Introduction in medical genetics 1

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Bratislava, 20.2.2017

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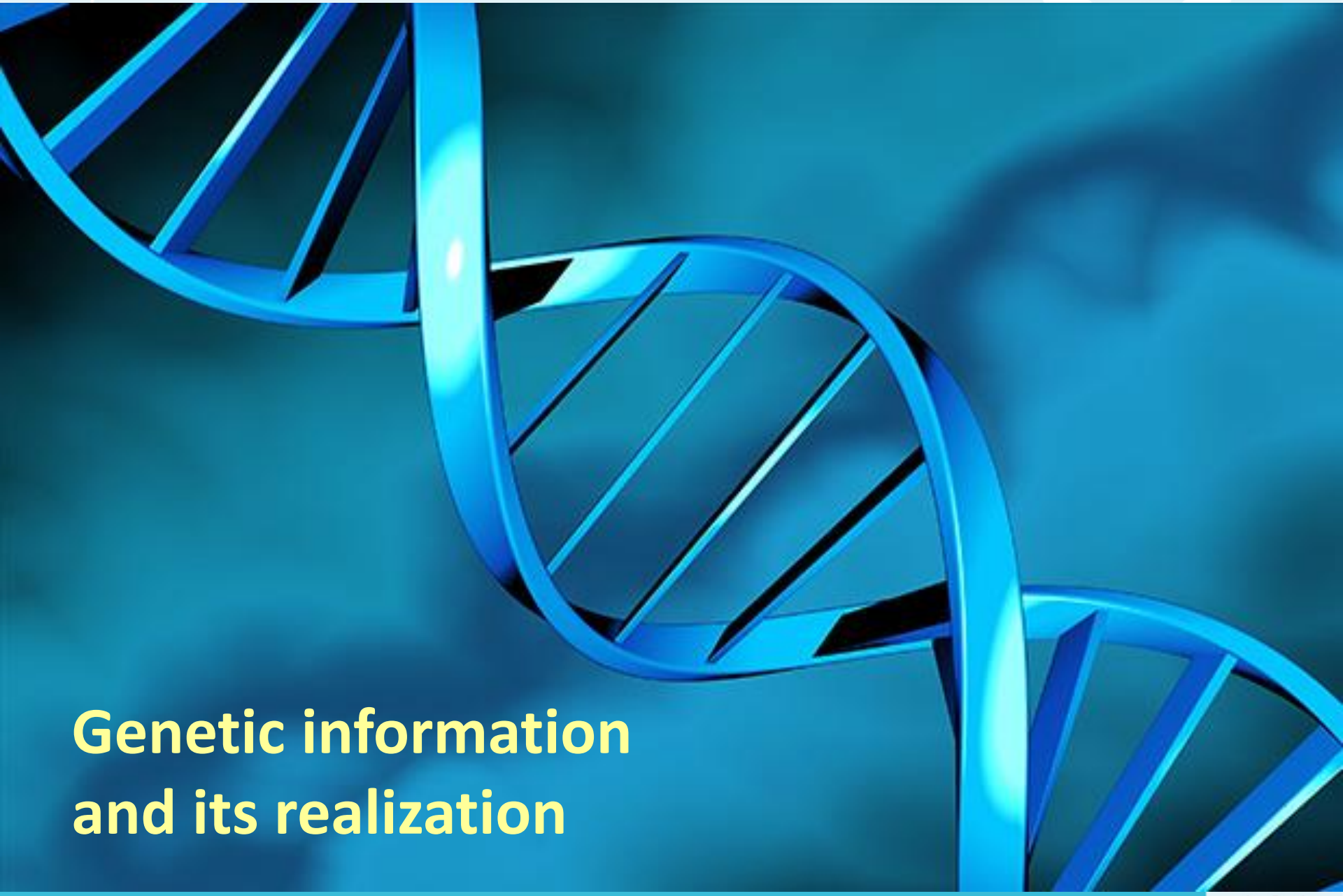
REPRODUKČNÁ GENETIKA


Genetic information
and its realization

Background and history

- **Medical genetics –** involves any application of genetics to medical practice

Includes:

- Studies of **inheritance of diseases in families**
- **Mapping of disease genes** to specific locations on chromosomes
- Analyses of **molecular mechanisms** through **which genes cause disease**
- The **diagnostics and treatment of genetic diseases**
- **Genetic counselling,** which involves the communication of information between clinical geneticist and patient and his/her family regarding to the risks, prognosis, treatment and prevention to the patient and his/her familie

Types of diseases

- **Disease based on the error (mutation) of genetic information**
  (single gene diseases - cystic fibrosis, hemofilia, ...)
- **Diseases with influence of environment in the etiology**
  (infections, medications ...)
- **Diseases with combination of the effect of mutation and environmental factors**
  (multifactorial diseases – diabetes mellitus, cardiovascular diseases, infertility, coeliac disease ...)

Marks of genetic disease

(Niel a Shull, 1954)

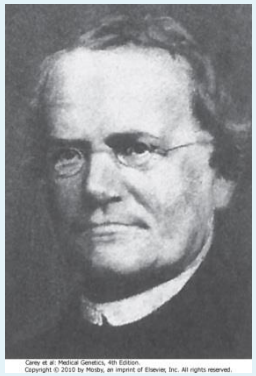
- Presentation of disease in the progeny according to the theoretical segregation models, when the influence of environmental factors in the etiology was excluded
- Disease is never present in biologically non-related persons of the family
- Clinical presentation of disease is demonstrated by the particular age and has a typical development, if no enhanced factors exist
- Disease occurs with higher concordance between monozygote twins than dizygotic twins
- The sick patient carry chromosomal abnormality with typical fenotype (clinical presentation), mental disability is often included. The same or similar disease can/cannot occur in the family.

Types of genetic diseases

- **Single gene diseases** – **mutation is present in one gene on one or both chromosomes**
  - rare frequency in the case of particular disease
  - remarkable and very typical occurence of disease at the level of pedigree
- **Chromosomal abnormalities** – **gain or loss of entire chromosome or its part or rearrangement of chromosomal structure**
  - Complex error in the genetic code
- **Multifactorial diseases** – **combination of the influence of genetic mutation and environmental factors**
  - Mutations and the interactions of many genes are included
  - Tendency to repeated occurence in the families, but the pedigrees are not typical
- **Acquired somatic genetic diseases** – **mutation present in somatic cell**

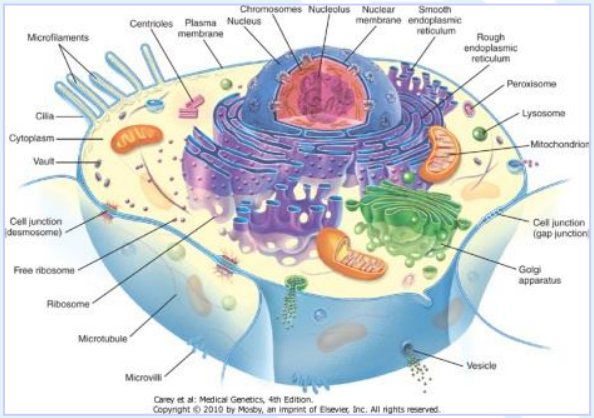
History

- **Johann Gregor Mendel** – a Czech monk – who is considered to be the "father" of genetics – formulates a series of fundamental principles of heredity (published his results in 1865)



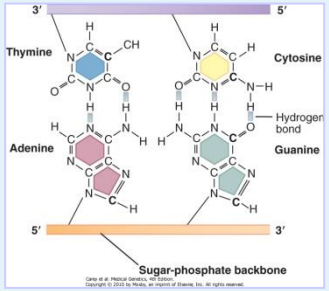
- Mendel´s principles where rediscovered in early 1900 by three different scientist
  - **Landsteiner** – discovered the ABO groups
  - **Garrod** – described alkaptonuria
  - **Johannsen** – coined the term gene to denote the basic unit of heredity

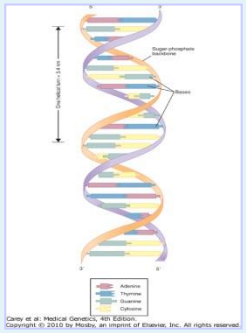
History



- **DNA –** in 1944, Avery showed that genes are composed of deoxyribonucleic acid (DNA)

- **DNA structure** – in 1953 **Watson** & **Crick,** specification of the physical structure of DNA (double helix)





- **The Human Genome Project** – a large collaborative venture begun in 1990, provided the complete human DNA sequence in the year 2003

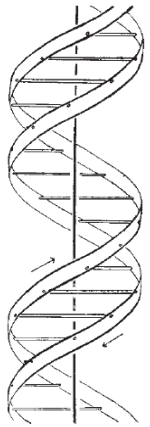
MOLECULAR STRUCTURE OF NUCLEIC ACIDS

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 Corey[1]. They kindly made their manuscript available to us in advance of publication. Their model consists of three intertwined chains, with the phosphates near the fibre axis, and the bases on the outside. In our opinion, this structure is unsatisfactory for two reasons: (1) We believe that the material which gives the X-ray diagrams is the salt, not the free acid. Without the acidic hydrogen atoms it is not clear what forces would hold the structure together, especially as the negatively charged phosphates near the axis will repel each other. (2) Some of the van der Waals distances appear to be too small.

Another three-chain structure has also been suggested by Fraser (in the press). In his model the phosphates are on the outside and the bases on the inside, linked together by hydrogen bonds. This structure as described is rather ill-defined, and for this reason we shall not comment on it.



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

We wish to put forward a radically different structure for the salt of deoxyribose nucleic acid. This structure has two helical chains each coiled round the same axis (see diagram). We have made the usual chemical assumptions, namely, that each chain consists of phosphate diester groups joining β-D-deoxyribofuranose residues with 3′,5′ linkages. The two chains (but not their bases) are related by a dyad perpendicular to the fibre axis. Both chains follow right-handed helices, but owing to the dyad the sequences of the atoms in the two chains run in opposite directions. Each chain loosely resembles Furberg's[2] model No. 1; that is, the bases are on the inside of the helix and the phosphates on the outside. The configuration of the sugar and the atoms near it is close to Furberg's 'standard configuration', the sugar being roughly perpendicular to the attached base. There is a residue on each chain every 3·4 A. in the z-direction. We have assumed an angle of 36° between adjacent residues in the same chain, so that the structure repeats after 10 residues on each chain, that is, after 34 A. The distance of a phosphorus atom from the fibre axis is 10 A. As the phosphates are on the outside, cations have easy access to them.

The structure is an open one, and its water content is rather high. At lower water contents we would expect the bases to tilt so that the structure could become more compact.

The novel feature of the structure is the manner in which the two chains are held together by the purine and pyrimidine bases. The planes of the bases are perpendicular to the fibre axis. They are joined together in pairs, a single base from one chain being hydrogen-bonded to a single base from the other chain, so that the two lie side by side with identical z-co-ordinates. One of the pair must be a purine and the other a pyrimidine for bonding to occur. The hydrogen bonds are made as follows: purine position 1 to pyrimidine position 1; purine position 6 to pyrimidine position 6.

If it is assumed that the bases only occur in the structure in the most plausible tautomeric forms (that is, with the keto rather than the enol configurations) it is found that only specific pairs of bases can bond together. These pairs are: adenine (purine) with thymine (pyrimidine), and guanine (purine) with cytosine (pyrimidine).

In other words, if an adenine forms one member of a pair, on either chain, then on these assumptions the other member must be thymine; similarly for guanine and cytosine. The sequence of bases on a single chain does not appear to be restricted in any way. However, if only specific pairs of bases can be formed, it follows that if the sequence of bases on one chain is given, then the sequence on the other chain is automatically determined.

It has been found experimentally[3,4] that the ratio of the amounts of adenine to thymine, and the ratio of guanine to cytosine, are always very close to unity for deoxyribose nucleic acid.

It is probably impossible to build this structure with a ribose sugar in place of the deoxyribose, as the extra oxygen atom would make too close a van der Waals contact.

The previously published X-ray data[5,6] on deoxyribose nucleic acid are insufficient for a rigorous test of our structure. So far as we can tell, it is roughly compatible with the experimental data, but it must be regarded as unproved until it has been checked against more exact results. Some of these are given in the following communications. We were not aware of the details of the results presented there when we devised our structure, which rests mainly though not entirely on published experimental data and stereochemical arguments.

It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material.

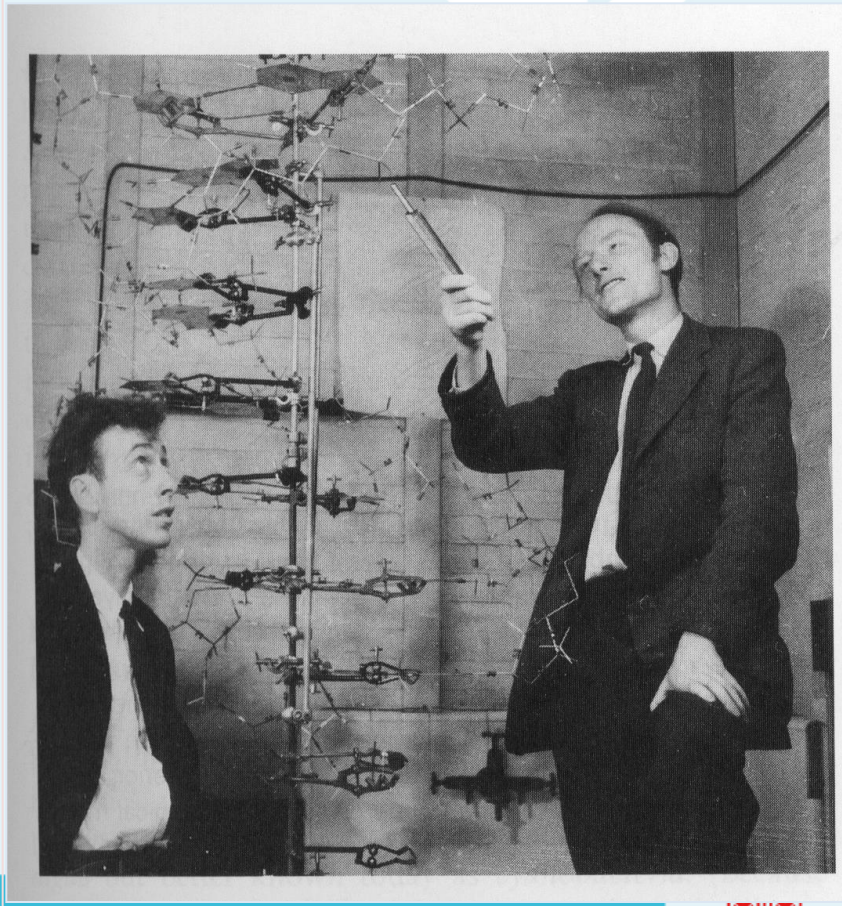
Full details of the structure, including the conditions assumed in building it, together with a set of co-ordinates for the atoms, will be published elsewhere.

We are much indebted to Dr. Jerry Donohue for constant advice and criticism, especially on interatomic distances. We have also been stimulated by a knowledge of the general nature of the unpublished experimental results and ideas of Dr. M. H. F. Wilkins, Dr. R. E. Franklin and their co-workers at King's College, London. One of us (J. D. W.) has been aided by a fellowship from the National Foundation for Infantile Paralysis.

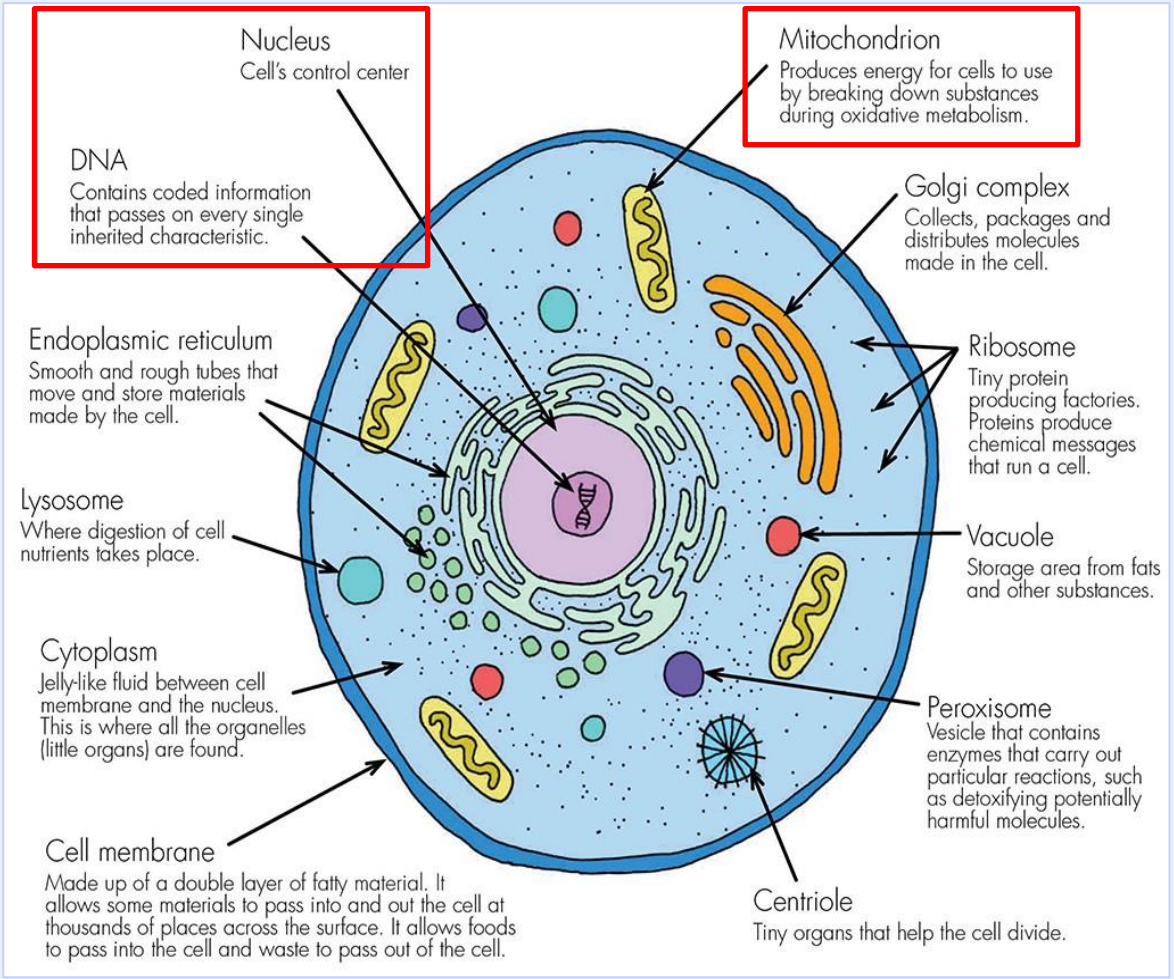
J. D. WATSON
F. H. C. CRICK

Medical Research Council Unit for the Study of the Molecular Structure of Biological Systems,
Cavendish Laboratory, Cambridge.
April 2.

[1] Pauling, L., and Corey, R. B., *Nature*, **171**, 346 (1953); *Proc. U.S. Nat. Acad. Sci.*, **39**, 84 (1953).
[2] Furberg, S., *Acta Chem. Scand.*, **6**, 634 (1952).
[3] Chargaff, E., for references see Zamenhof, S., Brawerman, G., and Chargaff, E., *Biochim. et Biophys. Acta*, **9**, 402 (1952).
[4] Wyatt, G. R., *J. Gen. Physiol.*, **36**, 201 (1952).
[5] Astbury, W. T., Symp. Soc. Exp. Biol. 1, Nucleic Acid, 66 (Camb. Univ. Press, 1947).
[6] Wilkins, M. H. F., and Randall, J. T., *Biochim. et Biophys. Acta*, **10**, 192 (1953).



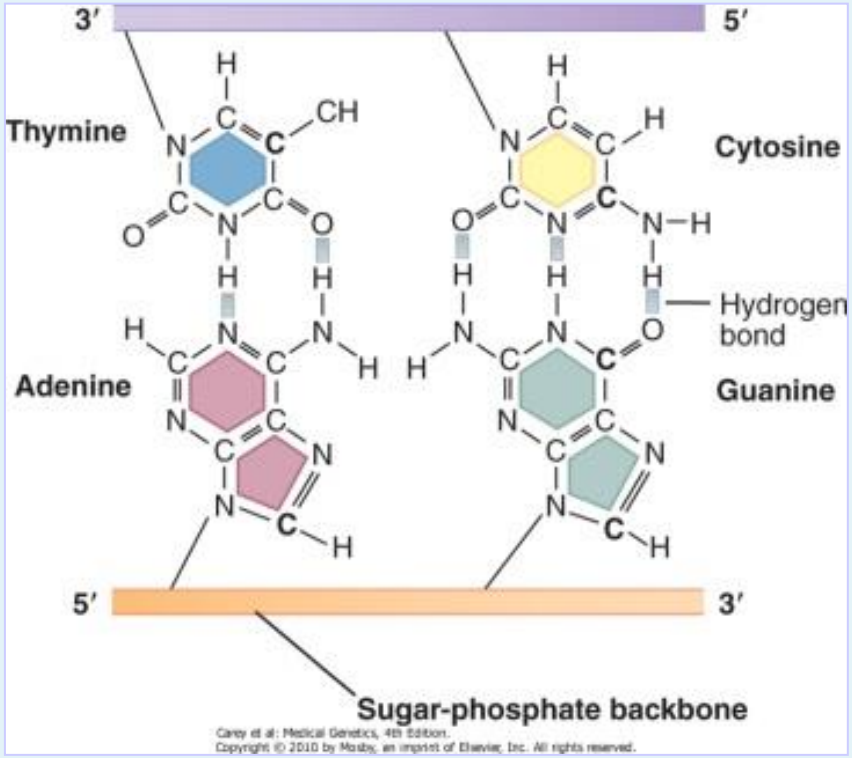
Human cell



Position of Homo sapiens in an animal kingdom

- Eucaryota
- Vertebrae
- Mammals
- Primates
- Homo sapiens

Structure of DNA



Nucleotide:

- **pentose sugar: deoxyribose**
- **a phosphate group**
- **4 types of nitrogenous base:**

  single carbon-nitrogen rings

  called **pyrimidines** - **cytosine C**

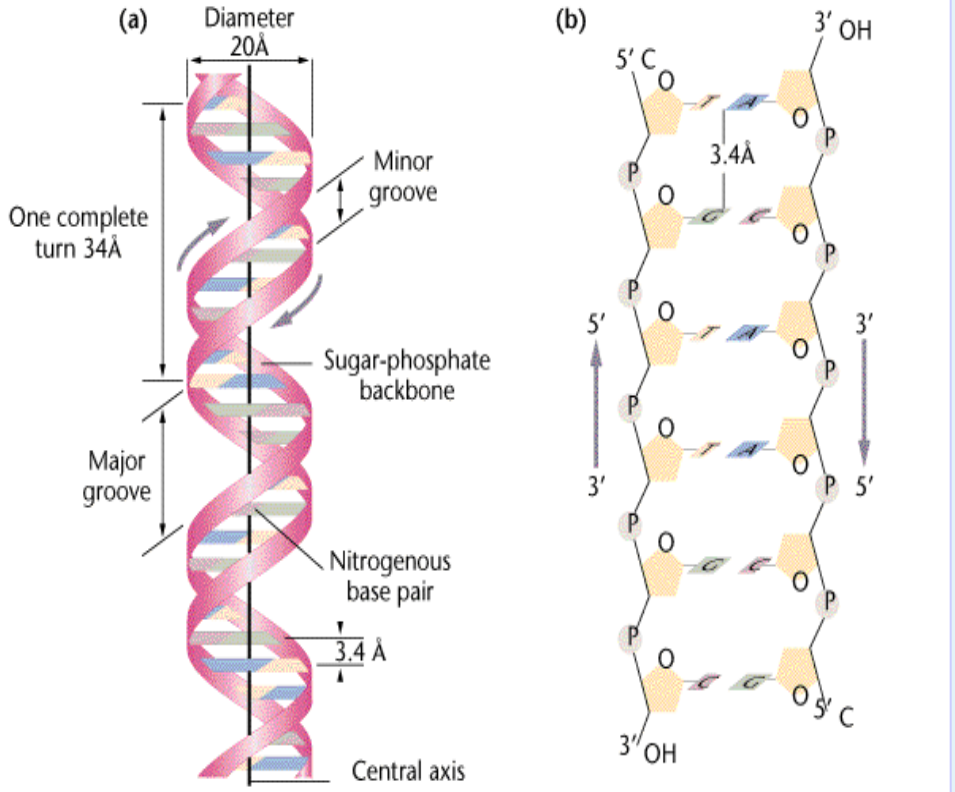
  - **thymine T**

  double carbon-nitrogen rings

  called **purines** - **adenine A**

  - **guanine G**

Structure of DNA



In non-denaturated conditions:

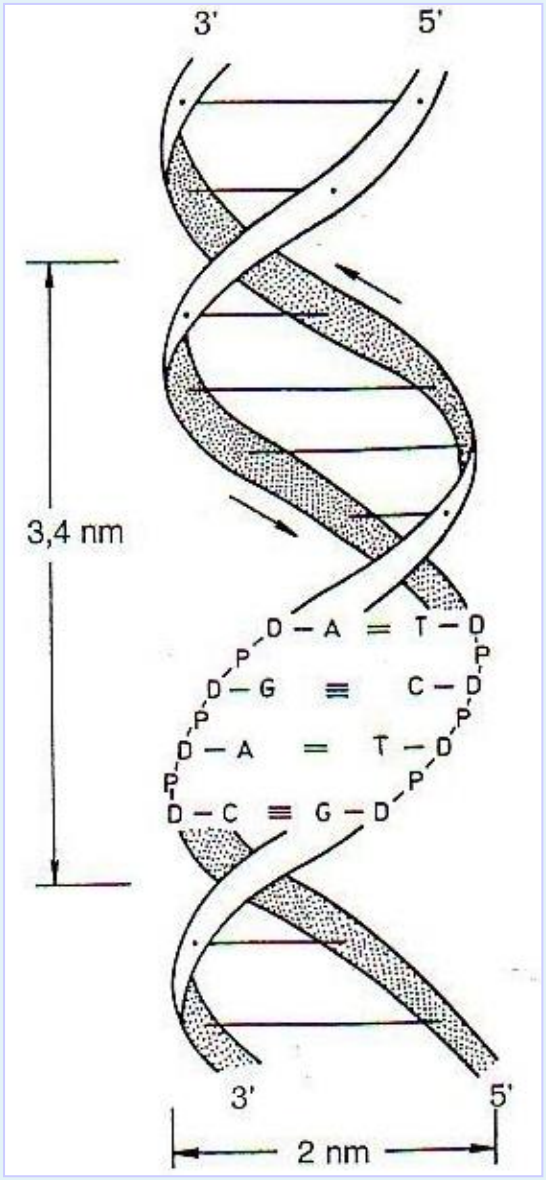
Double stranded DNA:

2 antiparallel strands of DNA: **5′→ 3′**

3′→ 5

3′→ 5′ - sense strand

5′→ 3′ - antisense strand



Structure of DNA

Complementarity of pairing bases A = T

G ≡ C

Bonds between nucleotides: covalent

Bonds between bases: hydrogen

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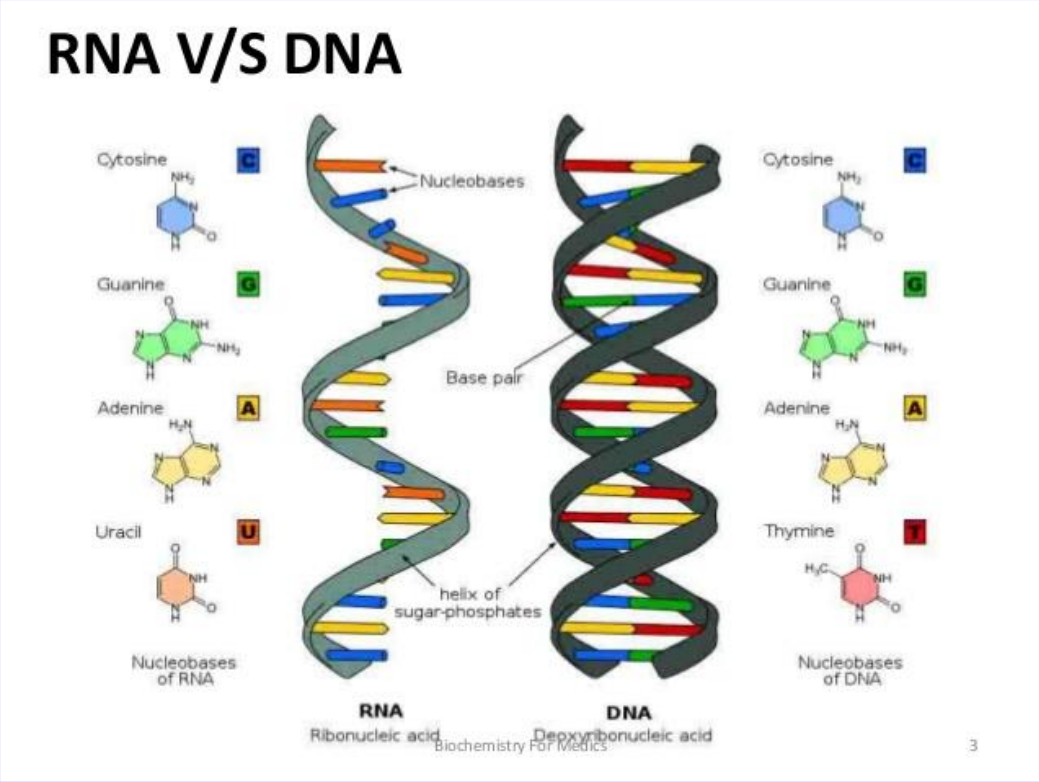
Mechanical and thermal stability of DNA:

Important for:

- genetic analysis methods (melting temperature)
- forensic medicine
- ancient DNA

Structure of RNA



Nucleotide:

- **sugar: ribose**
- **phosphate group**
- **nitrogenous base – adenine A**
  - **uracyl U**
  - **guanine G**
  - **cytosine C**

One strand of RNA 5´→ 3´

Types of RNA: **mRNA** (messenger RNA) – transcription of genetic information

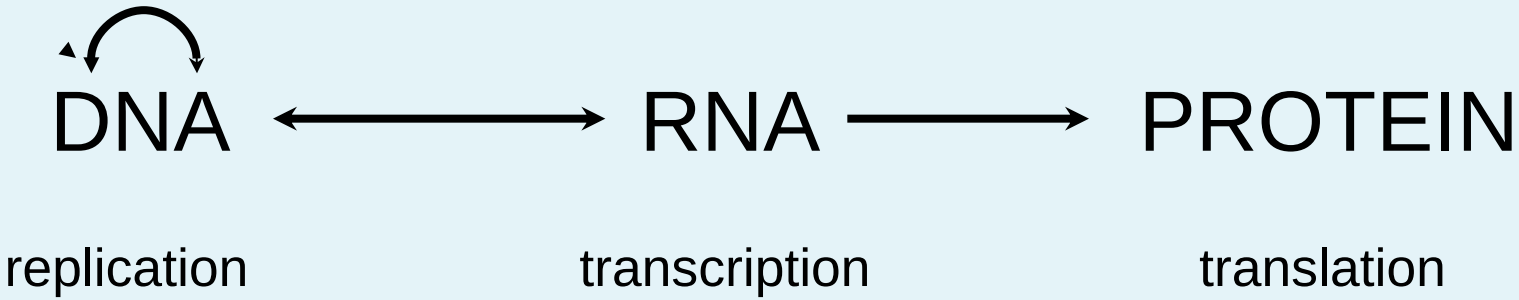
tRNA (translational RNA) – translation of genetic information into sequence of amino acids in protein

rRNA (ribosomal RNA) – participation in protein synthesis on ribosomes

microRNA – regulatory function

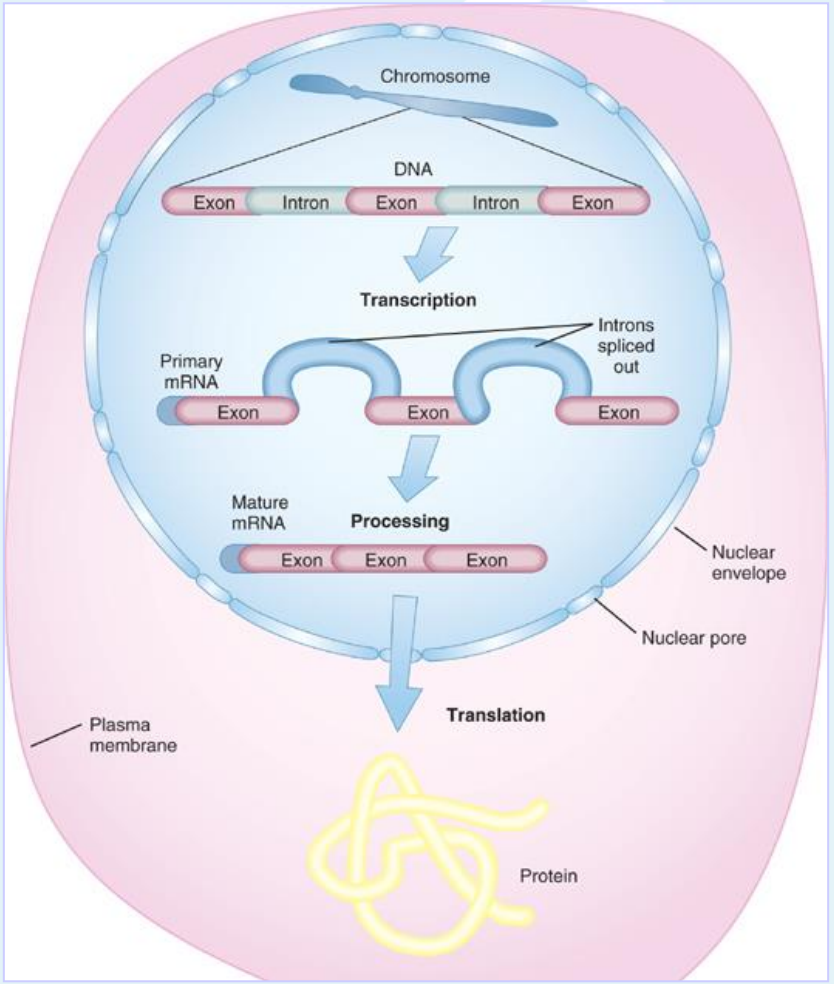
The central dogma of molecular biology

THE CENTRAL DOGMA:
DNA → RNA → PROTEIN



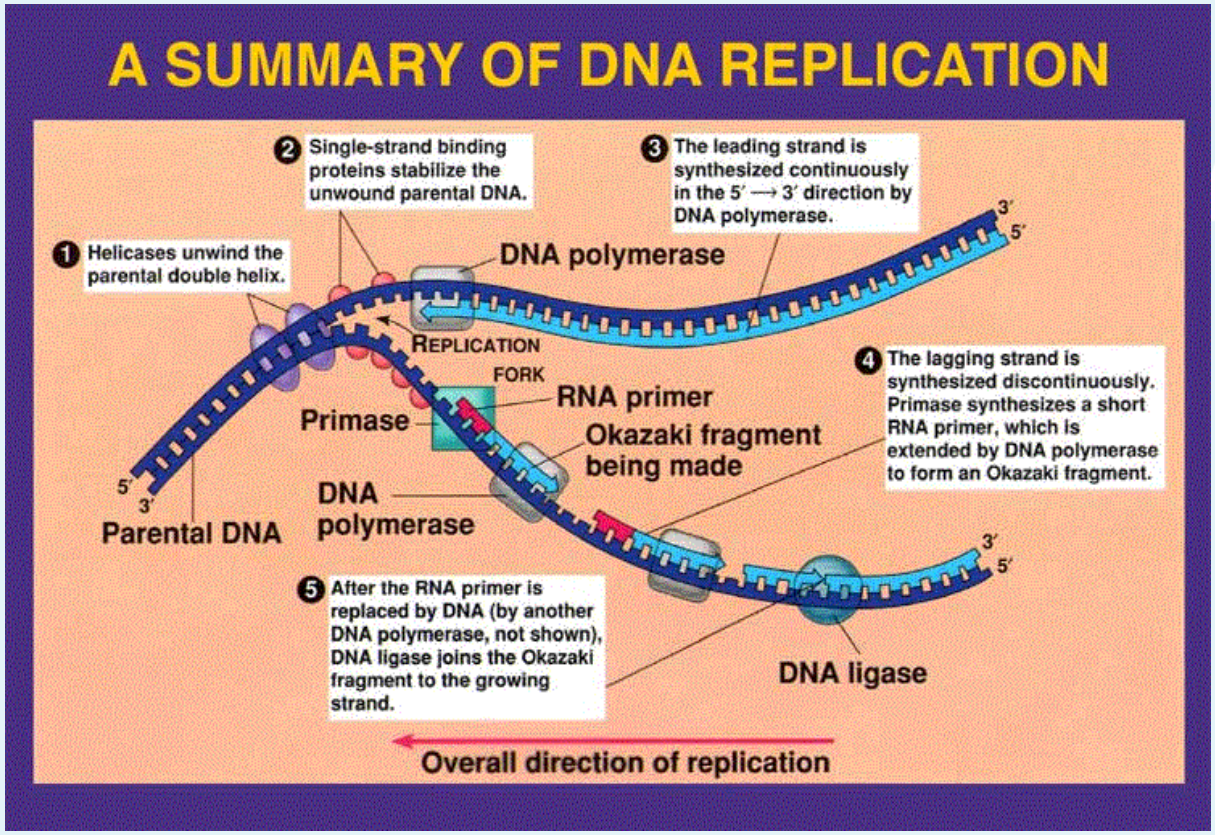
Realization of genetic information: from genes to proteins

- While **DNA is formed and replicated** in the **cell nucleus**, **protein synthesis takes place in the cytoplasm**
- The information contained in DNA must be transported to the cytoplasm and then used to dictate the composition of proteins
- This involves two processes: **transcription** and **translation**
- The DNA code is **transcribed** into mRNA, which then leaves the nucleus to be **translated** into proteins



DNA replication

- As cells divide to make copies of themselves, identical copies of DNA must be made and incorporated into the new cells.
- This is essential if DNA is to serve as the fundamental genetic material.



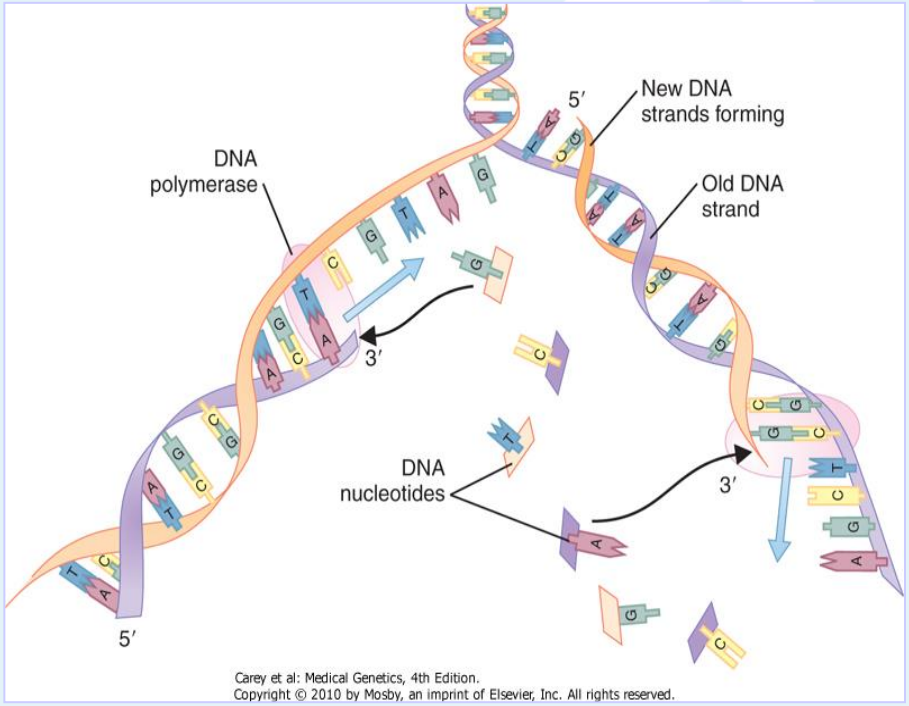
DNA Replication

- The single strand is said to be a **template** upon which the complementary strand is built. When replication is complete, a new double-stranded molecule identical to the original is formed

- Several different enzymes are involved in DNA replication. One enzyme unwinds the double helix, and another holds the strands apart. Key enzyme = **DNA polymerase**

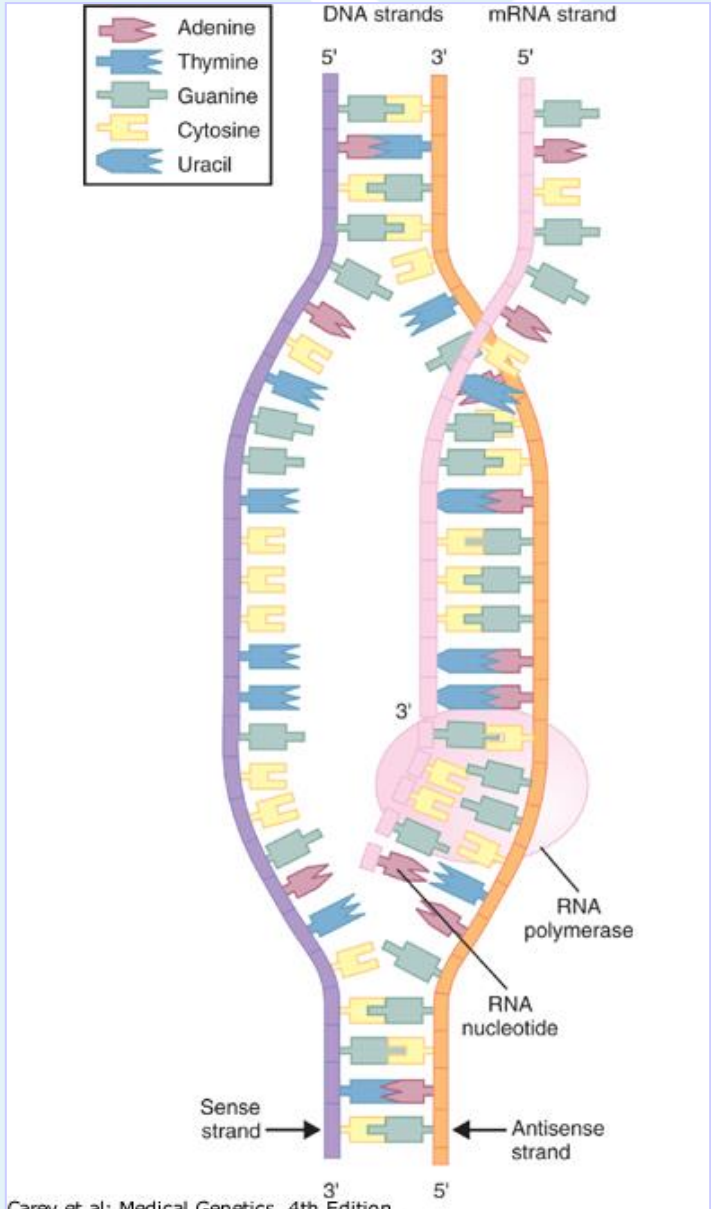
• **DNA replication** begins as the weak hydrogen bonds between bases break, producing single DNA strands with unpaired bases

• The consistent pairing of adenine with thymine and guanine with cytosine, known as **complementary base pairing,** is the key to accurate replication



Transcription

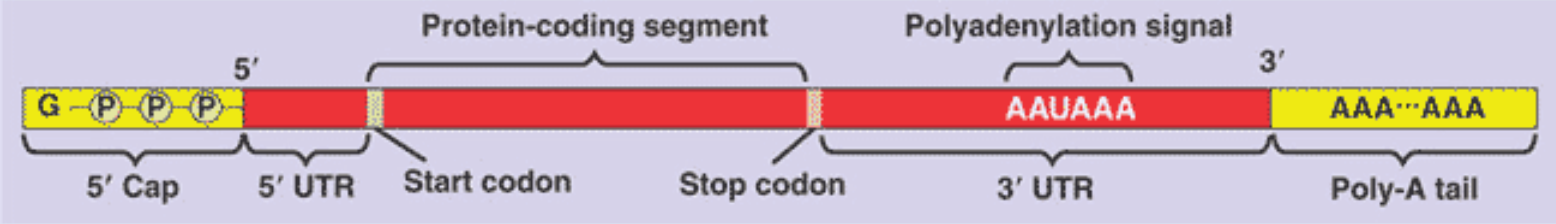
- **Transcription** is the process by which an RNA sequence is formed from a DNA template. The type of RNA produced by the transcription process is **messenger RNA (mRNA)**. This mRNA is a pre-cursor RNA **(pre-mRNA)**
- To initiate mRNA transcription, one of the **RNA polymerase** enzymes binds to a **promoter** site on the DNA



Carey et al: Medical Genetics, 4th Edition.

Transcription - mRNA

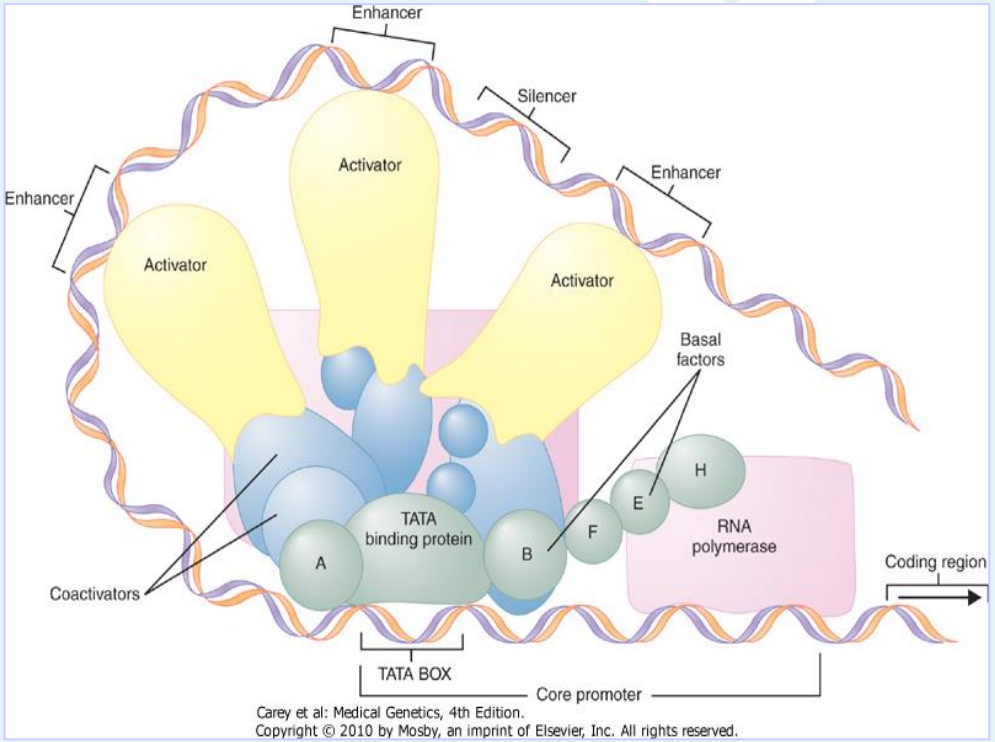
- RNA molecule is capped by the addition of a chemically modified guanine nucleotide. This **5' cap appears to help prevent the RNA molecule from being degraded.**
- Transcription continues until a group of bases called a **termination sequence** is reached
- Near this point, a series of 100 to 200 adenine bases are added to the 3' end of the RNA molecule- known as the **poly-A tail**, may be involved **in stabilizing the mRNA molecule**
- This mRNA molecule is termed the **primary transcript**



Transcription and the regulation of gene activity

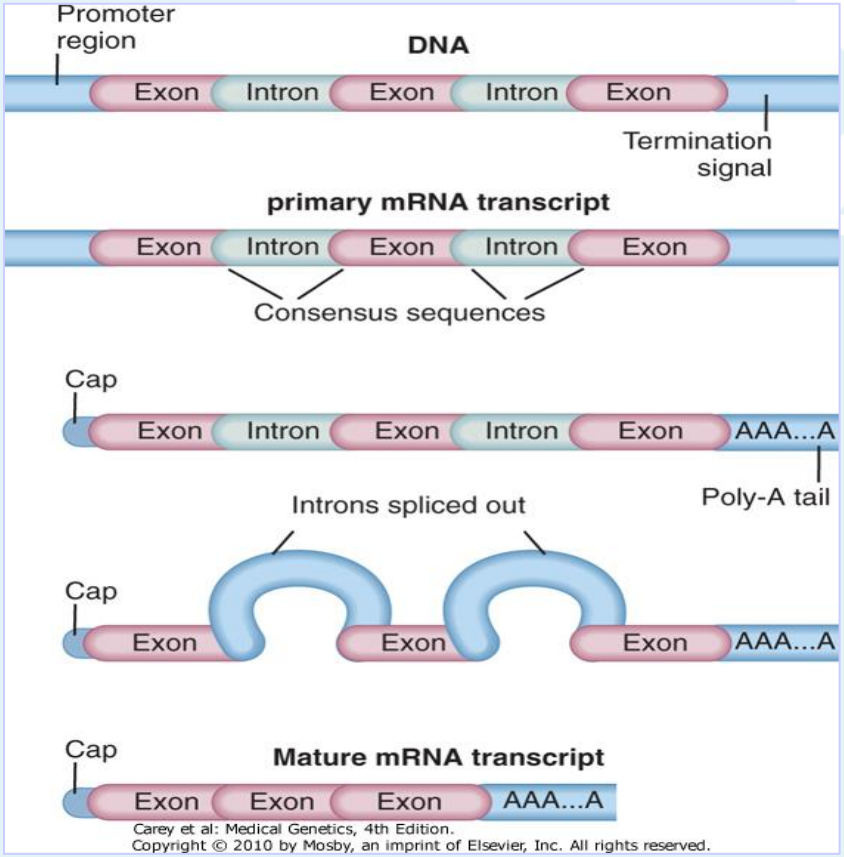
- Many different proteins participate in the process of transcription. These are termed **transcription factors.**

- Transcriptional activity of specific genes can be greatly increased by interaction with sequences called **enhancers - activators**.
- Whereas enhancers help to increase the transcriptional activity of genes, other DNA sequences, known as **silencers,** help to repress the transcription of genes through a similar series of interactions



Gene splicing

- Introns are spliced out of the primary mRNA transcript before the mature transcript leaves the nucleus. Exons contain the mRNA that specifies proteins.



Alternative pre-mRNA splicing

- Some genes contain **alternative splice sites**, which allow the same primary transcript to be spliced in different ways, ultimately producing different protein products from the same gene.
- Errors in gene splicing, like replication errors, are a form of mutation that can lead to genetic disease

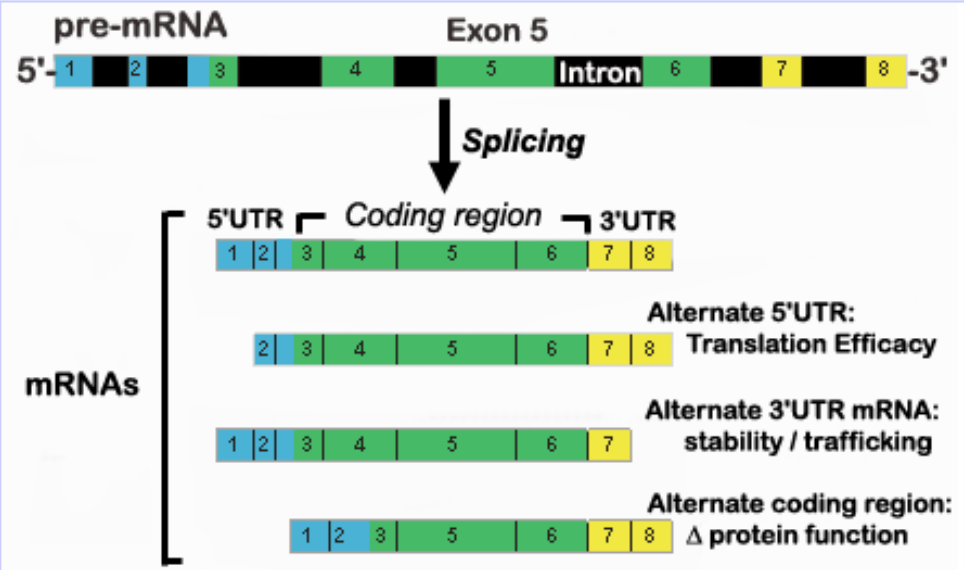
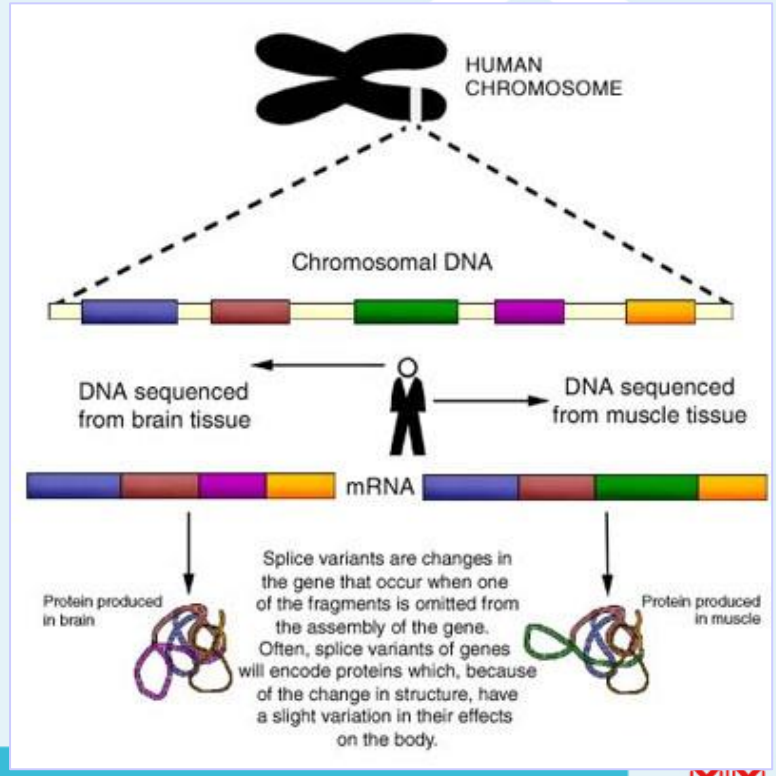
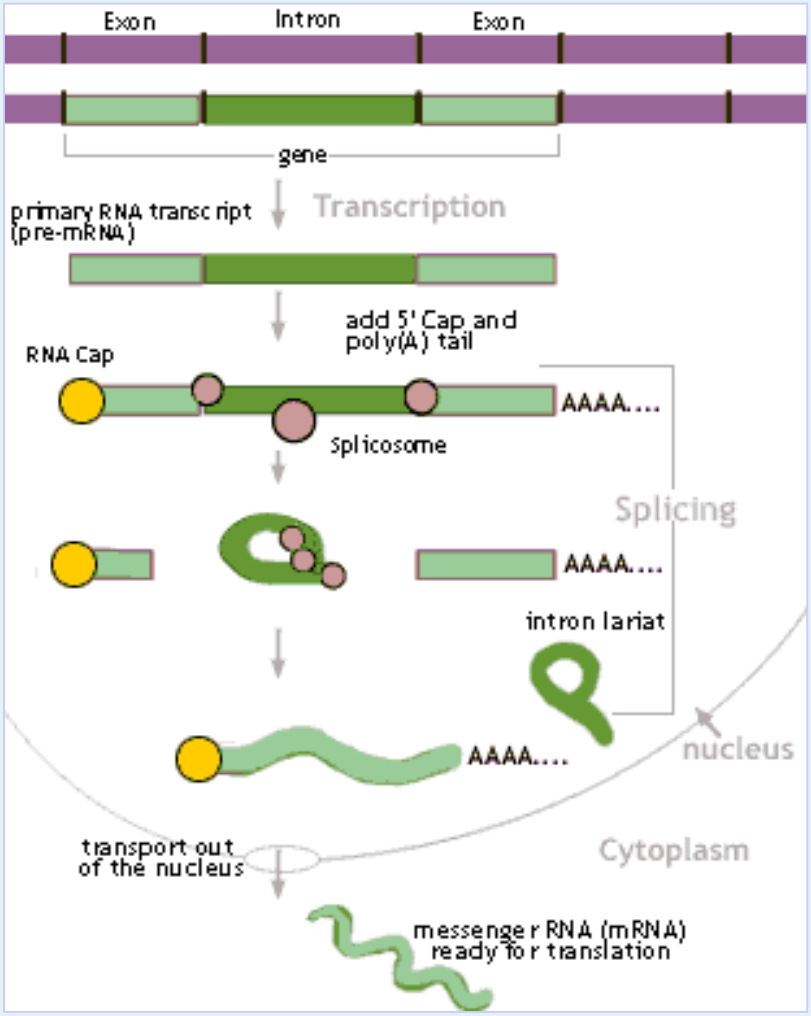


Figure 1. Alternative splicing can produce multiple mRNAs from a single gene



Processing pre-mRNA into mRNA - overview



- splicing of introns
- introduction of cap at the 5´-end of mRNA
- polyadenylation at 3´-end of mRNA

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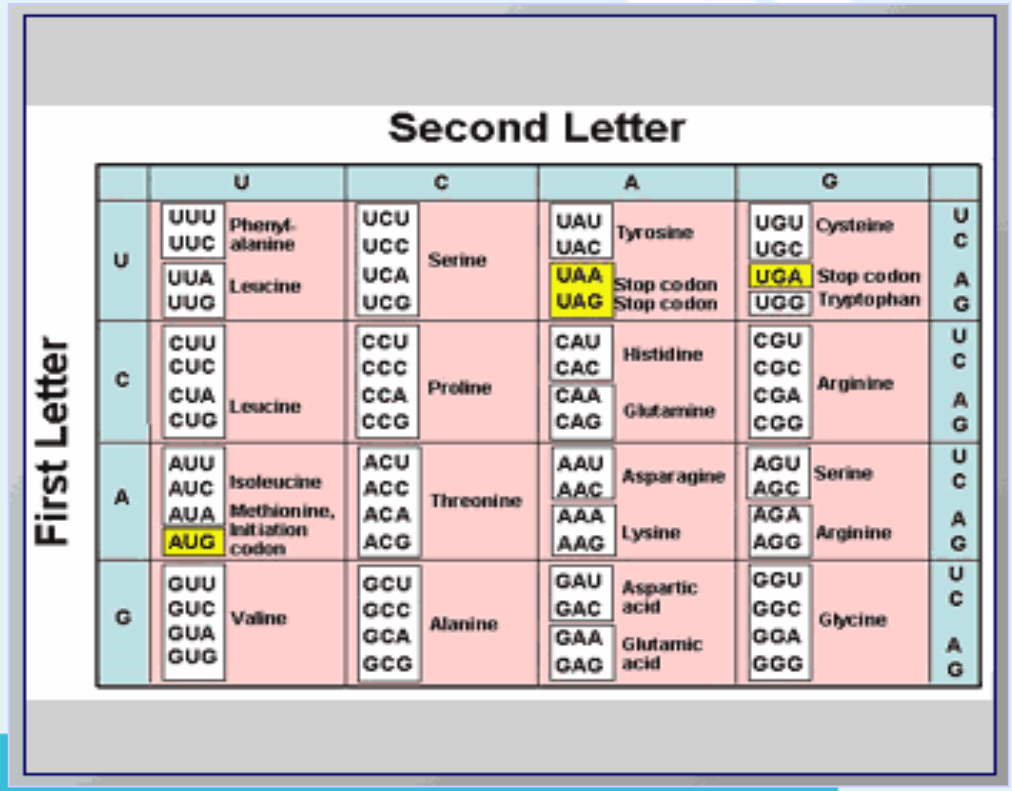
- transport out of the nucleus in cytoplasm
- mRNA is ready for translation

The genetic code

- Proteins are composed of one or more **polypeptides**, which are in turn composed of sequences of **amino acids**.
  The body contains 20 different types of amino acids, and the amino acid sequences that make up polypeptides must in some way be designated by the DNA after transcription into mRNA.

- The correspondence between specific codons and amino acids, known as the **genetic code.**



Features of genetic code

- **Universal** (exception - mt genom)

- **Degenerated** – some amino acids are coded for more than 1 one codon

  We have:

  64 codons – **61** of them have **coding function**

  - **3 STOP codons** (UAA, UAG, UGA) signal for the end of a gene

  20 amino acids

- **Non-overlapping** – each triplet codon codes for a specific amino acid (exception – some phags and bacteria)

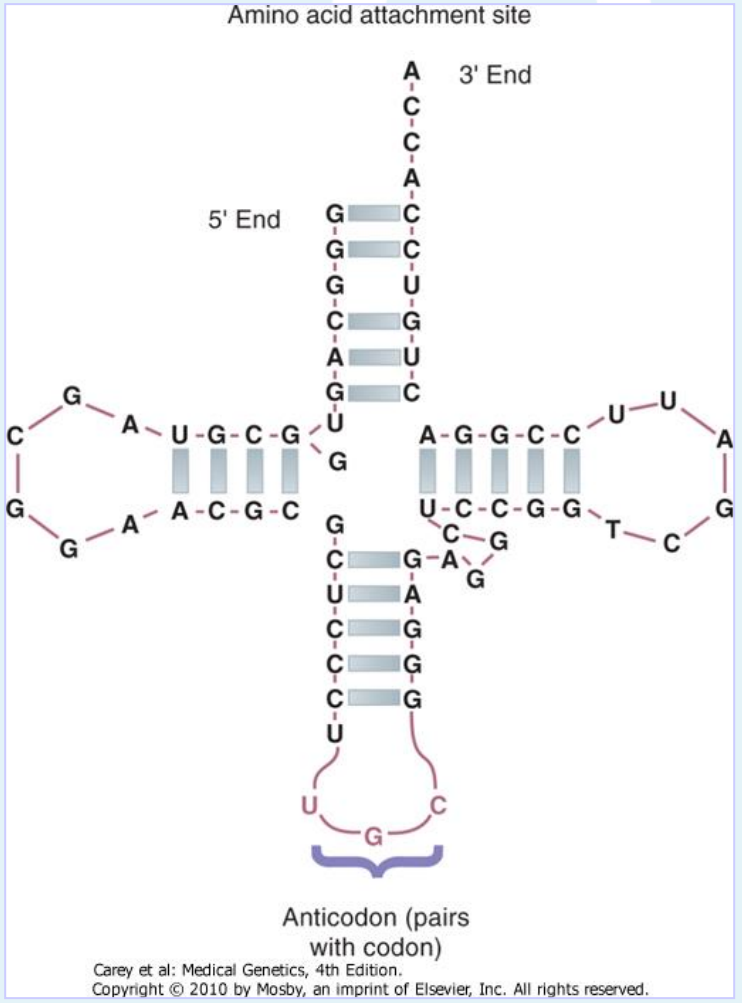
Second Letter

First Letter	U	C	A	G	
U	UUU Phenyl-alanine UUC UUA Leucine UUG	UCU UCC UCA Serine UCG	UAU Tyrosine UAC UAA Stop codon UAG Stop codon	UGU Cysteine UGC UGA Stop codon UGG Tryptophan	U C A G
C	CUU CUC CUA Leucine CUG	CCU CCC CCA Proline CCG	CAU Histidine CAC CAA Glutamine CAG	CGU CGC CGA Arginine CGG	U C A G
A	AUU AUC Isoleucine AUA Methionine, Initiation codon AUG	ACU ACC ACA Threonine ACG	AAU Asparagine AAC AAA Lysine AAG	AGU Serine AGC AGA Arginine AGG	U C A G
G	GUU GUC GUA Valine GUG	GCU GCC GCA Alanine GCG	GAU Aspartic acid GAC GAA Glutamic acid GAG	GGU GGC GGA Glycine GGG	U C A G

Translation

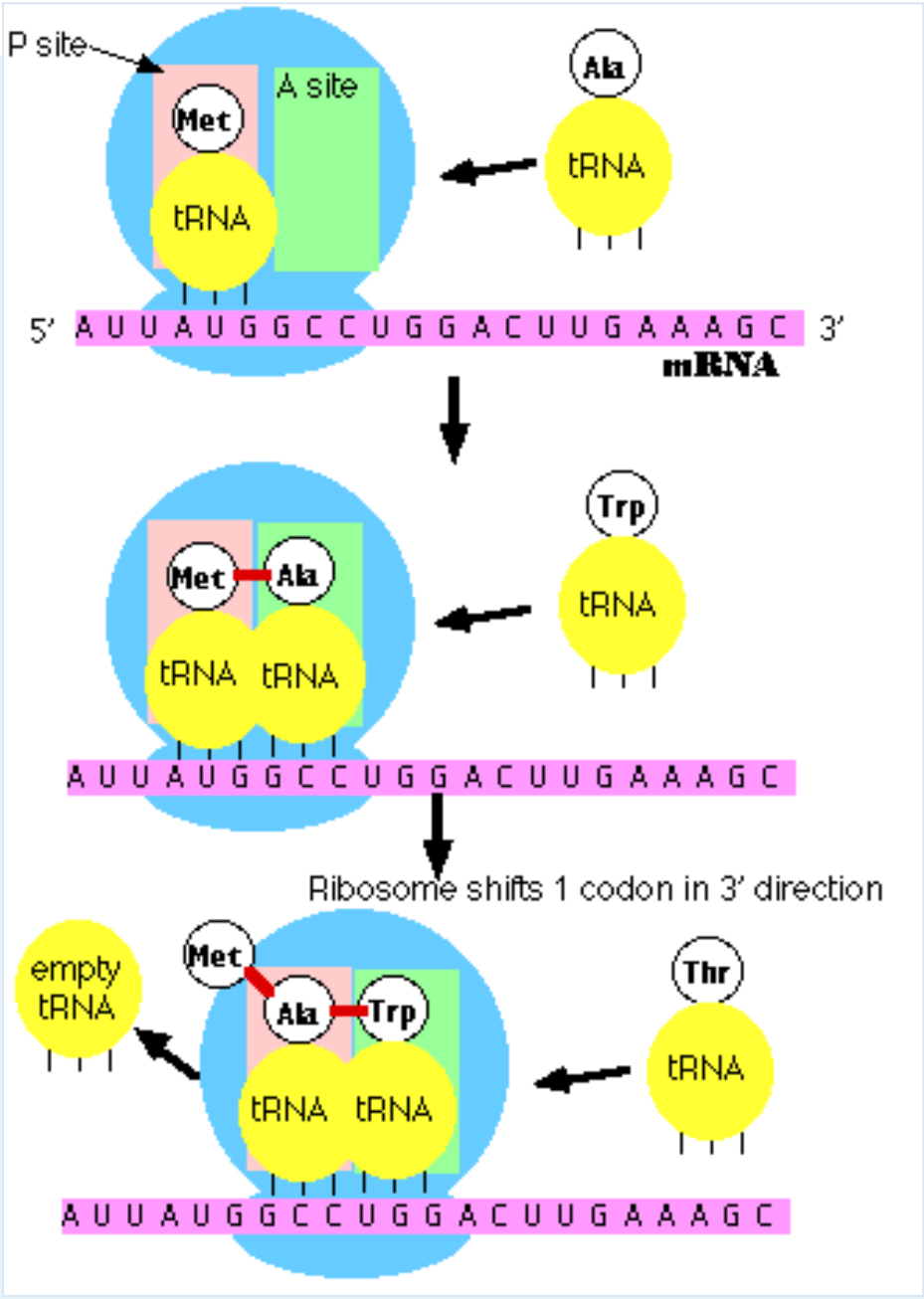
- **Translation** is the process in which **mRNA provides a template for the synthesis of a polypeptide.**

- **transfer RNA (tRNA),** which are cloverleaf-shaped RNA strands of about 80 nucleotides
- each tRNA molecule has a site at the 3' end for the attachment of a **specific amino acid** by a covalent bond.
- At the opposite end of the cloverleaf is a sequence of three nucleotides called the **anticodon**, **which undergoes complementary base pairing with an appropriate codon in the mRNA.**

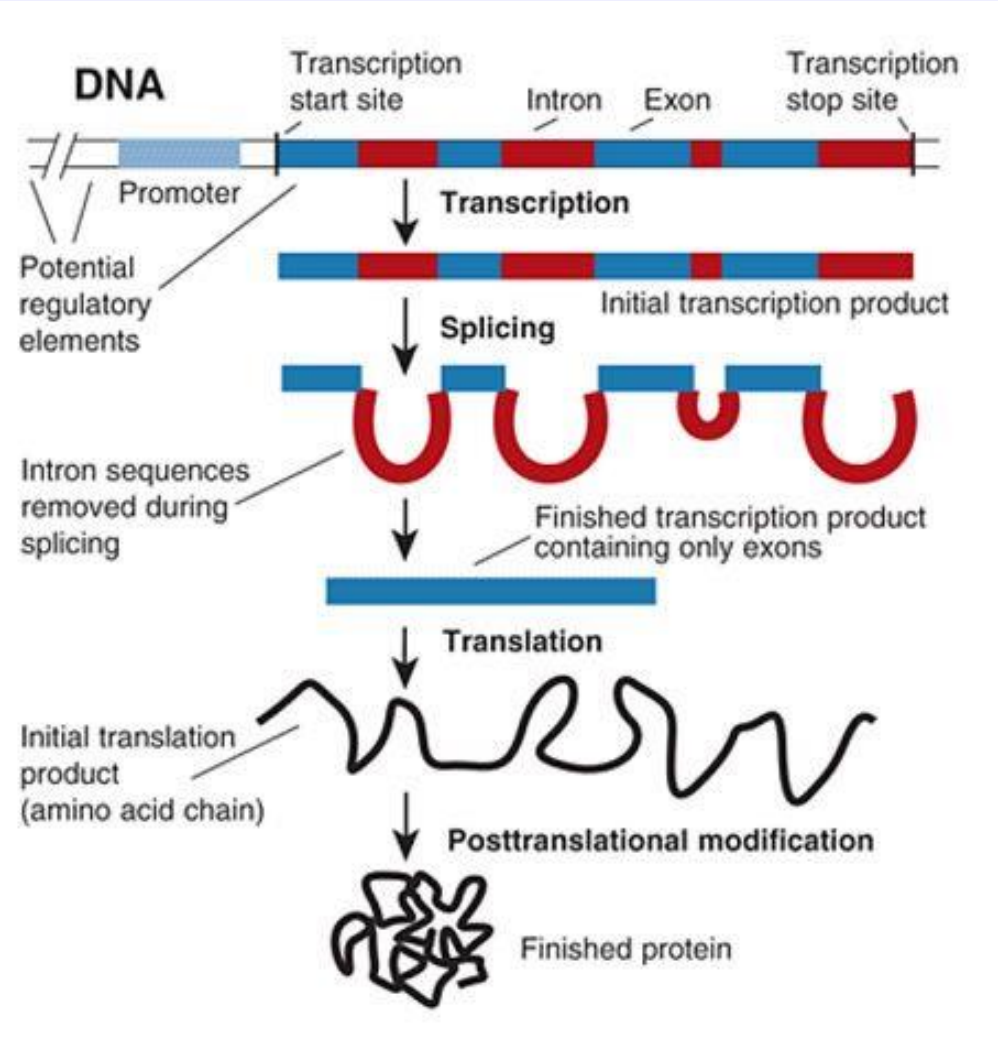


Translation

- The attached amino acid is then transferred to the polypeptide chain being synthesized.
- The cytoplasmic site of protein synthesis is the **ribosome**, which consists of enzymatic proteins and **ribosomal RNA (rRNA)**.
- **Posttranslational modification**



Realization of genetic information – the overview



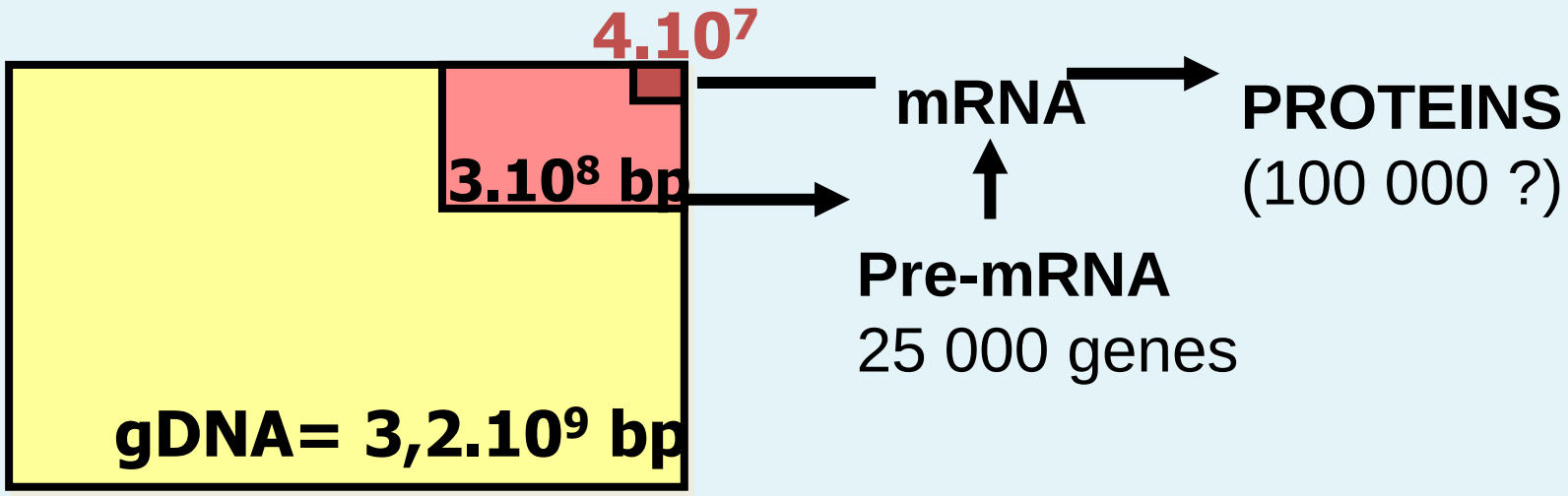
Vital Statistics of Human Genome

• Size of the genome	~ 3Gbp = 46 chromosomes
• Percent of genome classified as repeats	35%
• Number of annotated genes	20 000 – 25 000
• Total size of gene deserts	605Mbp
• Percent of base pairs spanned by genes	25.5-37.8%
• Percent of base pairs in intergenic DNA	74.5-63.6%
• Longest intergenic region (between annotated genes)	Chr 13(3,038,416 bp)

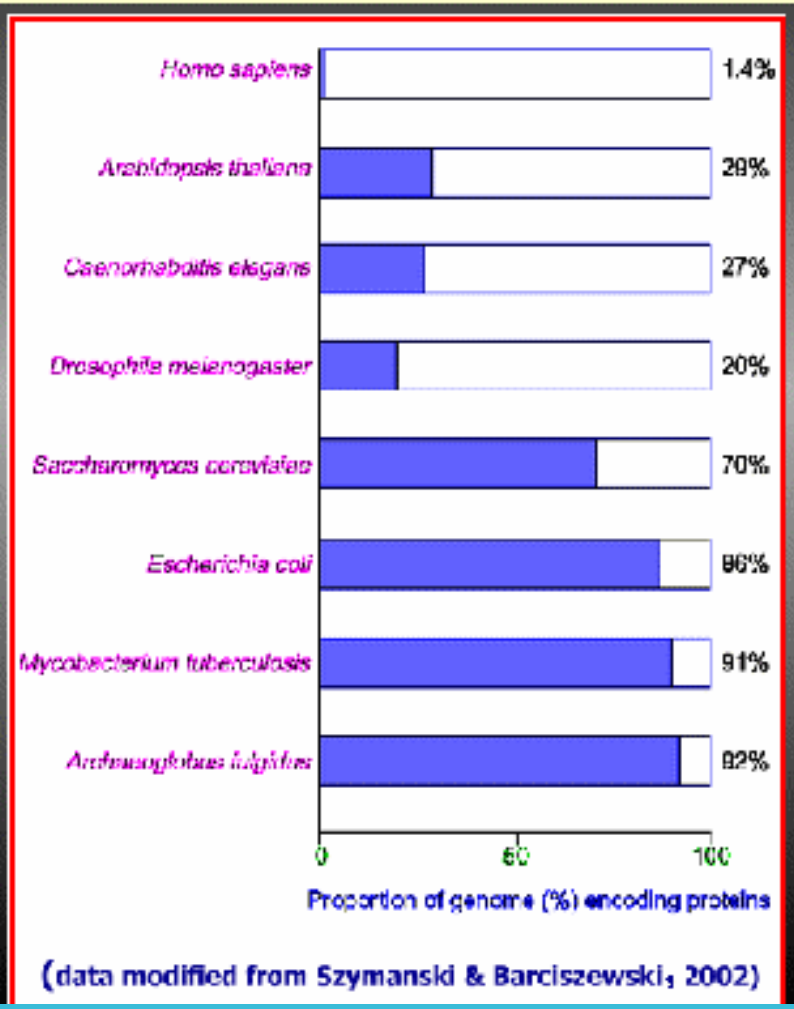
Celera Genomics

Human Genome

- Of the 3 billion base pairs of DNA in the genome, less than **1.5%** actually **encodes proteins** (= 232 000 exones = 10 exones/gene; almost the same number are pseudogenes)
- and only about **5% is thought to contain regulatory elements** that influence or determine patterns of gene expression during development or in different tissues
- **It means just 4.10^7 nukleotides have encoding function** (only 4-times more than in Saccharomyces)



Protein-coding sequences constitute a very small part of the genome in eukaryotes



(data modified from Szymanski & Barciszewski, 2002)

The vast majority of DNA in higher eukaryotes is unlikely to be JUST "JUNK"!

Genomes of different organism

Organism	Number of genes	Amount of DNA (bp)	chromosomes
Viruses	200	100 000	1
Mitochondria (human)	37	16 569	1
Escherichia coli	4000	$4,6.10^6$	1
Sacharomyces	5700	$1,2 .10^7$	32
Drosophyla	12000	$1,4.10^8$	10
Homo sapiens	25000	$3,2.10^9$	46
Oryza sativa	45000	$4,3.10^8$	24

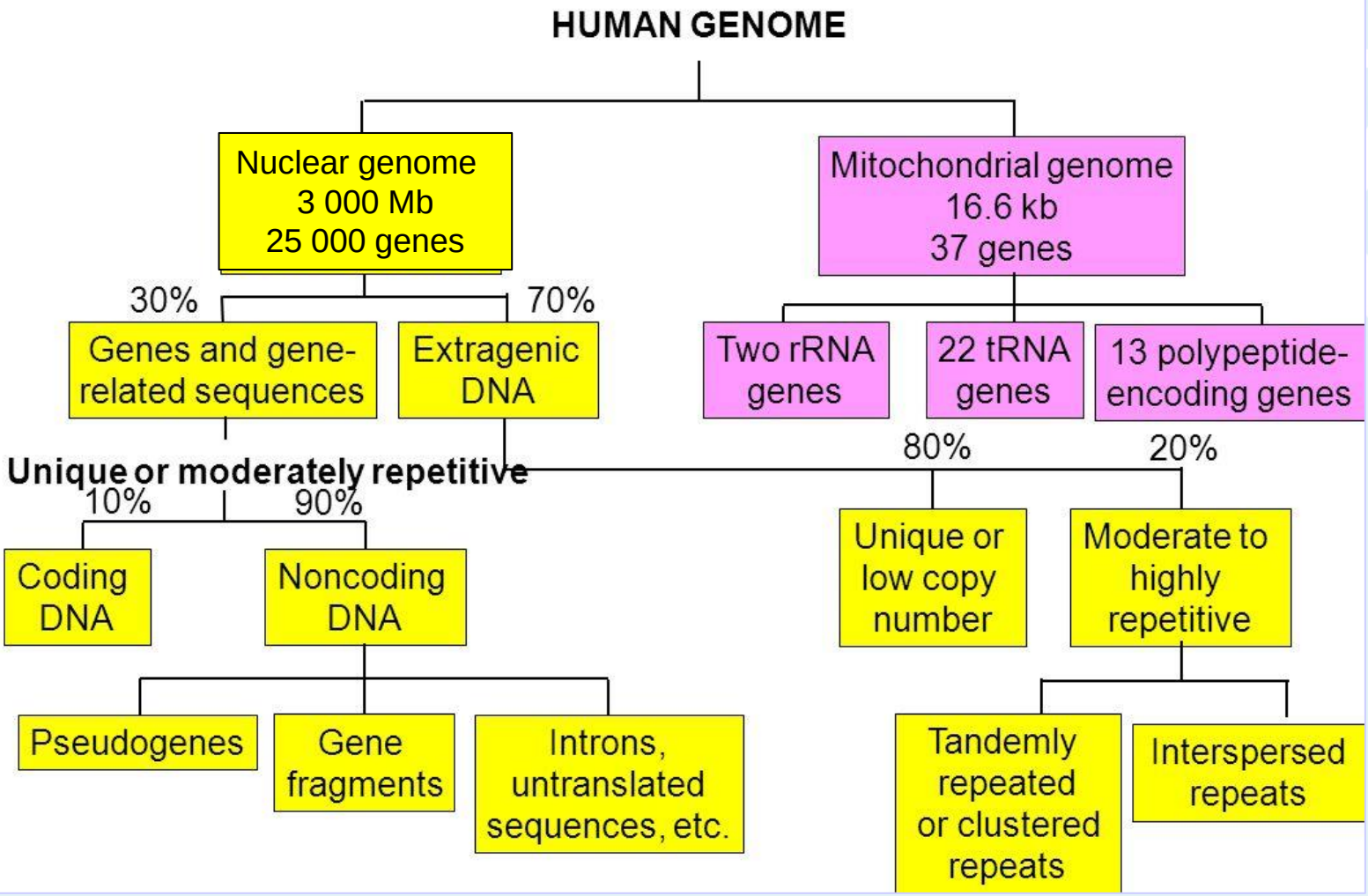
Organization of the Human Genome

- Only about half of the total linear length of the genome consists of so-called **single-copy** or **unique DNA**, that is, DNA whose nucleotide sequence is represented only once (or at most a few times)

- The rest of the genome consists of several classes of **repetitive DNA** and includes DNA whose nucleotide sequence is repeated, either perfectly or with some variation, hundreds to millions of times in the genome

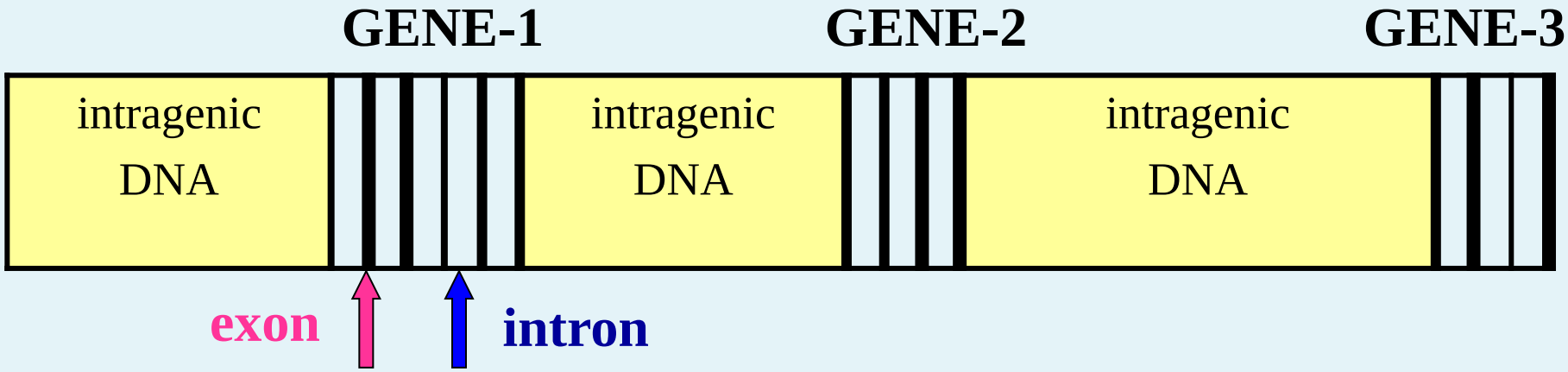
- Whereas most (but not all) of the estimated 25,000 genes in the genome are represented in single-copy DNA, **sequences in the repetitive DNA fraction contribute to maintaining chromosome structure** and are an important **source of variation between different individuals**; some of this variation **can predispose to pathological events**

Human Genome Organization

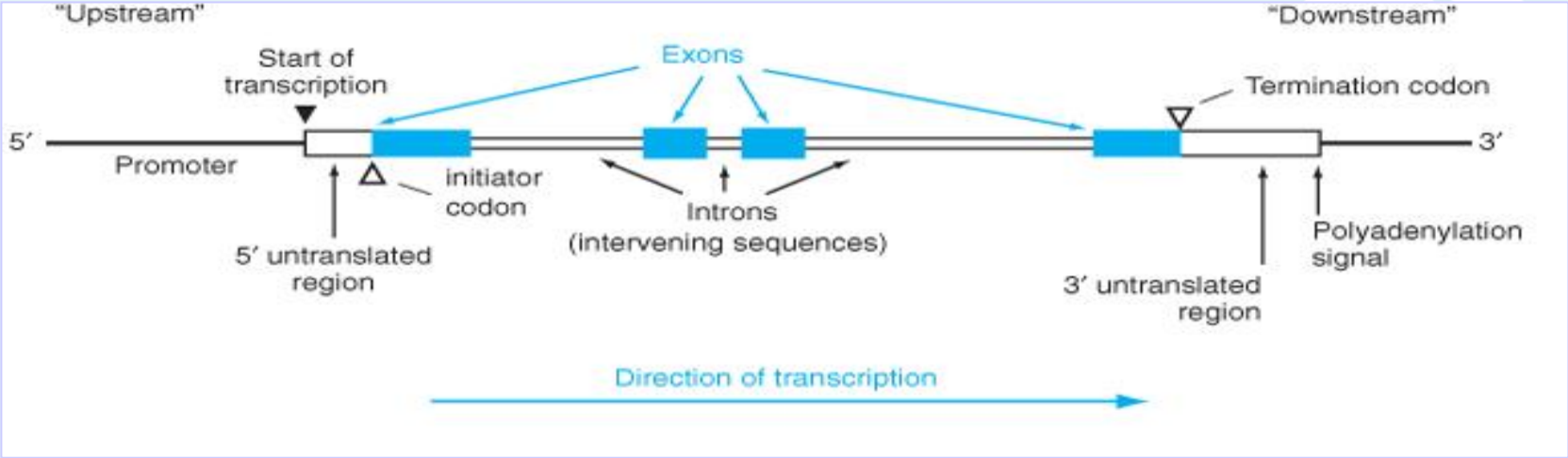


Human gene organization and structure

- the majority of genes are interrupted by one or more noncoding regions. These intervening sequences, called **introns**, are initially transcribed into RNA in the nucleus but **are not present in the mature mRNA** in the cytoplasm
- Introns alternate with **exons**, the segments of genes that **ultimately determine the amino acid sequence of the protein**, as well as certain flanking sequences that contain the 5' and 3' untranslated regions



Structural features of a typical human gene



- At the 5' end of each gene lies a **promoter** region that includes sequences responsible **for the proper initiation of transcription.**
- **The adjacent nucleotide sequences** provide the **molecular "start"** and **"stop" signals (termination codon)** for the synthesis of mRNA transcribed from the gene
- The regulatory elements, including **enhancers, silencers,** and **locus control regions**

Genetic variation: its origin and detection

- All genetic variation originates from the process known as **mutation**, which is defined as **a change in DNA sequence.**
- Mutations can affect either **germline cells** (cells that produce gametes) or **somatic cells** (all cells other than germline cells).
- **Mutations in somatic cells can lead to cancer** and are thus of significant concern.
- **Germline mutations can be transmitted from one generation to the next.**

Genetic variation: its origin and detection

- As a result of mutations, a gene can differ among individuals in terms of its DNA sequence. The **differing** sequences **(variants)** are referred to as **alleles**.
- **A gene's location on a chromosome** is termed a **locus** (from the Latin word for "place").
- If a person has **the same allele on both members of a chromosome pair,** he or she is said to be a **homozygote**.
- **If the alleles differ in DNA sequence,** the person is a **heterozygote**.
- The alleles that are present at a given locus are the person's **genotype**.

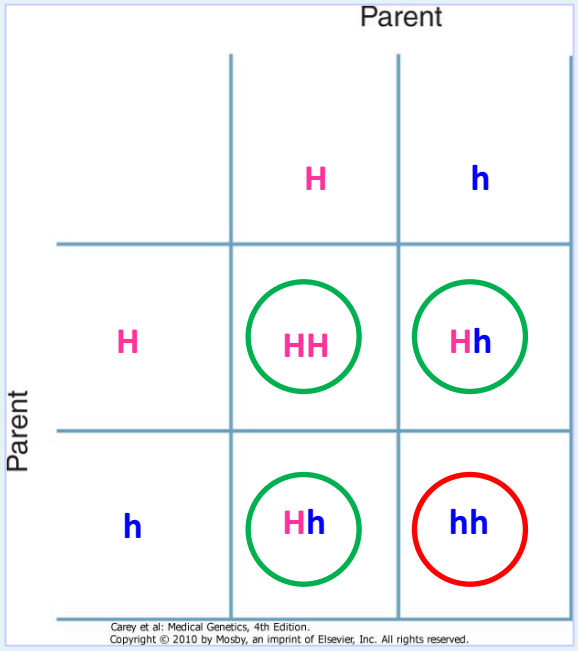
Genetic variation: its origin and detection

- In human genetics, the term **mutation** has often been reserved for DNA sequence changes that **cause genetic diseases** and are consequently relatively rare
- DNA sequence variants that are **more common in populations** (i.e., in which two or more alleles at a locus each have frequencies exceeding 1%), are said to be **polymorphic**
- Such **loci** are termed **polymorphisms,** although nowadays alleles that have a frequency less than 1% are often called polymorphisms as well
- **Many polymorphisms are now known to influence the risks for complex, common diseases such as diabetes and heart disease,** so the distinction between mutation and polymorphism has become increasingly blurred

Genetic variation: its origin and detection

- One of Gregor Mendel's important contributions to genetics was to show that the **effects of one allele at a locus can mask those of another allele at the same locus.**

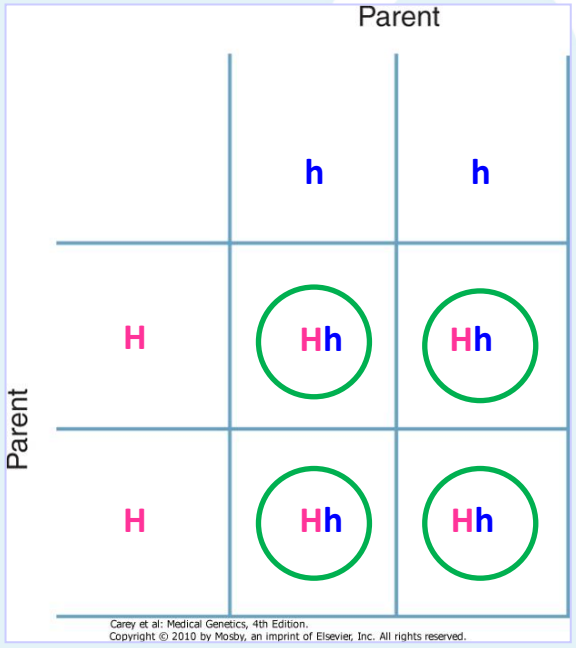
Punnett square illustrating a cross between *HH* and *hh* homozygote parents



H allele is **dominant**

h allele is **recessive**

Punnett square illustrating a cross between two *Hh* heterozygotes

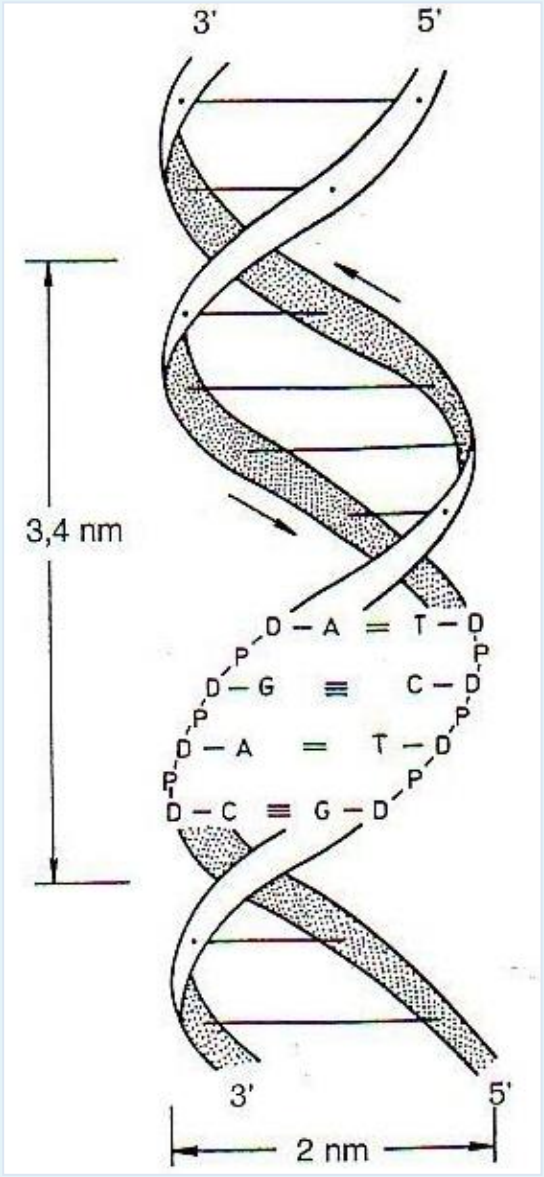


The Human Genome: the Chromosomal Basis of Heredity

- Physically, genes are composed of **deoxyribonucleic acid (DNA).** DNA provides the genetic blueprint for all proteins in the body. Thus, **genes ultimately influence all aspects of body structure and function.**

- Humans are estimated to have about **20,000 – 25,000 genes** (sequences of DNA that encode for ribonucleic acid [RNA] or proteins).

- An error (or **mutation**) in one of these genes **often leads to a recognizable genetic disease.**



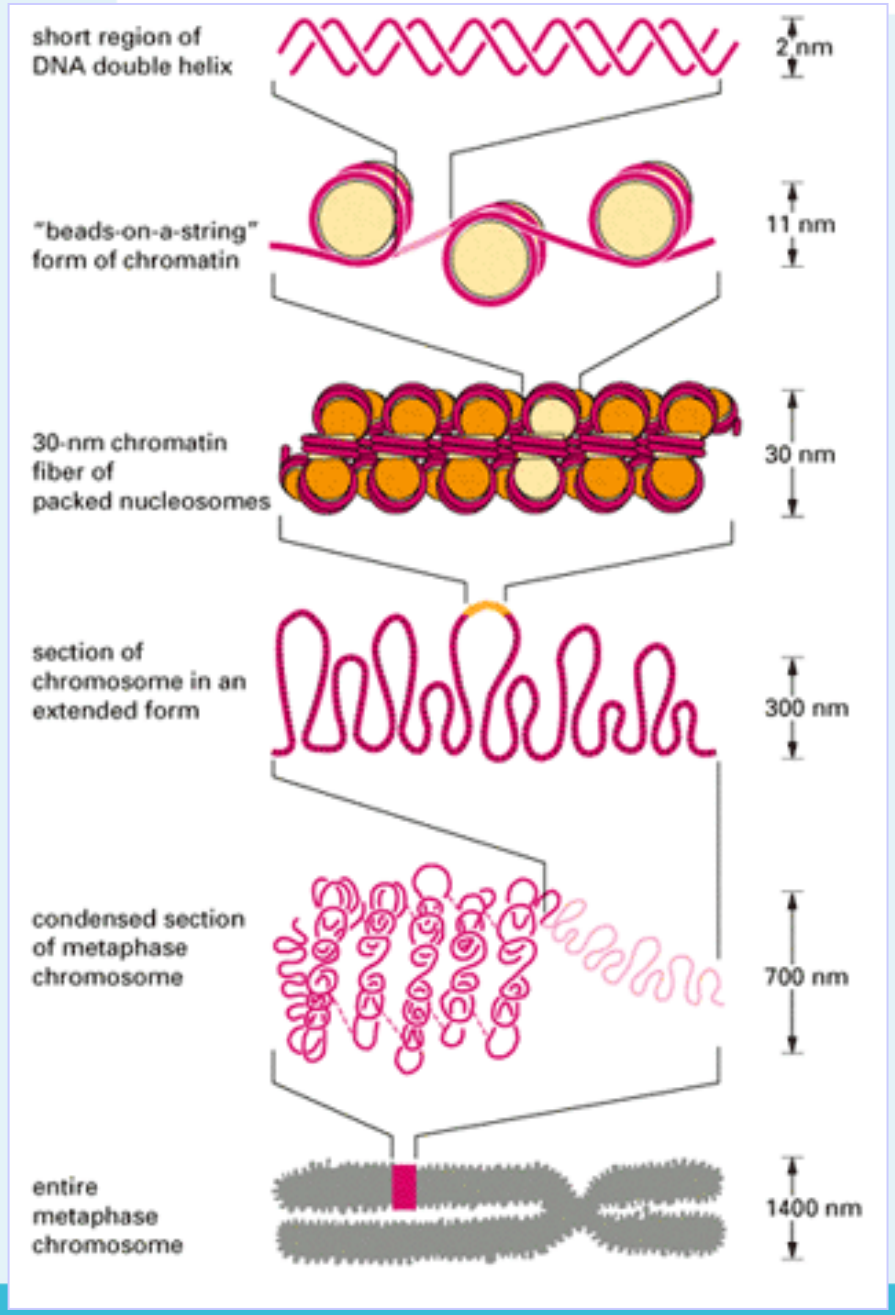
The Human Genome: the Chromosomal Basis of Heredity

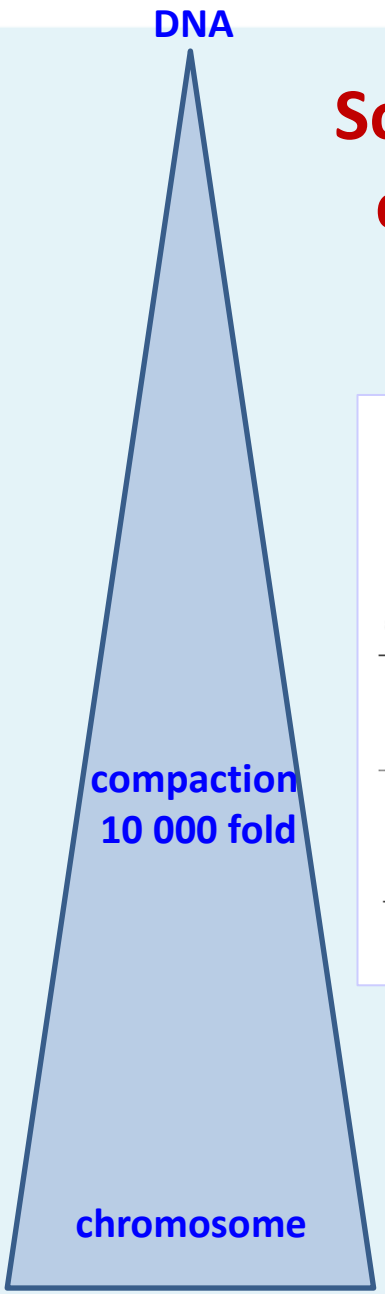
- Germinal cells - 3-billion-letter code (3.10^9 = 3Gbp) consist of (A, T, G, C), in relaxed state the length of DNA is about 2m

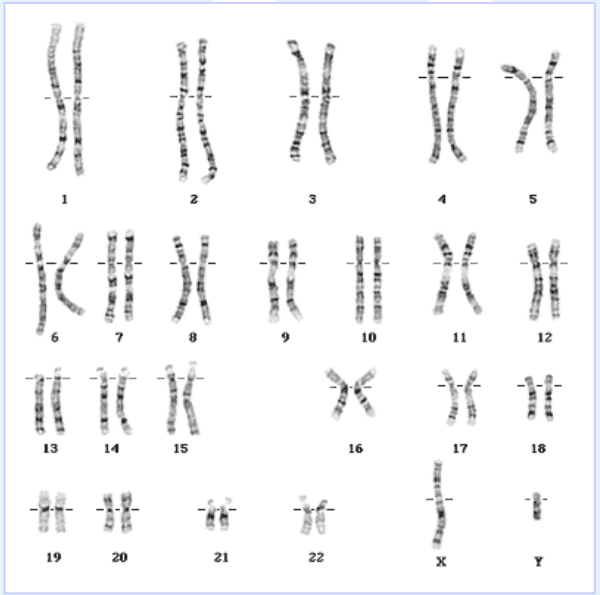
coiling and folding of DNA – protein (histone) complex into chromosome.

The length of the largest chromosome No. 1 is less than 0.5 mm

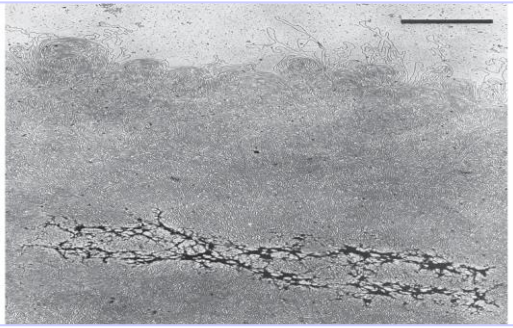
Solenoid structure of chromosome



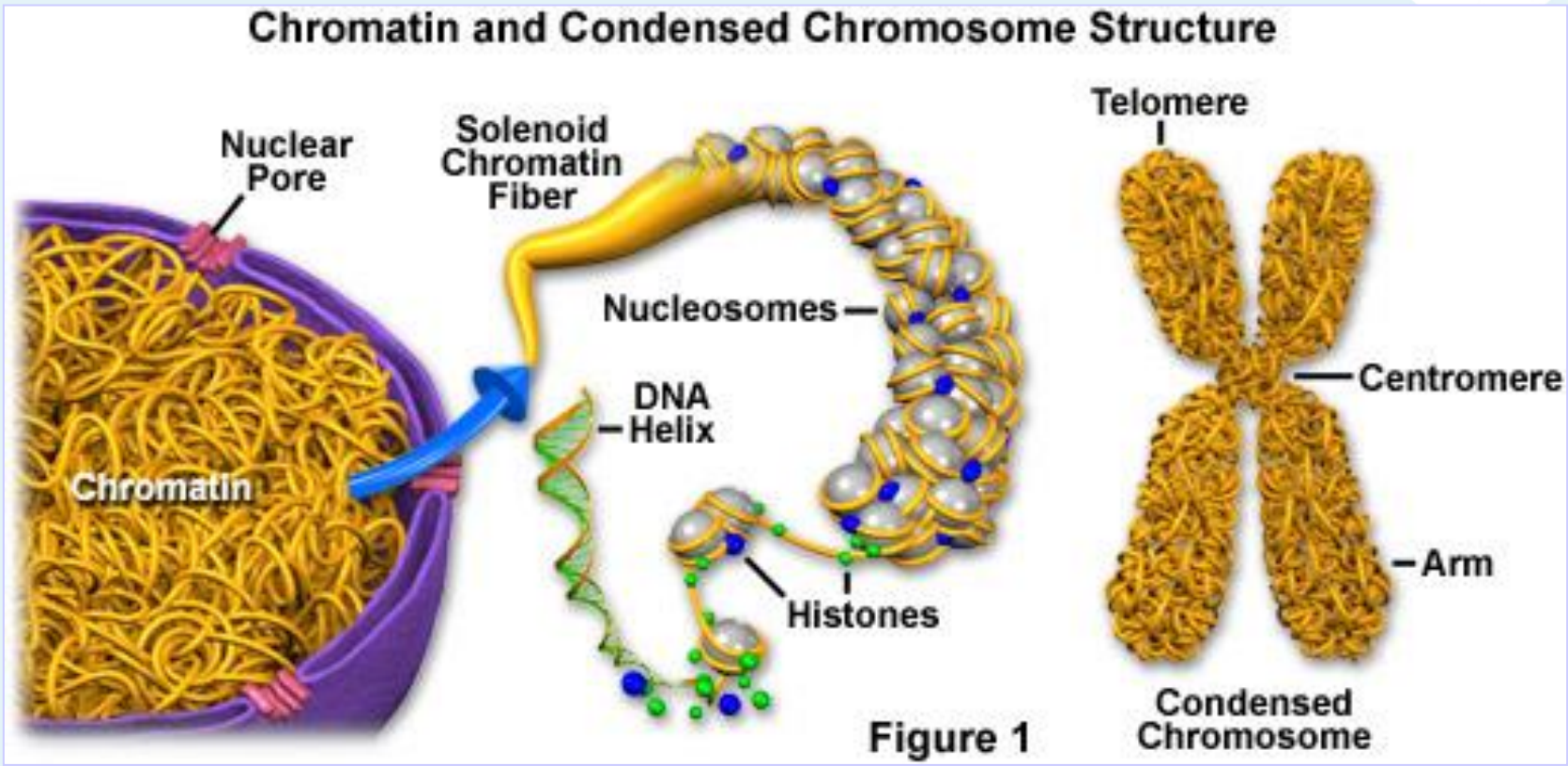




Chromatine and condensed chromosome structure



Electron micrograph of a protein-depleted human metaphase chromosome, showing the residual chromosome scaffold and loops of DNA.



Nuclear genome and chromosomes

Nuclear genome consists of 24 chromosomes:

22 autosomes

2 gonosomes X a Y

Each chromosome contain one molecule of DNA.

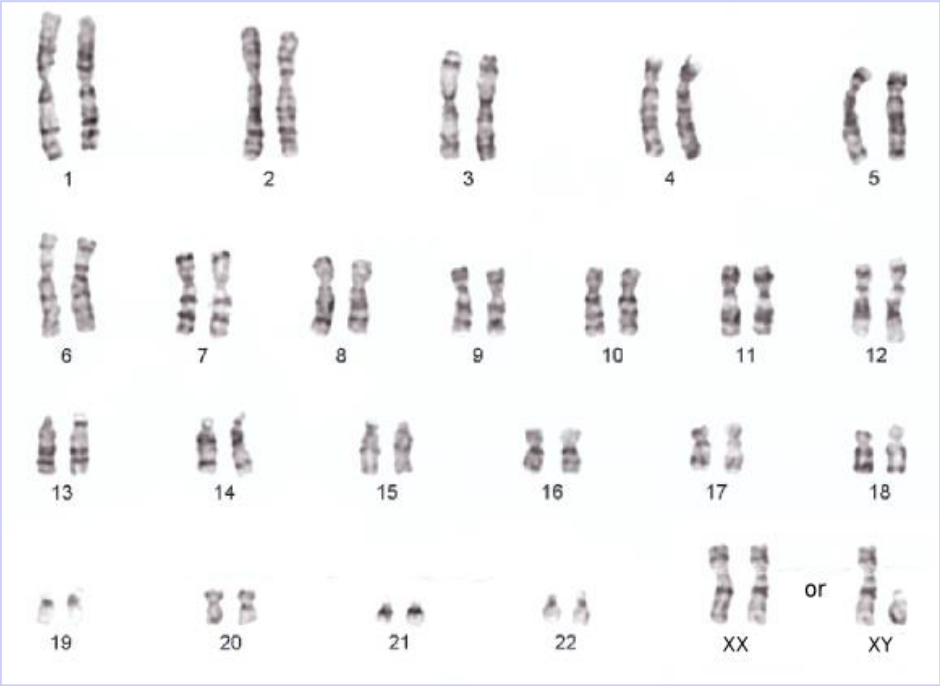
Gametes (oocytes and sperm) : **haploid genome** – 23 chromosomes

Somatic cells (cells of body): **diploid genome** – 46 chromosomes

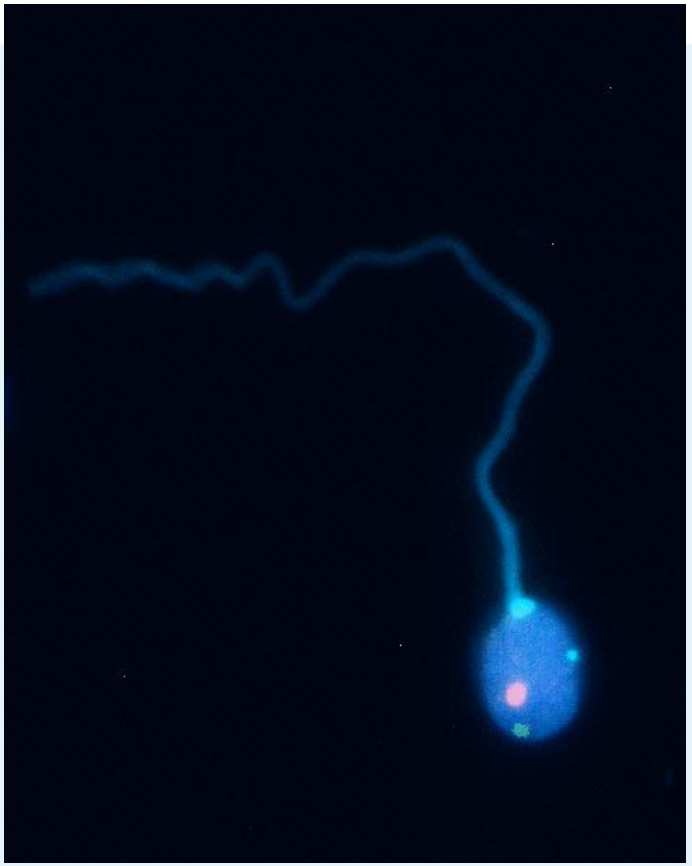
All chromosomes except of X and Y chromosomes exist as pairs of homollogical chromosomes with identical loci.

Locus – place of residency of the gene on the chromosome

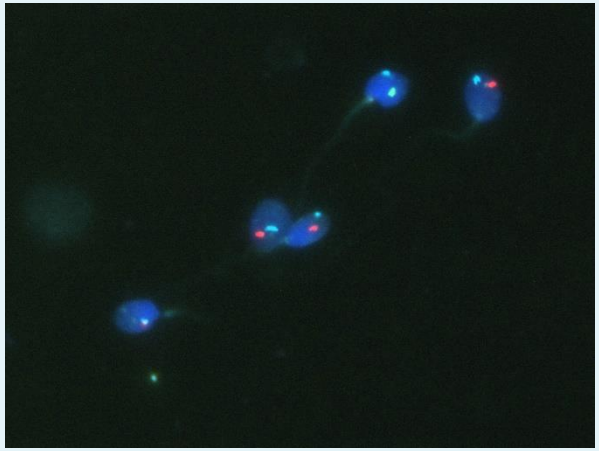
Alleles – variants of gene, which reside the same locus. Their difference is based on the structure and/or their function



Normal human female or male karyotype

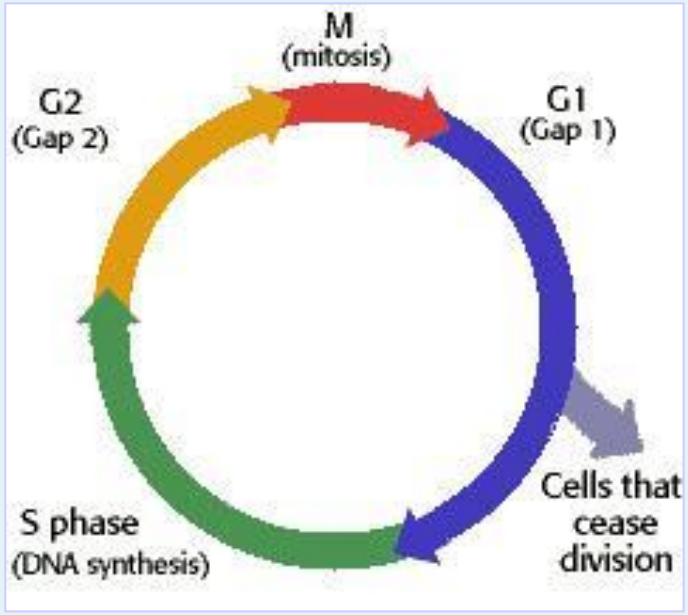


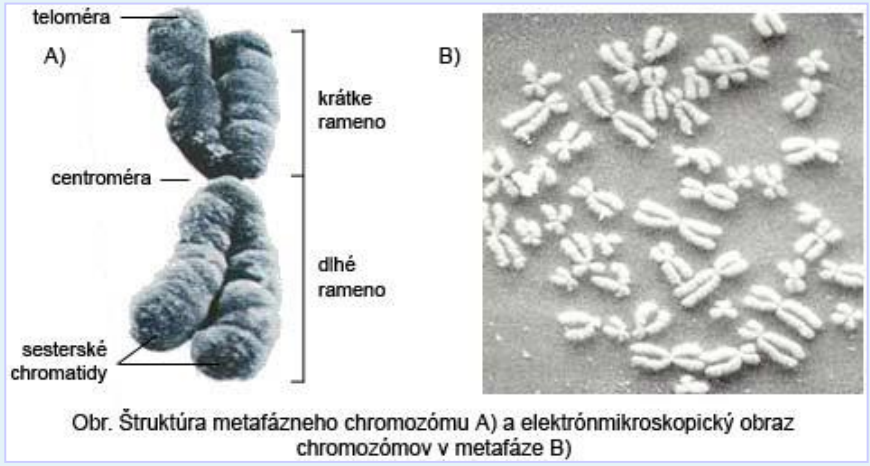
Diploid sperm:
1 chromosome X
1 chromosome Y
2 chromosomes 18



Normal sperm cells:
1 chromosome X and 1 chromosome 18
Or
1 chromosome Y and 1 chromosome 18

Organisation of chromatine during cell cycle





Obr. Štruktúra metafázneho chromozómu A) a elektrónmikroskopický obraz chromozómov v metafáze B)

Interphase – net of chromatine

- low condensation of chromatine
- transkriptional active

Metaphase of mitosis (meiosis)

– typical form of chromosomes

- much more condensed and packed chromatine
- transcriptional inactive

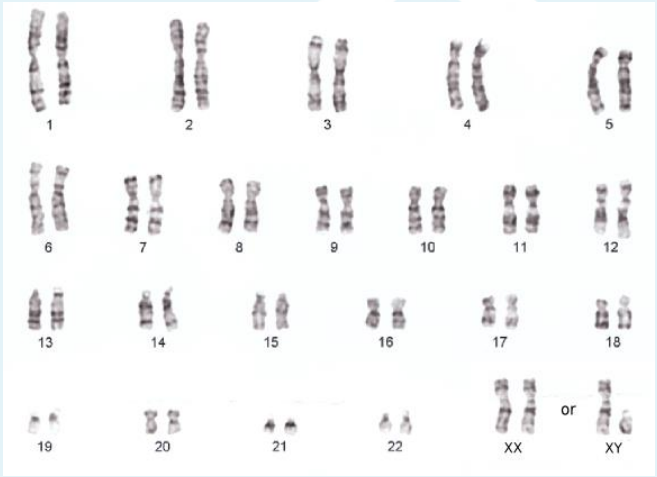
Types of chromatine

Euchromatine – present on many places on chromosomes

- diffuse staining
- genetic contains: transcriptional active and inactive regions, too

Heterochromatine – strongly condensed during all cell cycle

- dark stained regions of chromosomes
- genetic contain: repetitive sequences, which are transcriptional inactive



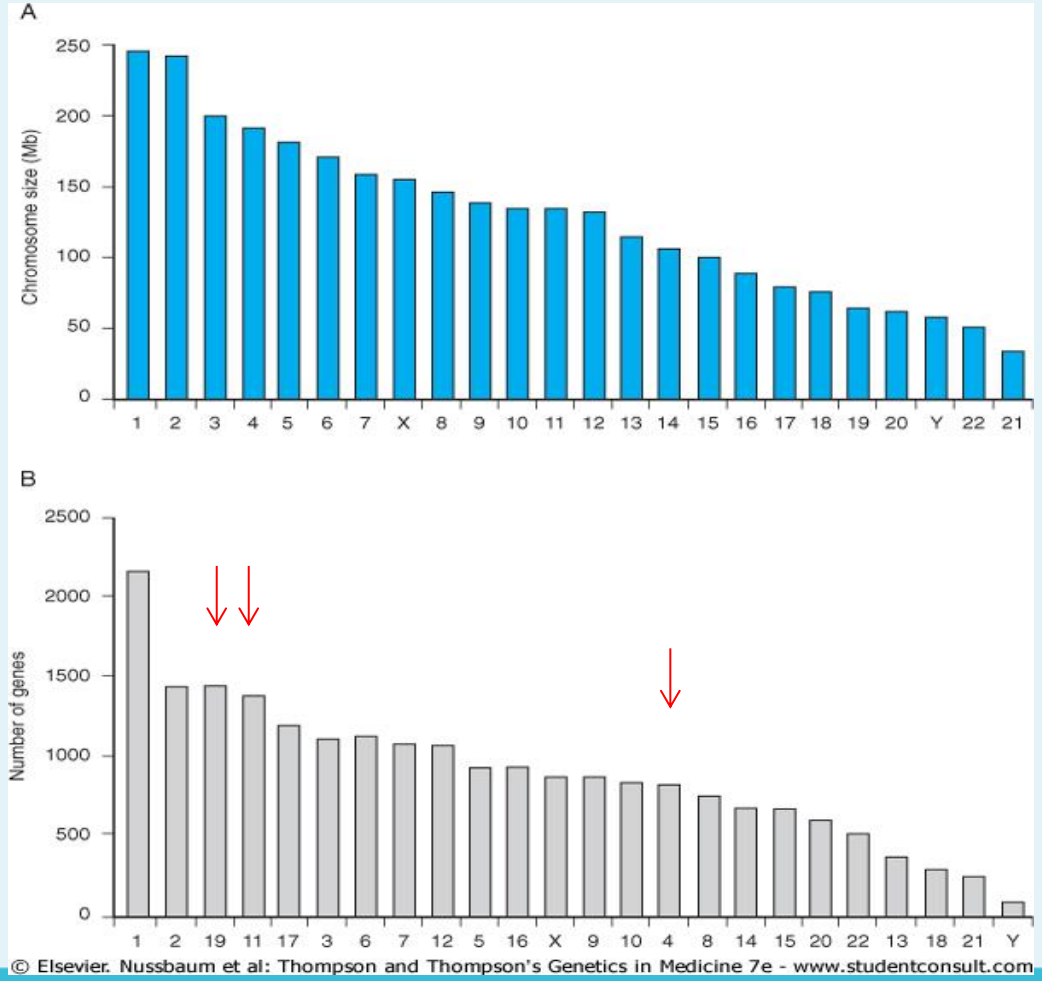
We recognize 2 types of heterochromatine:

facultative – active or inactive during development (ontogenesis)
(one of X chromosome of woman)

constitutive – always inactive (centromeric regions of chromosomes)

The Human Genome: the Chromosomal Basis of Heredity

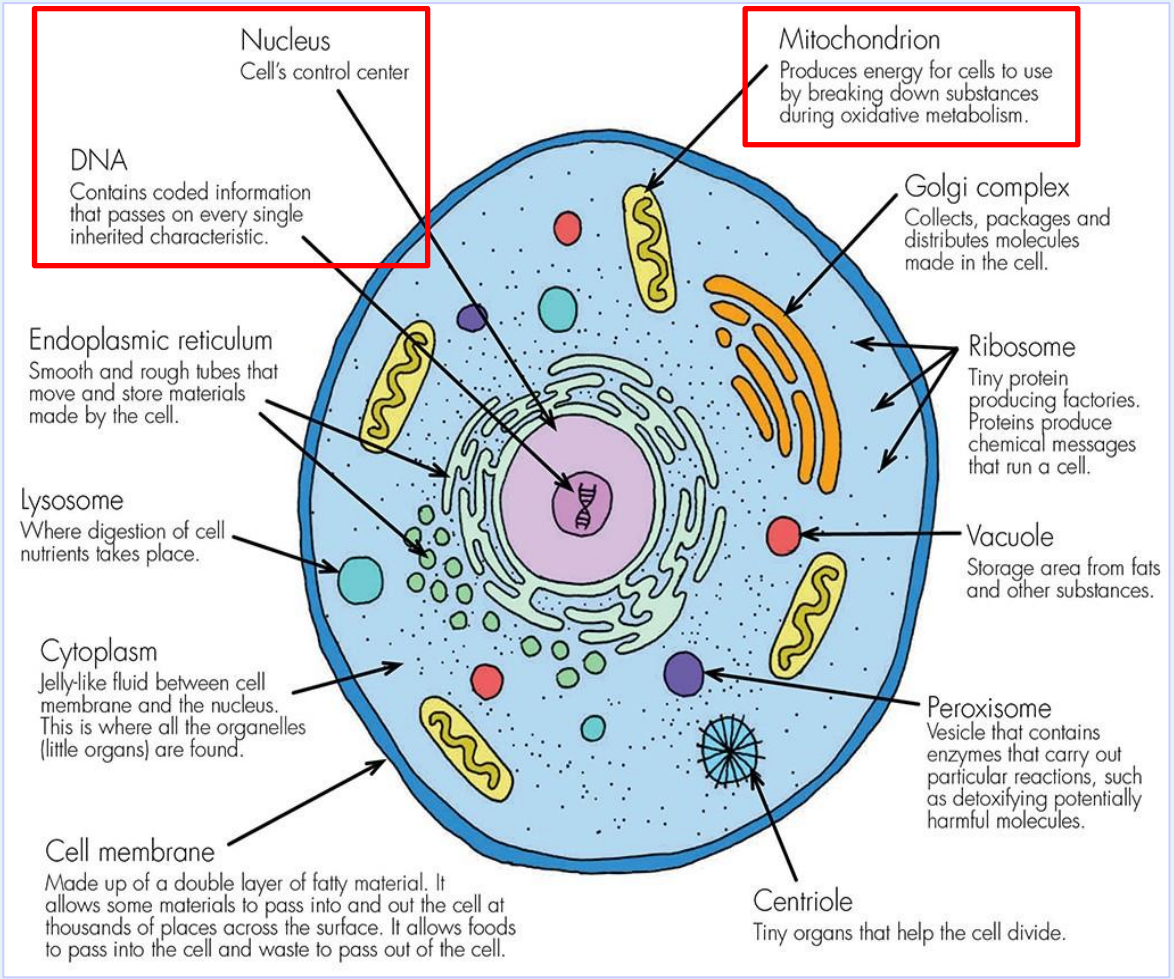
Size and gene content of the 24 human chromosomes



- **A:**
  Size of each human chromosome, in millions of base pairs (1 million base pairs = 1 Mb). Chromosomes are ordered left to right by size.

- **B:**
  Number of genes identified on each human chromosome. Chromosomes are ordered left to right by gene content

Human cell



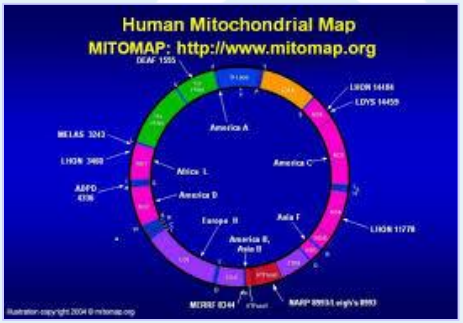
Position of Homo sapiens in an animal kingdom

- Eucaryota
- Vertebrae
- Mammals
- Primates
- Homo sapiens

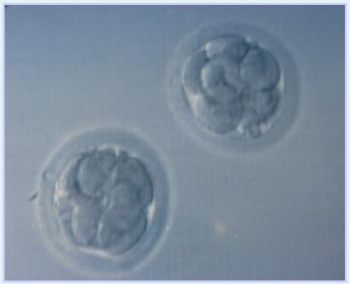
Impact of mitochondria and mtDNA on genetic diseases

1. Production of energy for cell metabolism

2. Mitochondrial diseases – maternal inheritance



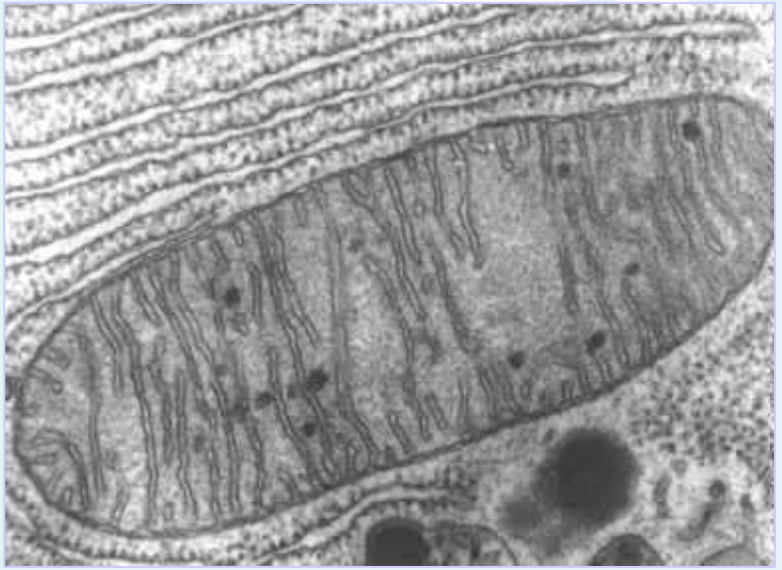
3. (In)fertility

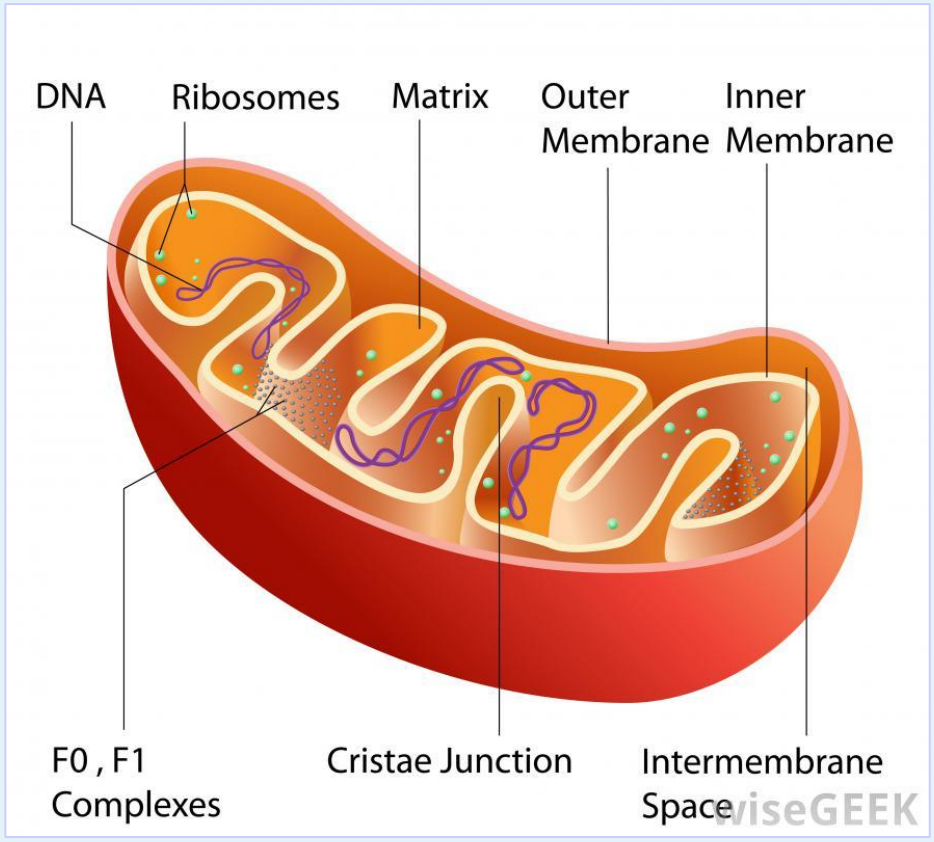


4. Origin of human based on maternal inheritance

Mitochondrie

- Energetické centrum bunky





mtDNA

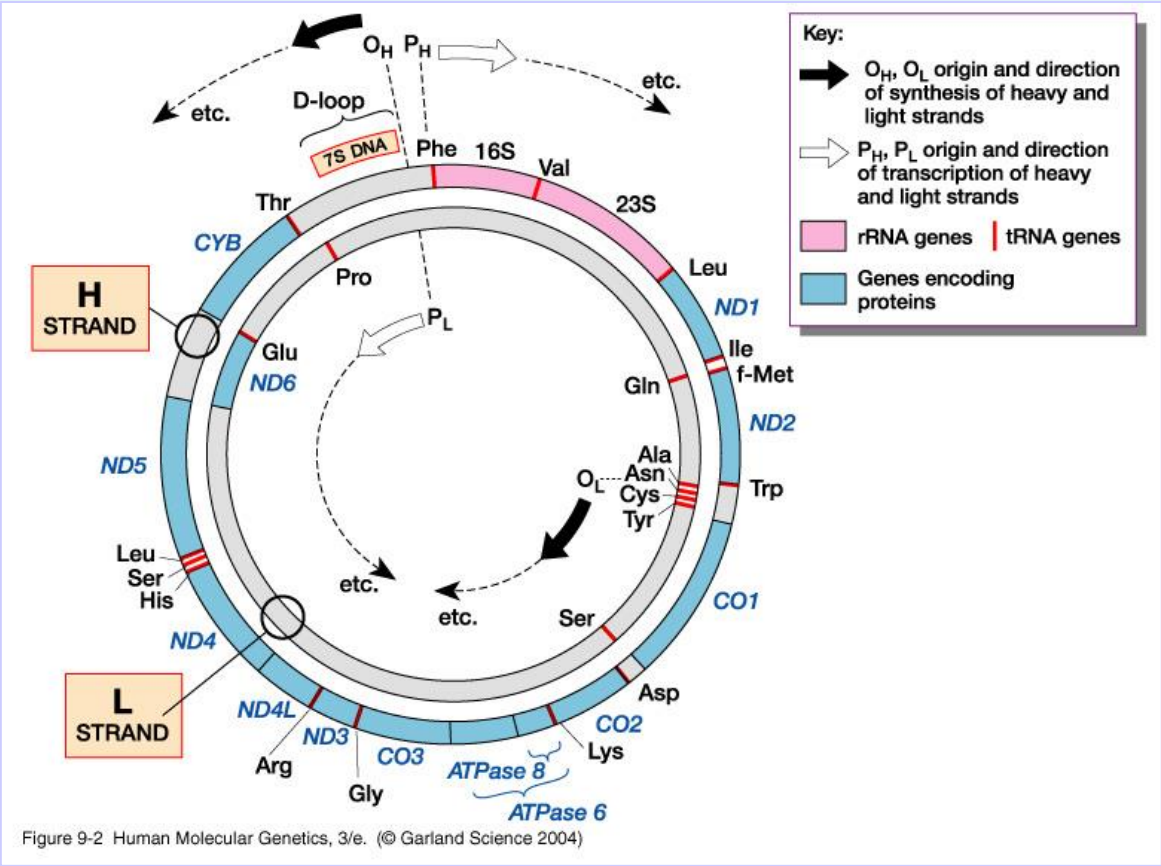


Figure 9-2 Human Molecular Genetics, 3/e. (© Garland Science 2004)

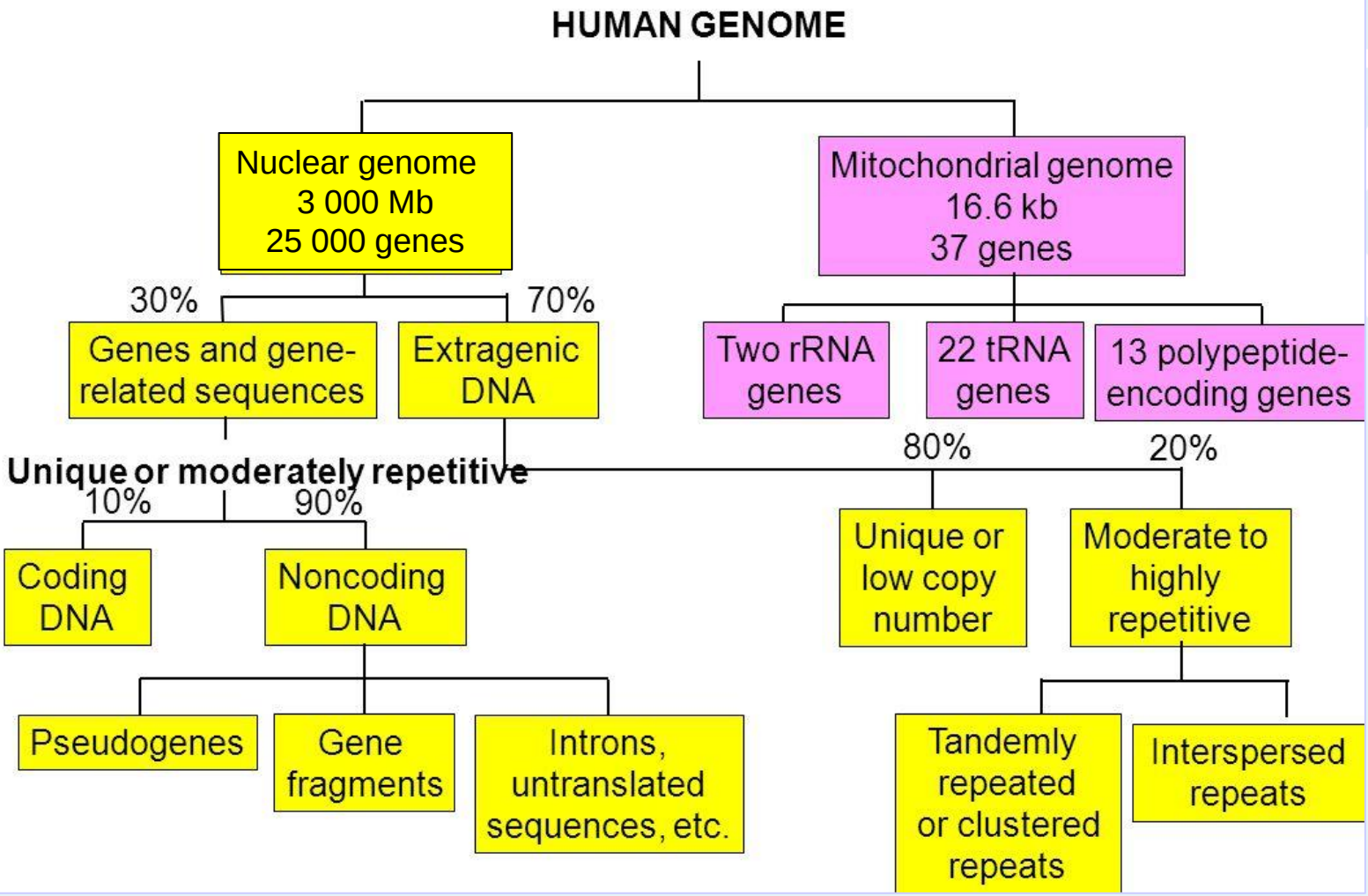
Circular dsDNA

Contains just **37 genes:**
- Genes for **tRNA**
- Genes for **rRNA**
- Genes encoding **proteins**

- The products of these genes function in mitochondria, although the majority of proteins within the mitochondria are, in fact, the products of nuclear genes (non-maternal inheritance)

The human nuclear and mitochondrial genomes		
	Nuclear Genome	**Mitochondrial Genome**
Size	3200 Mb	**16.6 kb**
No. of different DNA molecules	23 (in XX cells) or 24 (in XY cells); all linear	**One circular DNA molecule**
Total no. of DNA molecules per cell	46 in diploid cells, but varies according to ploidy	**Often several thousands up a few hundert thousands (but variable**
Associated protein	Present (histones & nonhistone proteins)	**Largely free of protein**
No. of genes **The percentage of coding DNA**	~ 25 000 ~ 3 %	37 ~ 93 %
Introns	Present in most of the genes	Not present
Recombination	Minimal one per each homolog in meiosis	**None**
Inheritance	Mendelian (autosomes and X chromosome); paternal (Y chromosome)	**Maternal** Mutations demonstrated in several maternally inherited as well as sporadic diseases

Human Genome Organization



Basic definitions

- **DNA** – biological macromolecule containing genetic information
- **Gene** – sequence of nucleotides of DNA encoding the sequence of amino acids in polypeptide (protein) or sequence of nucleotides in RNA
- **Chromosome** – structure occuring in nuclues, which contains DNA, proteins and other components
- **Karytype** – chromosomal make-up of biological species
- **Genome** – complete content of DNA
- **Locus** – position of the gene in DNA/chromosome
- **Allele** – alternative form of the gene residing on the same locus
- **Genotype** – genetic constitution of individual (of locus)
- **Fenotype** – features (morphological, biochemical, functional), which are a result of the work of genotype

Genotype + environment = fenotype

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Thank you for your attention

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