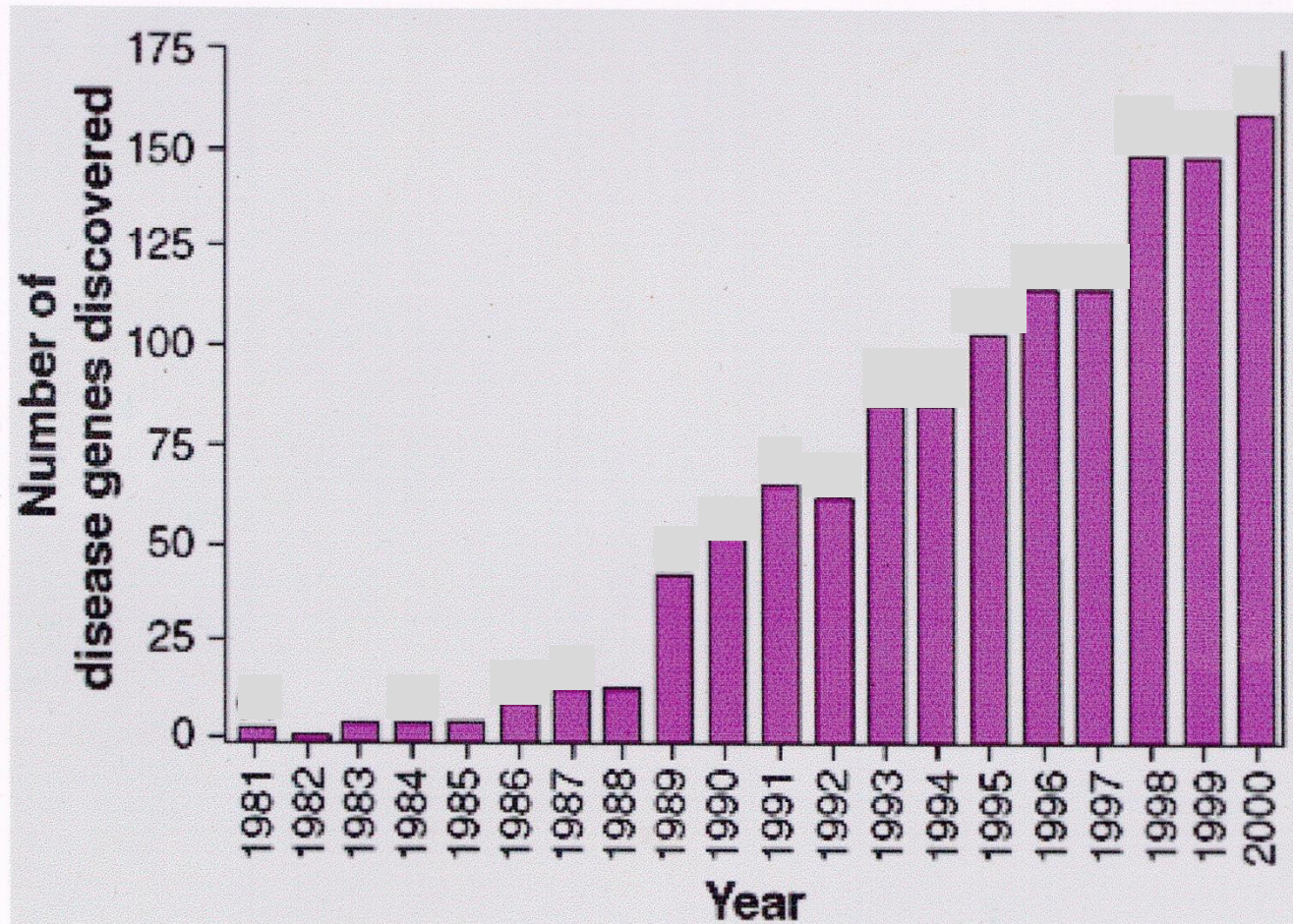
O que é o genoma?

Projetos Genoma



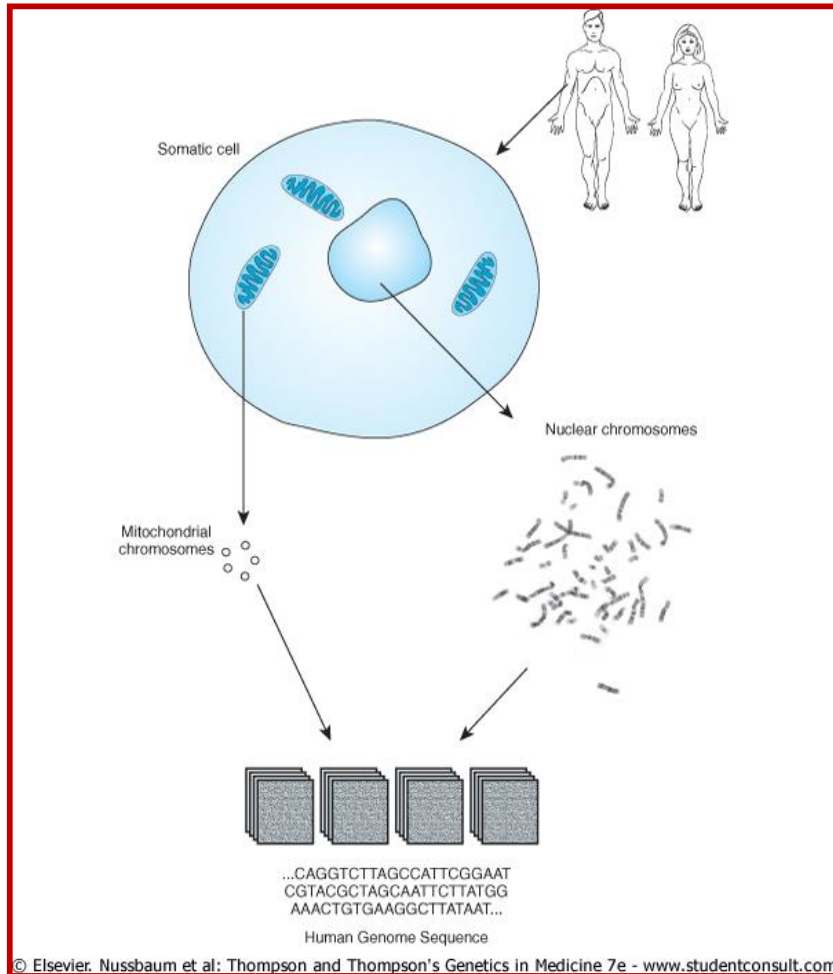
**Genoma: sequencia de DNA
de todos os cromossomos
nuclear e da mitocôndria de
um organismo**

Evolução da descoberta da origem genética de doenças humanas (1982-2000)



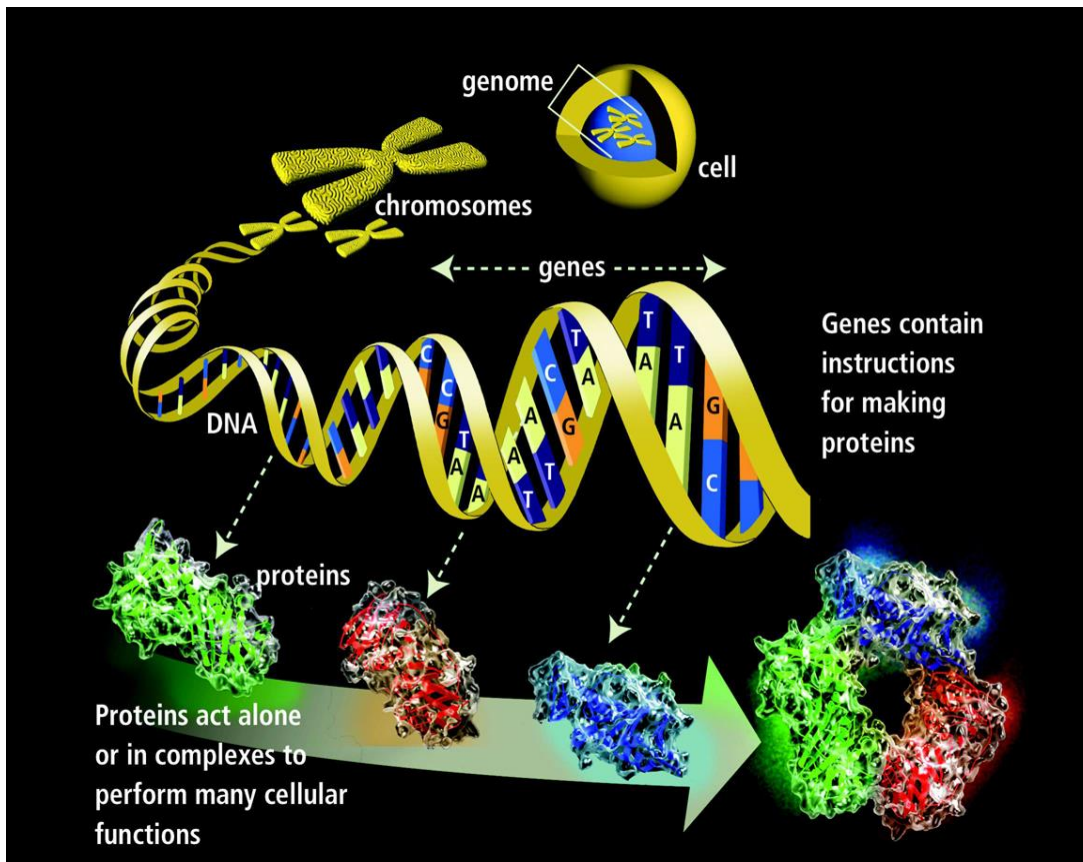
Onde estão os genes?

**Em todas as células
de nosso corpo e de
todos os seres vivos**



**Cromossomos nucleares e
mitocondriais**

DNA a molécula da vida



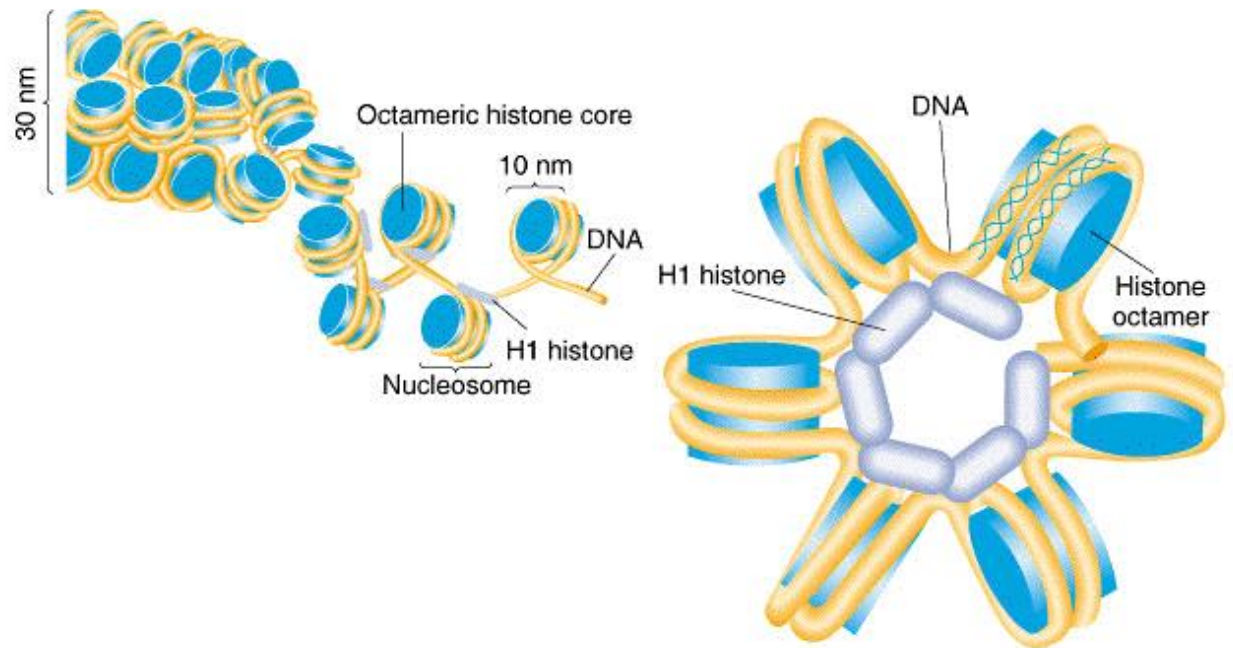
Cada célula humana tem:

46 cromossomos

2 metros de DNA

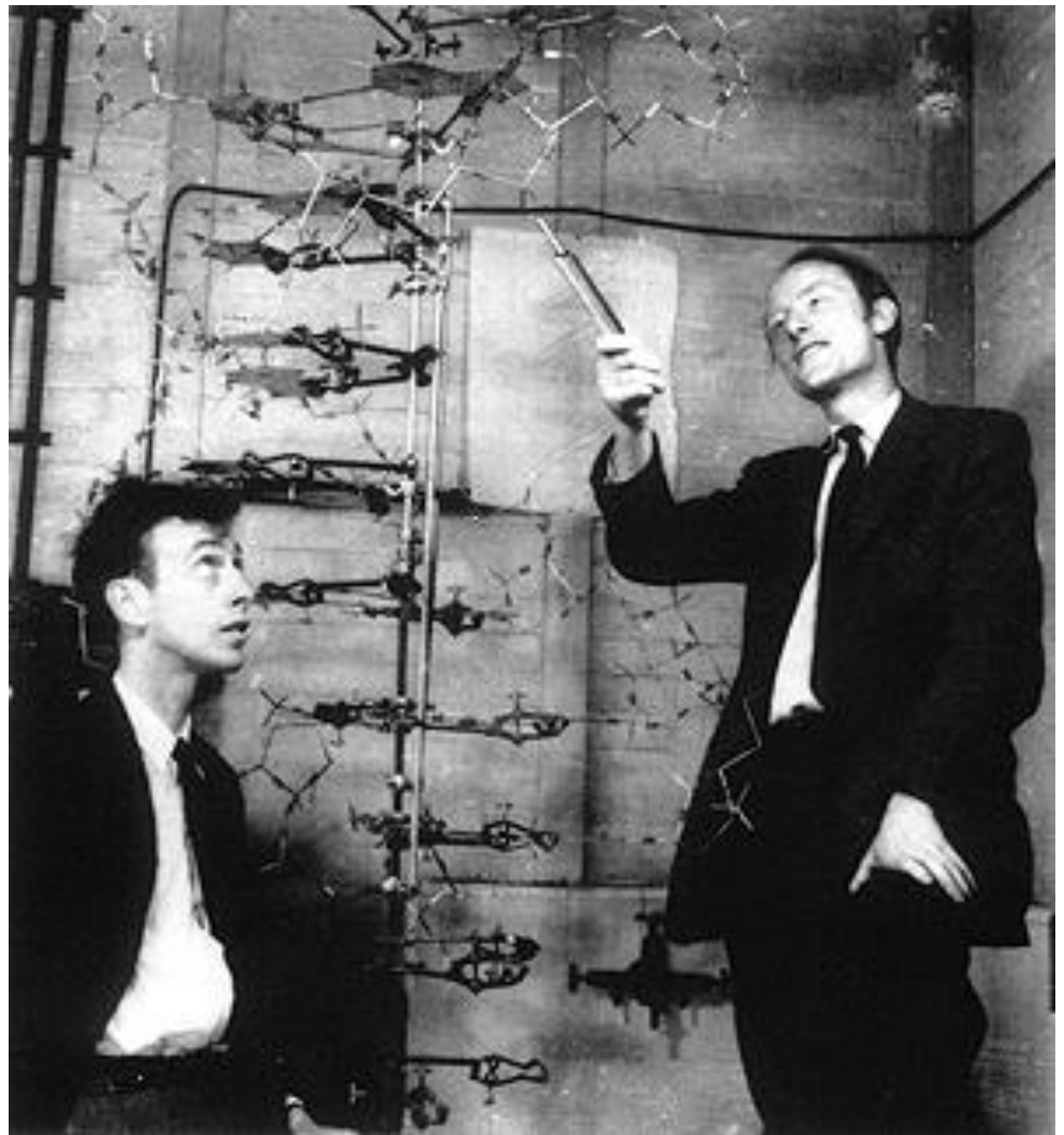
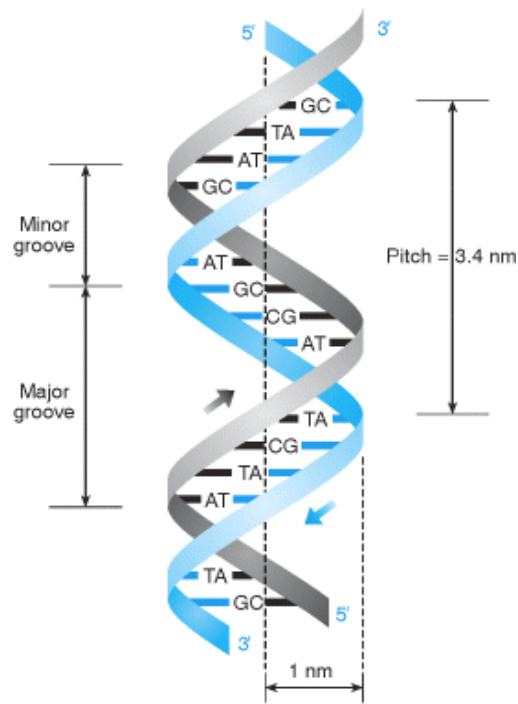
3 bilhões de subunidades de DNA (bases A, C, T, G)

~ 25.000 genes que codificam para RNA e proteínas responsáveis pelas funções biológicas



Modelo da dupla hélice do DNA

Watson e Crick 1953



equipment, and to Dr. G. E. R. Deacon and the captain and officers of R.R.S. *Discovery II* for their part in making the observations.

¹ Young, F. B., Gerrard, H., and Jevons, W., *Phil. Mag.*, **40**, 149 (1920).

² Longuet-Higgins, M. S., *Mon. Not. Roy. Astro. Soc., Geophys. Supp.*, **5**, 285 (1949).

³ Von Arx, W. S., *Woods Hole Papers in Phys. Oceanog. Meteor.*, **11** (3) (1950).

⁴ Ekman, V. W., *Arkiv. Mat. Astron. Fysik. (Stockholm)*, **2** (11) (1905).

MOLECULAR STRUCTURE OF NUCLEIC ACIDS

A Structure for Deoxyribose Nucleic Acid

WE wish to suggest a structure for the salt of deoxyribose nucleic acid (D.N.A.). This structure has novel features which are of considerable biological interest.

A structure for nucleic acid has already been proposed by Pauling and Corey¹. They kindly made their manuscript available to us in advance of publication.

is a residue on each chain even. We have assumed an adjacent residues in the same structure repeats after 10 residues, after 34 Å. The distance from the fibre axis is 10 Å. At the outside, cations have easy access.

The structure is an open one and is rather high. At lower water content we expect the bases to tilt so as to become more compact.

The novel feature of the structure is in which the two chains are held together by purine and pyrimidine bases. The bases are perpendicular to the fibre axis and are together in pairs, a single base on each chain, hydrogen-bonded to a single base on the other chain, so that the two lie side by side in the z-co-ordinates. One of the pairs is a purine for the other a pyrimidine for which two hydrogen bonds are made as compared with one for purine position 1 to pyrimidine position 6.

If it is assumed that the structure is the most stable one, the



This figure is purely diagrammatic. The two ribbons symbolize the two phosphate-sugar chains, and the horizontal rods the pairs of bases holding the chains together. The vertical line marks the fibre axis.

April 25, 1953: James Watson e Francis Crick publicaram o clássico paper que descreve pela primeira vez a estrutura de dupla hélice do DNA. Eles notaram que a estrutura sugeria o mecanismo de replicação do material genético.

Premio Nobel em Fisiologia e Medicina em 1962



Francis Harry
Compton Crick



James Dewey
Watson

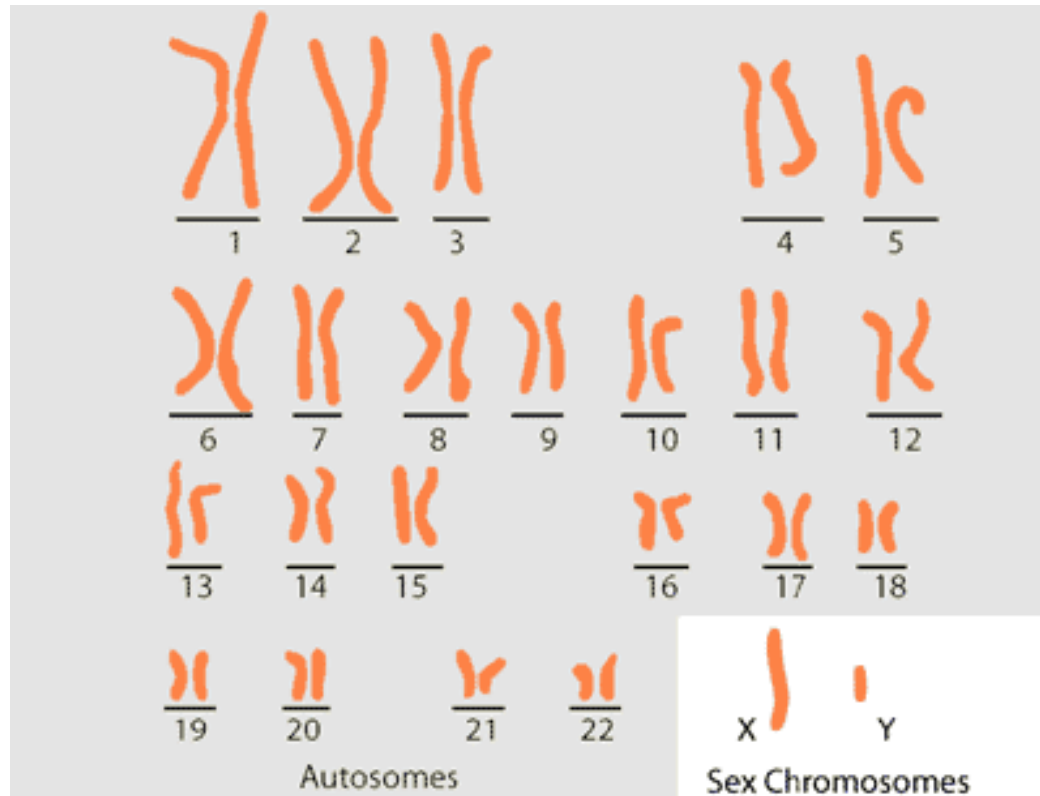


Maurice Hugh
Frederick Wilkins

The Nobel Prize in Physiology or Medicine 1962 was awarded jointly to Francis Harry Compton Crick, James Dewey Watson and Maurice Hugh Frederick Wilkins *"for their discoveries concerning the molecular structure of nucleic acids and its significance for information transfer in living material".*

Cromossomos Humanos

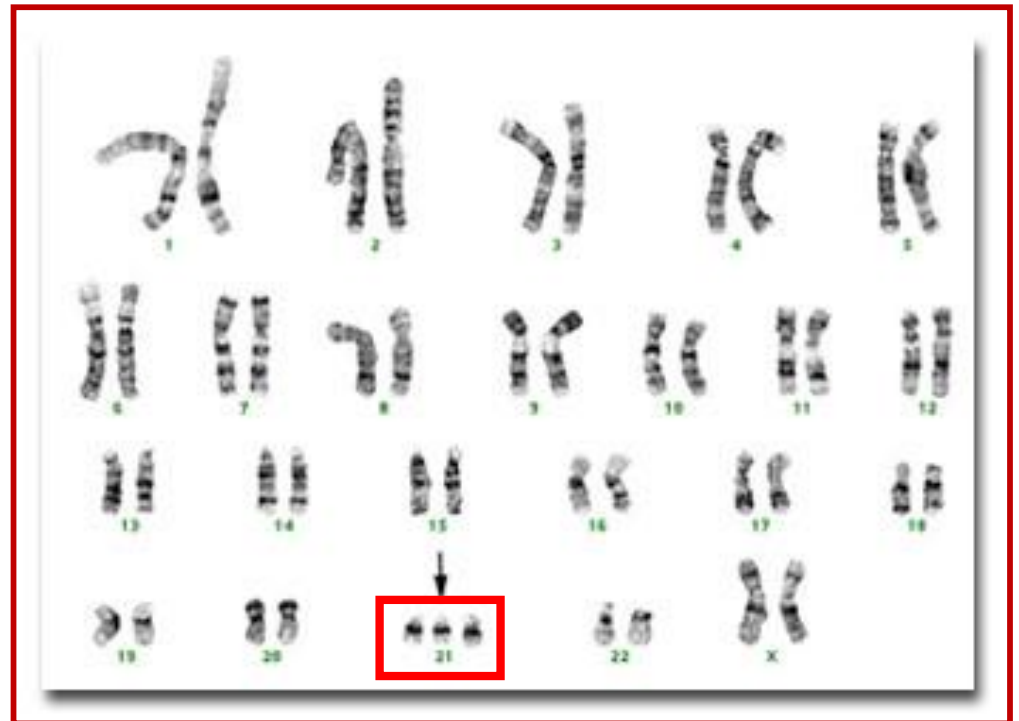
Cariótipo Humano



The Human Genome

The Human Genome is the total of the genetic information that is held in each human cell. It is usually made up of 46 chromosomes: 22 pairs of autosomes and 1 pair of sex chromosomes, which are usually X and X for females and X and Y for males.

Exemplo de transtorno cromossômico



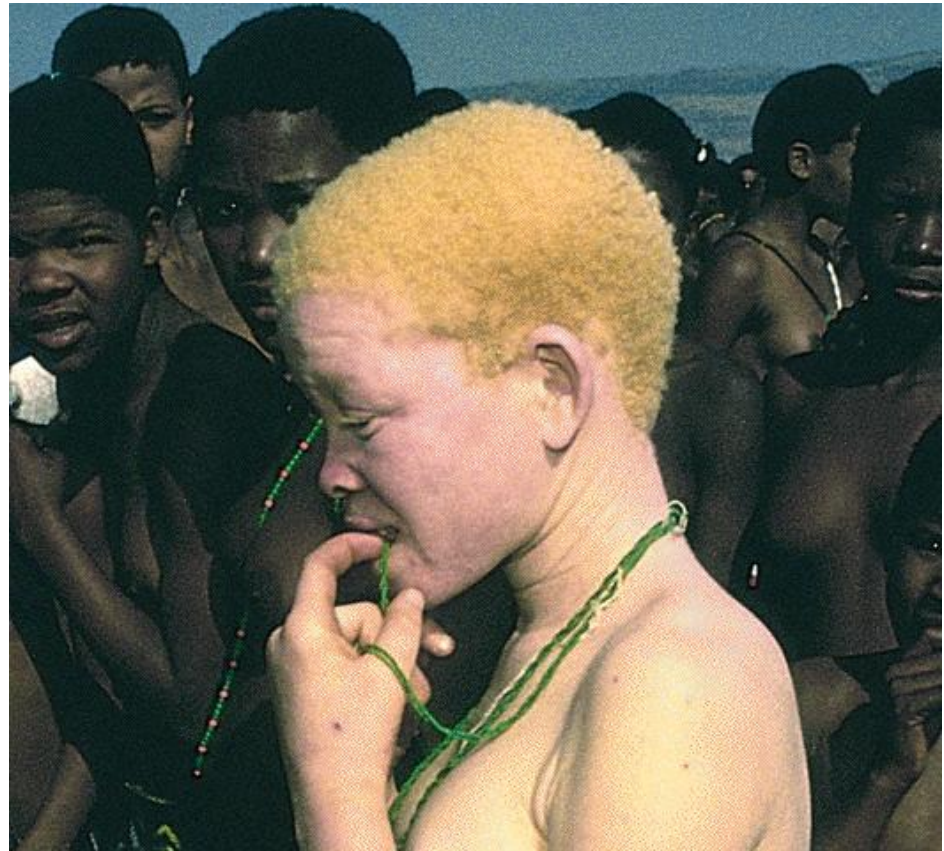
Síndrome de Down

Exemplos de doenças monogênicas



Acondroplasia: substituição de uma glicina por arginina no domínio transmembranar do receptor do fator de crescimento fibroblástico 3

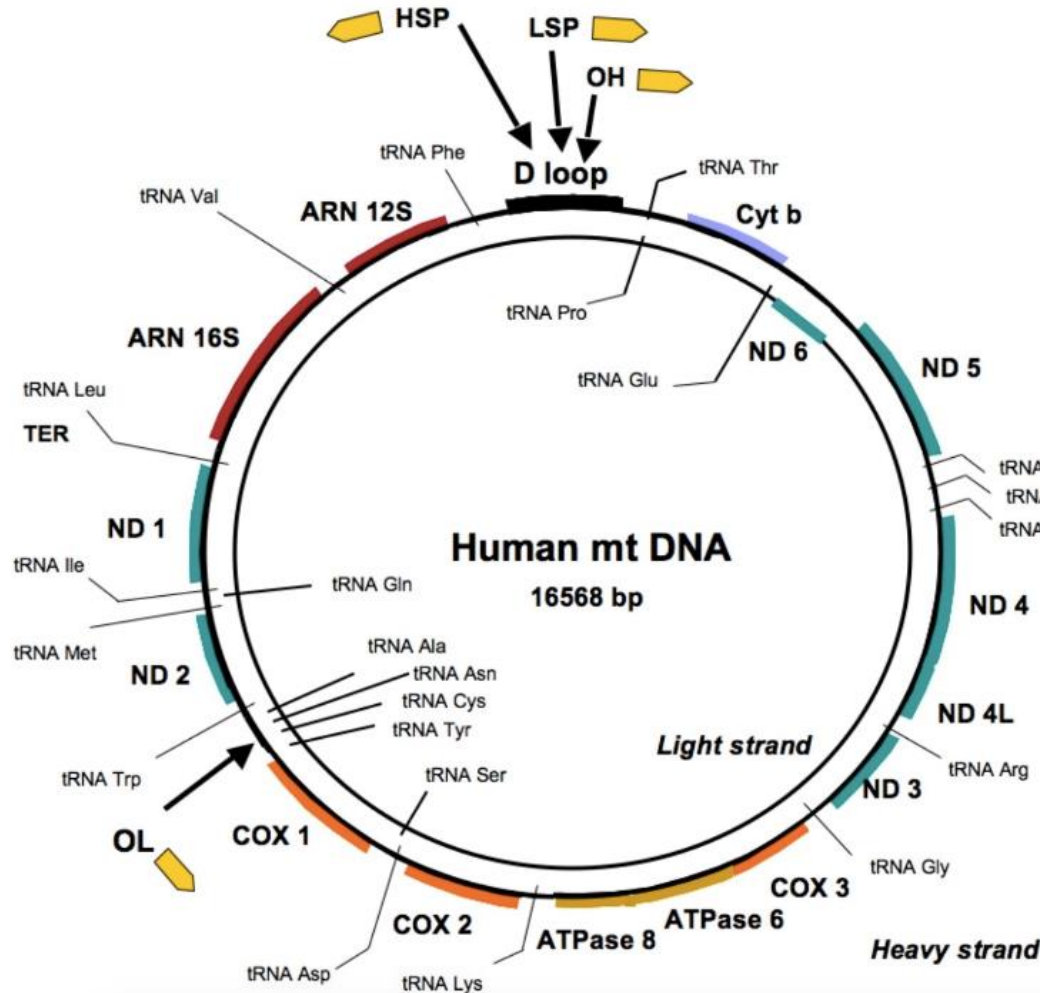
Albinismo: ausência ou defeito de uma enzima envolvida na produção de melanina.



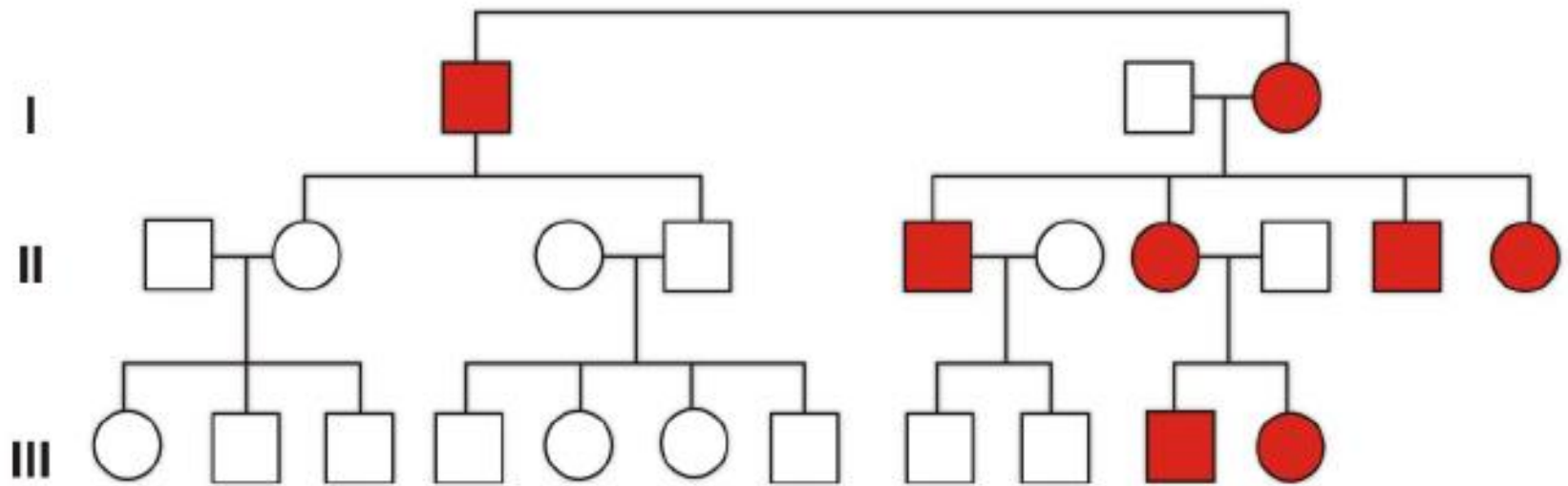
DNA mitochondrial (circular)

Codifica para algumas proteínas que participam da fosforilação oxidativa. Codifica também tRNA, rRNA para a síntese protéica mitocondrial

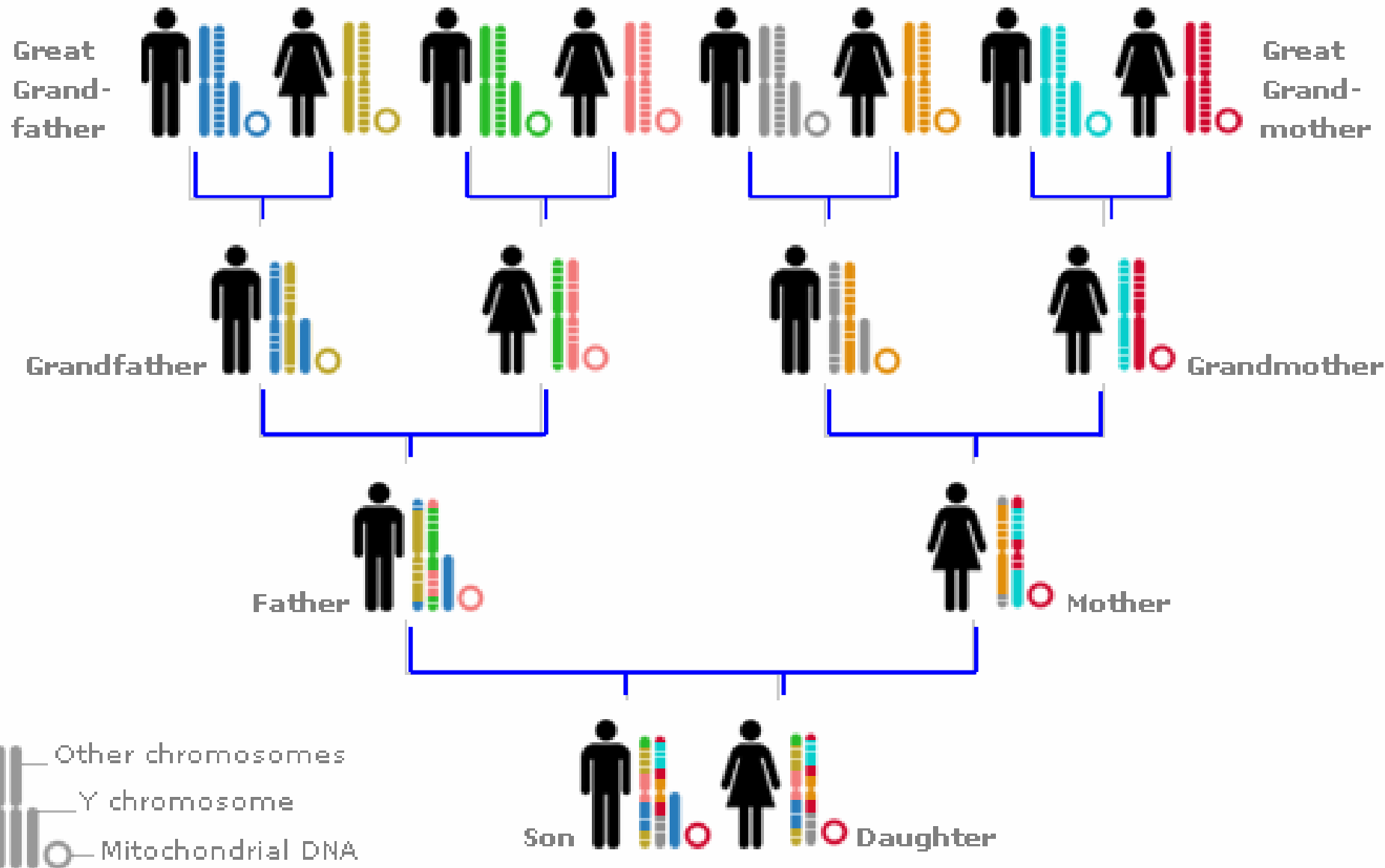
**37 genes
mitocondriais
humanos**



Padrão de herança mitocondrial (materna)



Herança mitocondrial e do cromossomo Y



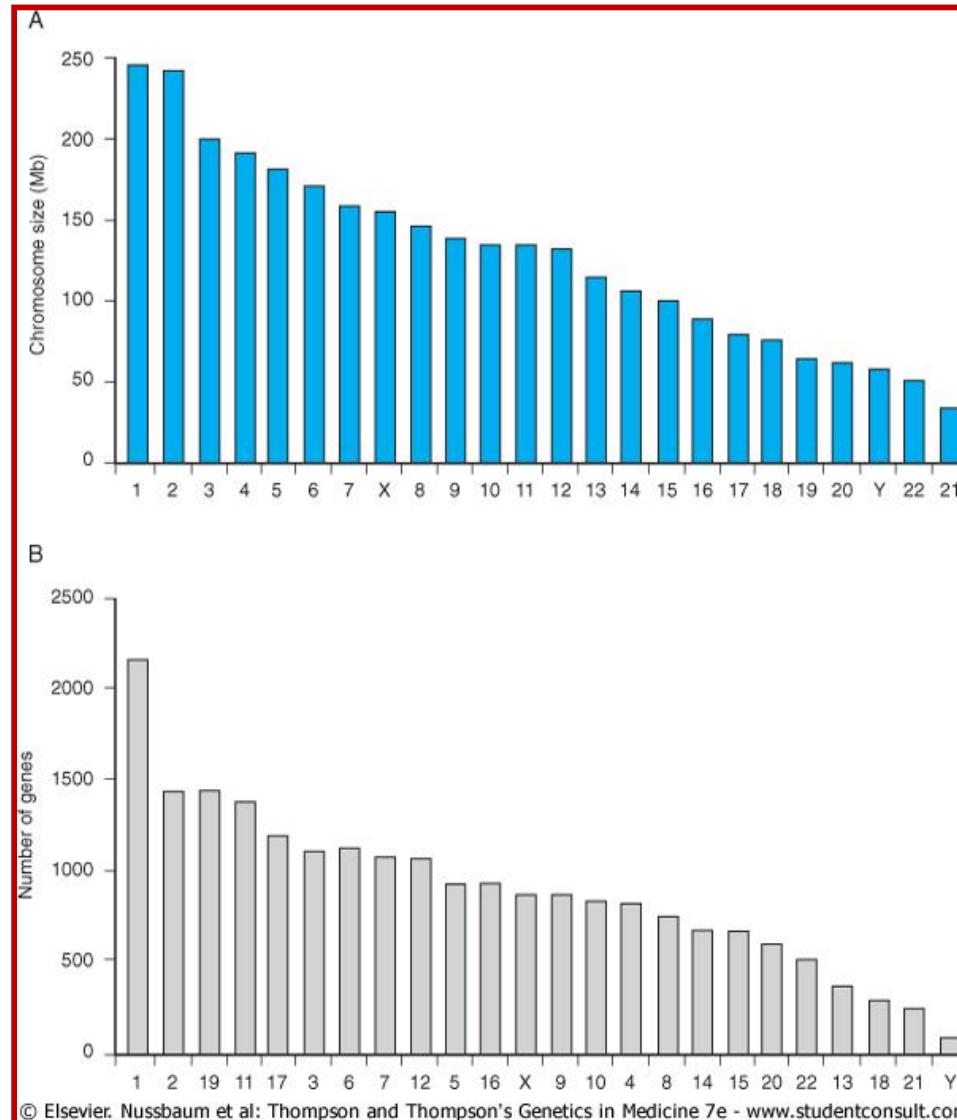
**Como os genes estão distribuídos
ao longo dos cromossomos ?**

Não há relação entre o tamanho do cromossomo e o número de genes no genoma humano

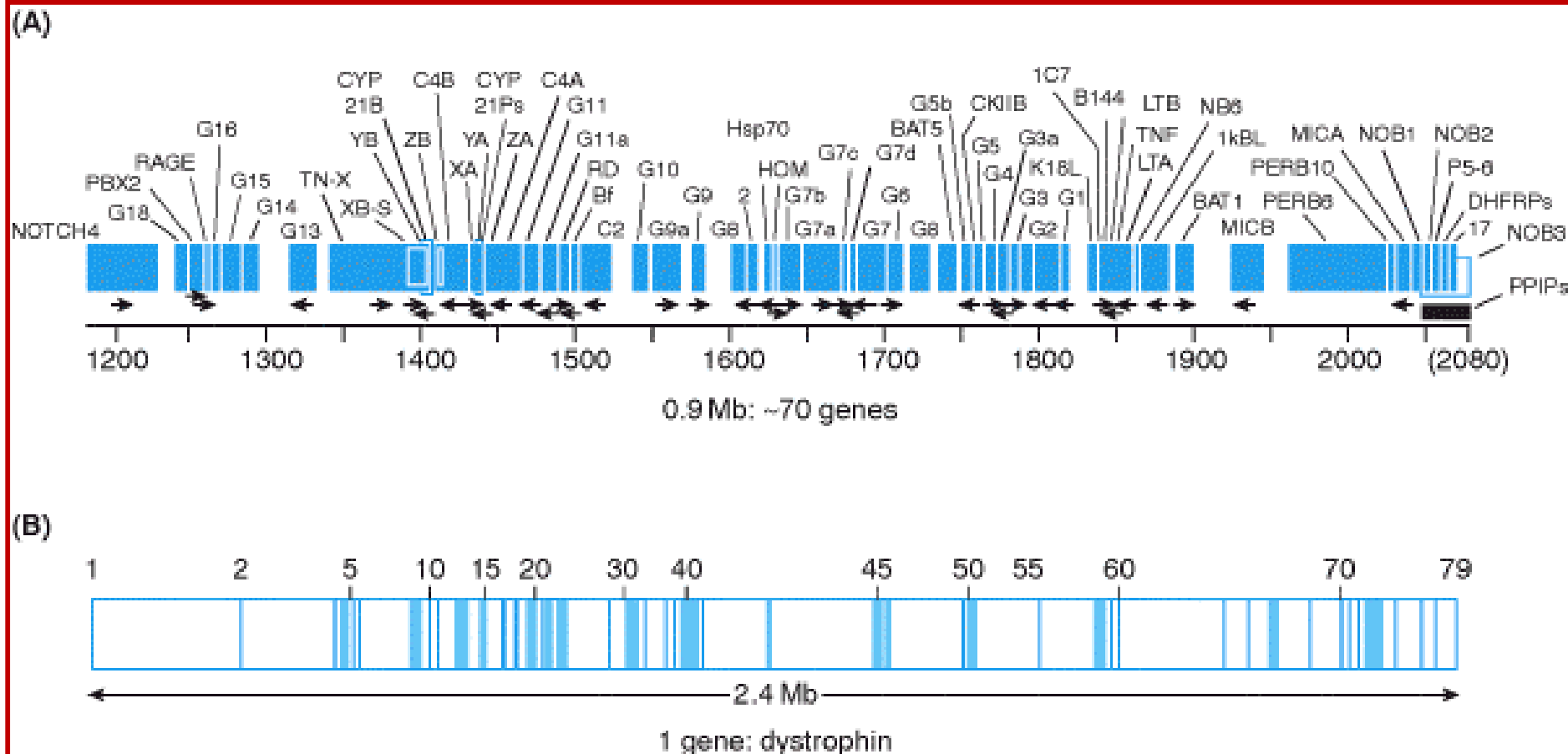
Tamanho dos cromossomos



Número de genes por cromossomo

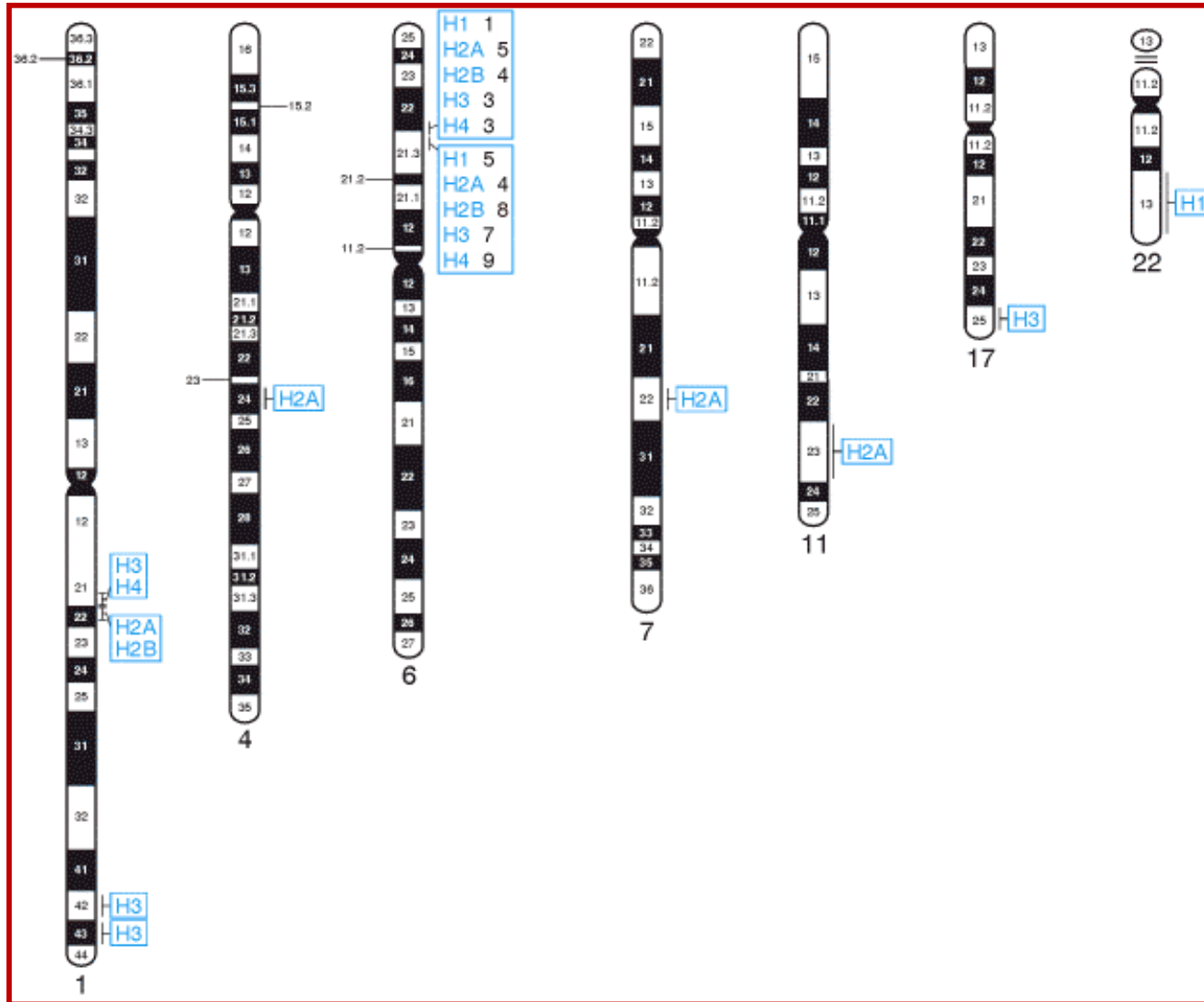


Contraste entre as densidades gênicas humanas (tamanho dos genes)



1 Mb = 1 milhão de nucleotídeos

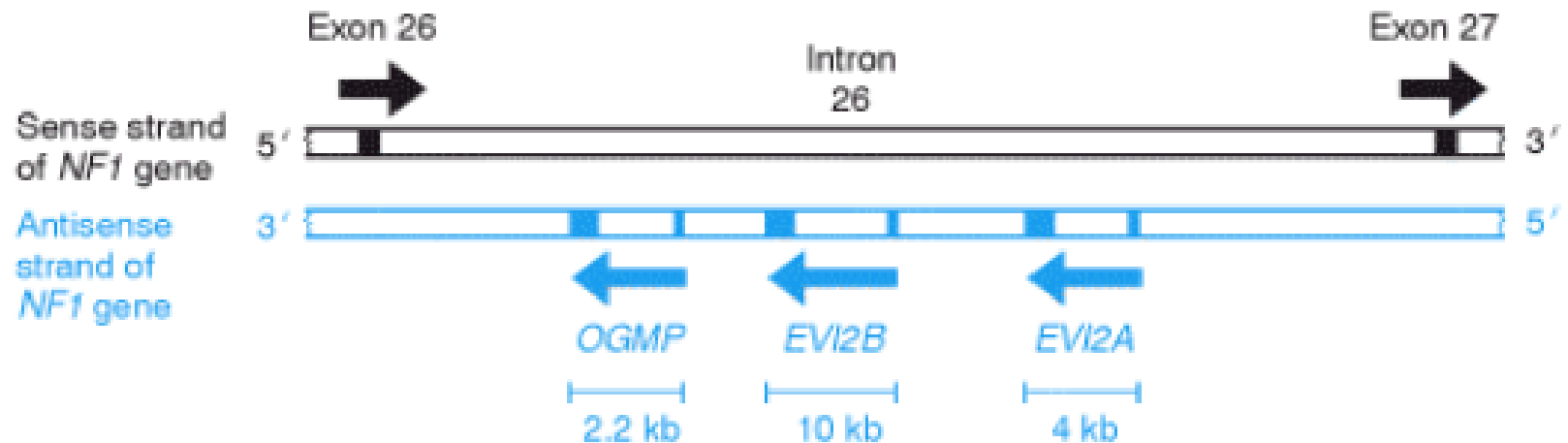
Genes Humanos envolvidos na síntese de histonas



Genes com funções semelhantes encontram-se dispersos no genoma. Várias cópias de genes fundamentais.

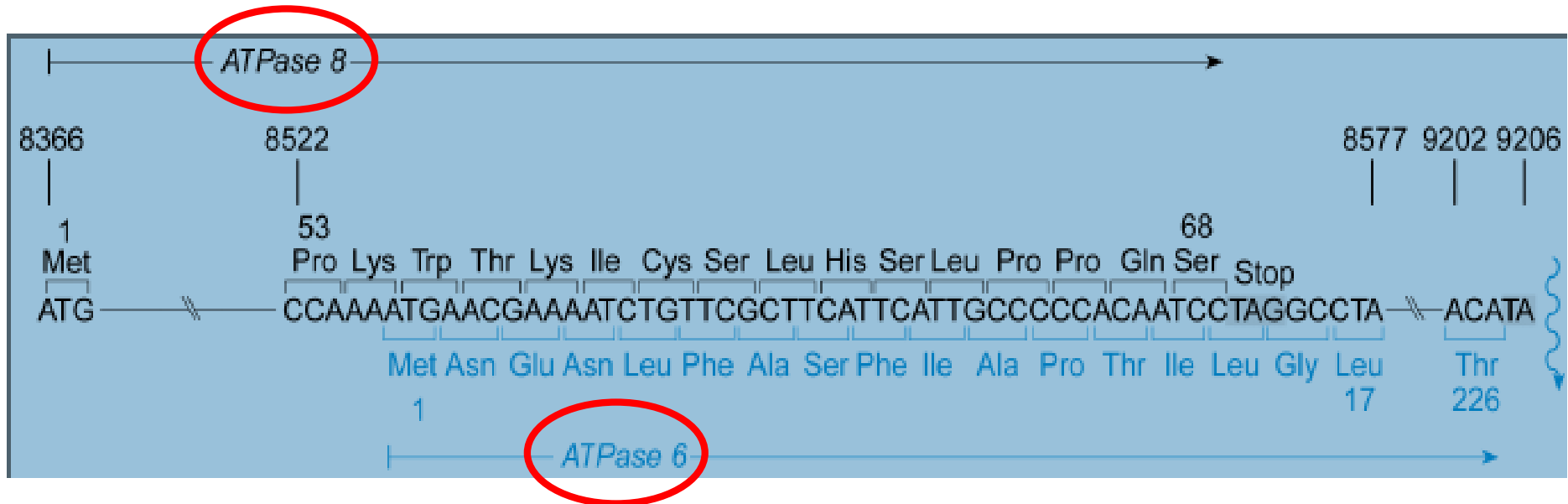
Peculiaridades da organização gênica:

Três genes dentro de um intron de outro gene no sentido oposto

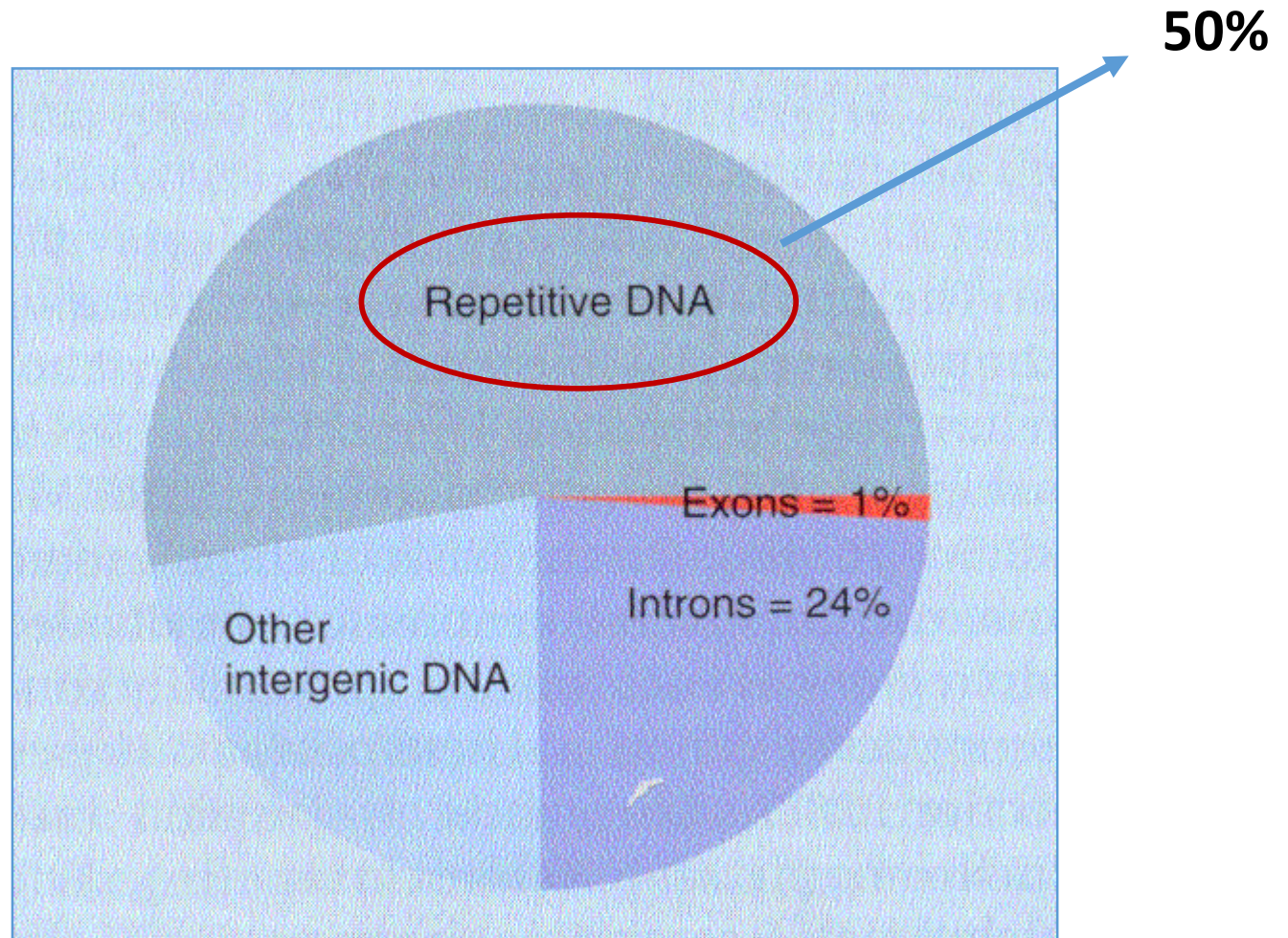


Peculiaridades da organização gênica:

Genes mitocondriais sobrepostos



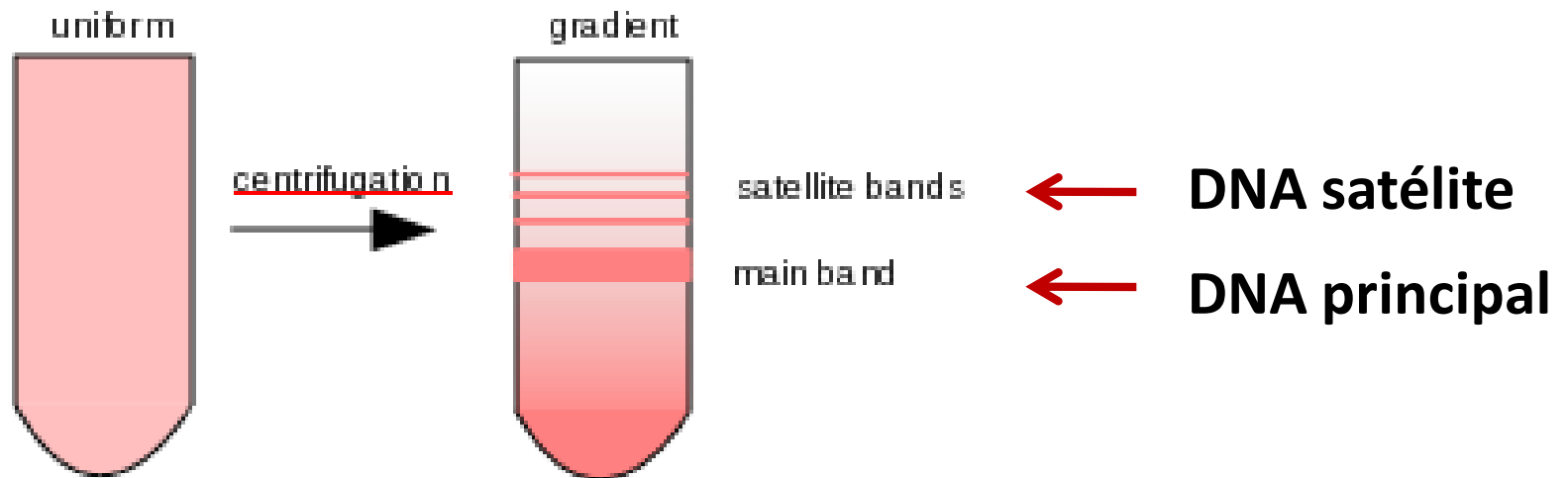
Genoma Humano: tipos de DNA



Sequências de DNA repetitivo

- **SINEs** (elemento nuclear intercalante curto)
Ex: Família Alu: tamanho 300 nucleotídeos.
Compõem 10 % do genoma humano.
- **LINEs** (elemento nuclear intercalante longo)
tamanho 6 Kb. Ocupa 20 % do genoma humano.
- Regiões centroméricas, teloméricas e transposons.

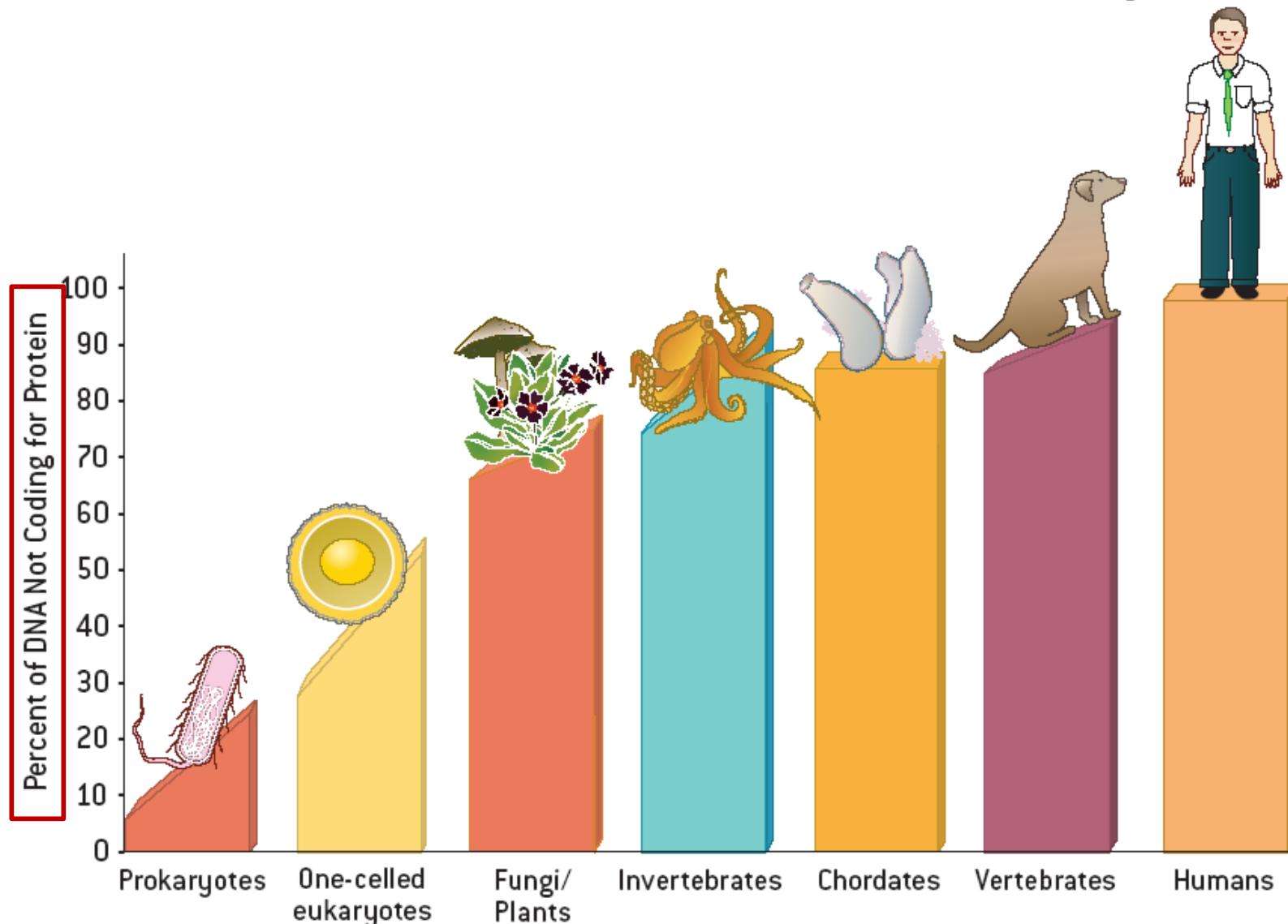
50% do genoma humano é constituído de DNA repetitivo (também chamado de DNA satélite)



Menos de 2 % do genoma humano codifica proteína

Como explicar a complexidade do genoma humano?

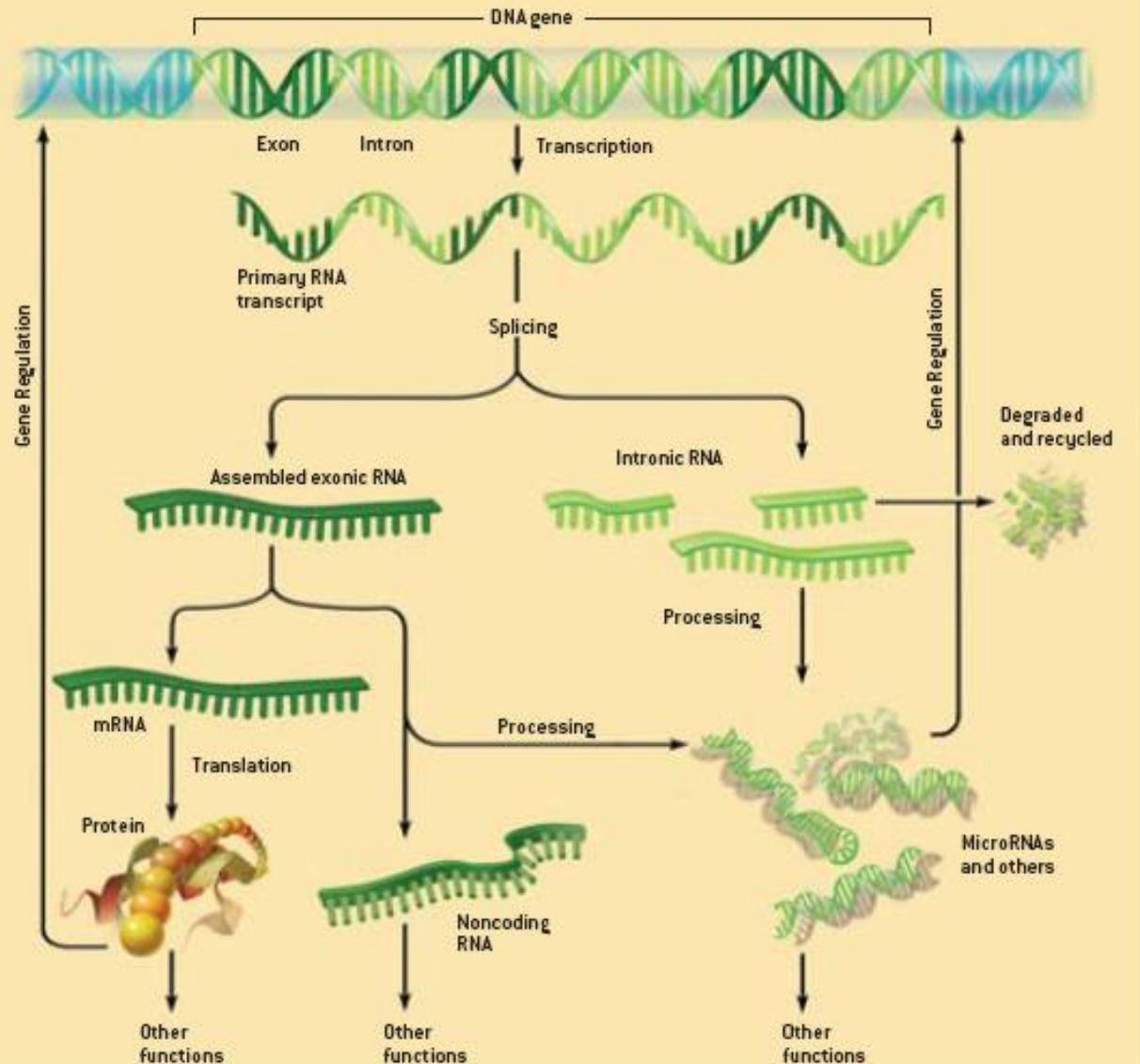
A quantidade de DNA não codificador de proteínas está relacionada a complexidade dos organismos



Visão da atividade gênica em eucariotos

NEW VIEW OF GENE ACTIVITY IN EUKARYOTES

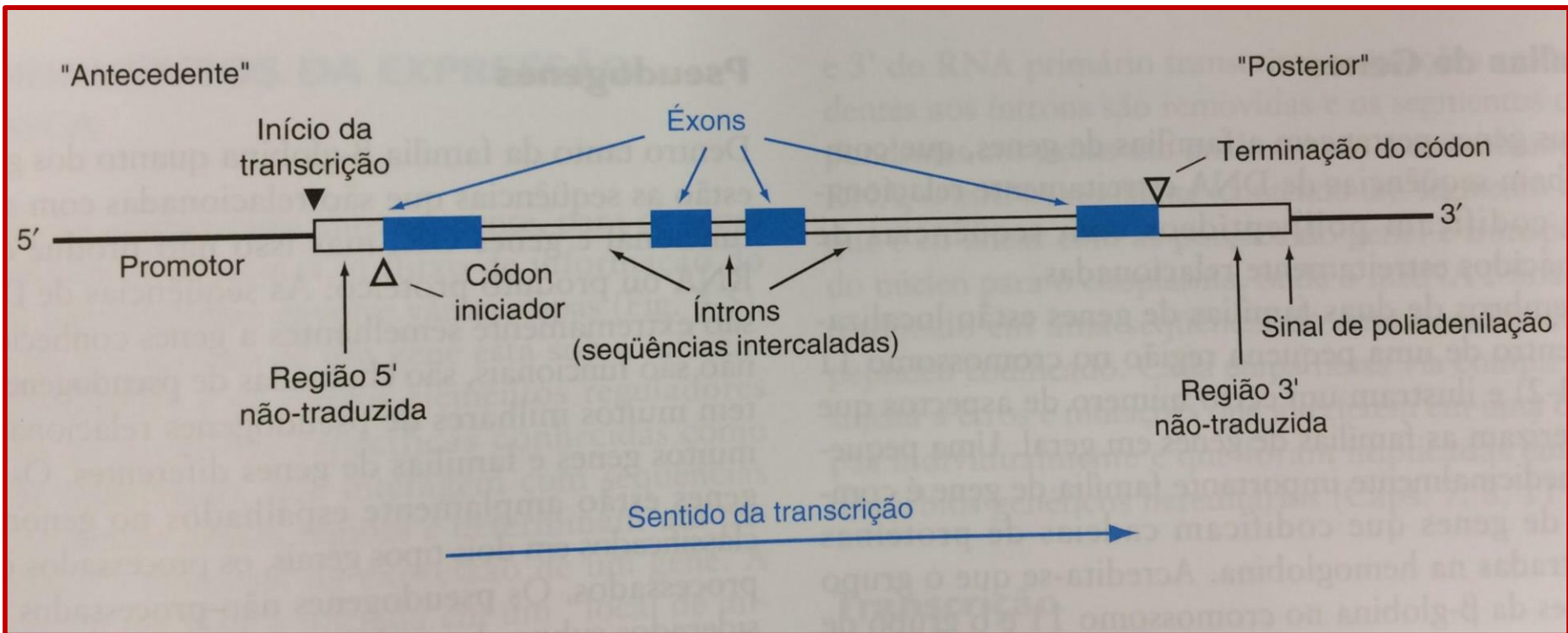
Some of the intronic RNA and even some of the assembled exonic RNA may play a direct regulatory role by interacting with the DNA, other RNA molecules or proteins. By modifying protein production at various levels, these noncoding RNAs may superimpose additional genetic instructions on a cell.



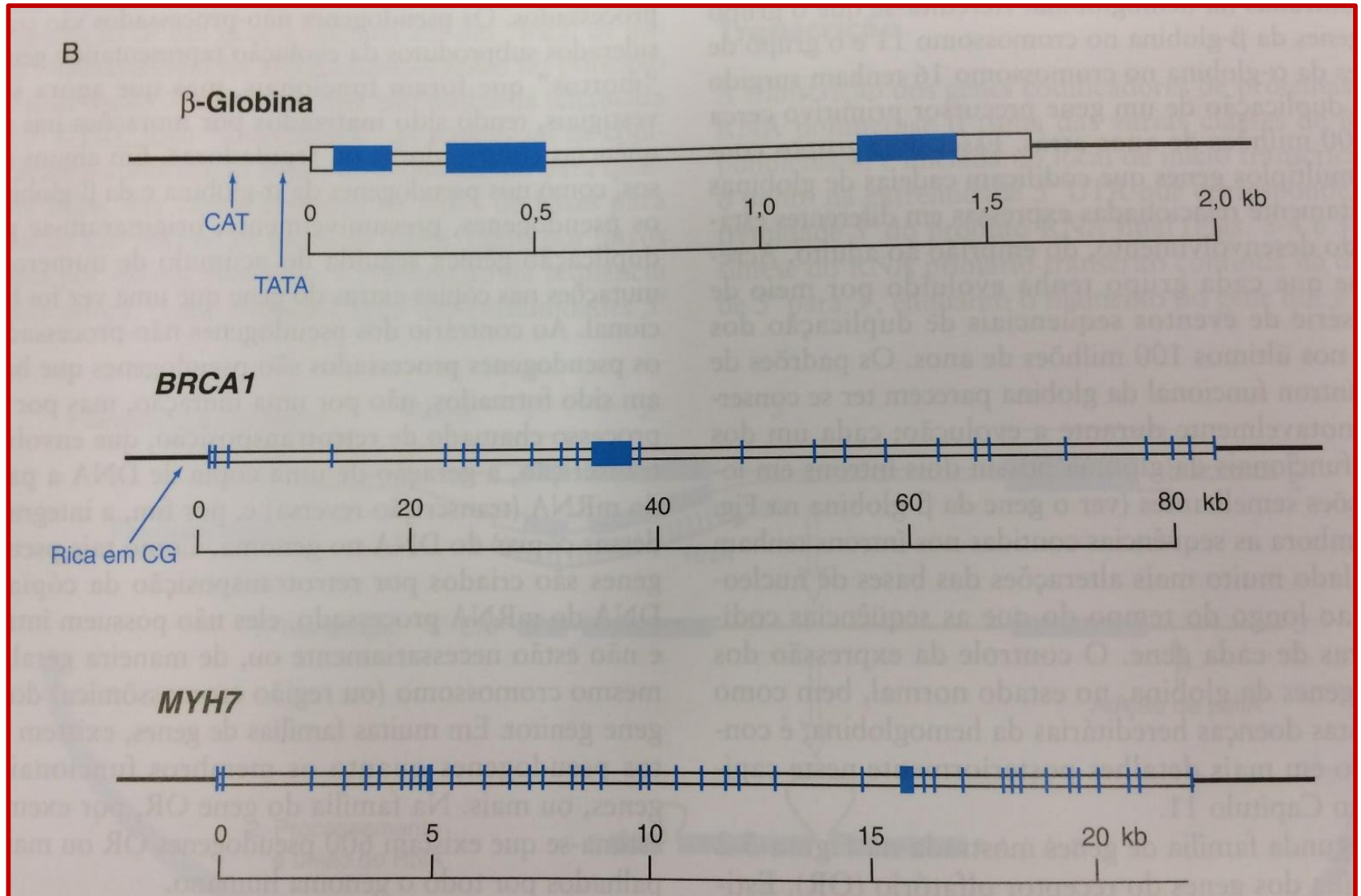
Papel do RNA não codificador (ncRNA) na expressão gênica

- Desenvolvimento embrionário
- Diferenciação celular
- Estabilidade genômica
- Estabilidade do mRNA
- Altera a estrutura da cromatina

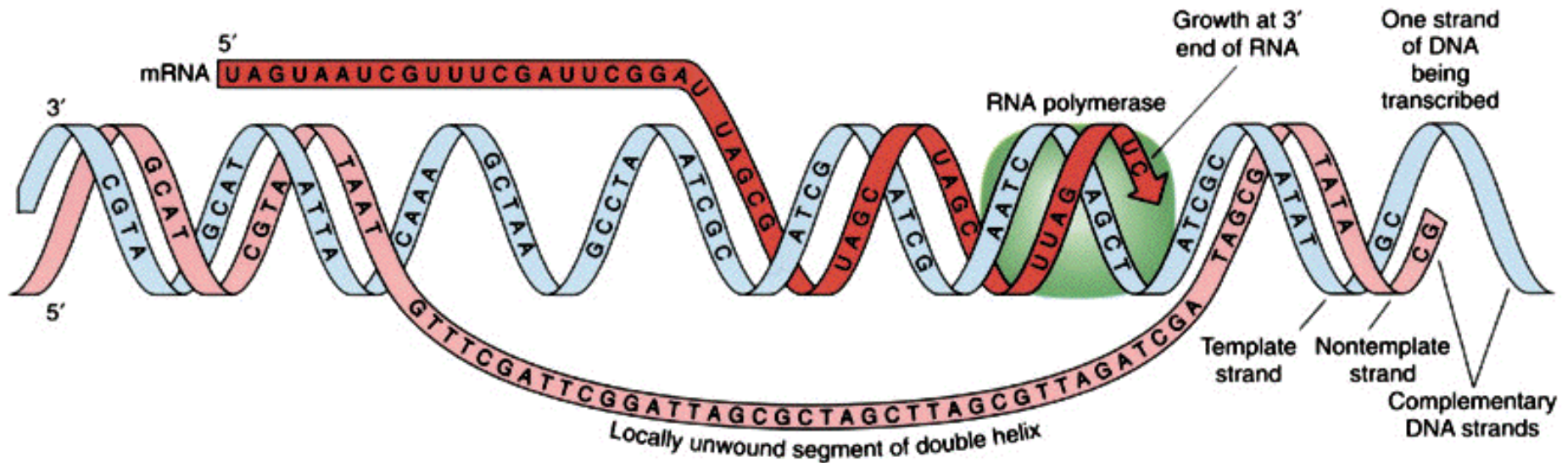
Um típico gene humano



Três genes humanos importantes na Medicina



A síntese do mRNA é fiel ao DNA

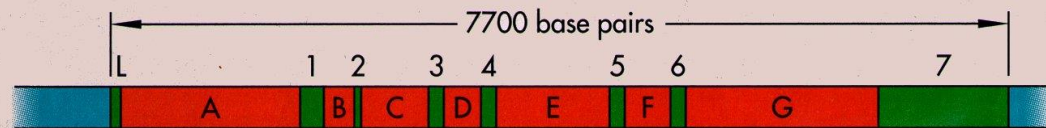
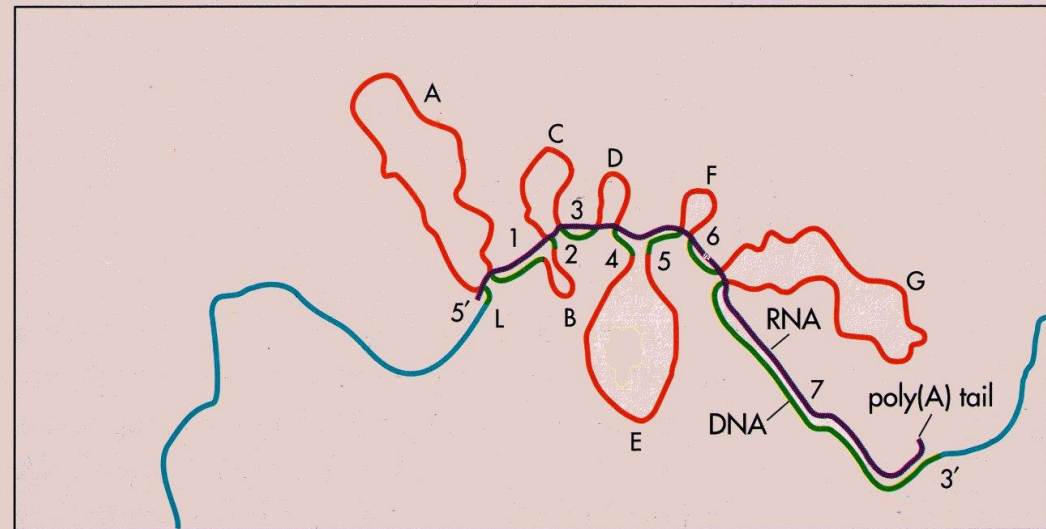
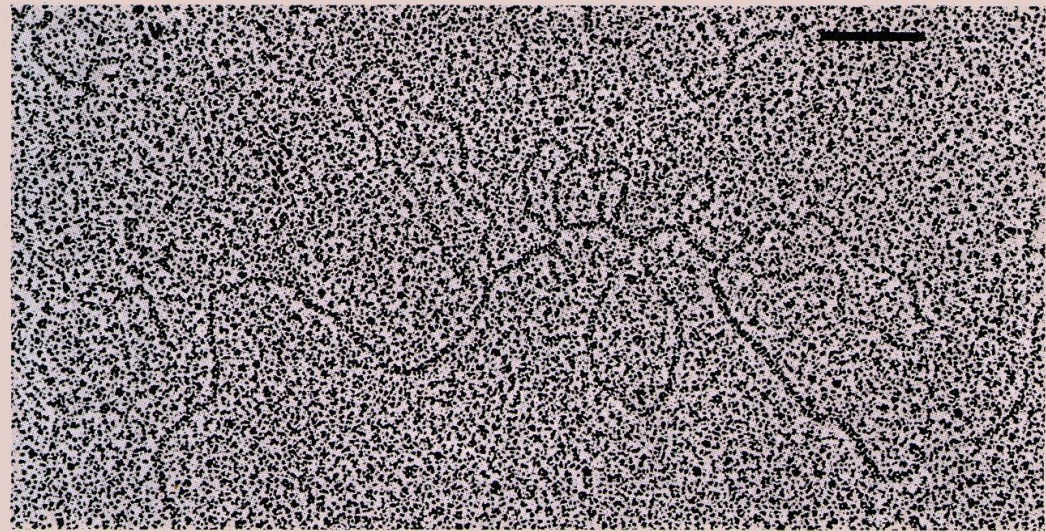


Nontemplate strand 5' – CTGCCATTGTCAGACATGTATACCCCGTACGTCTTCCCGAGCGAAAACGATCTGCGCTGC – 3' } DNA
 Template strand 3' – GACGGTAACAGTCTGTACATATGGGGCATGCAGAAGGGCTCGCTTTTGCTAGACGCGACG – 5' }
 5' – CUGCCAUUGUCAGACAUGUAUACCCCGUACGUCUUCCCGAGCGAAAACGAUCUGCGCUGC – 3' mRNA

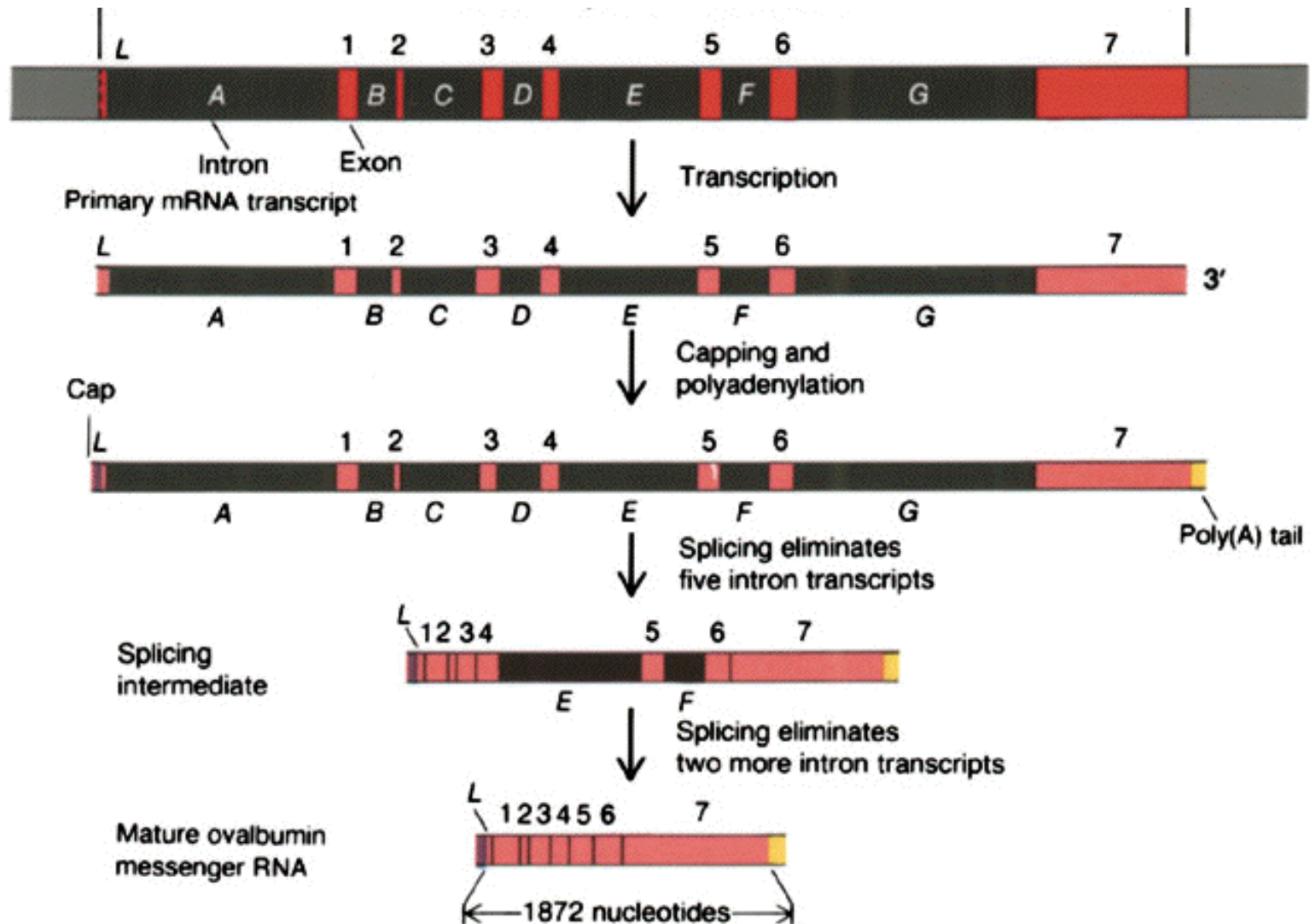
T → U

Descoberta do Processamento do RNA (Intron e Exon)

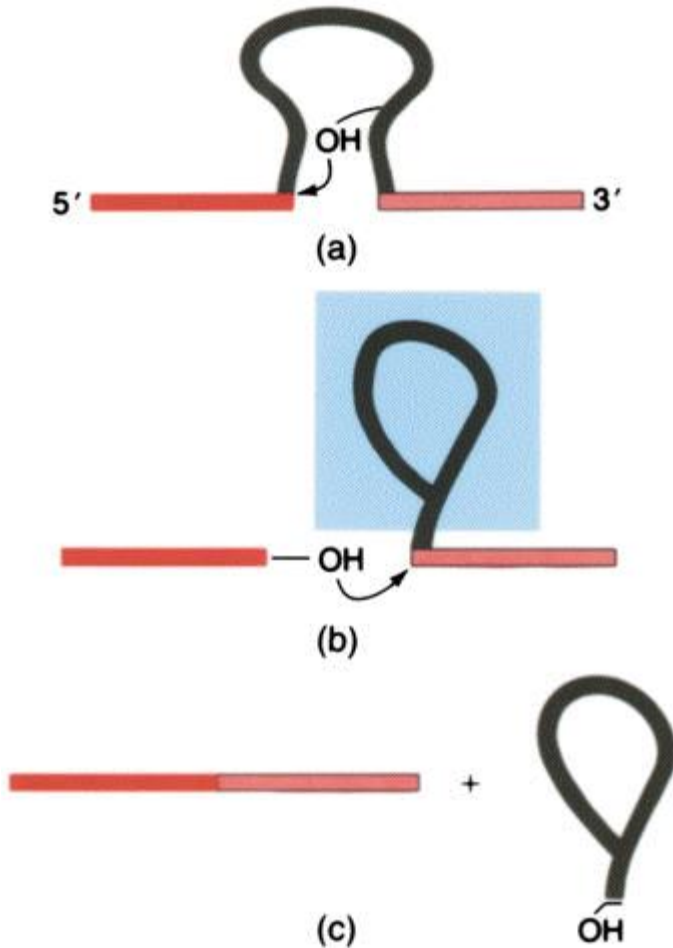
Hibridação
DNA-RNA →



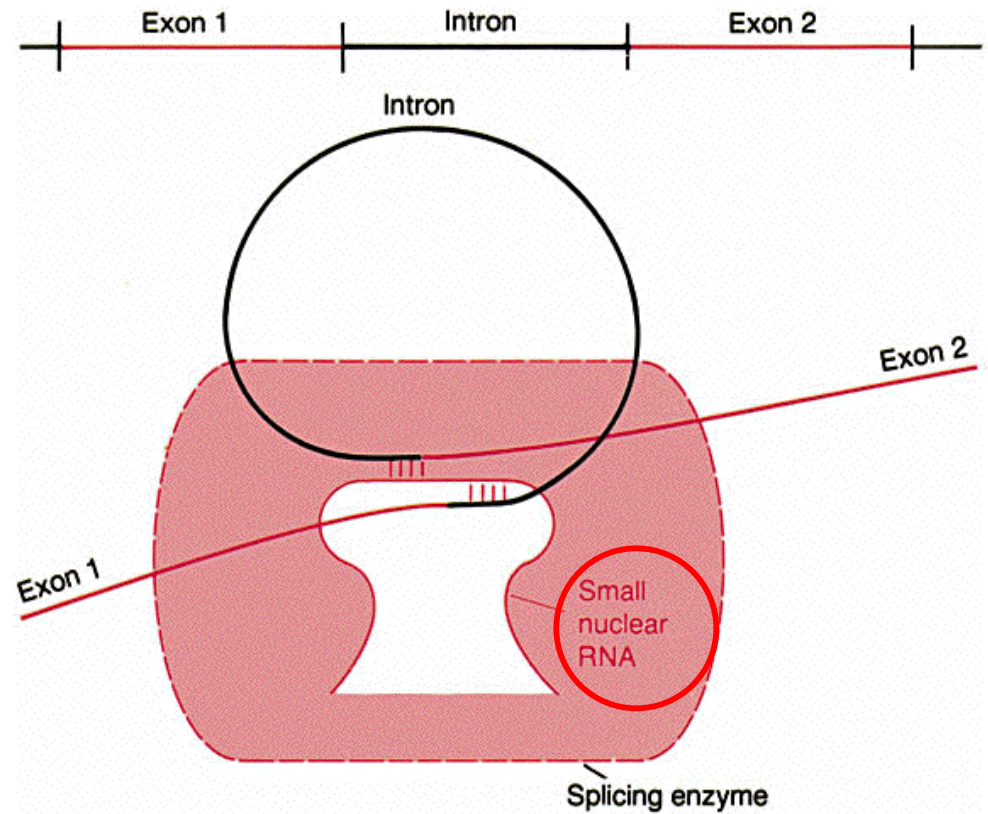
Passos do processamento do RNA



Mecanismos do processamento do RNA



Auto splicing



***Processamento por
spliceossomo***

Processamento alternativo do RNA

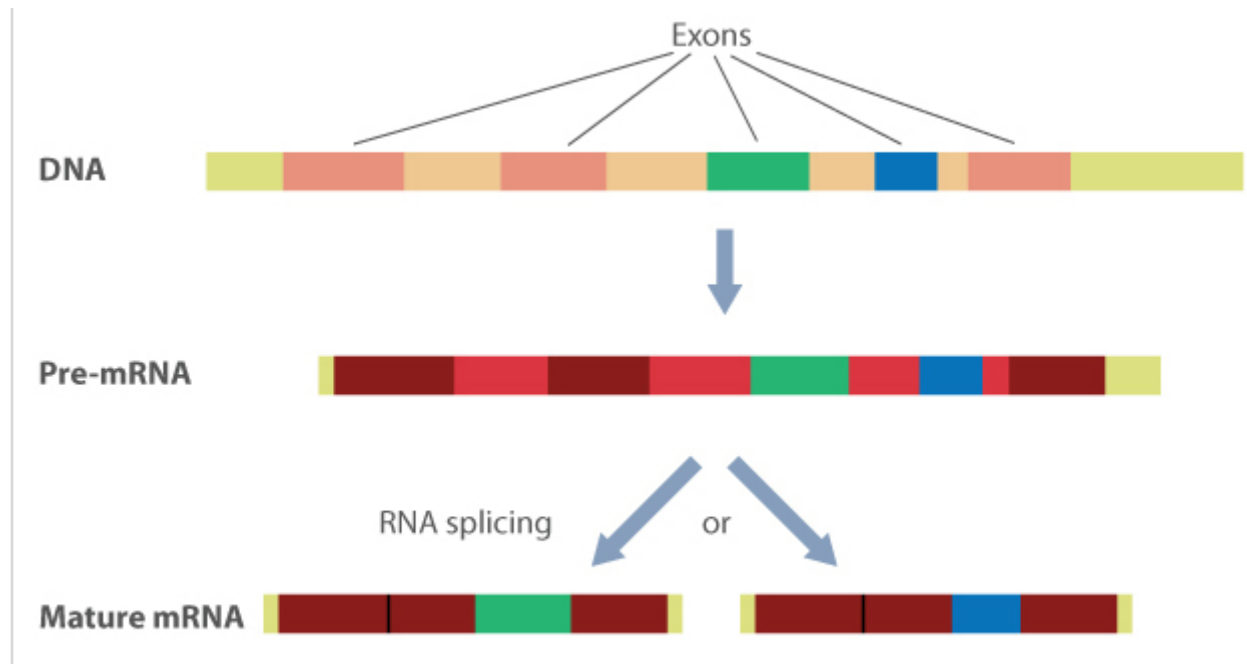
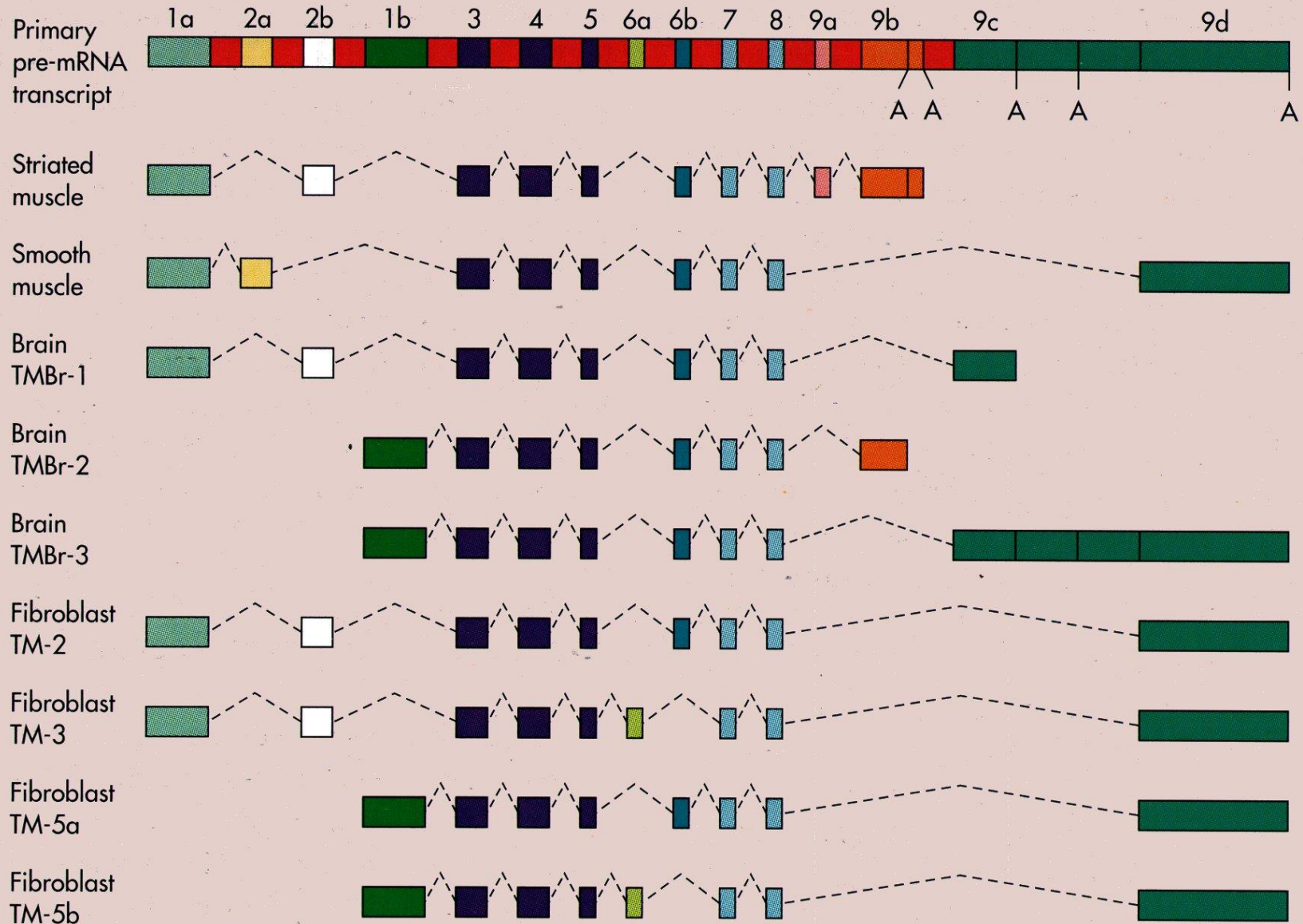


Figure 6: Alternative RNA splicing.
Production of two different mRNAs from the same gene.

**Produz 2 diferentes RNAs a partir do mesmo gene:
2 isoformas proteicas**

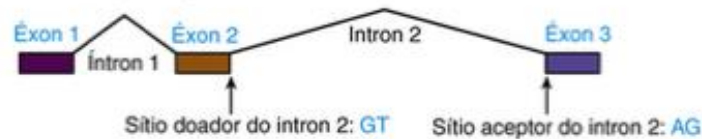
Processamento diferencial do gene da tropomiosina



Mutações que afetam o *splicing* normal do gene da β -globina causando a β -talassemia

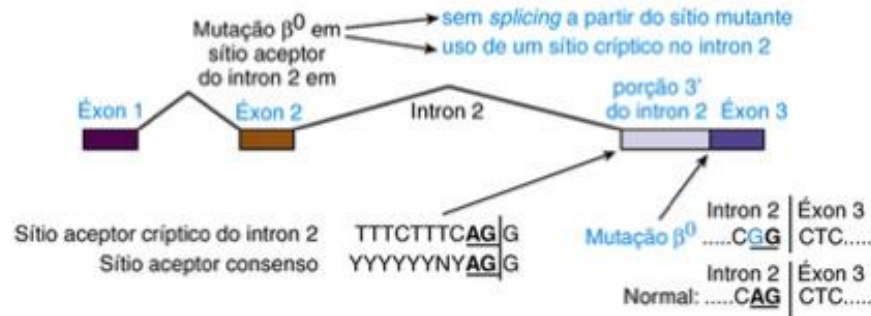
A

Padrão normal de *splicing*



B

Mutação que destrói um sítio de corte aceptor normal e ativa um sítio críptico

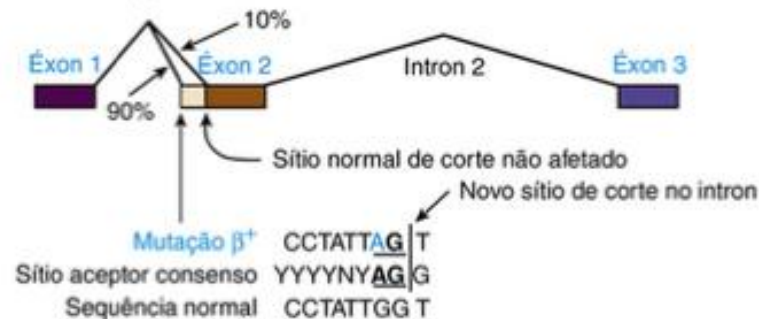


C

Mutação que cria um novo sítio de corte aceptor dentro de um intron

Mutação β^+ no intron 1 pb 110 em um sítio aceptor crítico

uso reduzido de um sítio normal não afetado
uso preferencial de um sítio mutante



NCBI: site para pesquisar doenças genética

The screenshot shows the NCBI Genomic Biology Homo sapiens website. At the top, there is a search bar with a dropdown menu set to 'All Databases (Entrez)' and buttons for 'Go' and 'Clear'. Below the search bar, on the left, is a section titled 'Browse your Genome' with a subtext 'Click on the Chromosome to show'. It features a dropdown menu set to 'Genes' and a grid of 22 chromosomes labeled 1 through 22, plus X and Y. Below this is a 'Find A Gene' section with a search bar, a dropdown menu set to 'Homo sapiens', and a 'Go' button. At the bottom left is 'The NCBI Handbook' section with a small NCBI logo and text describing it as an online guide to the use of NCBI resources. On the right side, there is a large banner for 'Human Genome Resources' featuring a DNA double helix. Below the banner is a paragraph of text about the challenge of piecing together genomic data, followed by a 'More...' link. Below this is a section titled 'Genes and Human Health' with a red background. It contains four sub-sections: 'Gene Database' (a new database of genes and associated information), 'RefSeq' (reference sequences of chromosomes, genomic contigs, mRNAs, and proteins), 'OMIM' (a guide to human genes and inherited disorders), and 'dbSNP' (a database of single nucleotide polymorphisms). Below this is another section titled 'Reagents' with a red background, containing two sub-sections: 'Full-Length cDNA Clones' (NIH Mammalian Gene Collection) and 'Molecular Probes' (a new NCBI database providing sequences of molecular probes).

NCBI Genomic Biology Homo sapiens

Search All Databases (Entrez) for Go Clear

Browse your Genome
Click on the Chromosome to show

Genes

1 2 3 4 5 6 7 8
9 10 11 12 13 14 15 16
17 18 19 20 21 22 X Y

Find A Gene

Search for
from Homo sapiens Go

The NCBI Handbook
An online guide to the use of NCBI resources. Titles of selected chapters that refer to human genome resources are shown below.

Human Genome Resources

A challenge facing researchers today is that of piecing together and analyzing the plethora of data currently being generated through the Human Genome Project and scores of smaller projects. NCBI's Web site serves as an integrated, one-stop, genomic information infrastructure for biomedical researchers from around the world so that they may use these data in their research efforts. [More...](#)

Genes and Human Health

- ▶ **Gene Database**
A new database of genes and associated information is now available for searching in Entrez.
- ▶ **RefSeq**
Reference sequences of chromosomes, genomic contigs, mRNAs, and proteins for human and major model organisms.
- ▶ **OMIM**
A guide to human genes and inherited disorders maintained by Johns Hopkins University and collaborators.
- ▶ **dbSNP**
A database of single nucleotide polymorphisms (SNPs) and other nucleotide variations.

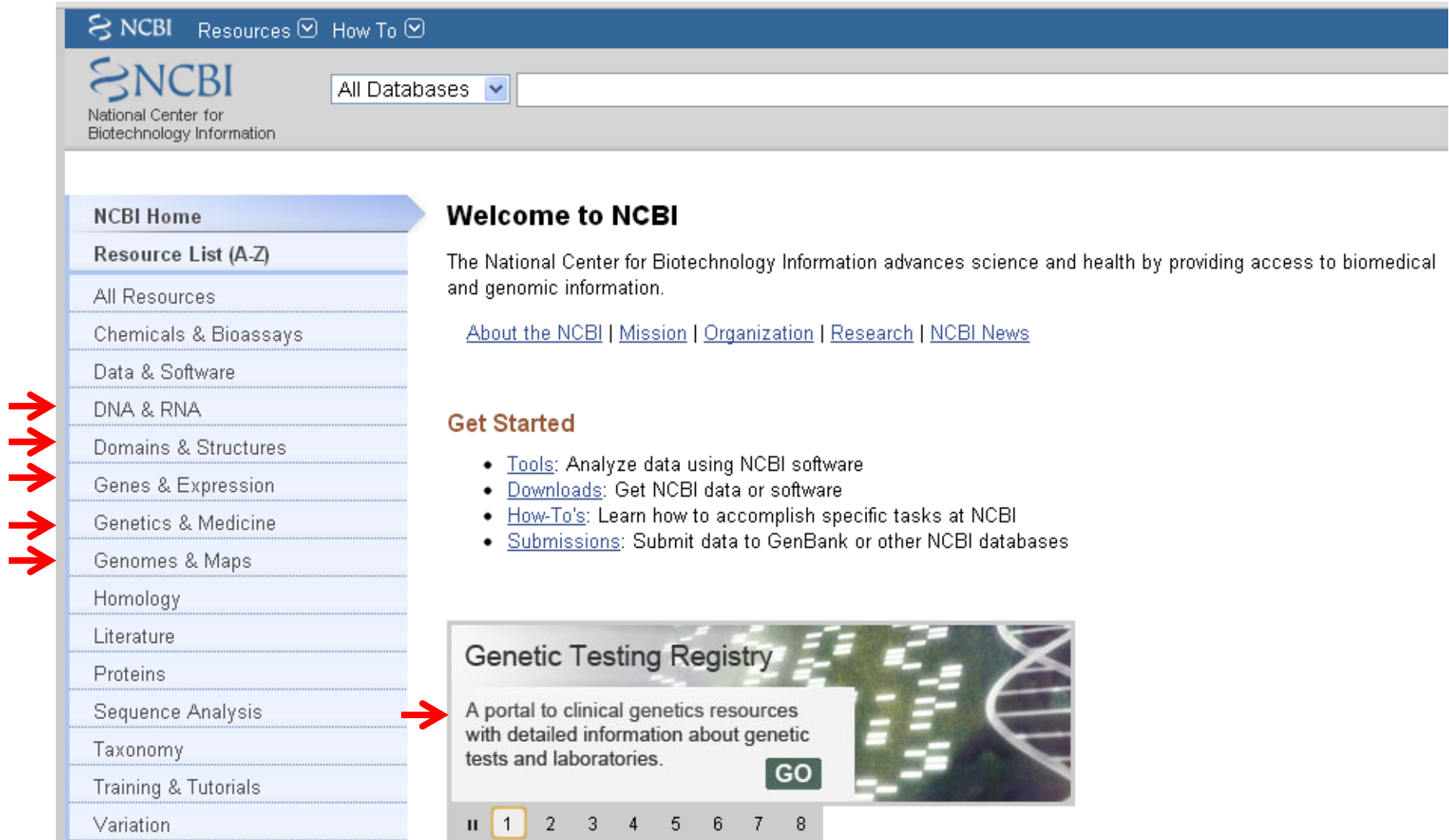
Reagents

- ▶ **Full-Length cDNA Clones**
The NIH Mammalian Gene Collection (MGC) provides sequence-verified cDNA clone reagents for most
- ▶ **Molecular Probes**
A new NCBI database provides sequences of molecular probes, their biomedical applications, and

National Center for Biotechnology Information

<http://www.ncbi.nlm.nih.gov/>

Sequências de DNA são submetidas ao NCBI



The screenshot shows the NCBI homepage. On the left is a vertical navigation menu with items: NCBI Home, Resource List (A-Z), All Resources, Chemicals & Bioassays, Data & Software, DNA & RNA, Domains & Structures, Genes & Expression, Genetics & Medicine, Genomes & Maps, Homology, Literature, Proteins, Sequence Analysis, Taxonomy, Training & Tutorials, and Variation. Red arrows point to 'DNA & RNA' and 'Sequence Analysis'. The main content area has a 'Welcome to NCBI' section with a description and links. Below that is a 'Get Started' section with links to Tools, Downloads, How-To's, and Submissions. At the bottom is a 'Genetic Testing Registry' banner with a 'GO' button and a pagination bar showing '1' as the active page.

NCBI Resources How To

NCBI
National Center for
Biotechnology Information

All Databases

NCBI Home

Resource List (A-Z)

All Resources

Chemicals & Bioassays

Data & Software

DNA & RNA

Domains & Structures

Genes & Expression

Genetics & Medicine

Genomes & Maps

Homology

Literature

Proteins

Sequence Analysis

Taxonomy

Training & Tutorials

Variation

Welcome to NCBI

The National Center for Biotechnology Information advances science and health by providing access to biomedical and genomic information.

[About the NCBI](#) | [Mission](#) | [Organization](#) | [Research](#) | [NCBI News](#)

Get Started

- [Tools](#): Analyze data using NCBI software
- [Downloads](#): Get NCBI data or software
- [How-To's](#): Learn how to accomplish specific tasks at NCBI
- [Submissions](#): Submit data to GenBank or other NCBI databases

Genetic Testing Registry

A portal to clinical genetics resources with detailed information about genetic tests and laboratories.

GO

1 2 3 4 5 6 7 8

National Center for Biotechnology Information <http://www.ncbi.nlm.nih.gov/>

Bibliografia

Thompson & Thompson
Genética Médica

Strachan & Read
Genética Molecular humana

Exercícios

1. Que tipo de herança ocorre para o DNA mitocondrial e para o cromossomo Y humanos?
2. A quantidade de sequência de DNA não codificadoras de proteínas aumenta proporcionalmente com a complexidade dos organismos. Comente e explique.
3. O que você entende por processamento do RNA tecido-específico? De exemplo para a espécie humana.
4. O processamento do RNA pode ser afetado por mutação? Explique.
5. Qual é a relevância do DNA repetitivo?