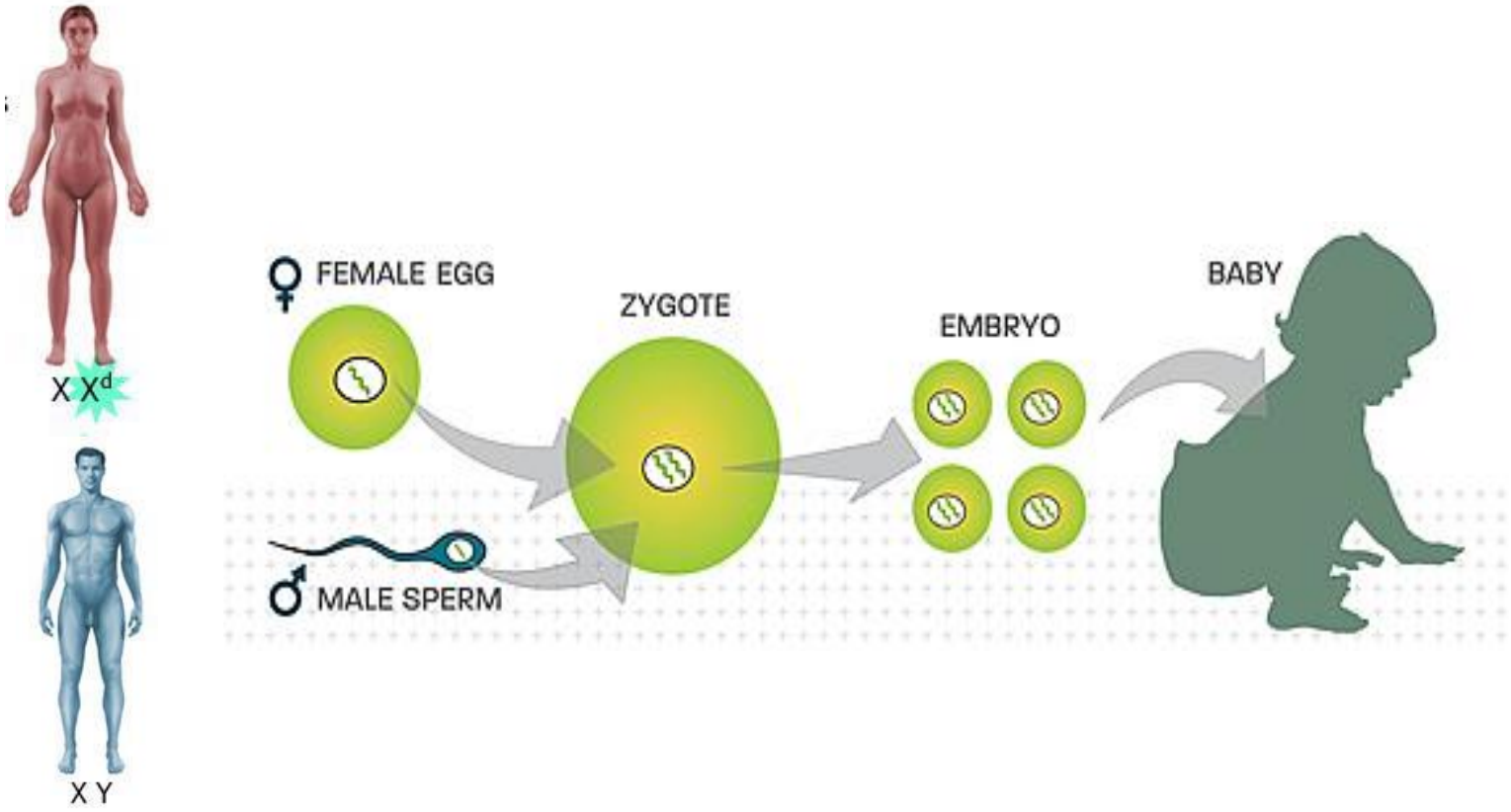
CURS 1

- INTRODUCERE ÎN GENETICA MEDICALĂ

- ADN – PURTĂTORUL INFORMAŢIEI GENETICE

- CROMOZOMII UMANI

GENETICA = știinta EREDITĂTII și VARIABILITAȚII



Ereditatea - proprietatea unui individ de a transmite la urmași caracterele sale personale, precum și cele ale speciei cãreia îi aparține.

EREDITATEA = proces informational bazat pe stocarea, expresiaa, transmiterea informației genetice.

EREDITATE **VARIABILITATE**

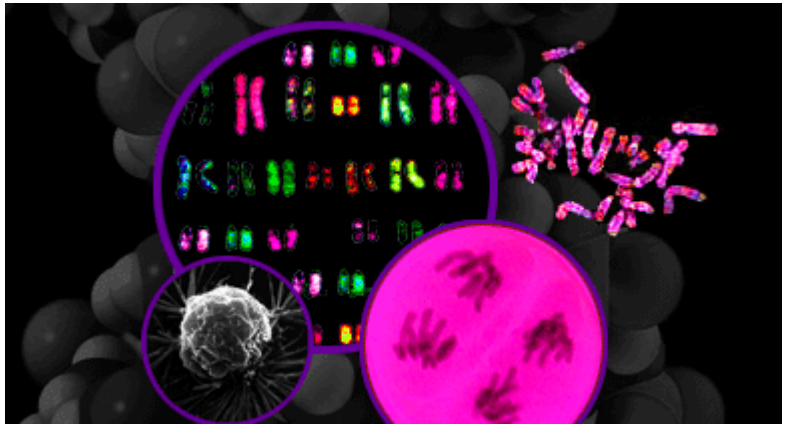
- **Mutații**
- **Recombinari genetice**
- **Migrații**

doi indivizi neinruditi ADN identic 99,9%

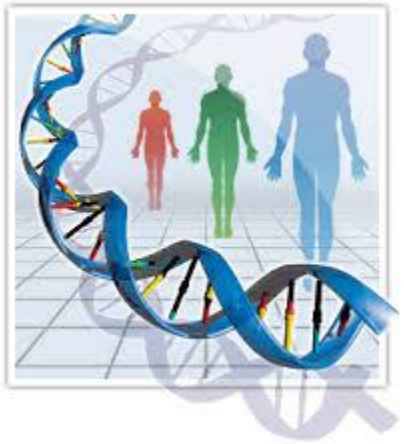
Variabilitate = ansamblul fenomenelor care produc diferențele genetice individ/ populații

GENETICA UMANA

- **Știință fundamentală**



- **Știință aplicativă – Genetica Medicală**

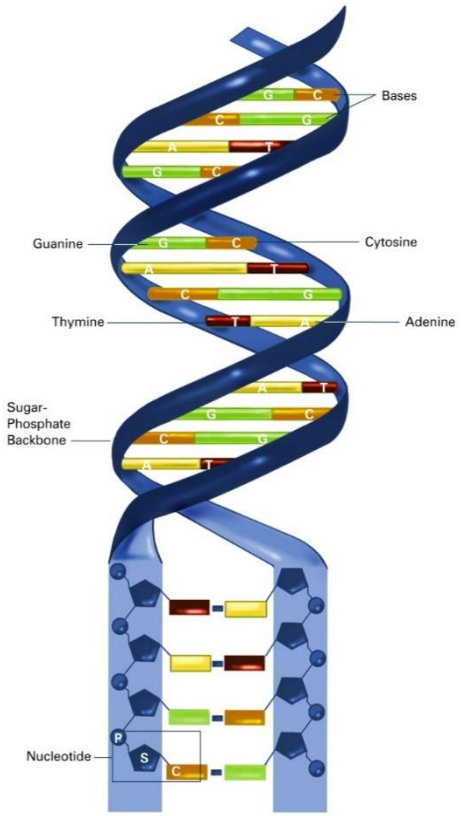


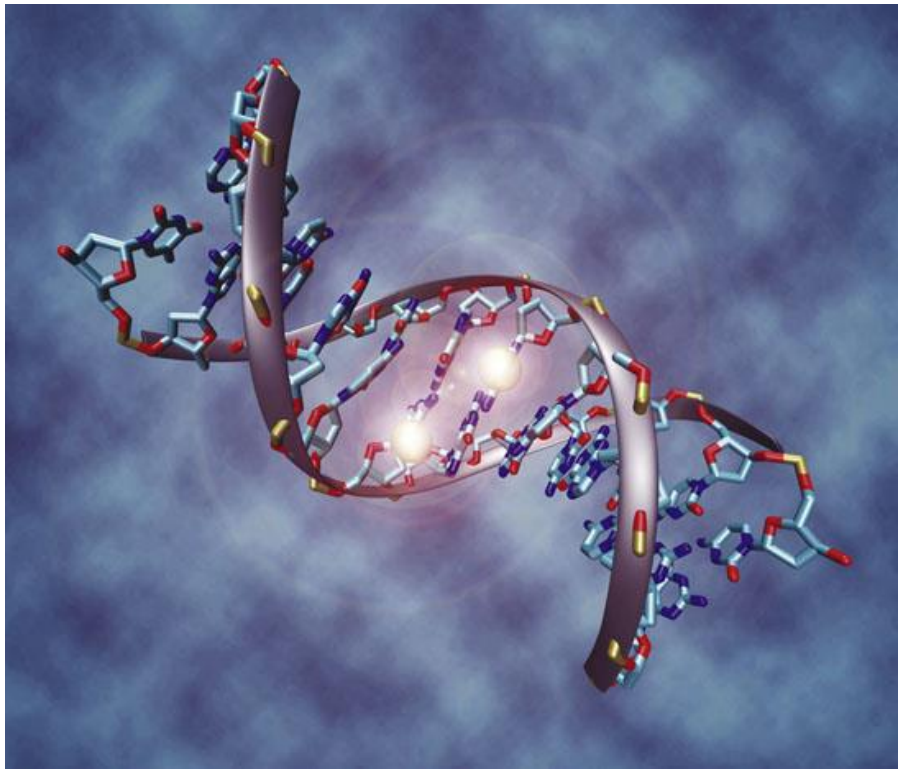
- **Știință medico-sociala**

GENETICA MEDICALA

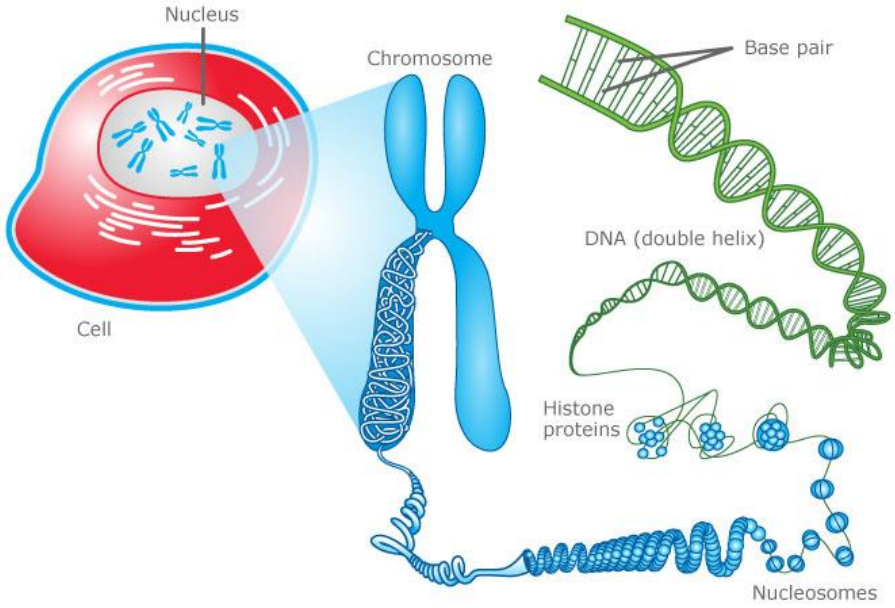
- **GENETICA CLINICĂ**
- **CITOGENETICA**
- **GENETICA BIOCHIMICA**
- **GENETICA MOLECULARĂ**

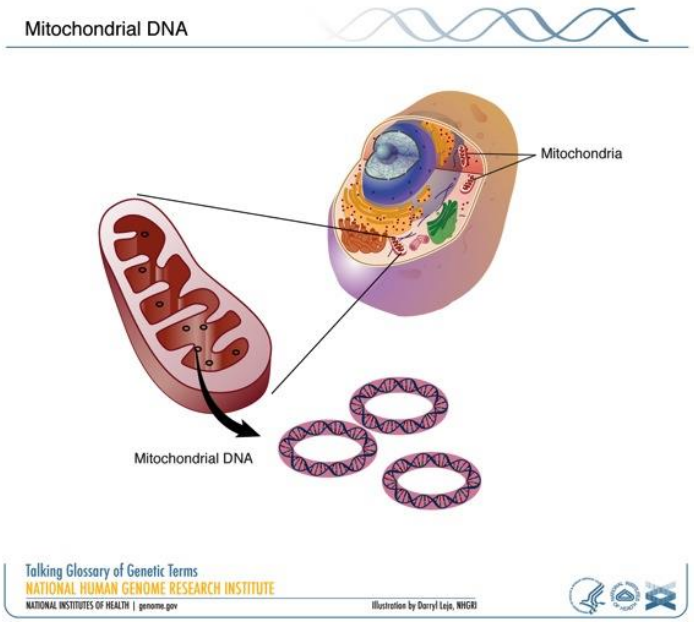
Acidul dezoxiribonucleic (ADN) este substratul molecular al eredității.

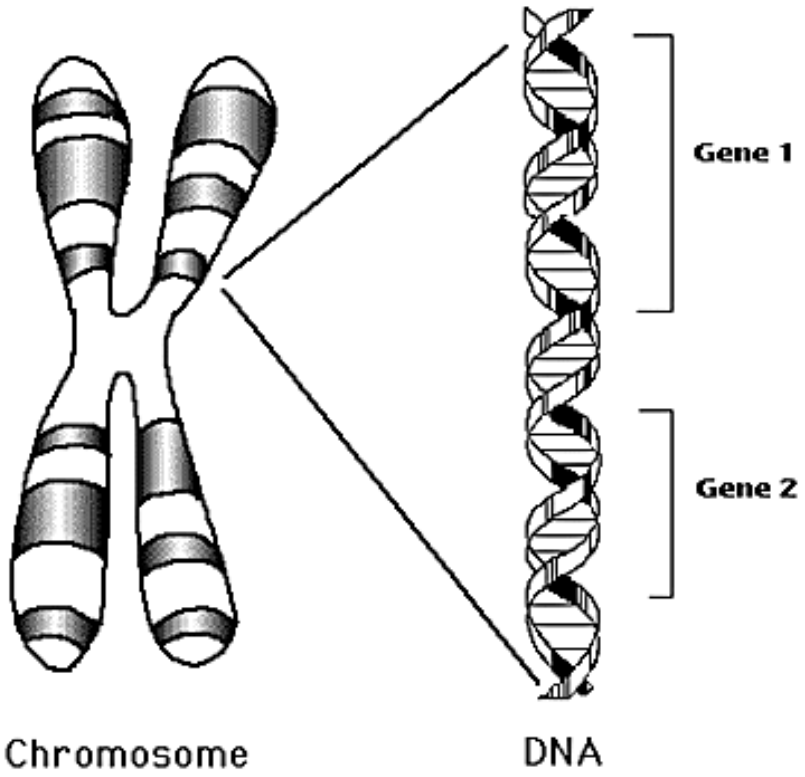




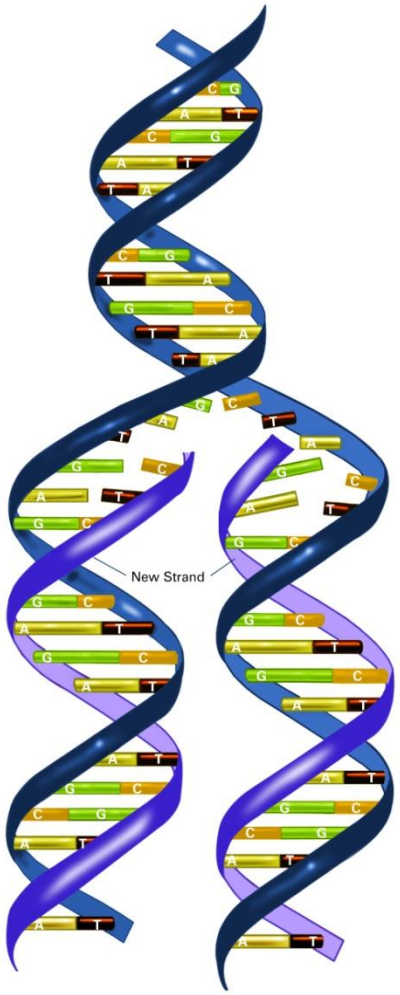
Genomul uman este alcătuit dintr-un genom nuclear și un genom mitocondrial



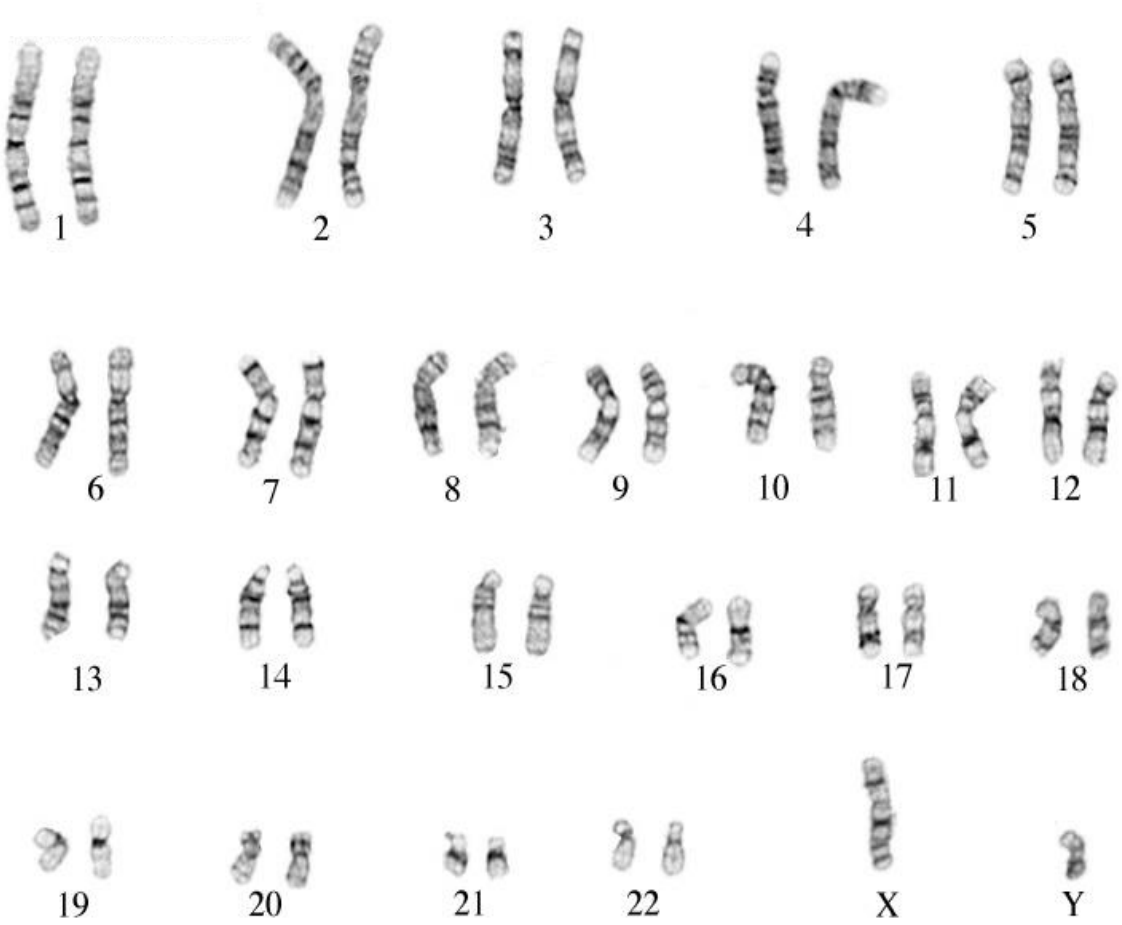




Genes



Numãrul și forma cromozomilor sunt elemente caracteristice fiecãrei specii.

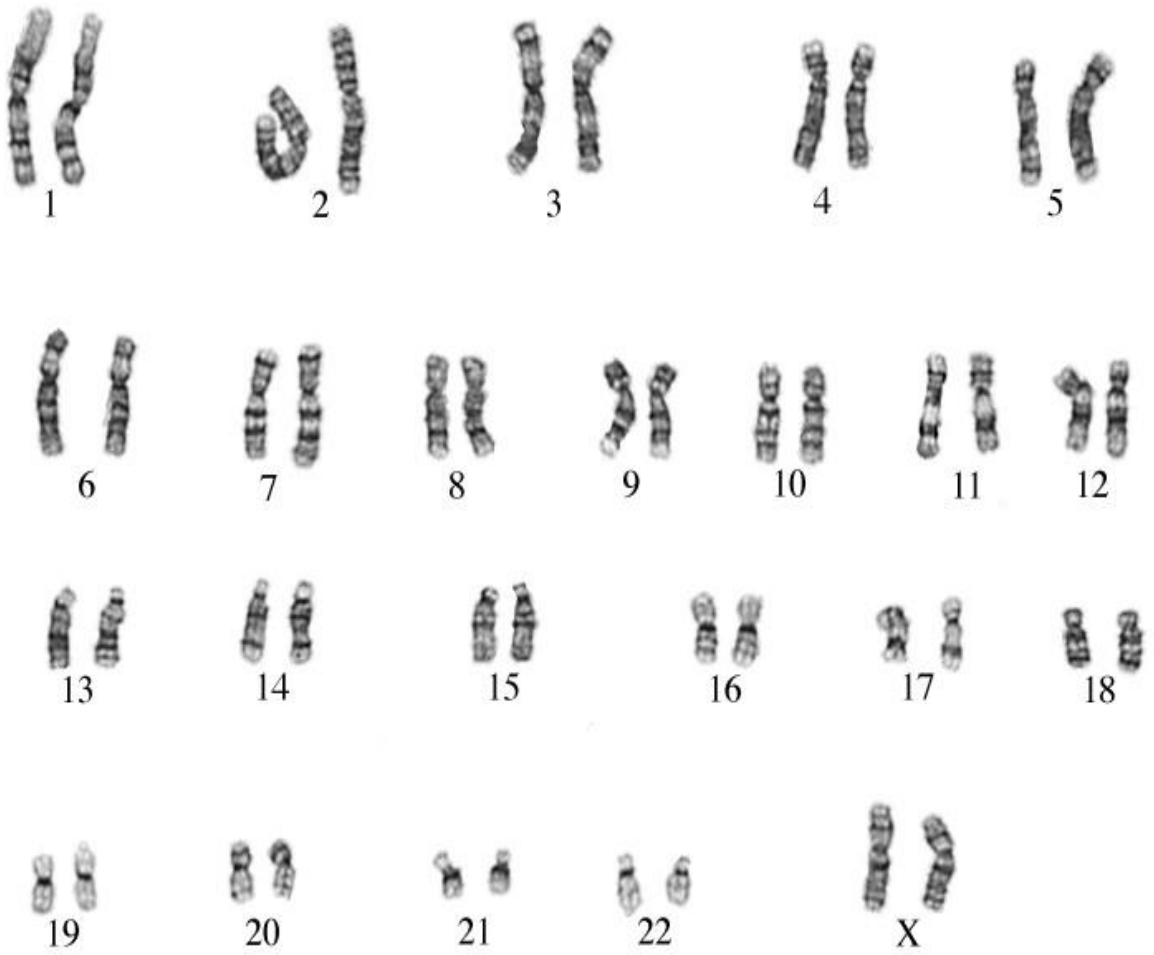


46 de cromozomi (2n = numãr diploid),

44 autozomi

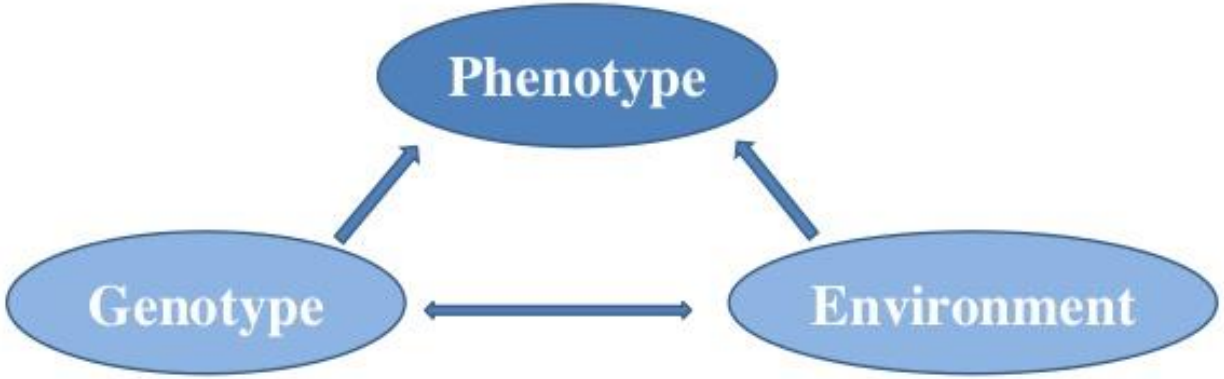
2 cromozomi sexuali

Cariotip uman normal 46,XY



Cariotip uman normal 46,XX

Genetic Architecture of Complex Traits



$$P = G + E + GE$$

GENOTIP - structura unică și caracteristică a unui individ/ constituția genetică

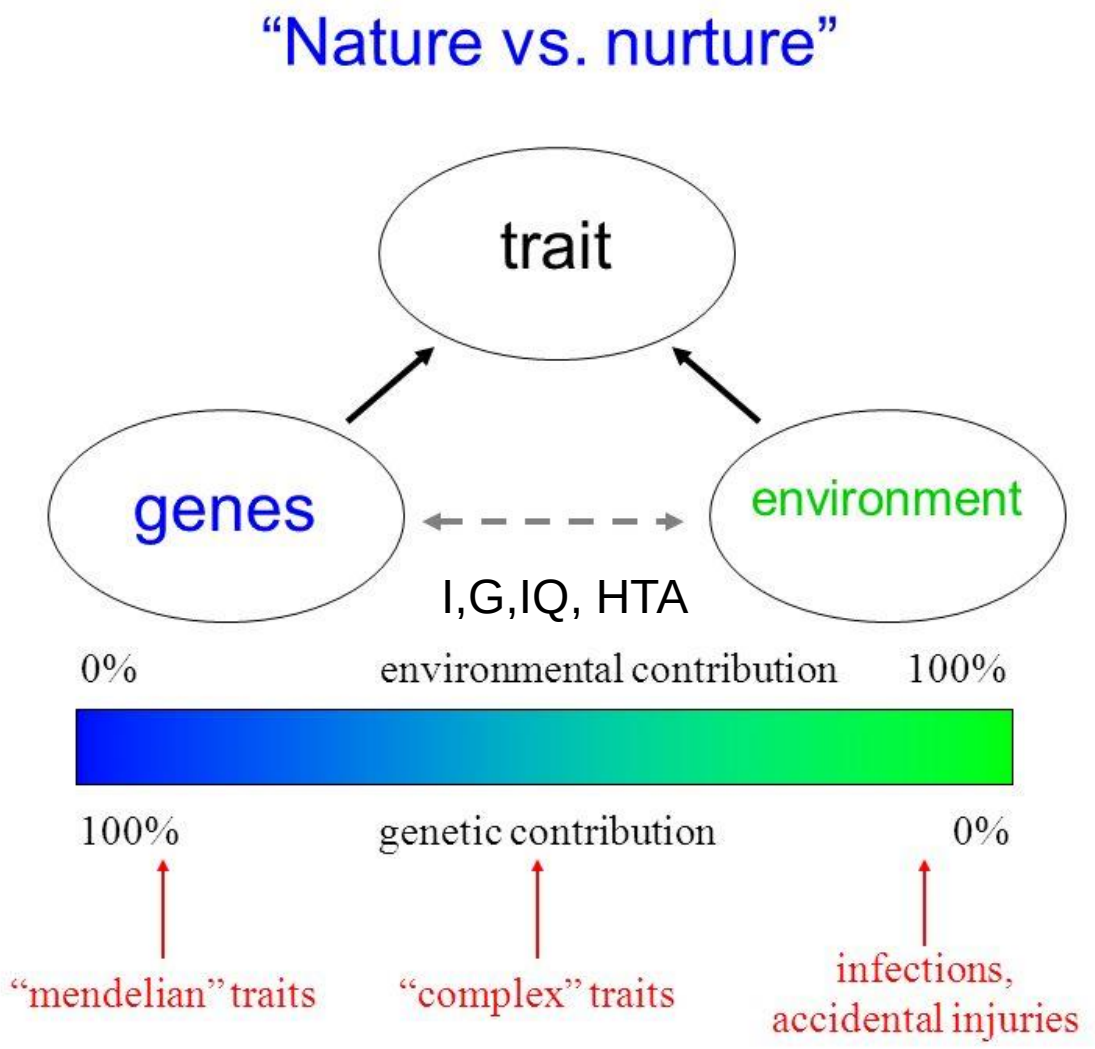
FENOTIP – ansamblul unic de caractere manifeste (observabile) și specifice ale unui organism, produse prin interacțiunea permanentã, dar în proporții diferite, dintre ereditate (genotip) și mediu

Om - Unicitate bio-psiho-sociala

Grupe sangvine

Hemofilie

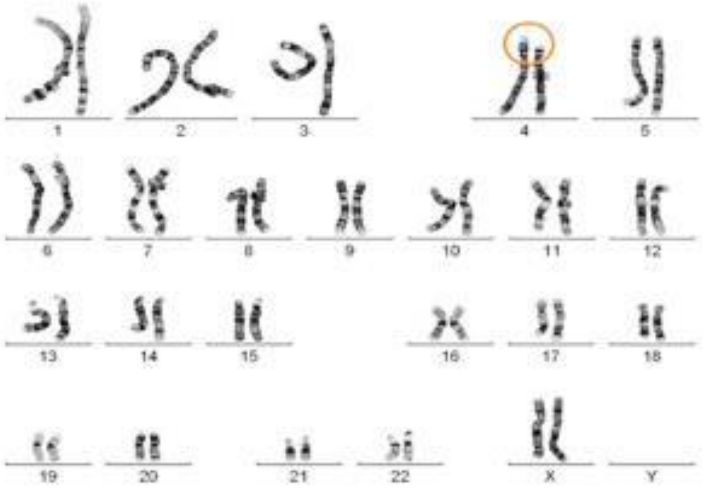
Fenilcetonurie



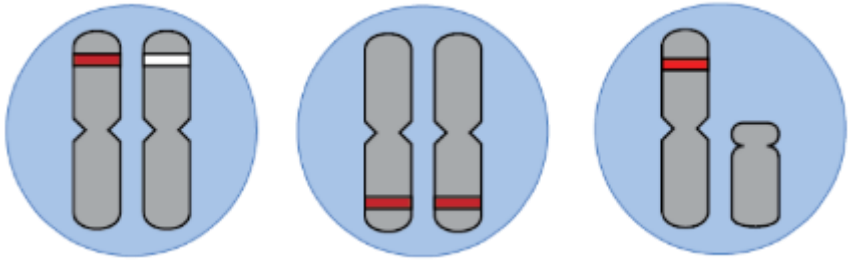
Caractere	**pur ereditare**	**multifactoriale**	**pur ecologice**

TIPURI DE AFECȚIUNI GENETICE

Boli CROMOZOMIALE

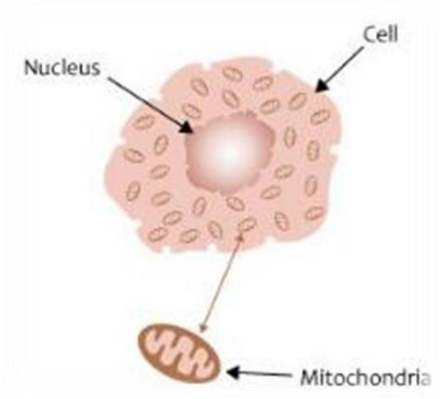


Boli MONOGENICE

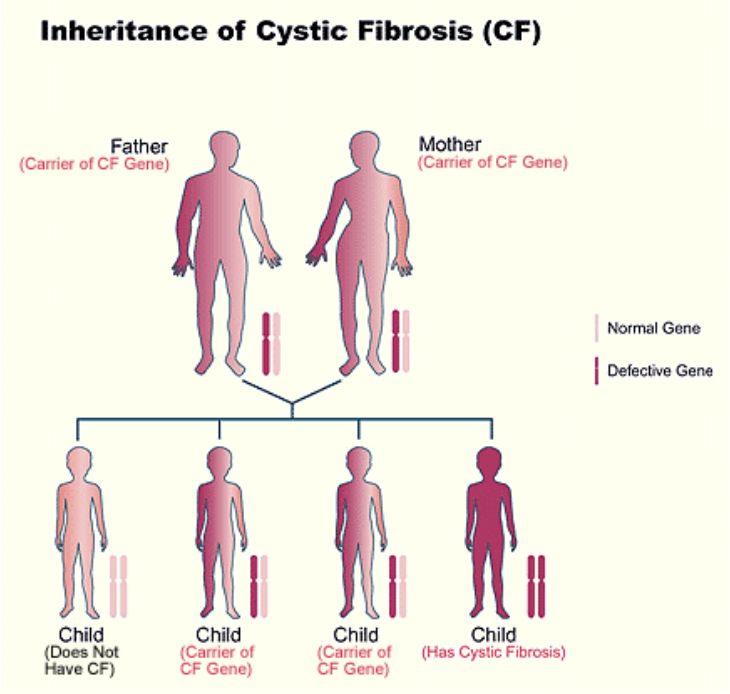


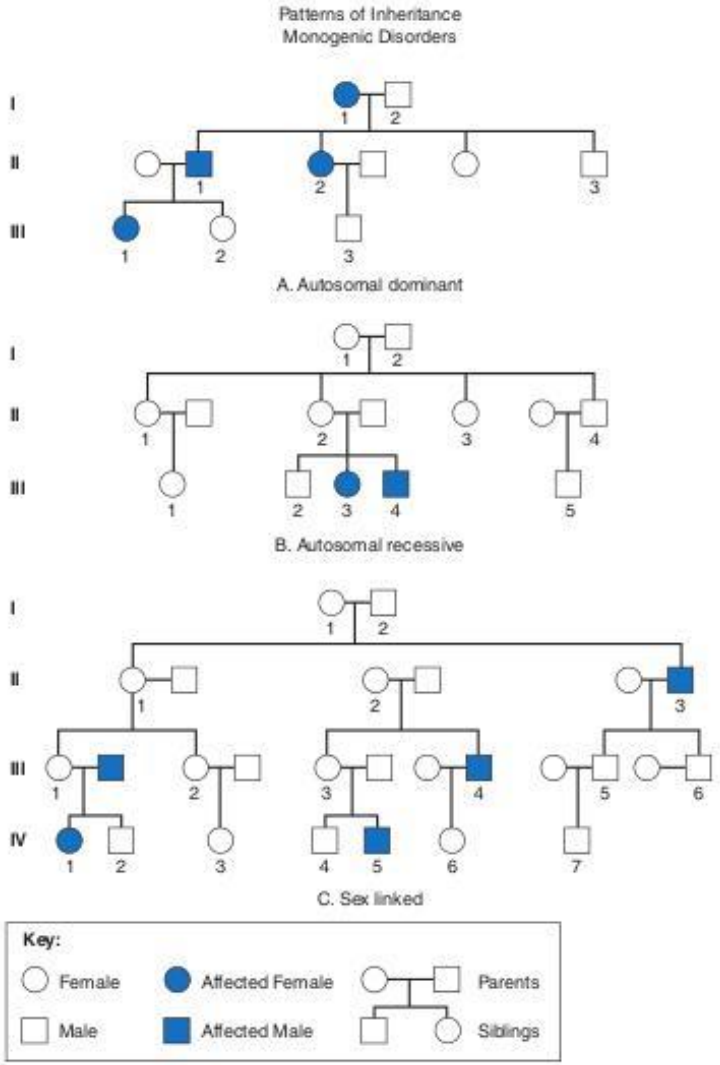
HETEROZIGOT HOMOZIGOT HEMIZIGOT

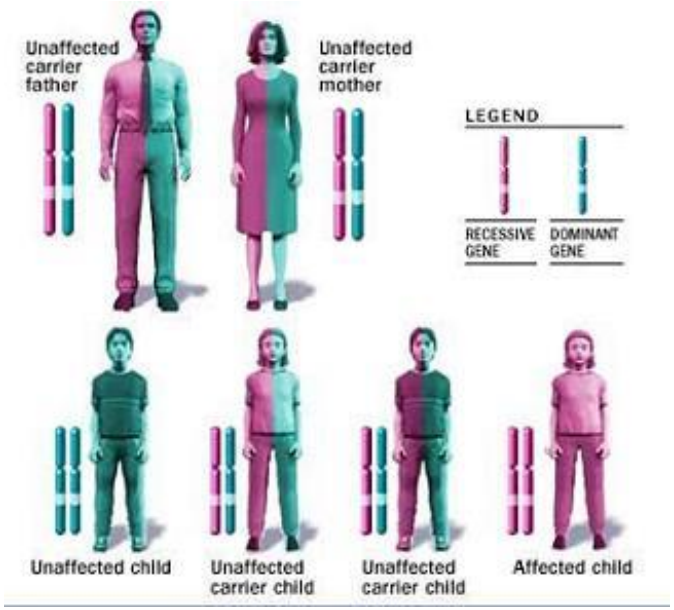
Boli MITOCONDRIALE

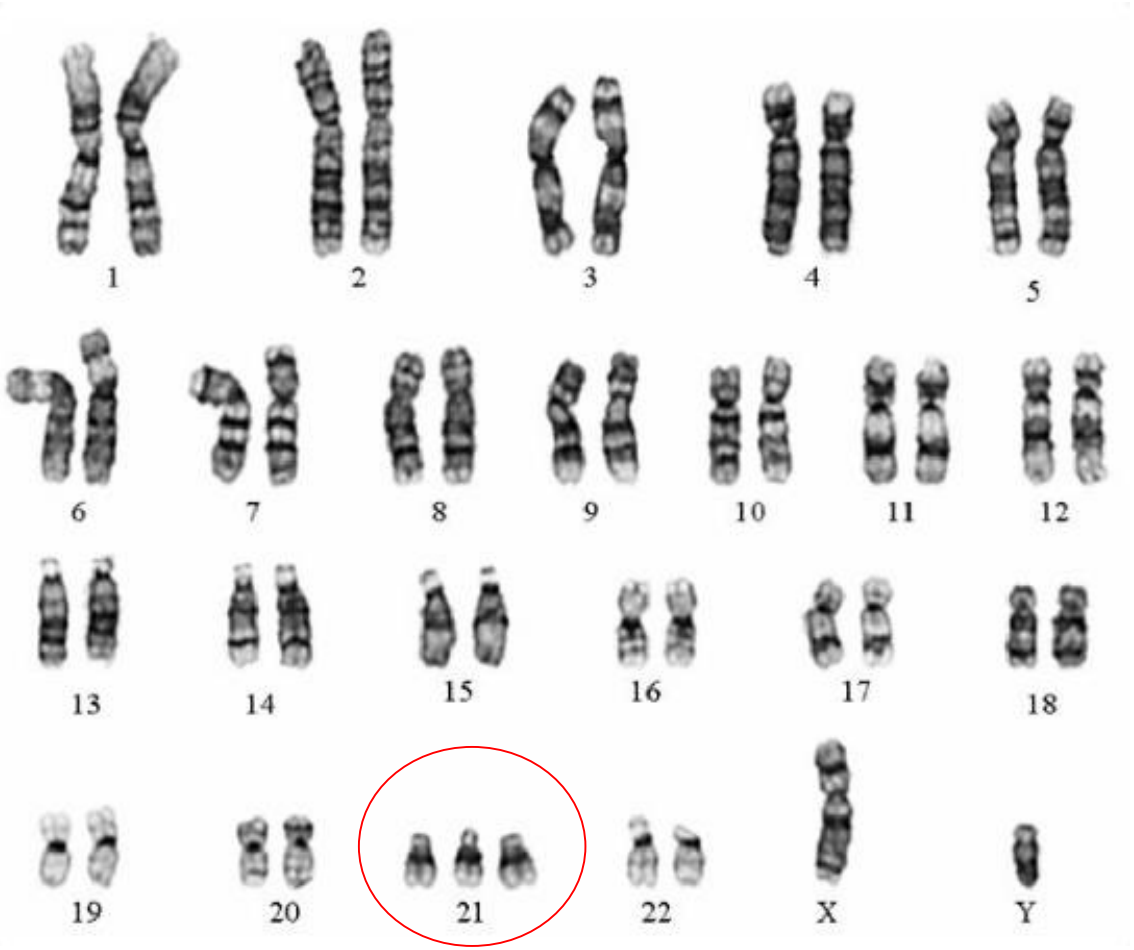


Boli MULTIFACTORIALE


Inheritance of Cystic Fibrosis (CF)
Father
(Carrier of CF Gene)
Mother
(Carrier of CF Gene)
Normal Gene
Defective Gene
Child
(Does Not Have CF)
Child
(Carrier of CF Gene)
Child
(Carrier of CF Gene)
Child
(Has Cystic Fibrosis)


Patterns of Inheritance
Monogenic Disorders
A. Autosomal dominant
B. Autosomal recessive
C. Sex linked
Key:
Female
Male
Affected Female
Affected Male
Parents
Siblings


Unaffected carrier father
Unaffected carrier mother
LEGEND
RECESSIVE GENE
DOMINANT GENE
Unaffected child
Unaffected carrier child
Unaffected carrier child
Affected child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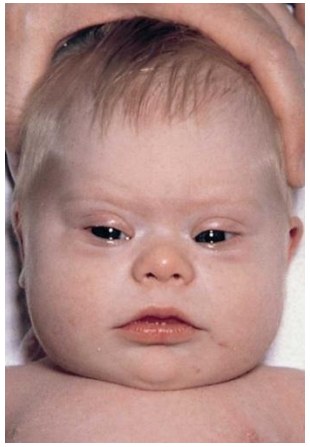
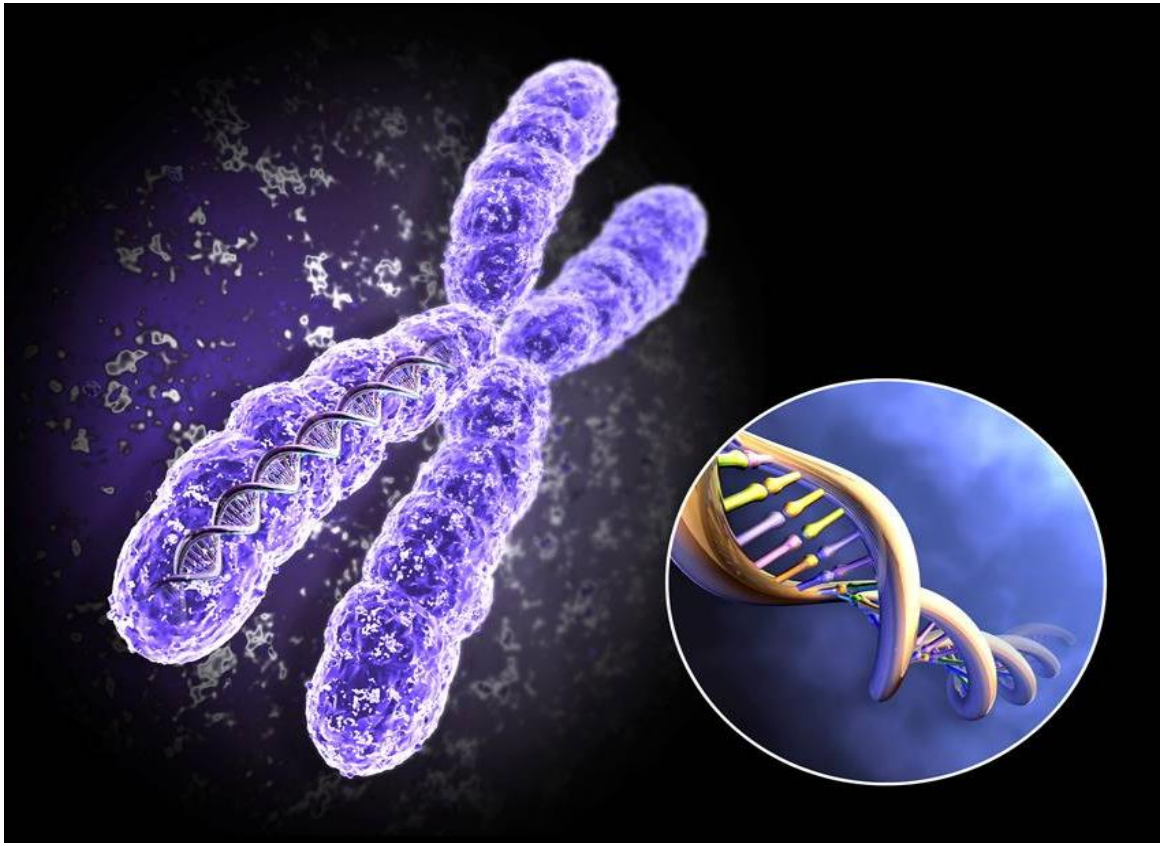


ADN - ul substratul molecular al ereditatii



DNA - double helix

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, J. B., Gerrard, R., and Bevan, W., *Phil. Mag.*, **40**, 349 (1949).

2 Longuet-Higgins, M. S., *Mon. Not. Roy. Astro. Soc., Geophys. Supp.*, **6**, 235 (1949).

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

4 Neuman, A. W., *Arkiv. Mat. Astron. Fysik* (Stockholm), **B 111** (1905).

MOLECULAR STRUCTURE OF NUCLEIC ACIDS

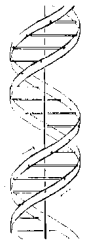
A Structure for Deoxyribose Nucleic Acid

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 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.

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.



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

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.

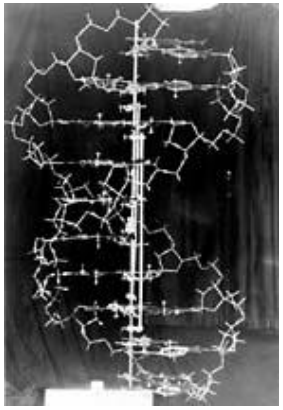
The previously published X-ray data[5,6] on deoxyribose nucleic acid are insufficient for a rigorous test of our structure. So far as we can tell, it is roughly compatible with the experimental data, but it must be regarded as unproved until it has been checked against more exact results. Some of these 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

Watson and Crick (1953/62)

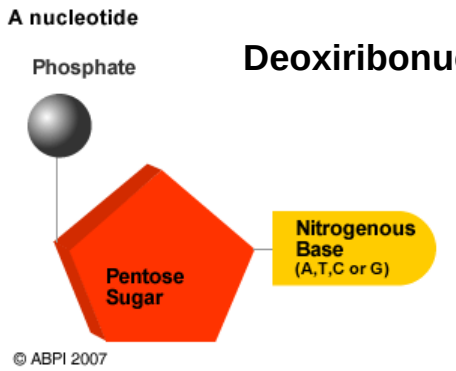


The original DNA model by Watson and Crick. Photo: Cold Spring Harbor Laboratory Archives

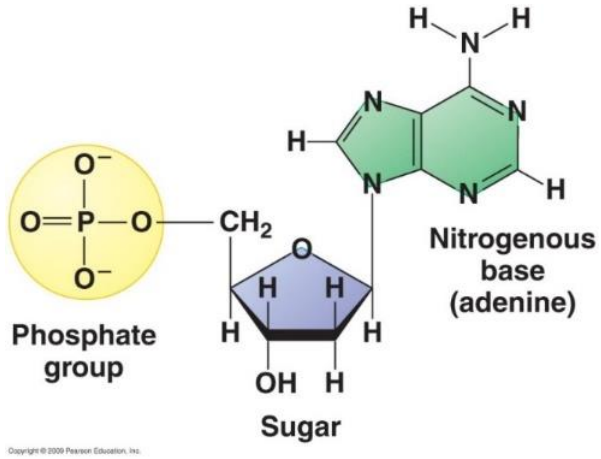
STRUCTURA PRIMARĂ A ADN

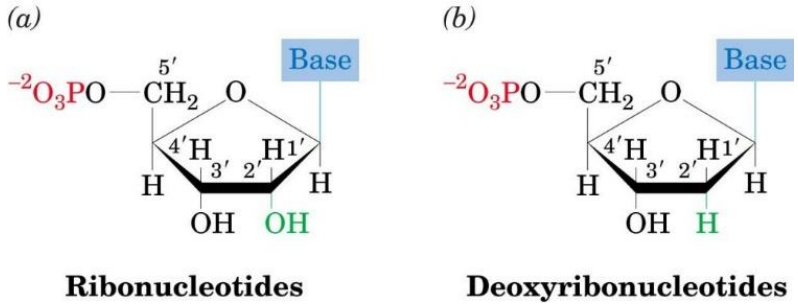
ADN este macropolimer de deoxiribonucleotide.

Unitatea structuralã a ADN este dezoxiribonucleotidul.



Deoxiribonucleotidul





Structura primară a ADN

Nucleotid

Nucleozid

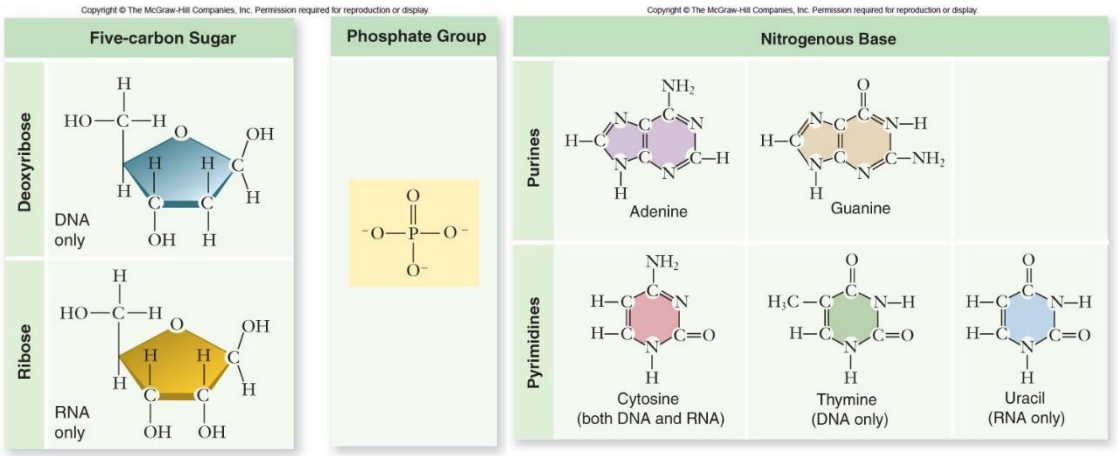
Grup fosfat

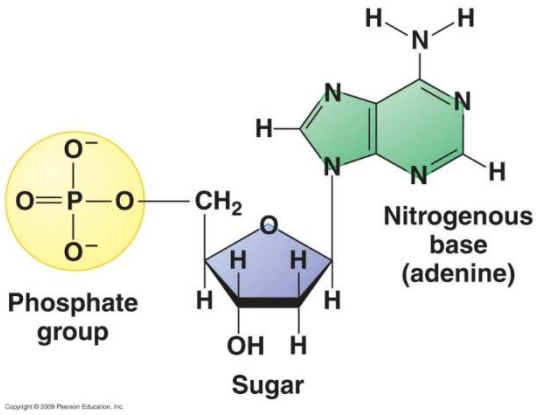
pentoza

baza azotata

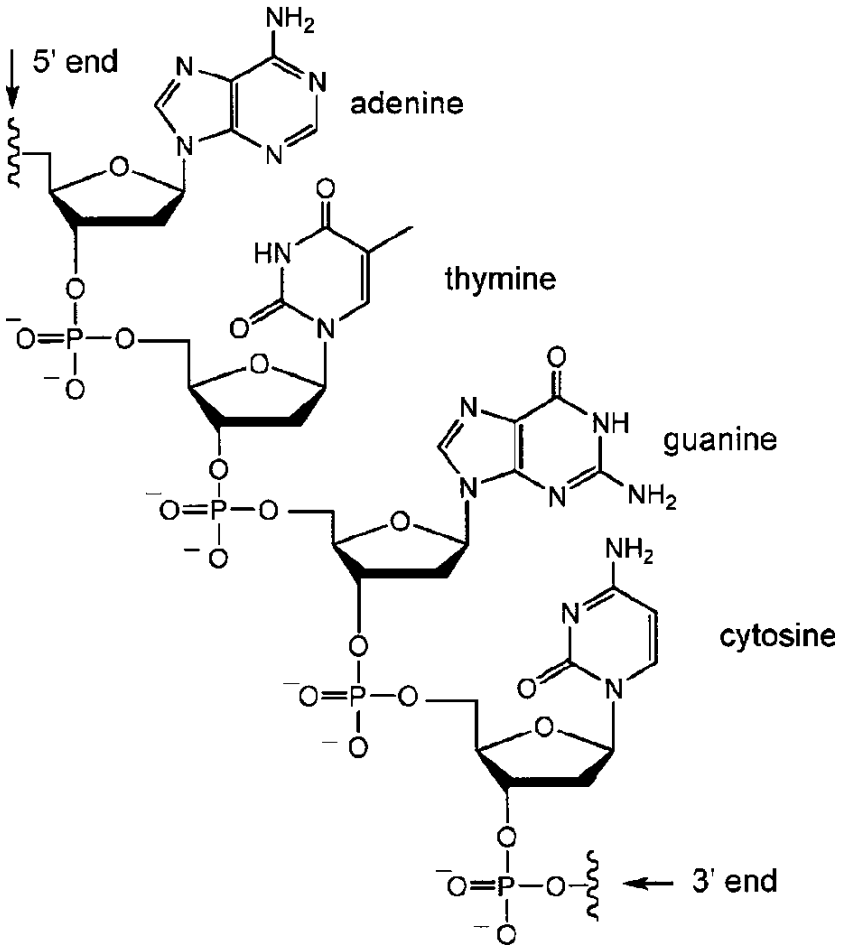
Un dezoxiribonucleotid este alcătuit din trei elemente distincte :

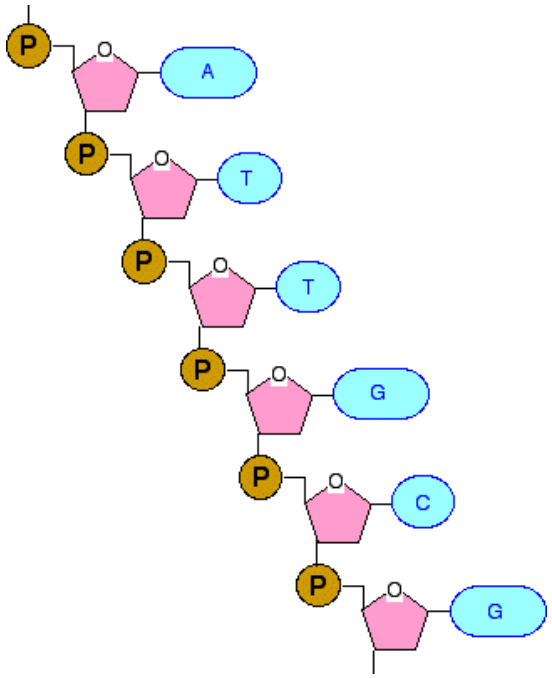
- **un glucid cu cinci atomi de carbon (o pentozã) - D-2-DEZOXIRIBOZA**
- **o bază azotată, care poate fi purinică (adenina (A), guanina (G)) sau pirimidinică (timina (T), citozina (C)), se leagã la C1 dezoxiribozei, alcãtuind împreunã un nucleozid**
- **un grup fosfat care se leagã la C5 al dezoxiribozei**





- **Caracter acid şi numeroase sarcini negative**
- **Polimerizare 3'-5' fosfodiester**
- **Catena continuă liniară- structura primară**
- **Liberate de aşezare totală a nucleotidelor**
- **Succesiunea nucleotidelor repezintă informaţia genetică codificată**
- **sensul de citire determinat de polaritatea 5'→3'**





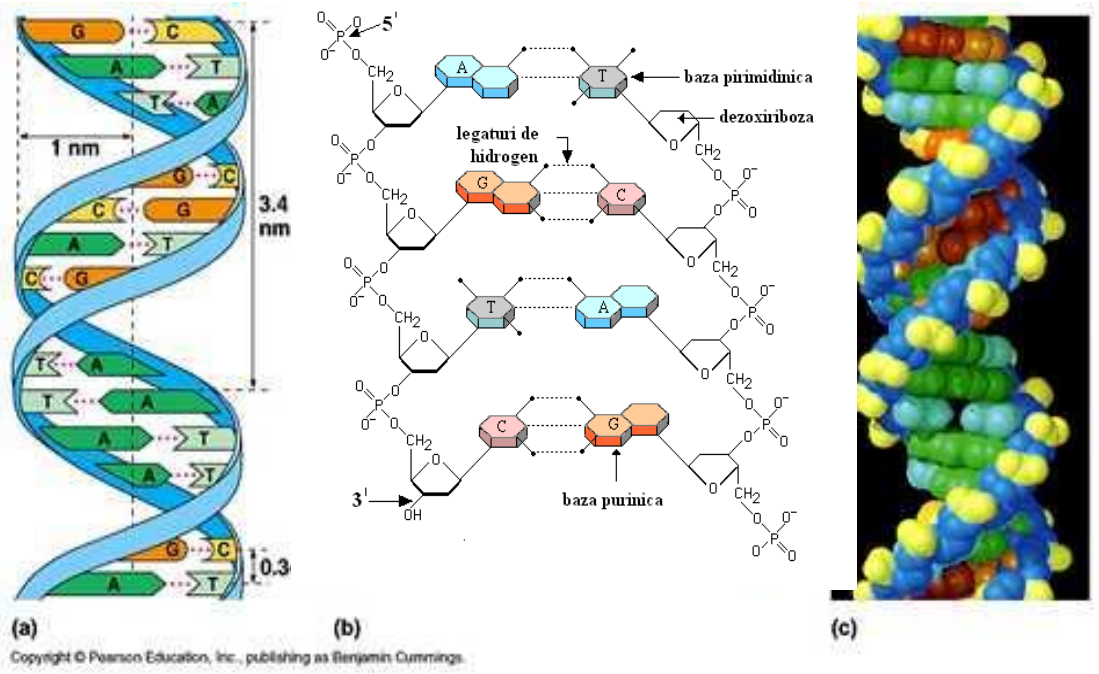
5‘- ATTGCG - 3‘

STRUCTURA SECUNDARĂ A ADN

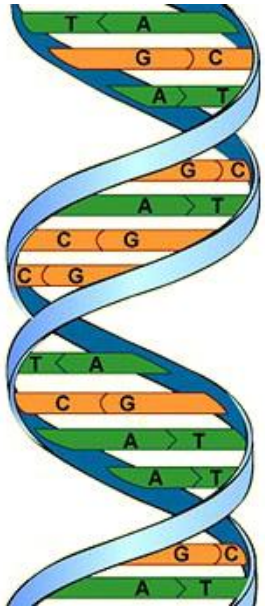
- **dubla spirală elicoidală**

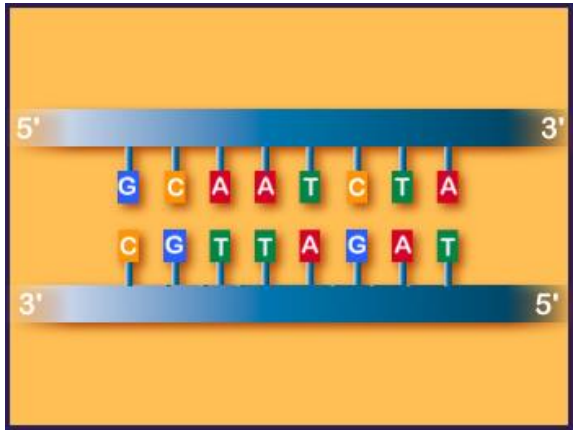
- două catene polinucleotidice, legate între ele prin bazele azotate, în mod complementar și înfășurate plectonemic pentru a forma o dublă spirală elicoidală (o elice dublă) orientată spre dreapta, cu diametrul de 2 nm și pasul elicei de 3.4 nm.

- bazele azotate sunt situate spre interiorul moleculei și se leagă complementar: o bază purinică se unește cu o bază pirimidinică: A-T și G-C (formând un cuplu sau o pereche de baze, prescurtat pb) prin punți de hidrogen.



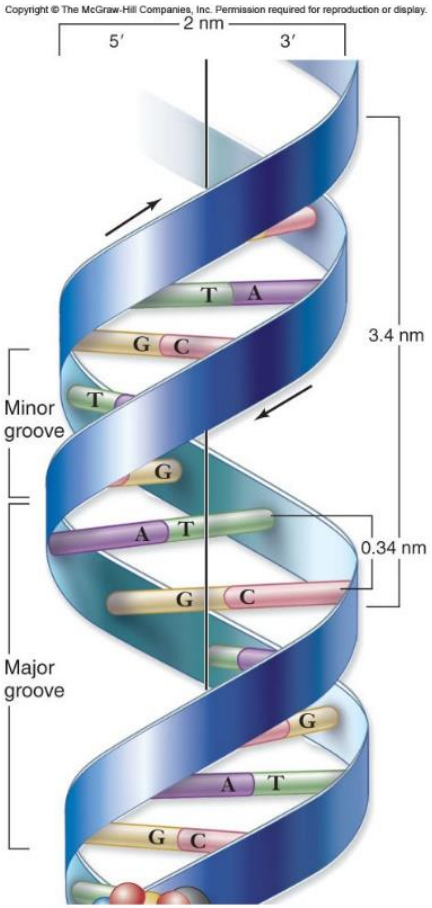
Secvența nucleotidelor unei catene determină cu necesitate secvența nucleotidelor celeilalte catene. Deci cele două catene ale ADN nu sunt identice, ci complementare, antiparalele și strict codeterminate.

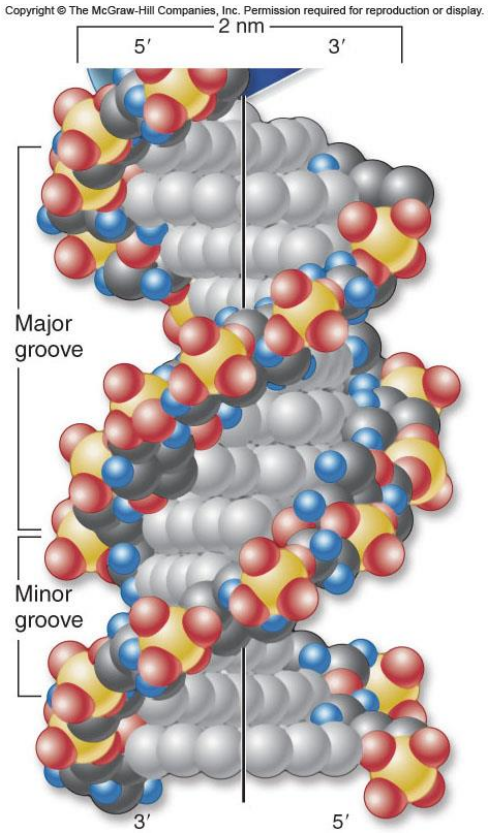




- dublã spiralã elicoidalã coaxialã (o elice dublã), orientatã spre dreapta (dextrogir)

- **prezintã două șanțuri laterale (incizuri): unul mai mic (12 Å) unde se vor fixa proteine histonice și altul mai mare (24 Å) unde se vor fixa factori de transcripție**





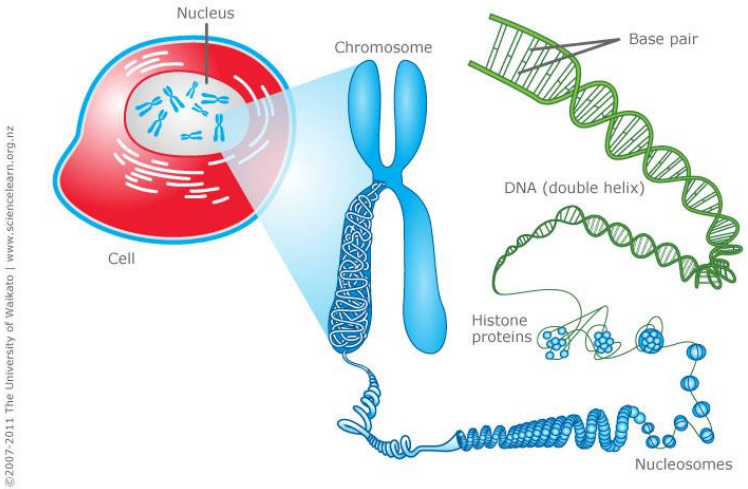
ORGANIZAREA ADN ÎN CELULĂ

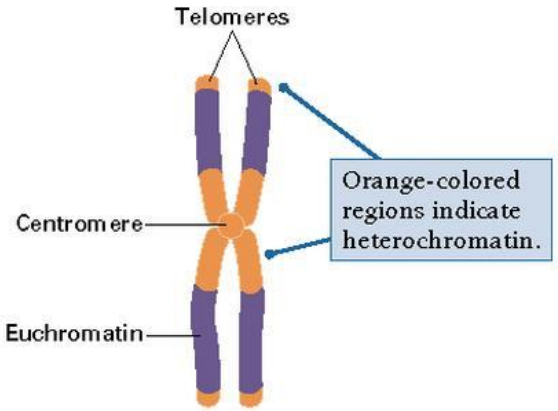
ADN

Nucleu - 99,5% — **INTERFAZA - filamente de cromatina**

Mitocondrii - 0,5% — **DIVIZIUNE - CROMOZOMI**

CROMATINA = ADN+ PROTEINE HISTONICE + proteine nonhistonice+ ARN



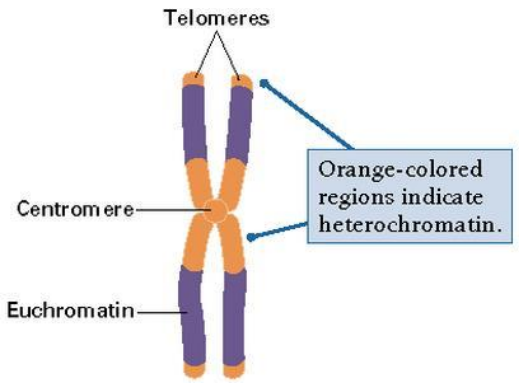


La începutul diviziunii, membrana nucleară și nucleolii dispar, iar fibrele de cromatină se spiralizează, se condensează și formează cromozomii; la sfârșitul diviziunii, aceștia se despiralizează, pentru ca în interfază să revină la configurația filamentelor de cromatină.

ORGANIZAREA ADN ÎN CELULĂ

Cromatina se prezintă sub forma a două unităţi morfo - funcţionale distincte:

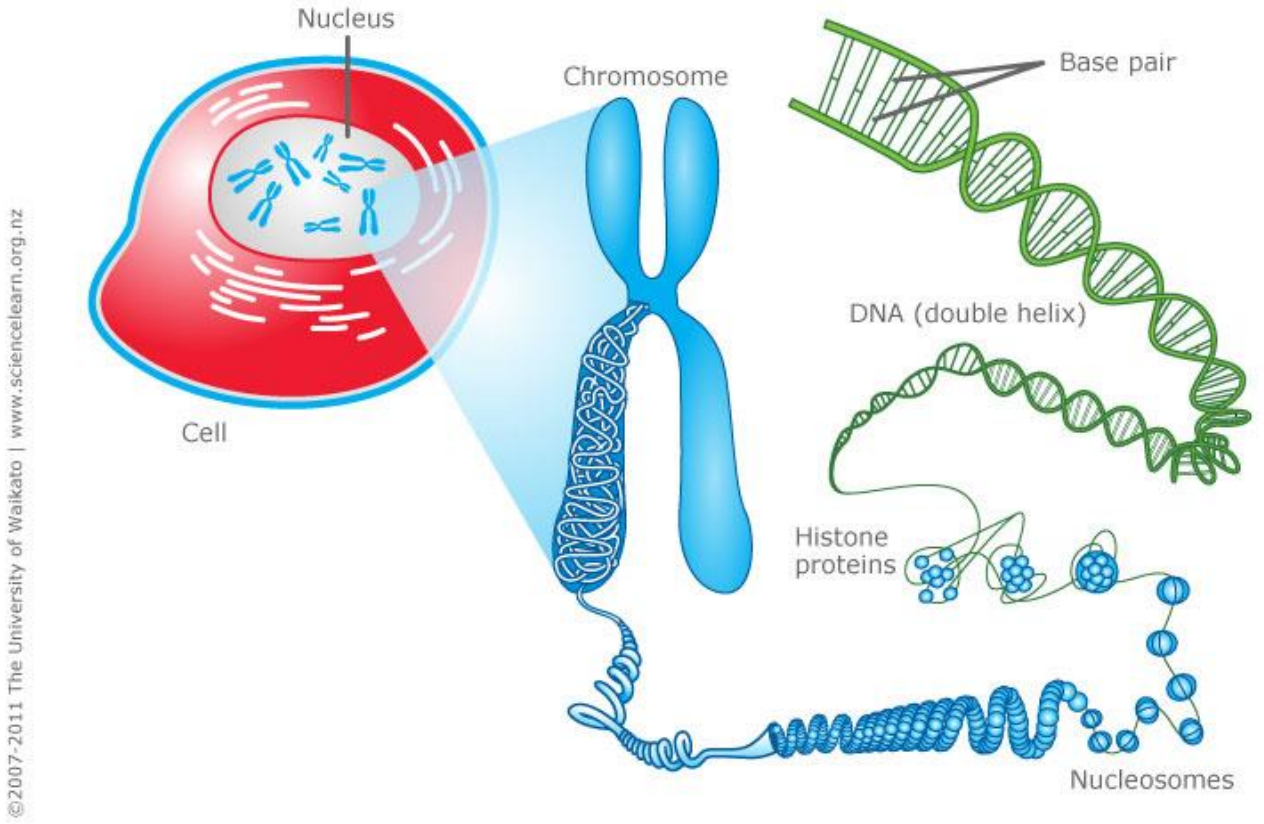
- **eucromatina**
- **heterocromatina**



Caracteristici	Eucromatina	Heterocromatina
Condensare	Fin dispersată	Puternic condensata
Colorare	Slabă, difuză	Intensă
Compoziţie	C-G, ADN nerepetitiv, p. nonhistonice	A-T, ADN repetitiv, histone
Concentraţie gene	Mare	Foarte mică-absentă
Replicare S	Precoce	Tardivă
Activitate genică	Activă transcripţional	Inactivă transcripţional

SISTEMUL IERARHIZAT DE FIBRE DE CROMATINĂ

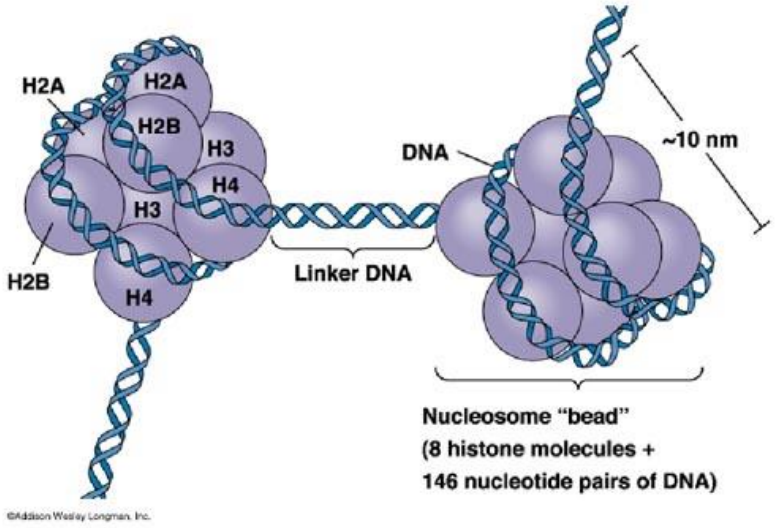
Moleculele de ADN suferă o compactare de 10.000 de ori pentru a încăpea cu ușurință în spațiul mic, de circa 10 µm diametru, al nucleului, formând un sistem ierarhizat de fibre de cromatină (4 niveluri de condensare).



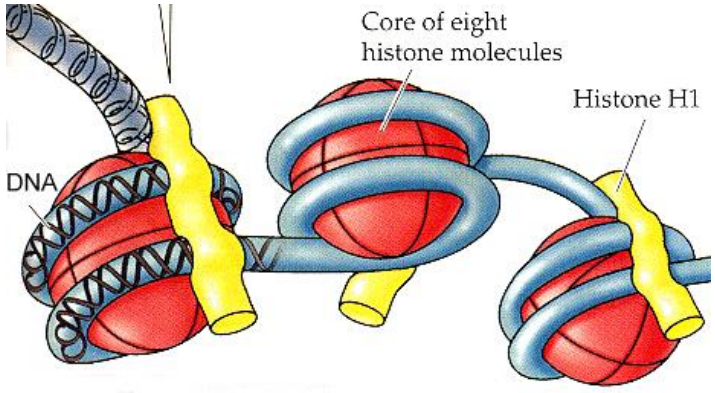
Impachetarea ADN - Nivelul I – FILAMENTUL CU NUCLEOZOMI

NUCLEOZOMUL- unitatea fundamentala a cromatinei

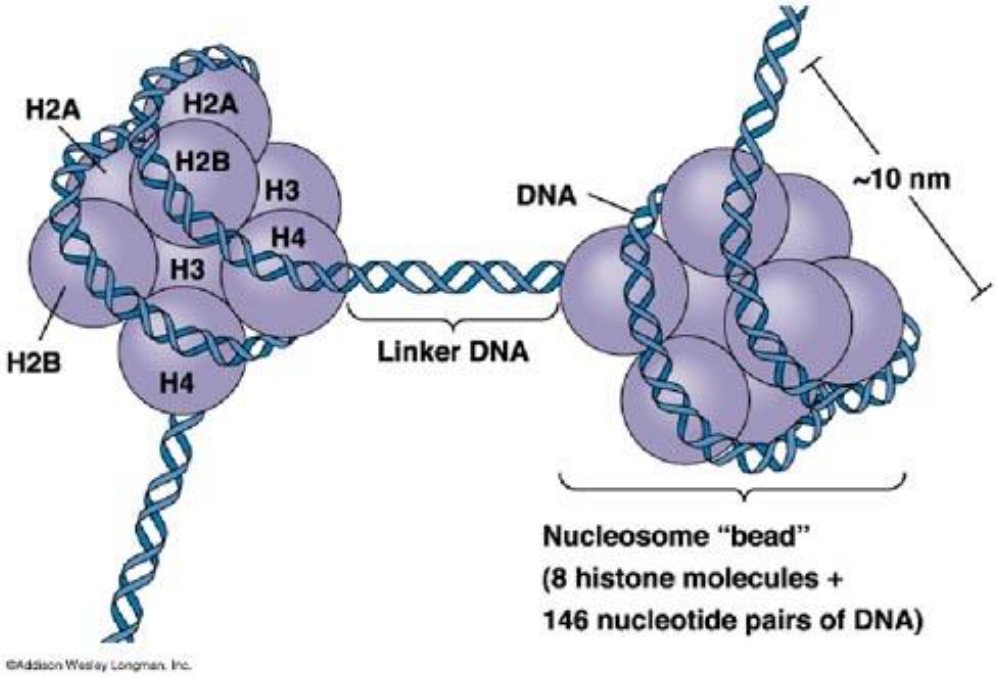
Primul nivel de organizare supramoleculară a ADN este filamentul cu nucleozomi, cu diametrul de 10 nanometri.

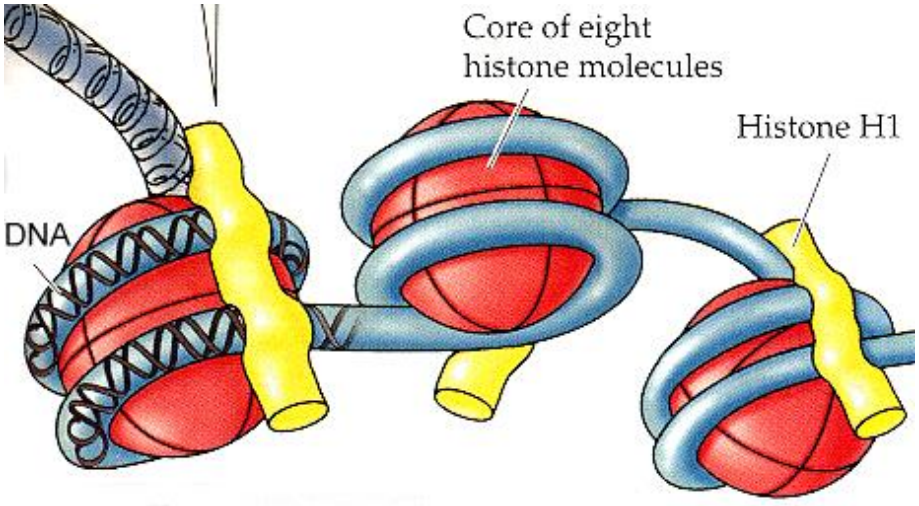


Nucleozomul este unitatea fundamentală (repetitivă) a structurii cromatinei, fiind alcătuit dintr-un miez histonic cilindric (format din 8 molecule, câte două din histonele H2A, H2B, H3 și H4) în jurul căruia se înfășoară (1 tur Și 3/4) o secvență de ADN (de 147 pb).

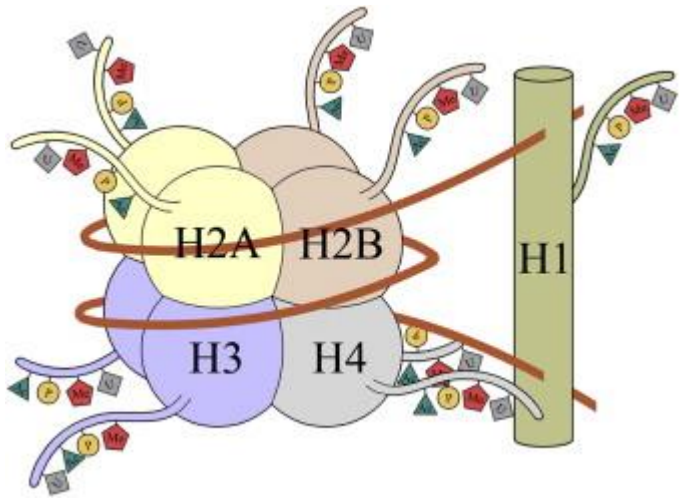


Nucleozomii sunt legați între ei printr-un segment de ADN liber (linker) de 60~80 pb), formând filamentul cu nucleozomi, asemãnãtor unui șirag de mãrgele pe o sfoarã.





Histonele sunt proteine bazice, de mici dimensiuni, prezente la toate eucariotele, cu mare afinitate pentru ADN, fixându-se pe mica incizurã și neutralizând sarcinile acide.



Roluri:

1) - **structural (intră în strcutura nucleozomilor)**

2) **reglarea epigenetică a expresiei genelor (acetilare, metilare la nivelul capetelor terminale)**

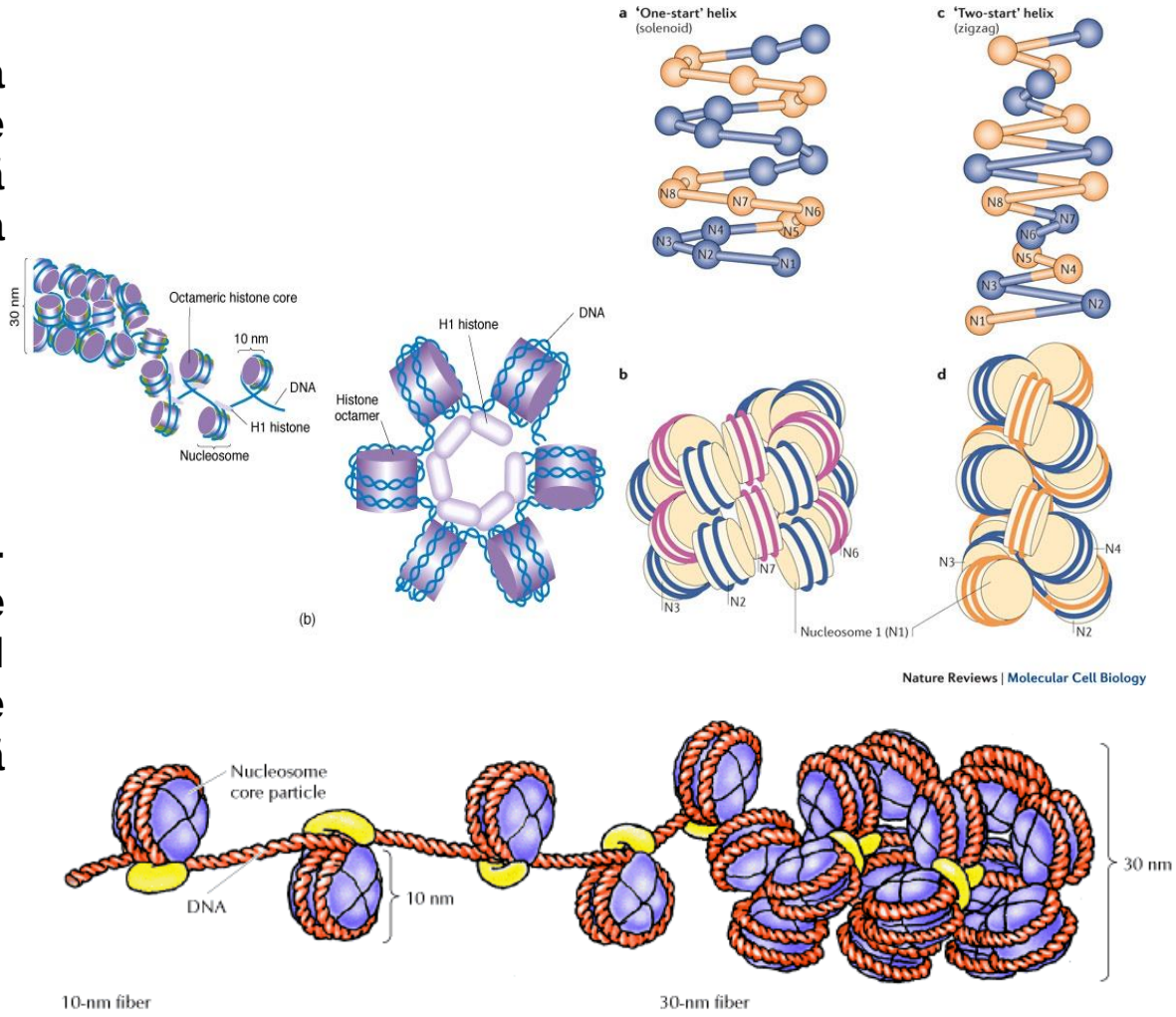
Dupã numãrul și tipul de aminoacizi se deosebesc cinci tipuri de histone prezente la toate eucariotele: H1, H2A, H2B, H3 și H4.

Impachetarea ADN

Nivelul II – Fibra solenoidală de 30 nm.

Al doilea nivel de compactare a cromatinei este fibra de cromatinã de 30 nm. Ea rezultã prin spiralizarea în solenoid a filamentului cu nucleozomi.

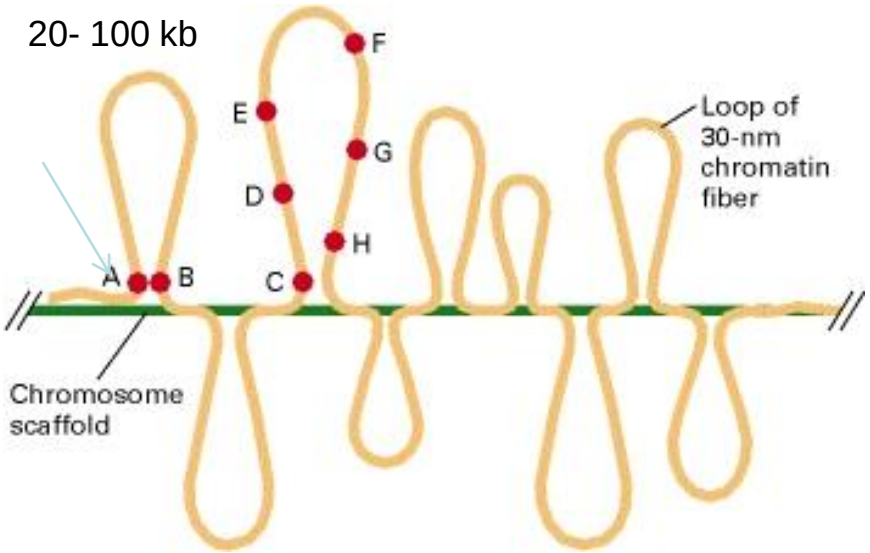
Această structură (cu pasul de 6-8 nucleozomi) este stabilizatã de histona H1 (fixatã în interiorul solenoidului), care prin cele două brațe laterale conectează nucleozomii învecinați.



Impachetarea ADN

Nivelul III - Fibra de cromatinã de 30 nm în bucle laterale

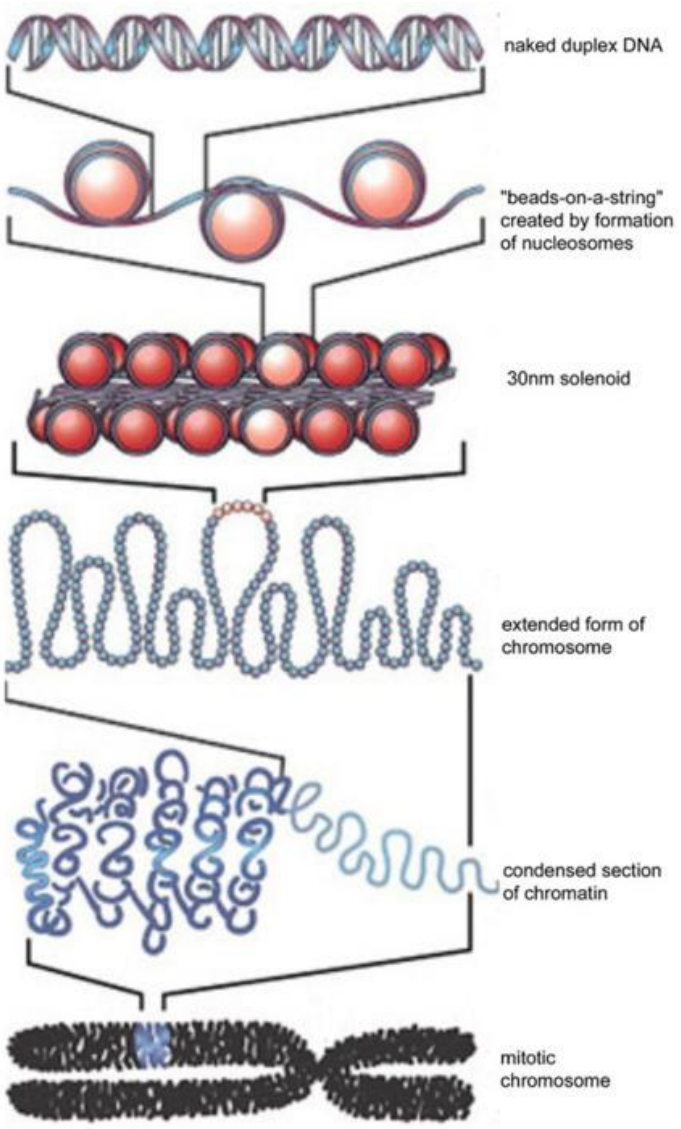
Al treilea nivel de organizare rezultã prin plierea fibrei de cromatinã de 30 nm în bucle laterale de lungimi diferite (20-100 kb); se formeazã fibra pliatã în bucle laterale, cu un diametru de 300 nm.



Buclele sunt atașate în spiralã, prin anumite situsuri de ancorare din structura fibrei de ADN, la un schelet. sau matrice proteicã (nonhistonicã).

Proteinele nehistonice sunt proteine acide și neutre, numeroase și puțin abundente. Unele proteine nehistonice au un rol structural formând matricea cromozomilor, dar majoritatea au roluri funcționale, intervenind specific în reglarea sau modularea activității genelor.

Impachetarea ADN
Nivelul IV - Cromatida de 700 nm



Cromatida unui cromozom se formează prin puternica spiralizare și condensare a fibrei pliate în bucle laterale. Astfel, se asigurã o compactare de 20:1, iar prin continuarea condensării cromozomul metafazic atinge o grosime de 700 nm, gradul maxim de compactare a fibrei de bazã a cromatinei (30 nm).

Fiecare cromatidã a unui cromozom conține deci o singurã moleculã de ADN, organizatã în mai multe structuri succesive și ierarhizate de împachetare.

Se realizează astfel o împachetare (compactare) a genomului diploid (~2m lungime) în cromozomi (lungime totalã în metafazã ~230 mm) și nucleu (10 µm diametru).