

# Genetics and Bioinformatics

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# INTRODUCTION

## Fundamental principles

**Inheritable Trait (Character)** : qualitative or quantitative feature transmissible to the next generations

**Evolution** : Modification of traits from generation to generation driven by natural selection and genetic drift

**Heredity** : transmission of inherited traits from one individual to its progeny

**Genetics**: science that studies individuals' inherited characters, their transmission throughout generations and their alterations (mutations).

# I – The emergence of Molecular Biology

- Classical genetics



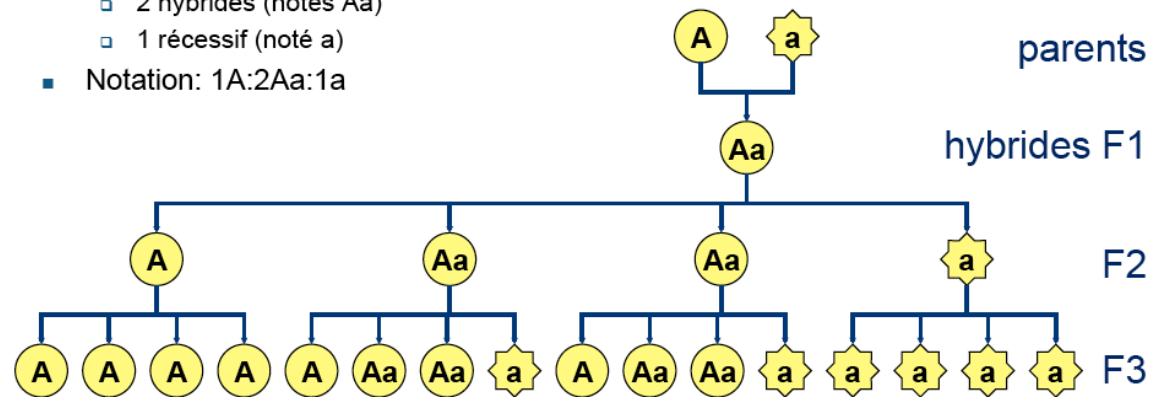
Gregor Mendel (1822 - 1884)

Heredity's (Mendel's) laws (1866)

*Law n°1 : Law of Dominance (uniformity of characters at first generation).*

*Law n°2 : Law of Segregation of parental gene versions (alleles)*

- 2 hybrides (notés Aa)
- 1 récessif (noté a)
- Notation: 1A:2Aa:1a



# I – The emergence of Molecular Biology

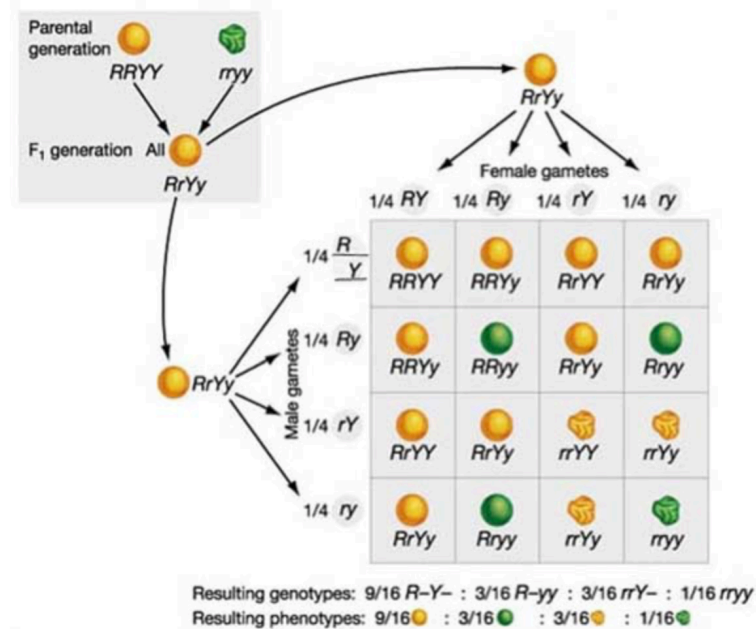
- Classical genetics



Gregor Mendel (1822 - 1884)

Heredity's (Mendel's) laws (1866)

*Law n°3 : Law of independent assortment (genes for different traits are sorted separately in gametes).*



Genes and alleles : (concepts 1 to 6) : <http://www.dnaftb.org/1/>



# I – The emergence of Molecular Biology

- Classical genetics

Gregor Mendel (1822 - 1884)

- Chromosome is the support of heredity (1910)

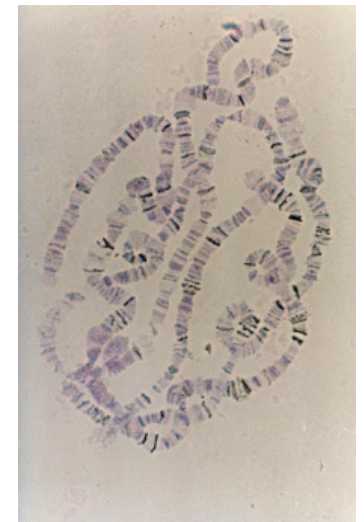


Thomas Morgan (1866 - 1945)

Chromosomal theory of heredity

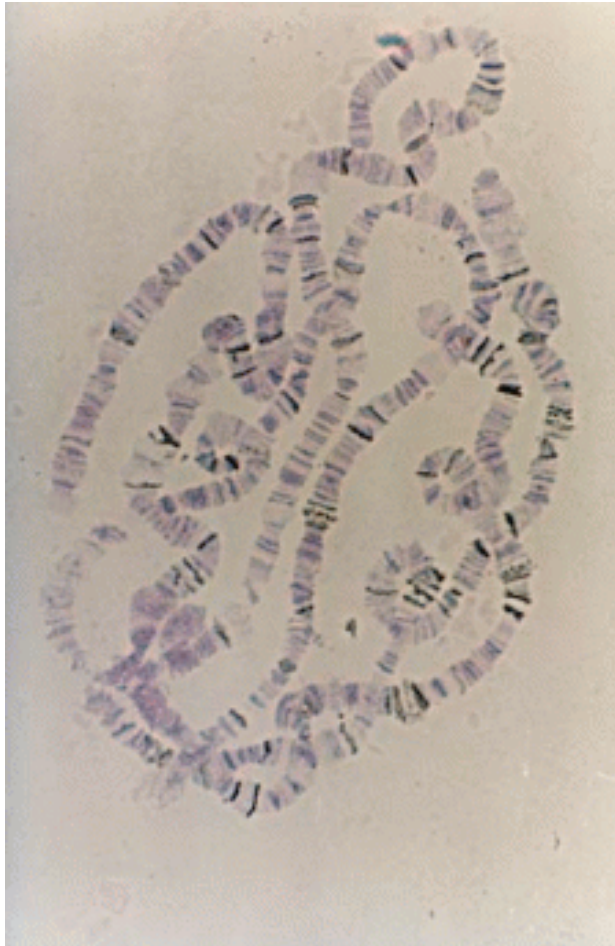


*Drosophila melanogaster*

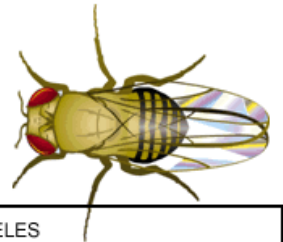
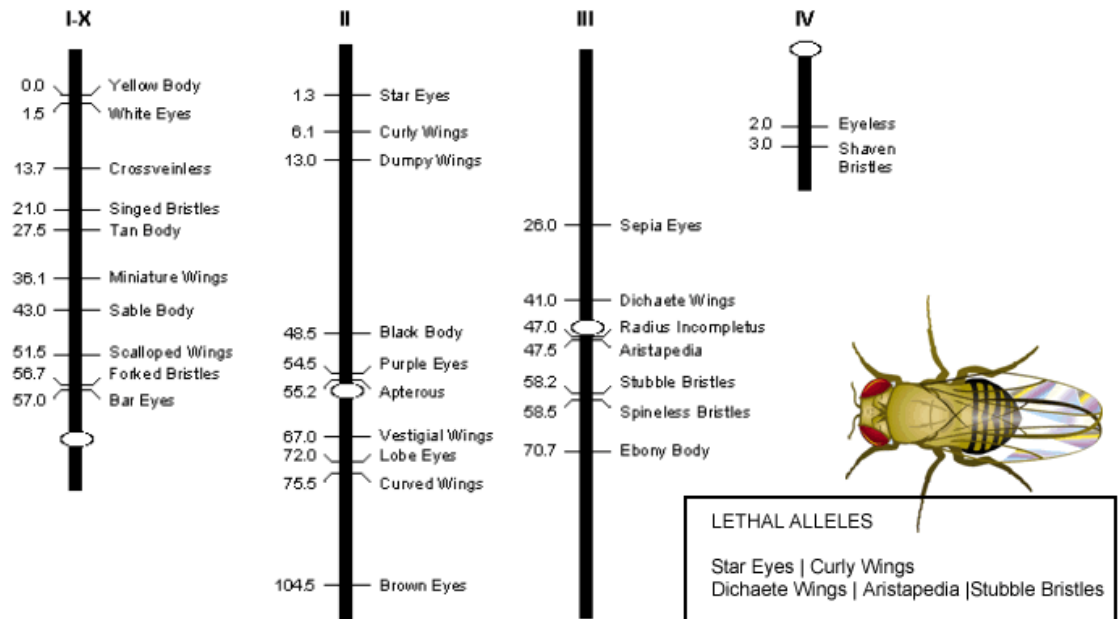


*Polytene chromosomes*

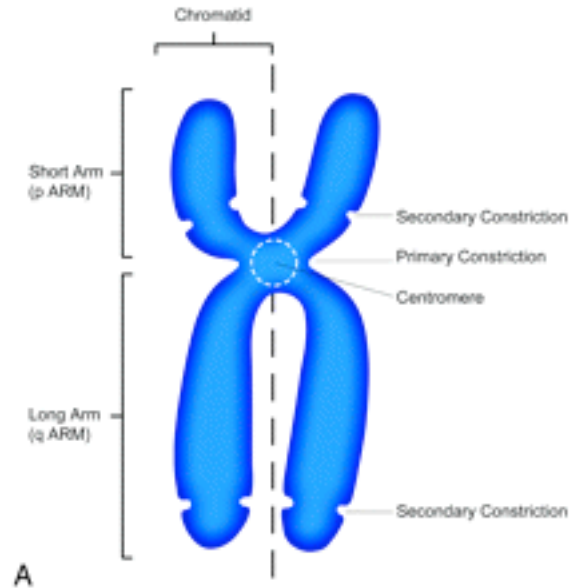
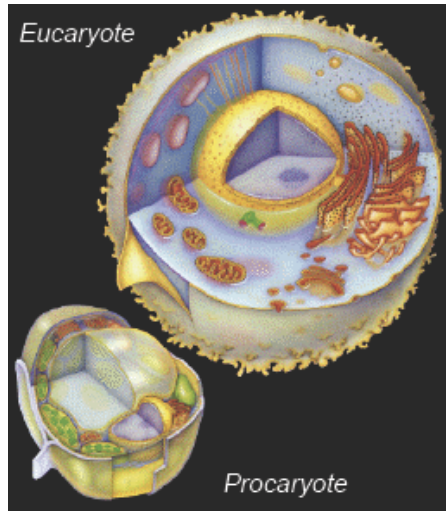
- Chromosome is the support of heredity (Thomas Morgan)



Drosophila Chromosome Map



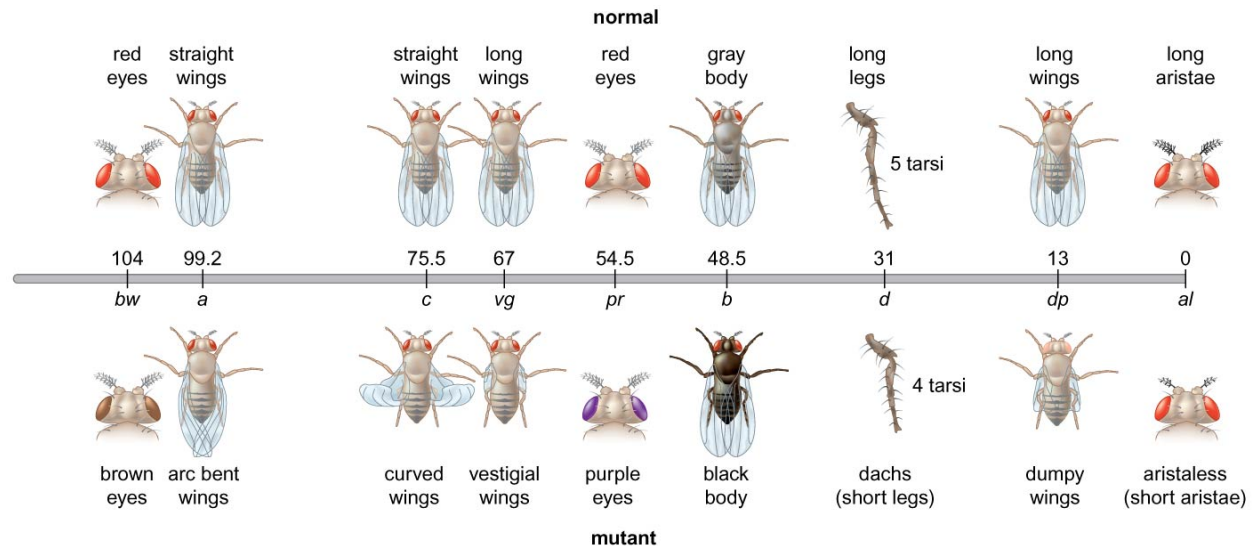
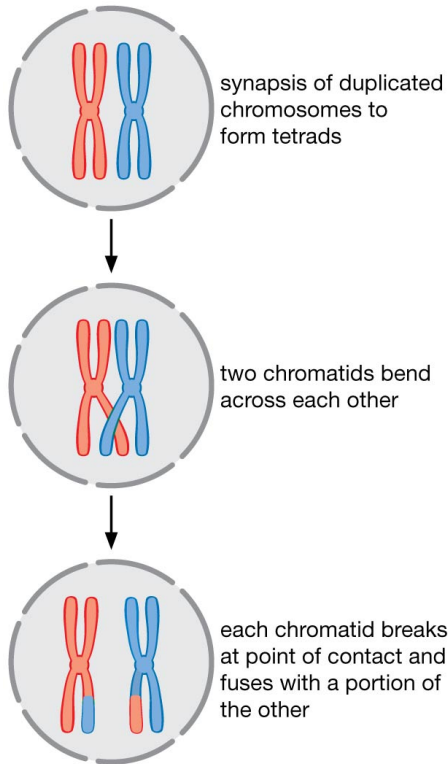
- Chromosome is the support of heredity



Genes and Chromosomes : (concepts 7 to 14) : <http://www.dnafb.org/1/>

<https://www.youtube.com/watch?v=PLaDJMx88FI>

- Chromosome is the support of heredity



→ The further apart the loci are, the greater the chances that they get separated during meiosis by crossing-over

# I – The emergence of Molecular Biology

- Classical genetics  
Gregor Mendel (1822 - 1884)
- Chromosome is the support of inheritance  
Thomas Morgan (1866 - 1945)  
Alfred Sturtevant (1891 - 1970)
- DNA is the support of inheritance  
Fred Griffith (1877 - 1941)  
Oswald Avery (1877 – 1955)
- Composition and structure of DNA  
Alfred Hershey (1908-1997)  
Martha Chase (1927-2003)



Erwin Chargaff (1905 - 1992)

$$A+T / C+G = K$$

$$A / T = C / G = 1$$

[https://www.youtube.com/watch?v=a3\\_1AOXCMmo](https://www.youtube.com/watch?v=a3_1AOXCMmo)

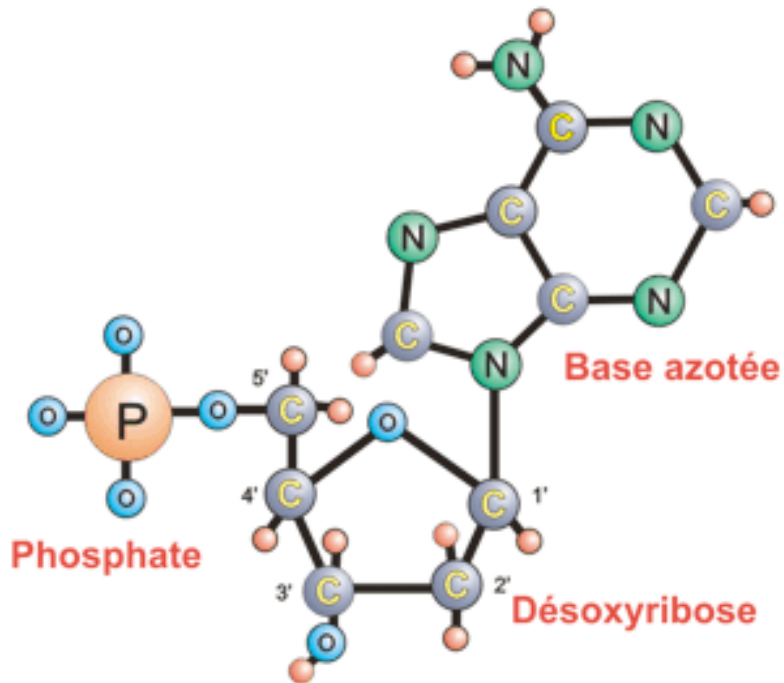


## II – Structure of nucleic acids

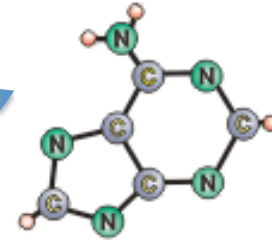
### II.I Simple molecules

Desoxyribonucleic acid (DNA)

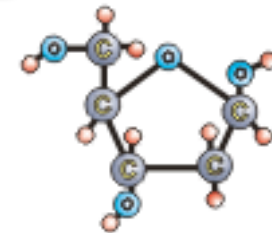
= polymers of small sub-units called **nucleotides**



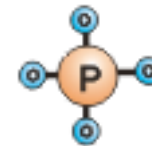
**BASE**



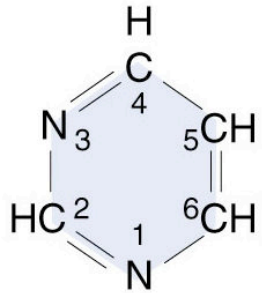
**SUGAR**



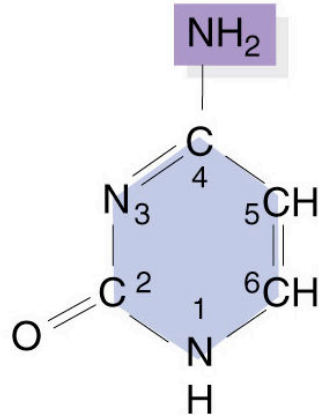
**PHOSPHORIC ACID**



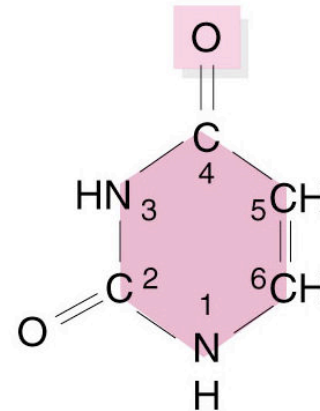
## II.I.1 Nitrogenous bases



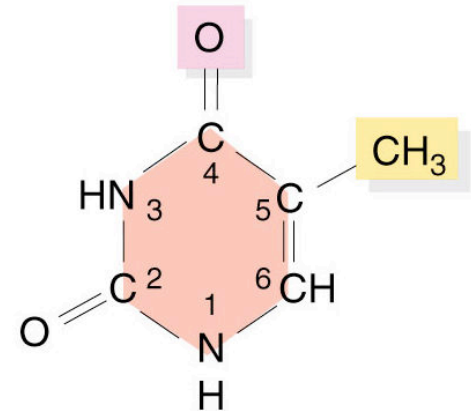
**Pyrimidine**



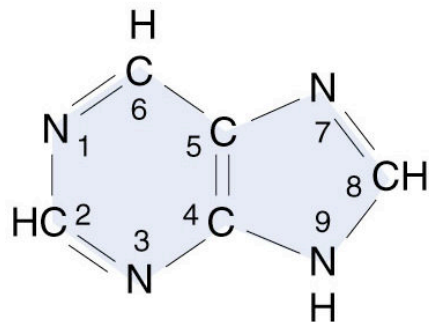
**Cytosine (C)**  
*2-oxy-4-amino-pyrimidine*



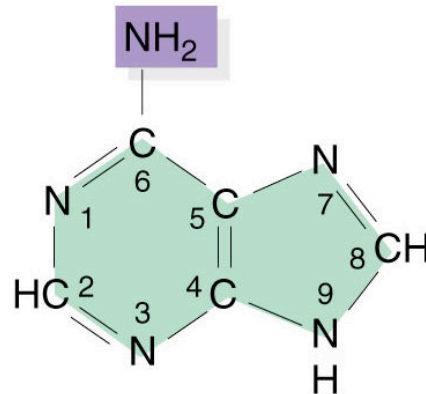
**Uracil (U)**  
**(found in RNA)**  
*2,4-dioxy-pyrimidine*



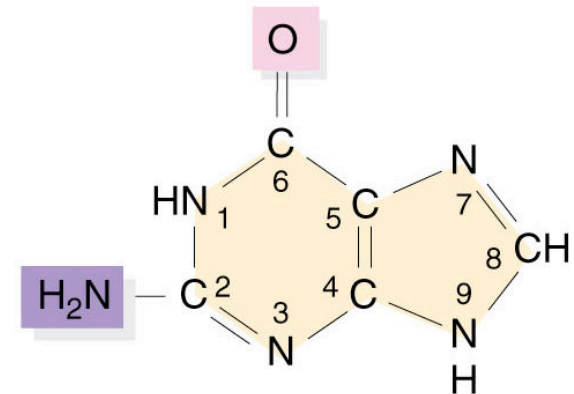
**Thymine (T)**  
**(found in DNA)**  
*2,4-dioxy-5-méthyl-pyrimidine*



**Purine**



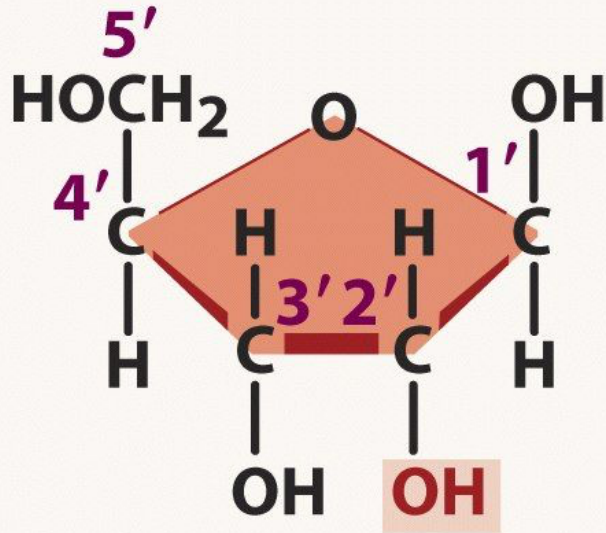
**Adenine (A)**  
*6-amino-purine*



**Guanine (G)**  
*2-amino-6-oxy-purine*

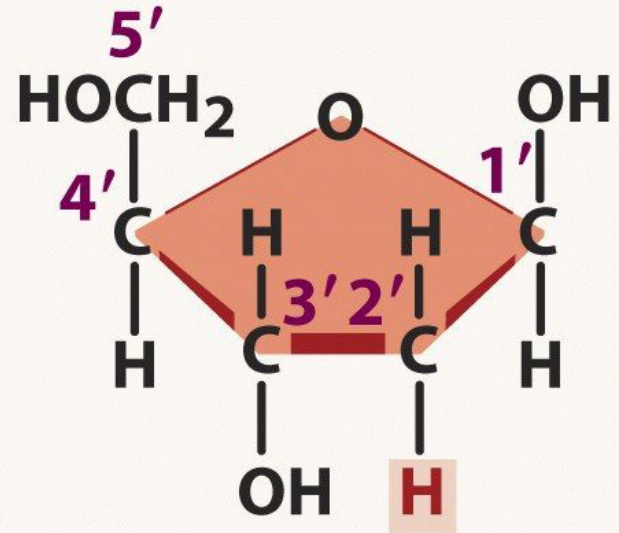
## II.1.2 Sugars

### Sugars



**Ribose**

RNA



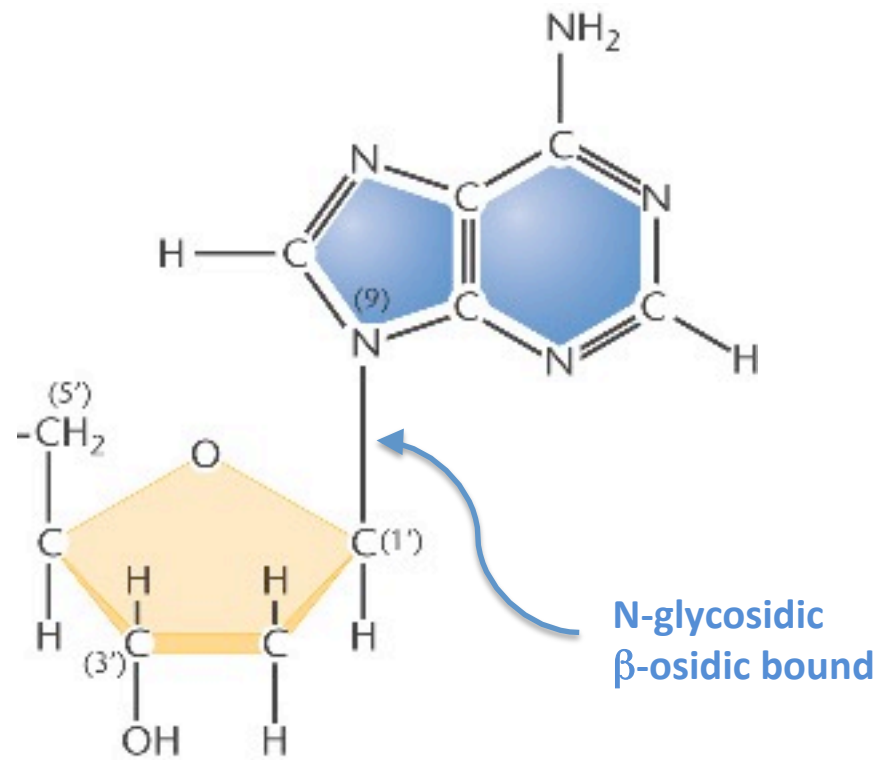
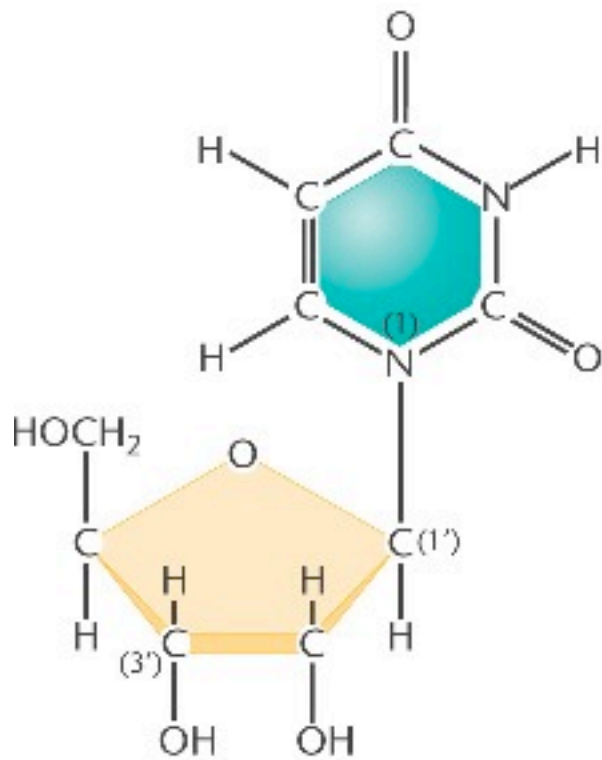
**Deoxyribose**

DNA

## II.2 Nucleosides

### NucleoSides

SUGAR + BASE

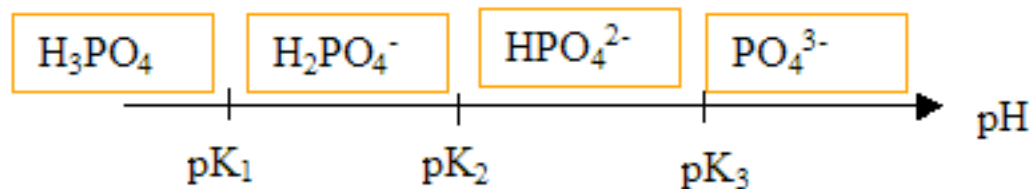
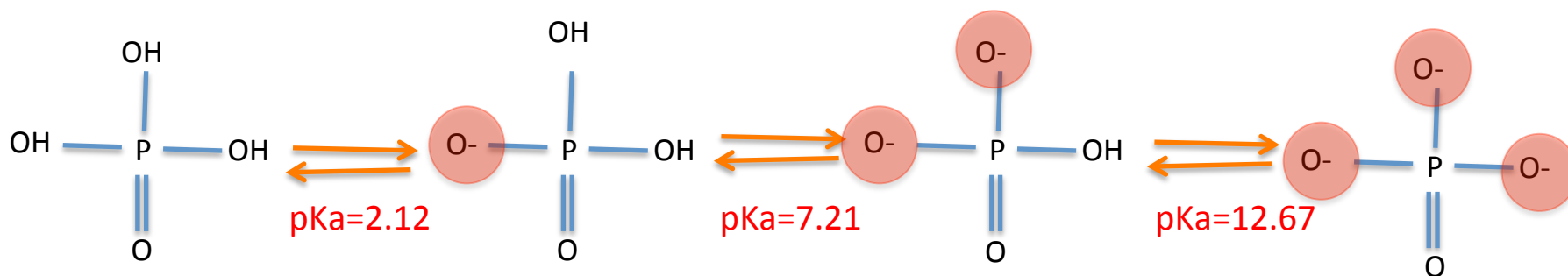
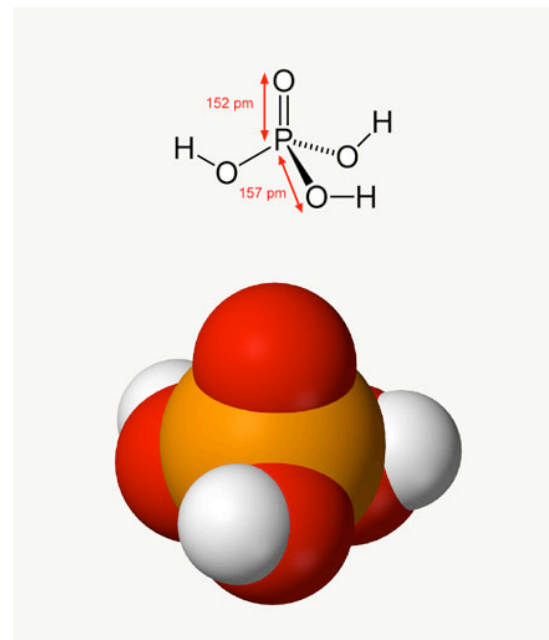


## II.2 Nucleosides

	<b>Base</b>	<b>Ribonucleoside</b>	<b>Desoxyribonucleoside</b>
Purines	Adénine Guanine	<b>Adénosine</b> <b>Guanosine</b>	Désoxyadénosine Désoxyguanosine
Pyrimidines	Uracile Cytosine Thymine	<b>Uridine</b> <b>Cytidine</b> Thymine ribonucléoside	Désoxyuridine Désoxycytidine Désoxythymidine ou thymidine

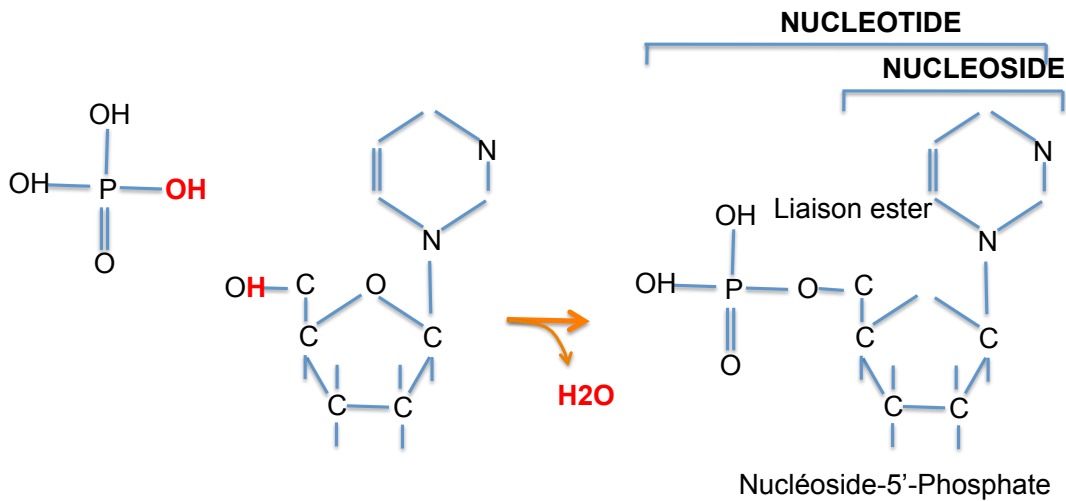
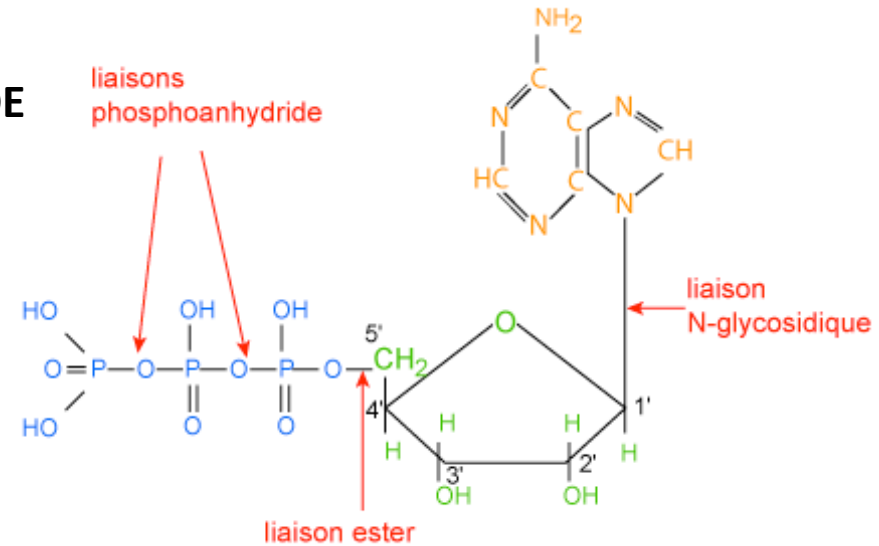


## II.3 Phosphoric Acid



## II.4 Nucleotides

**SUGAR + BASE + PHOSPHATE = NUCLEOTIDE**



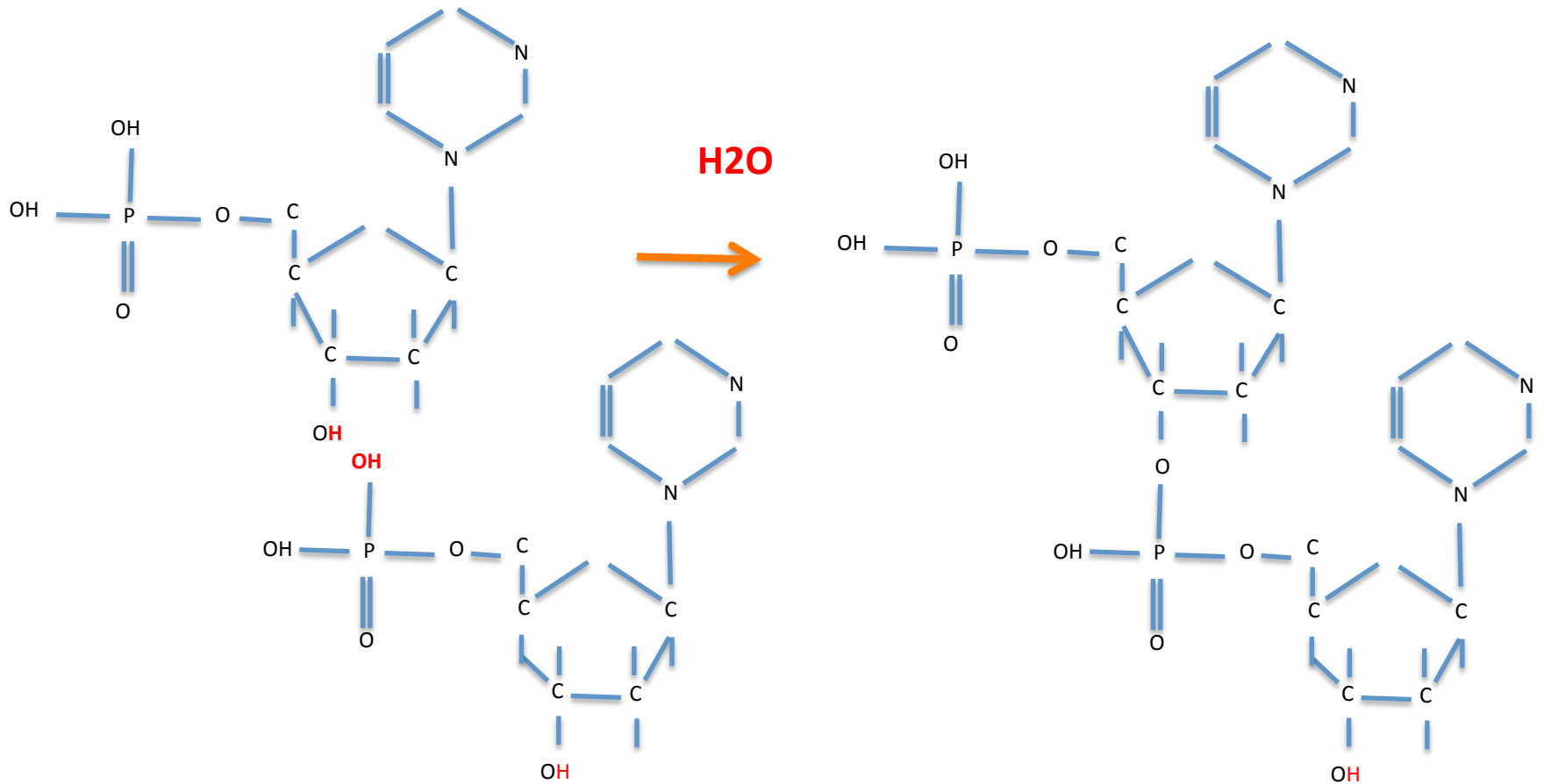
## II.4 Nucleotides

### NucleoTides : nucleosides-5'-Monophosphate

Base	RibonucleoTide	DesoxyribonucleoTide
Adénine	Adé <b>no</b> sine-5'-Monophosphate (AMP)	Désoxyadénosine-5'-Monophosphate (dAMP)
Guanine	Guan <b>o</b> sine-5'-Monophosphate (GMP)	Désoxyguanosine-5'-Monophosphate (dGMP)
Uracile	Urid <b>i</b> ne-5'-Monophosphate (UMP)	Désoxyuridine-5'-Monophosphate (dUMP)
Cytosine	Cytid <b>i</b> ne-5'-Monophosphate (CMP)	Désoxycytidine-5'-Monophosphate (dCMP)
Thymine	Thymine riboside -5'-Monophosphate (TMP)	Désoxythymidine -5'-Monophosphate (dTMP)

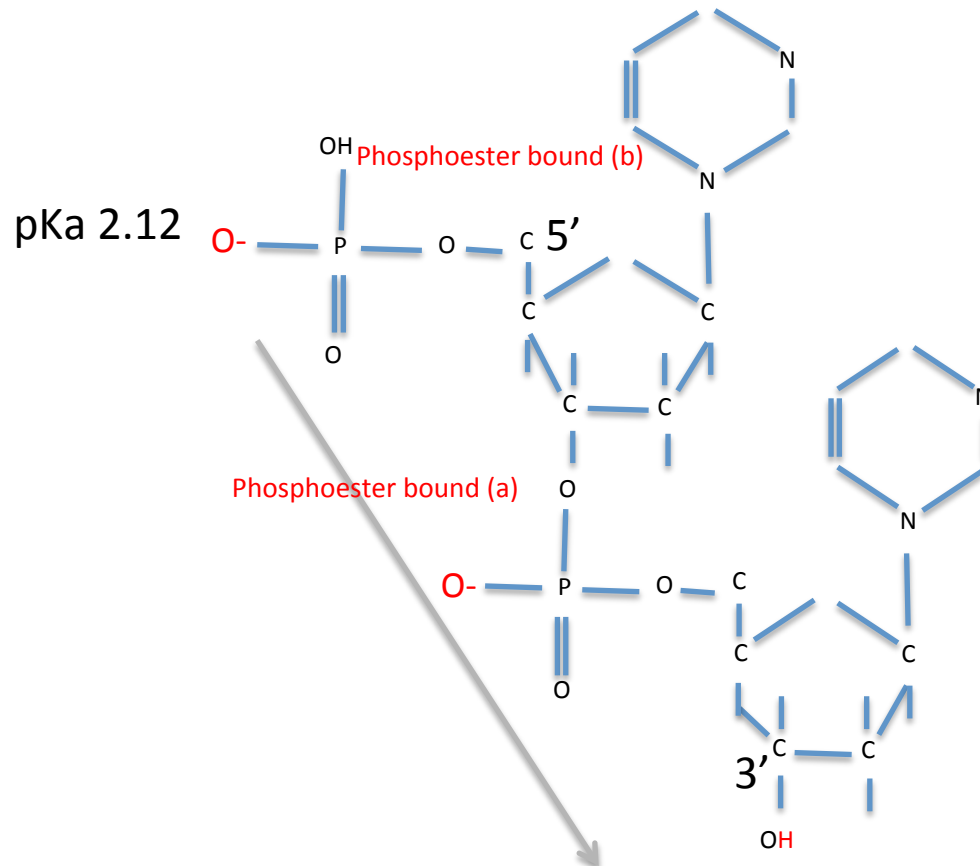
## II.5 Phosphodiester bound

Polynucleotidic chain



## II.5 Phosphodiester bound

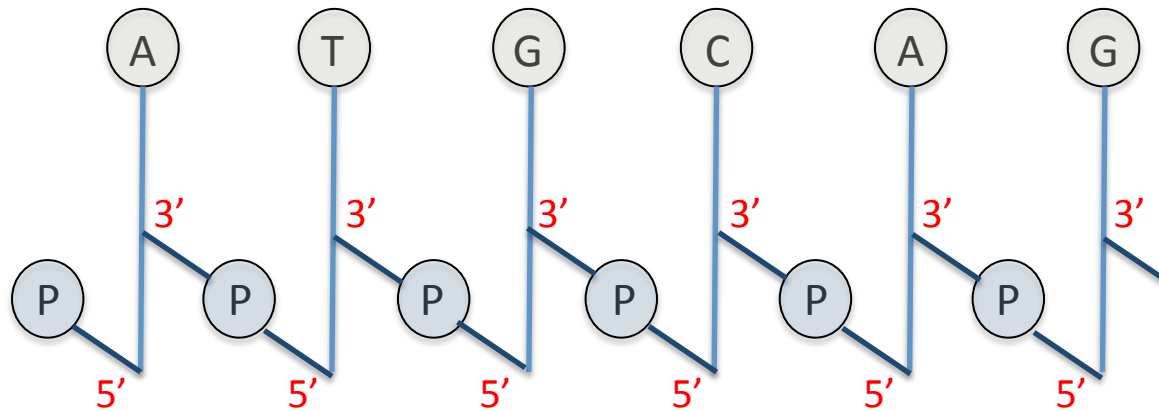
Polynucleotidic chain





## II.5 Phosphodiester bound

Polynucleotidic chain

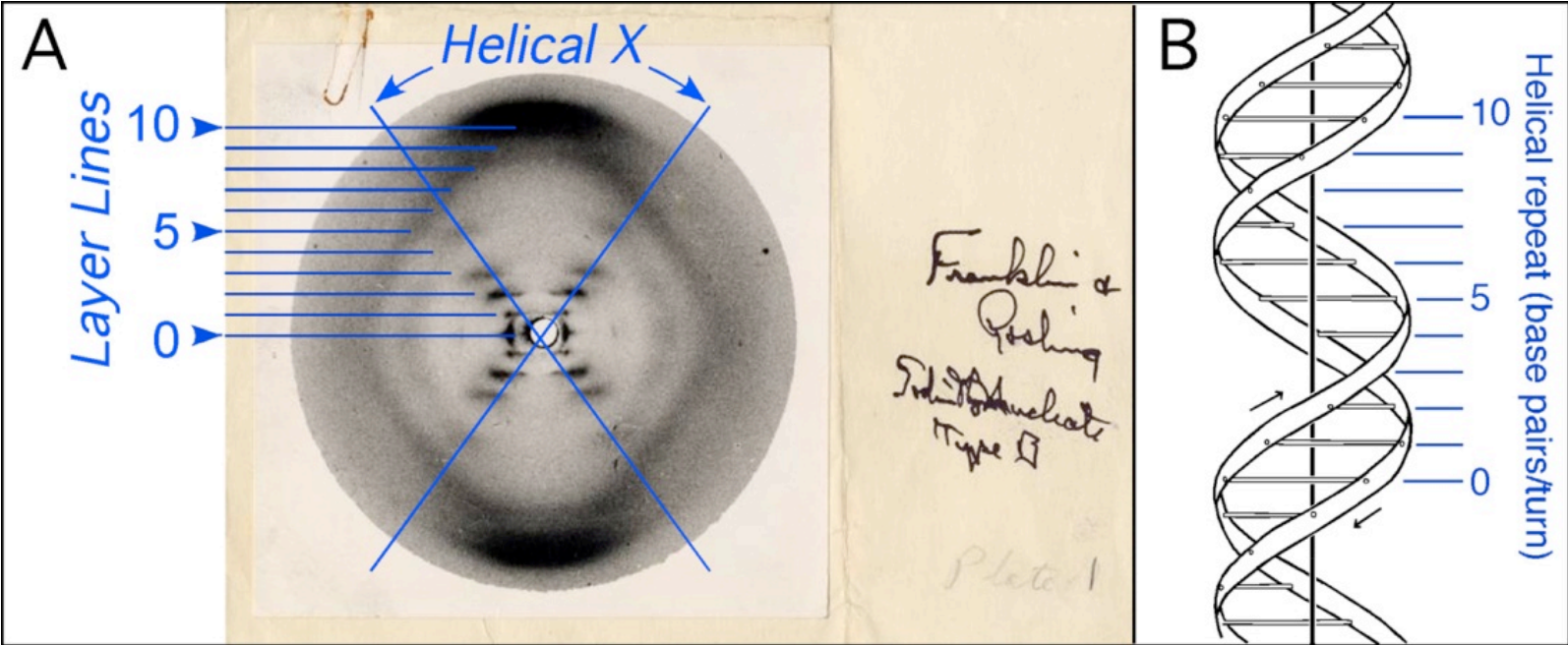


p5'dAp5'dTp5'dGp5'dCp5'dAp5'dG

ou 5'-dATGCAG-3'  
5'-ATGCAG-3'

# II.6 Secondary Structure of DNA

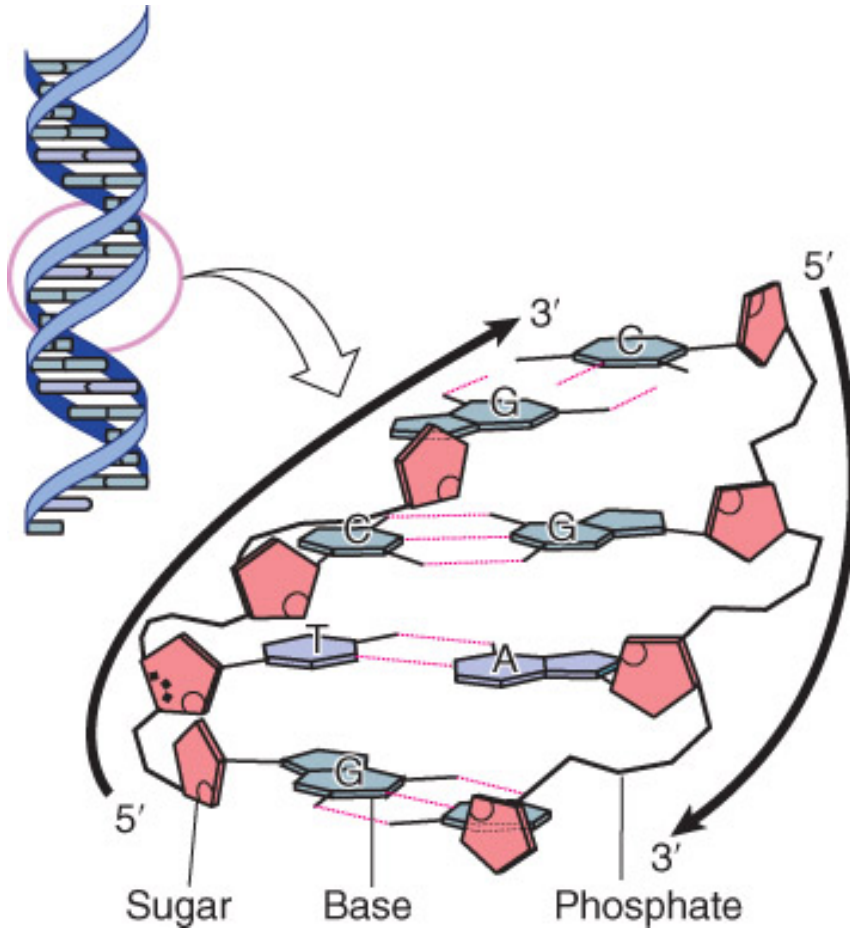
Secondary Structure : The Watson et Crick model



Rosalind Franklin

## II.6 Secondary Structure of DNA

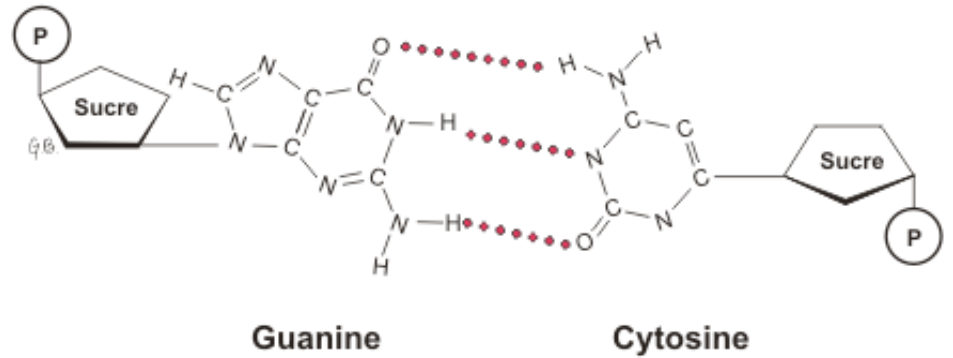
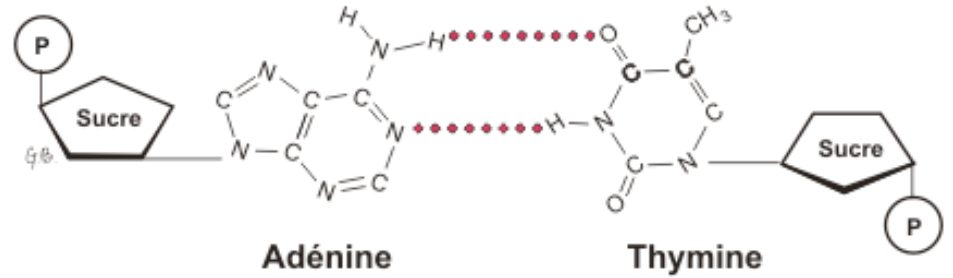
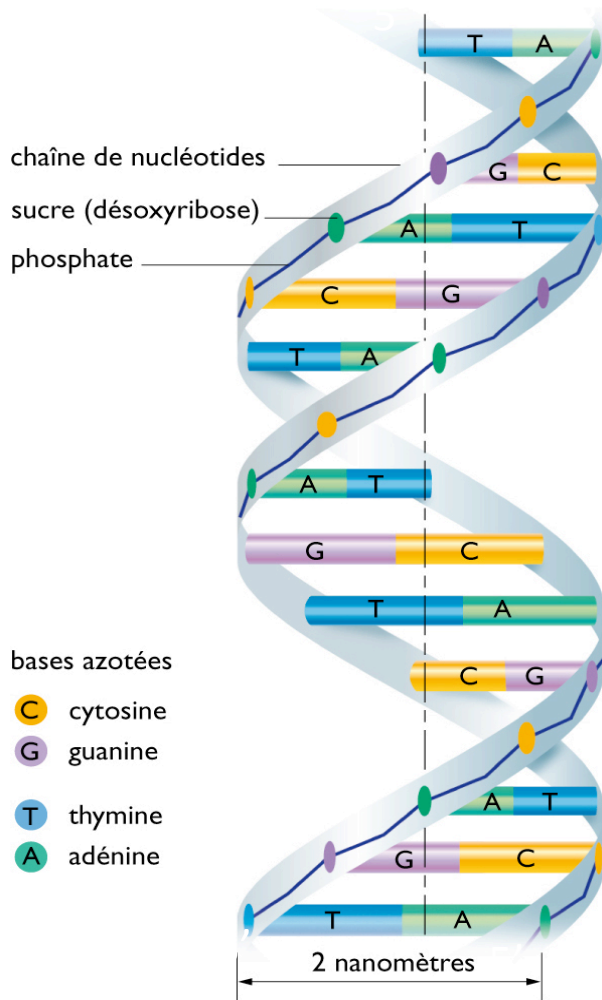
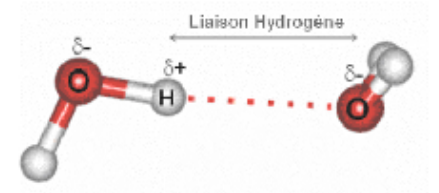
The Molecule of DNA : secondary structure (Watson-Crick Model)



- **Double stranded** (2 strands of polynucleotide chains)
- **Antiparallel**
- **Helicoidal**
- Bases (inside) Sugar/phosphates (outside)
- **Complementary !**

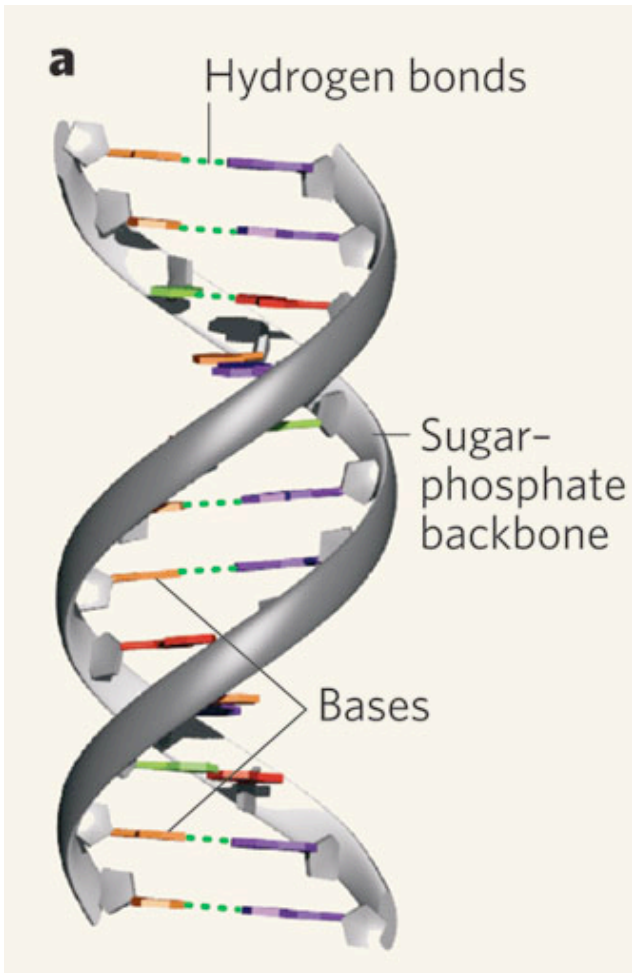
# II.6 Secondary Structure of DNA

## Rules of complementarity



## II.6 Secondary Structure of DNA

The DNA molecule : secondary structure and stability



<https://www.youtube.com/watch?v=q6PP-C4udkA>

[https://www.youtube.com/watch?v=o\\_-6JXLYS-k](https://www.youtube.com/watch?v=o_-6JXLYS-k)

## **Problem**

The proportion of nitrogenous bases in a single stranded DNA was calculated. The G/C content of that molecule is 39,8%.

1. Calculate the proportion of each of the 4 bases (A, T, G, C) in the molecule.
2. Propose a 20 nucleotide long double-stranded DNA molecule that fits this criteria.

### III. Structure of genomes

In cells, the molecule of DNA is associated to specialized proteins that will determine the structure by imposing a series of constraints : **Chromosome**

The structuration of DNA will have an impact on :

- its size

DNA is highly compacted in all types of genomes				
Compartment	Shape	Dimensions	Type of Nucleic Acid	Length
TMV	filament	0.008 x 0.3 $\mu\text{m}$	One single-stranded RNA	2 $\mu\text{m}$ = 6.4 kb
Phage fd	filament	0.006 x 0.85 $\mu\text{m}$	One single-stranded DNA	2 $\mu\text{m}$ = 6.0 kb
Adenovirus	icosahedron	0.07 $\mu\text{m}$ diameter	One double-stranded DNA	11 $\mu\text{m}$ = 35.0 kb
Phage T4	icosahedron	0.065 x 0.10 $\mu\text{m}$	One double-stranded DNA	55 $\mu\text{m}$ = 170.0 kb
<i>E. coli</i>	cylinder	1.7 x 0.65 $\mu\text{m}$	One double-stranded DNA	1.3 mm = 4.2 x 10 <sup>3</sup> kb
Mitochondrion (human)	oblate spheroid	3.0 x 0.5 $\mu\text{m}$	~10 identical double-stranded DNAs	50 $\mu\text{m}$ = 16.0 kb
Nucleus (human)	spheroid	6 $\mu\text{m}$ diameter	46 chromosomes of double-stranded DNA	1.8 m = 6 x 10 <sup>6</sup> kb

- its accessibility (protection, replication, transcription, etc..)

### III. Structure of genomes

The genome of each organism is organized into a specific number of chromosomes, whose shape is characteristic

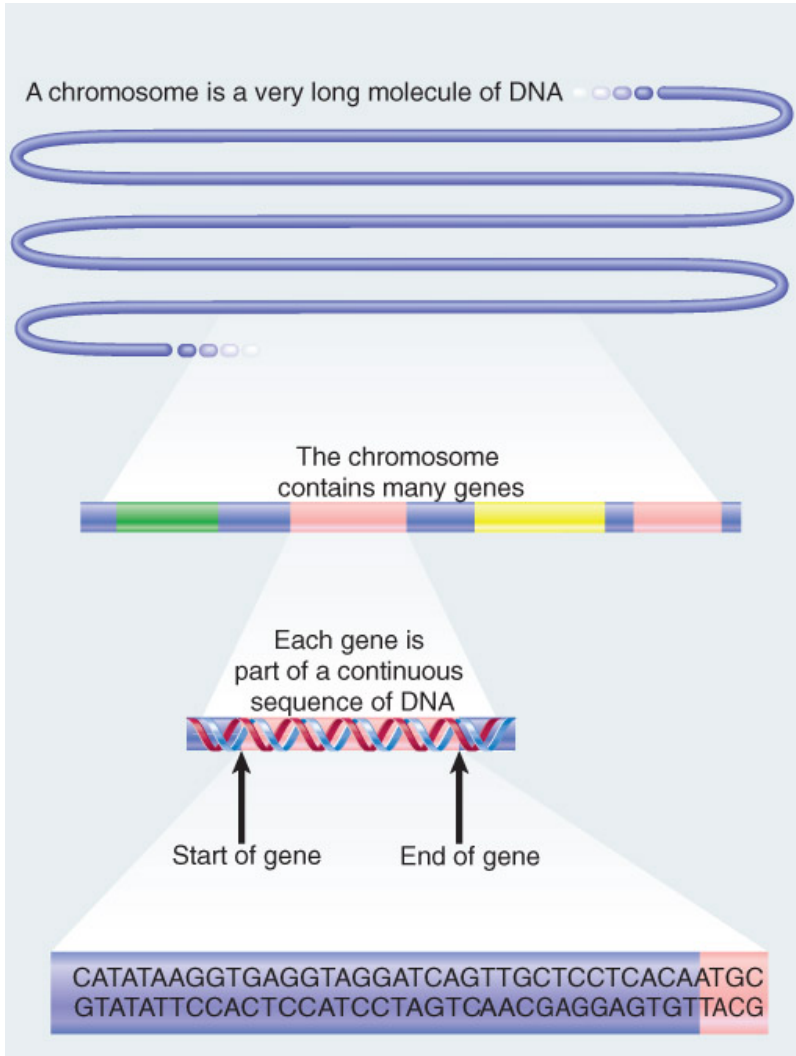
**TABLE 8-1** Variation in Chromosome Makeup in Different Organisms

Species	Number of Chromosomes	Chromosome Copy Number	Form of Chromosome(s)	Genome Size (Mb)
<b>Prokaryotes</b>				
<i>Mycoplasma genitalium</i>	1	1	Circular	0.58
<i>Escherichia coli</i> K-12	1	1	Circular	4.6
<i>Agrobacterium tumefaciens</i>	4	1	3 circular, 1 linear	5.67
<i>Sinorhizobium meliloti</i>	3	1	Circular	6.7
<b>Eukaryotes</b>				
<i>Saccharomyces cerevisiae</i> (budding yeast)	16	1 or 2	Linear	12.1
<i>Schizosaccharomyces pombe</i> (fission yeast)	3	1 or 2	Linear	12.5
<i>Caenorhabditis elegans</i> (roundworm)	6	2	Linear	97
<i>Arabidopsis thaliana</i> (weed)	5	2	Linear	125
<i>Drosophila melanogaster</i> (fruit fly)	4	2	Linear	180
<i>Tetrahymena thermophilus</i> (protozoa)	5	2	Linear	125
Micronucleus				
Macronucleus	225	10–10,000	Linear	
<i>Fugu rubripes</i> (fish)	22	2	Linear	393
<i>Mus musculus</i> (mouse)	19+X and Y	2	Linear	2600
<i>Homo sapiens</i>	22+X and Y	2	Linear	3200



### III. Structure of genomes

What's a gene? : a gene is a region of DNA (sequence of bases) coding for a polypeptide (+ proximal upstream regulatory regions)



Allele : one of the versions of a gene

Locus : position of a gene on the chromosome

In an individual, or a population, more than one allele can be found at a single locus

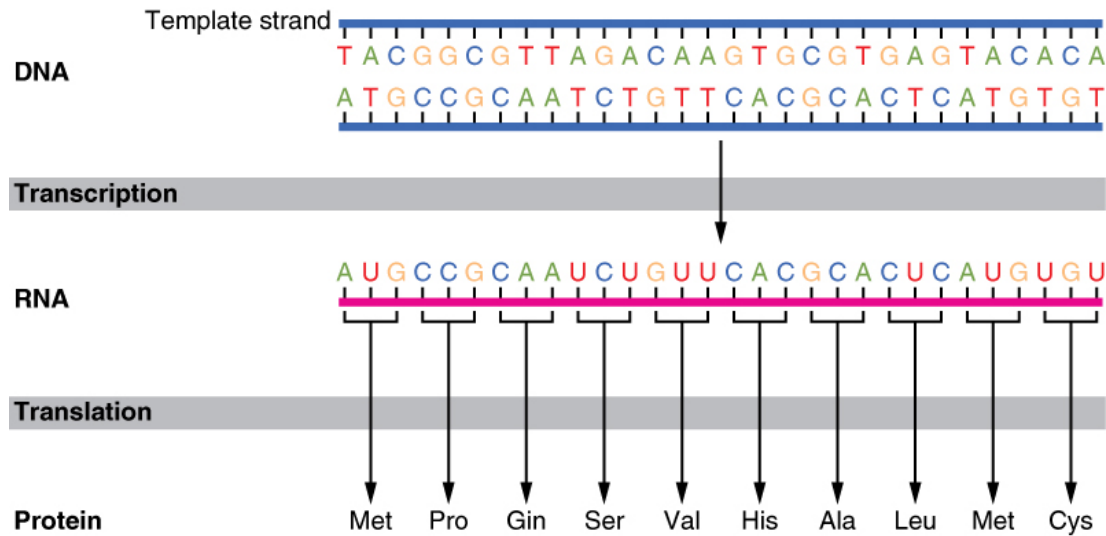
Each allele has a different phenotype	
Allele	Phenotype of homozygote
$w^+$	red eye (wild type)
$w^{bl}$	blood
$w^{ch}$	cherry
$w^{bf}$	buff
$w^h$	honey
$w^a$	apricot
$w^e$	eosin
$w^l$	ivory
$w^z$	zeste (lemon-yellow)
$w^{sp}$	mottled, color varies
$w^1$	white (no color)

# The gene

## The genetic code

Genetic Code : the relation between the sequence of nucleotides in the DNA and the sequence of amino acids in the polypeptides

Genetic Information : genes + regulatory sequences



The genetic code is redundant but unambiguous

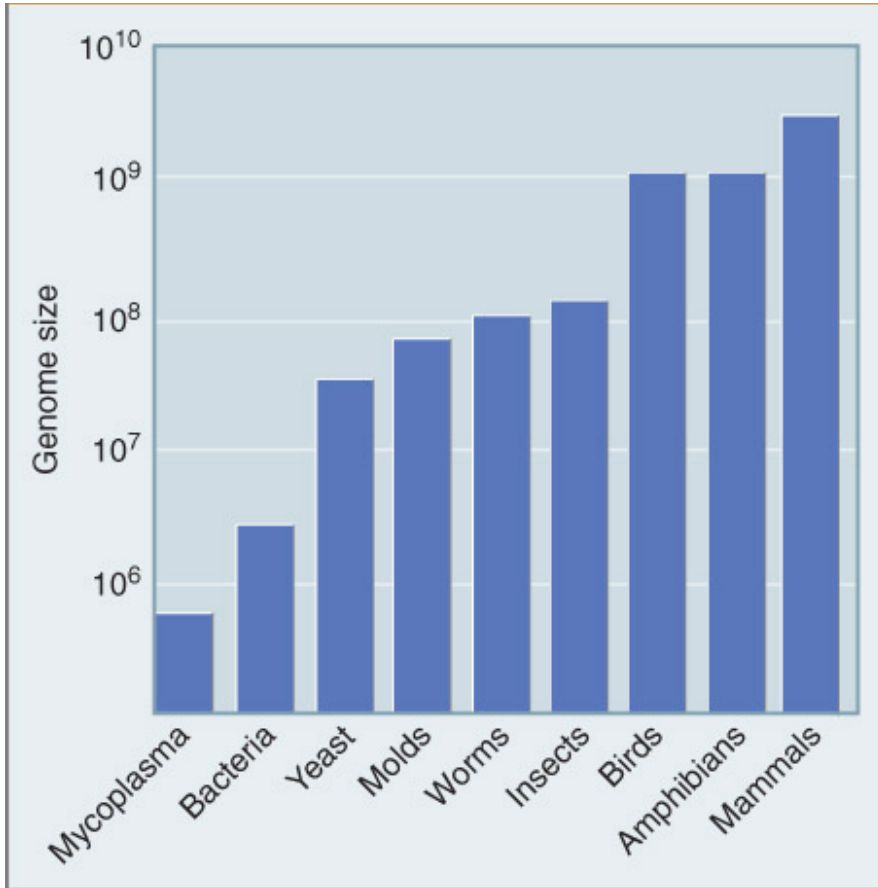
		Seconde lettre					
		U	C	A	G		
Premi re lettre	U	UUU } Phe UUC } UUA } Leu UUG }	UCU } UCC } Ser UCA } UCG } *	UAU } Tyr UAC } UAA Stop UAG Stop	UGU } Cys UGC } UGA Stop UGG Trp	U C A G	
	C	CUU } CUC } Leu CUA } CUG } *	CCU } CCC } Pro CCA } CCG } *	CAU } His CAC } CAA } Gln CAG }	CGU } CGC } Arg CGA } CGG } *	U C A G	
	A	AUU } Ile AUC } AUA } AUG Met	ACU } ACC } Thr ACA } ACG } *	AAU } Asn AAC } AAA } Lys AAG }	AGU } Ser AGC } AGA } Arg AGG }	U C A G	
	G	GUU } Val GUC } GUA } GUG } *	GCU } GCC } Ala GCA } GCG } *	GAU } Asp GAC } GAA } Glu GAG }	GGU } GGC } Gly GGA } GGG } *	U C A G	

**Troisi me lettre : wobble**



### III. Structure of genomes

The size of the genome is roughly correlated to the complexity of the organism



C-value : size of a genome in bas pairs (bp) or pico-gram

### III. Structure of genomes

The number of genes roughly increases with the complexity of the organism

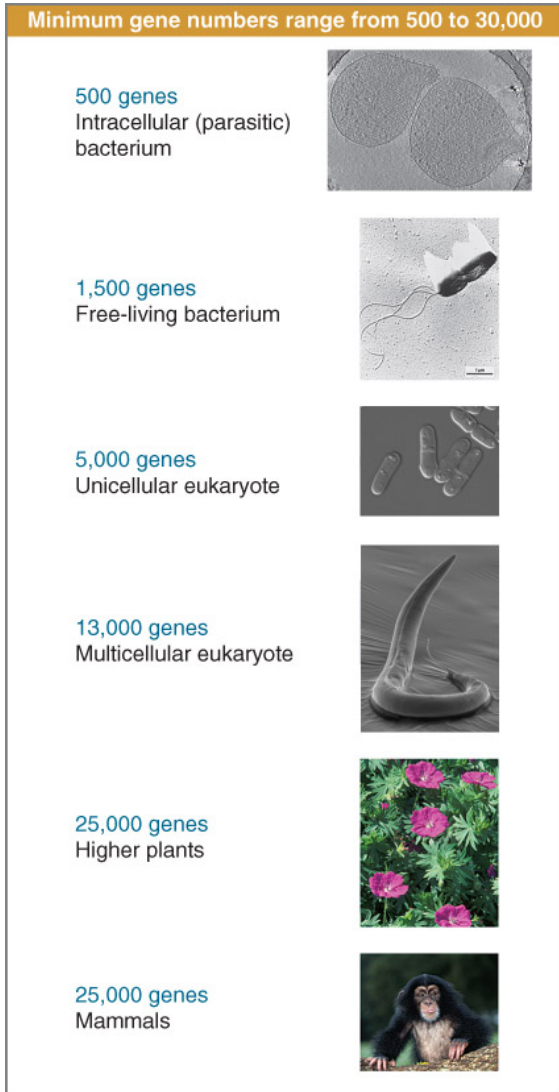


TABLE 8-2 Comparison of the Gene Density in Different Organisms' Genomes

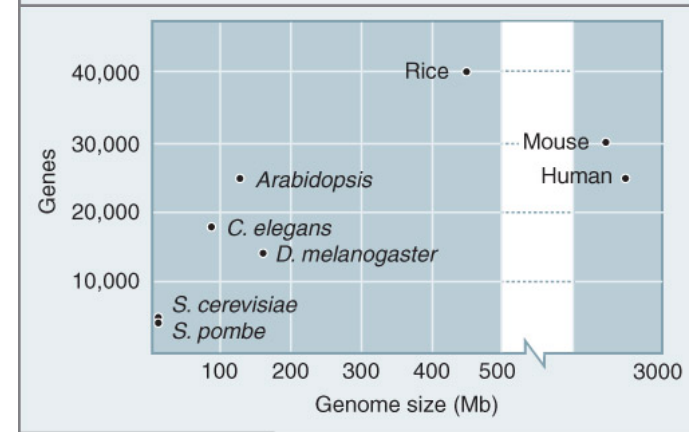
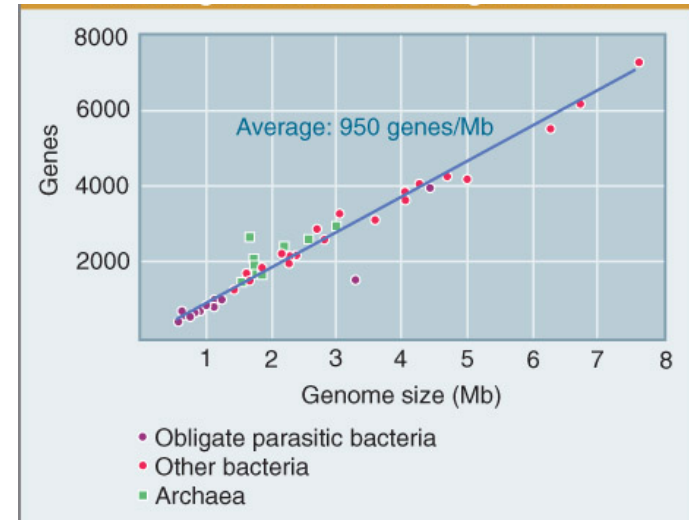
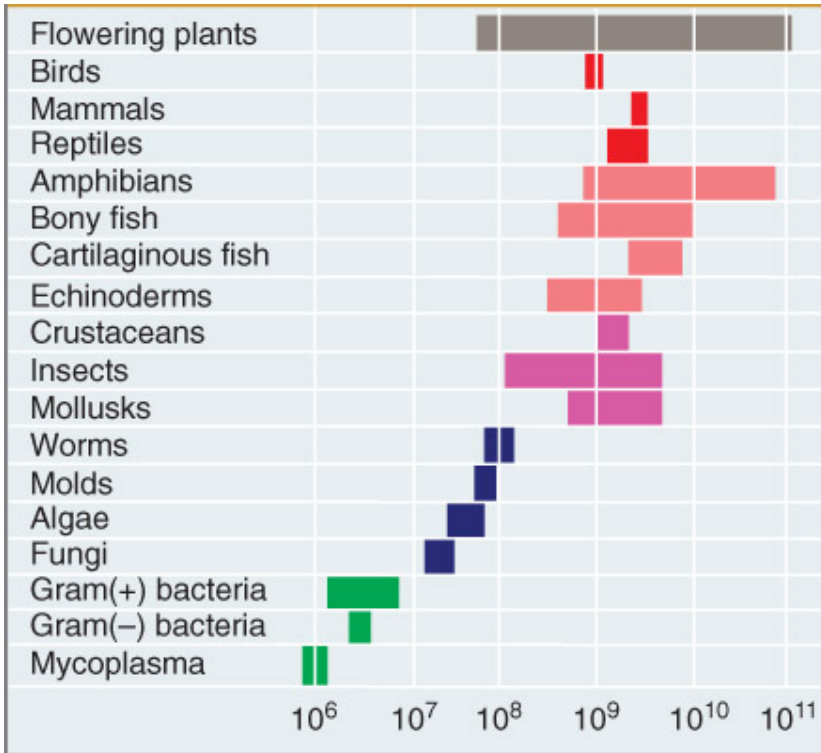
Species	Genome Size (Mb)	Approximate Number of Genes	Gene Density (genes/Mb)
<b>Prokaryotes (bacteria)</b>			
<i>Mycoplasma genitalium</i>	0.58	500	860
<i>Streptococcus pneumoniae</i>	2.2	2300	1060
<i>Escherichia coli</i> K-12	4.6	4400	950
<i>Agrobacterium tumefaciens</i>	5.7	5400	960
<i>Sinorhizobium meliloti</i>	6.7	6200	930
<b>Eukaryotes (animals)</b>			
<b>Fungi</b>			
<i>Saccharomyces cerevisiae</i>	12	5800	480
<i>Schizosaccharomyces pombe</i>	12	4900	410
<b>Protozoa</b>			
<i>Tetrahymena thermophila</i>	125	27,000	220
<b>Invertebrates</b>			
<i>Caenorhabditis elegans</i>	103	20,000	190
<i>Drosophila melanogaster</i>	180	14,700	82
<i>Ciona intestinalis</i>	160	16,000	100
<i>Locusta migratoria</i>	5000	nd	nd
<b>Vertebrates</b>			
<i>Fugu rubripes</i> (pufferfish)	393	22,000	56
<i>Homo sapiens</i>	3200	20,000	6.25
<i>Mus musculus</i> (mouse)	2600	22,000	8.5
<b>Plants</b>			
<i>Arabidopsis thaliana</i>	120	26,500	220
<i>Oryza sativa</i> (rice)	430	~45,000	~100
<i>Zea mays</i> (corn)	2200	>45,000	>20
<i>Triticum aestivum</i> (wheat)	16,000	nd	nd
<i>Fritillaria assyriaca</i> (tulip)	~120,000	nd	nd

nd, Not determined.



### III. Structure of genomes

The C-value paradox : There is not a strict correlation between the size of the genome and the complexity of the organism or the number of genes



[https://bio.libretexts.org/TextMaps/Genetics/Book%3A\\_Working\\_with\\_Molecular\\_Genetics\\_\(Hardison\)/Unit\\_1%3A\\_Genes%2C\\_Nucleic\\_Acids%2C\\_Genomes\\_and\\_Chromosomes/4%3A\\_Genomes\\_and\\_Chromosomes/4.5%3A\\_Sizes\\_of\\_genomes\\_-\\_The\\_C%E2%80%91value\\_paradox](https://bio.libretexts.org/TextMaps/Genetics/Book%3A_Working_with_Molecular_Genetics_(Hardison)/Unit_1%3A_Genes%2C_Nucleic_Acids%2C_Genomes_and_Chromosomes/4%3A_Genomes_and_Chromosomes/4.5%3A_Sizes_of_genomes_-_The_C%E2%80%91value_paradox)

### III. Structure of genomes

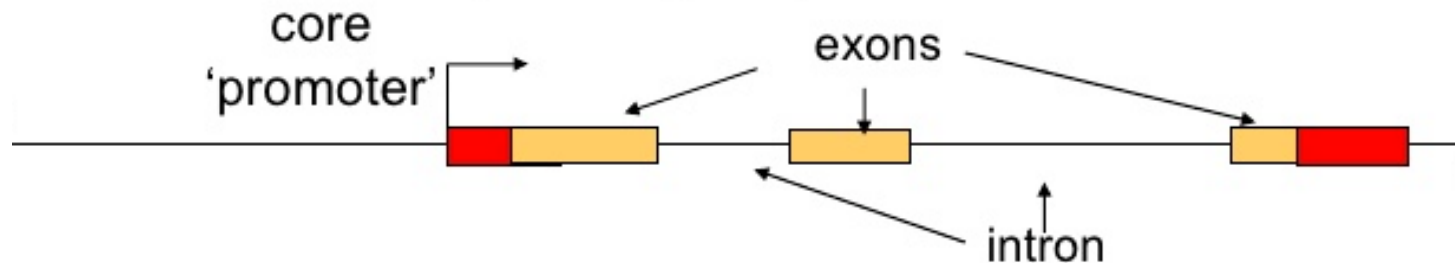
#### Structure of genes

In **procaryotes**, genes are not interrupted (monocistronic)



→ ADN et ARNm sont colinéaires

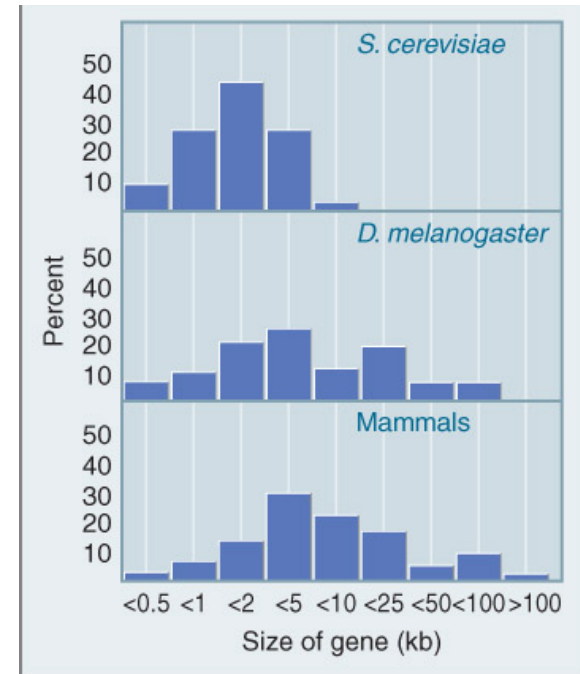
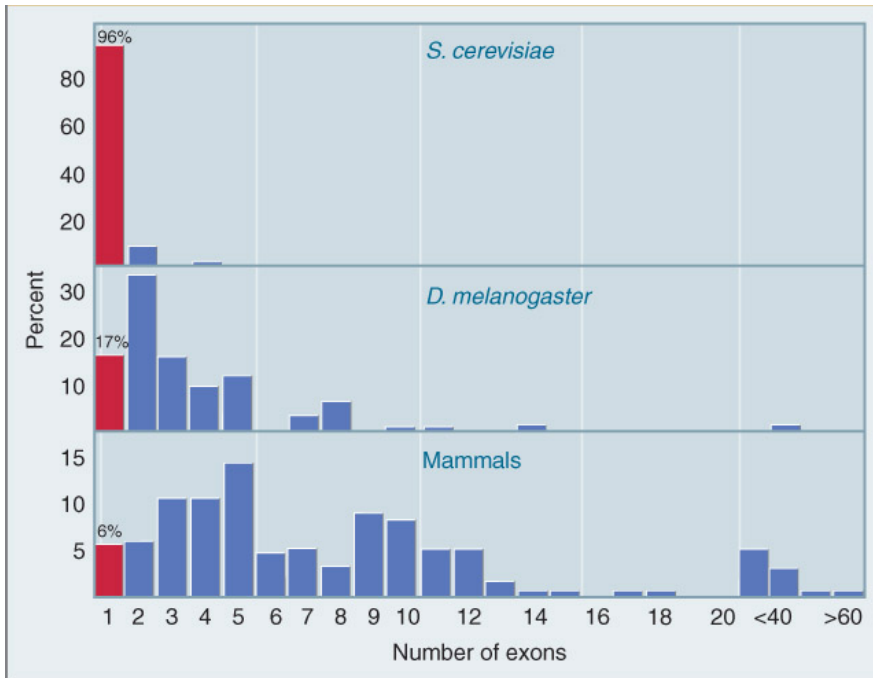
In eukaryotes, genes are longer and mostly interrupted (introns/exons)





### III. Structure of genomes

#### Structure of genes

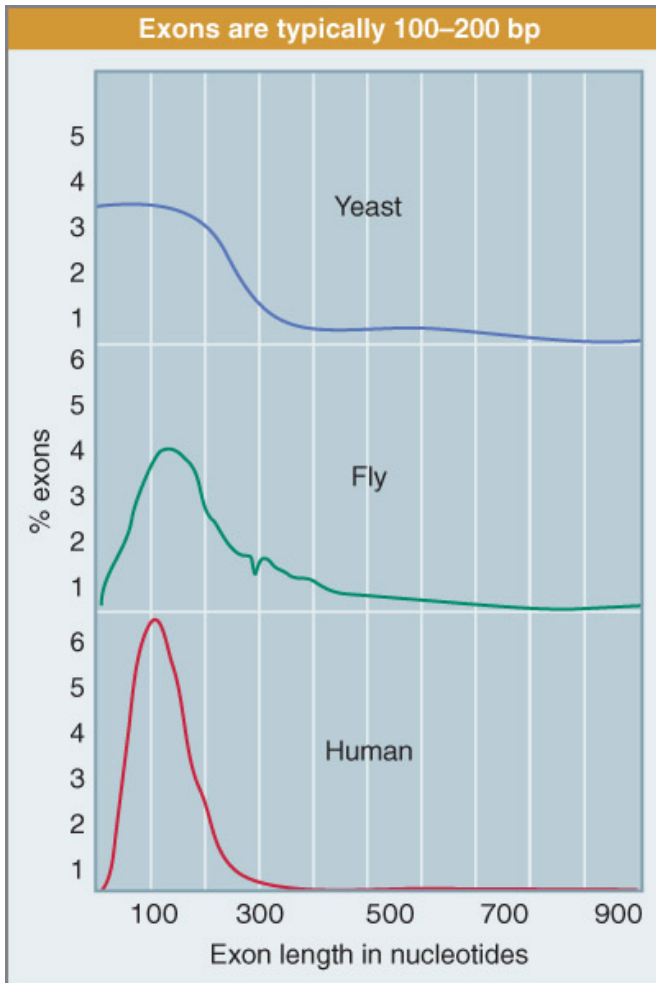


During evolution, genes went from mostly short and uninterrupted to mostly longer and interrupted

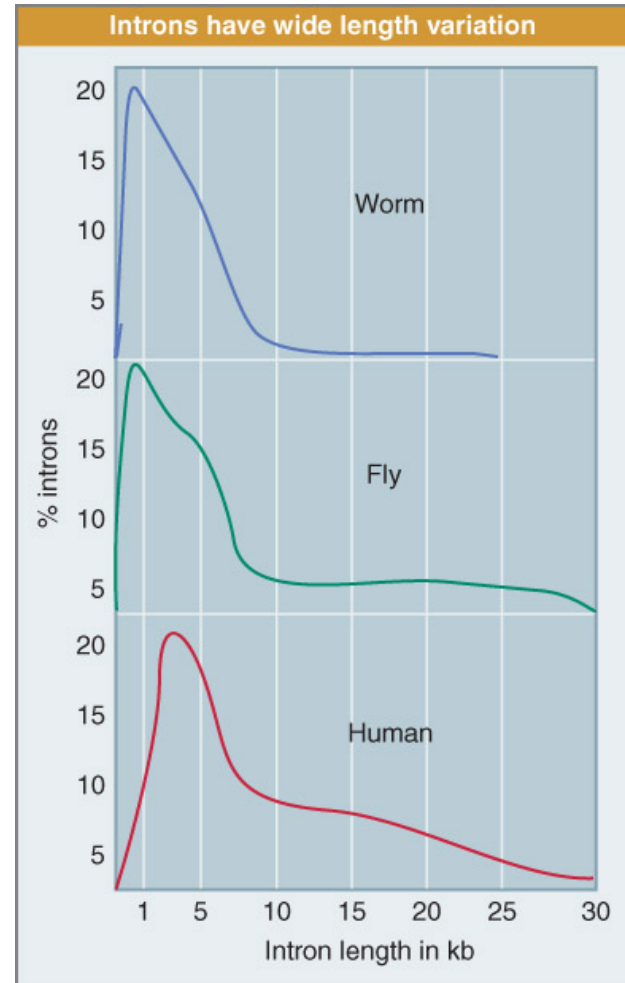
### III. Structure of genomes

#### Structure of genes

exons are short and with constant sizes throughout evolution

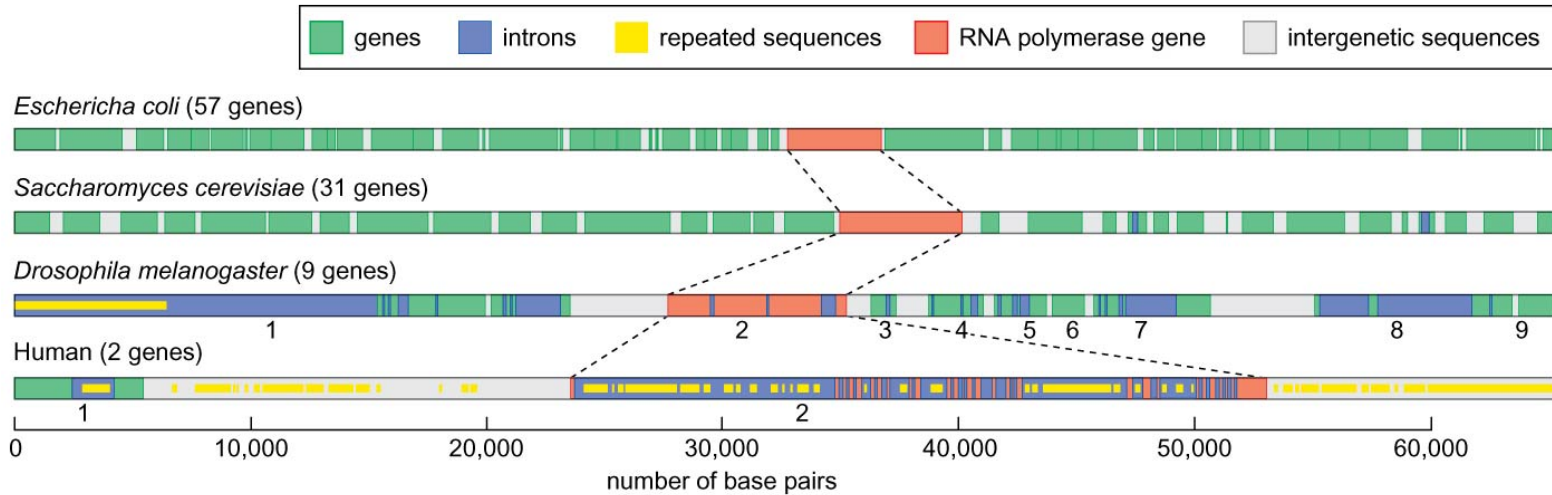


introns are more variable in size and become longer throughout evolution



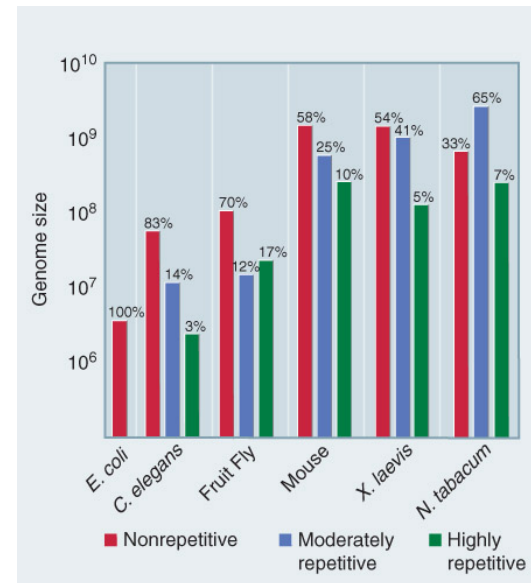
### III. Structure du génome

More complex organisms have lower gene densities



Moderately or highly repeated DNA (junk DNA) : in general, non coding (transposons, satellite DNA, low complexity DNA)

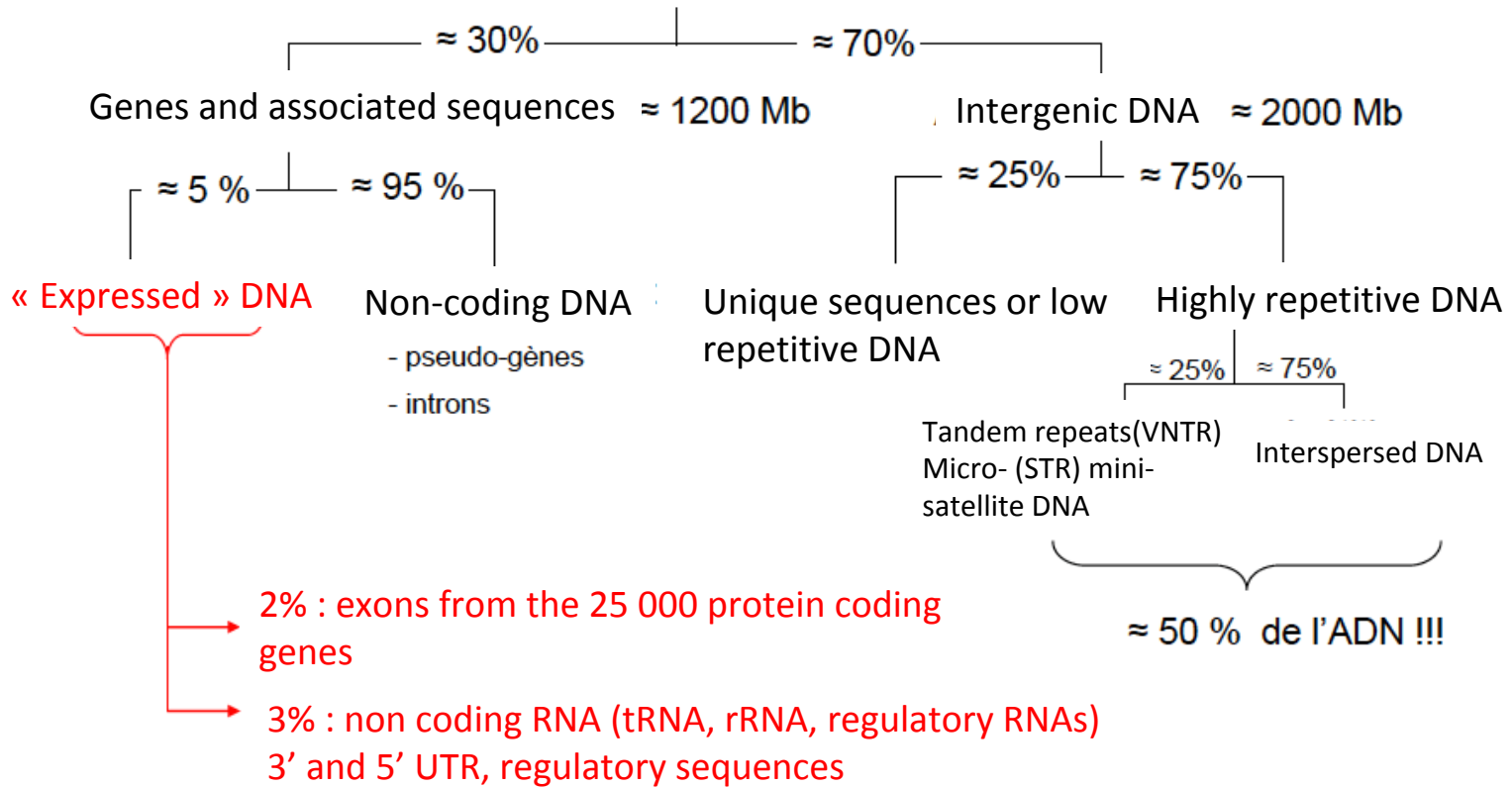
Non repeated DNA : coding regions (genes)



### III. Structure du génome

#### Classical composition of a superior eukaryote genome

The majority of DNA is non coding!



## IV. Mutations

Mutations are modifications of the DNA sequence

**Spontaneous mutations** (mistakes during replication)

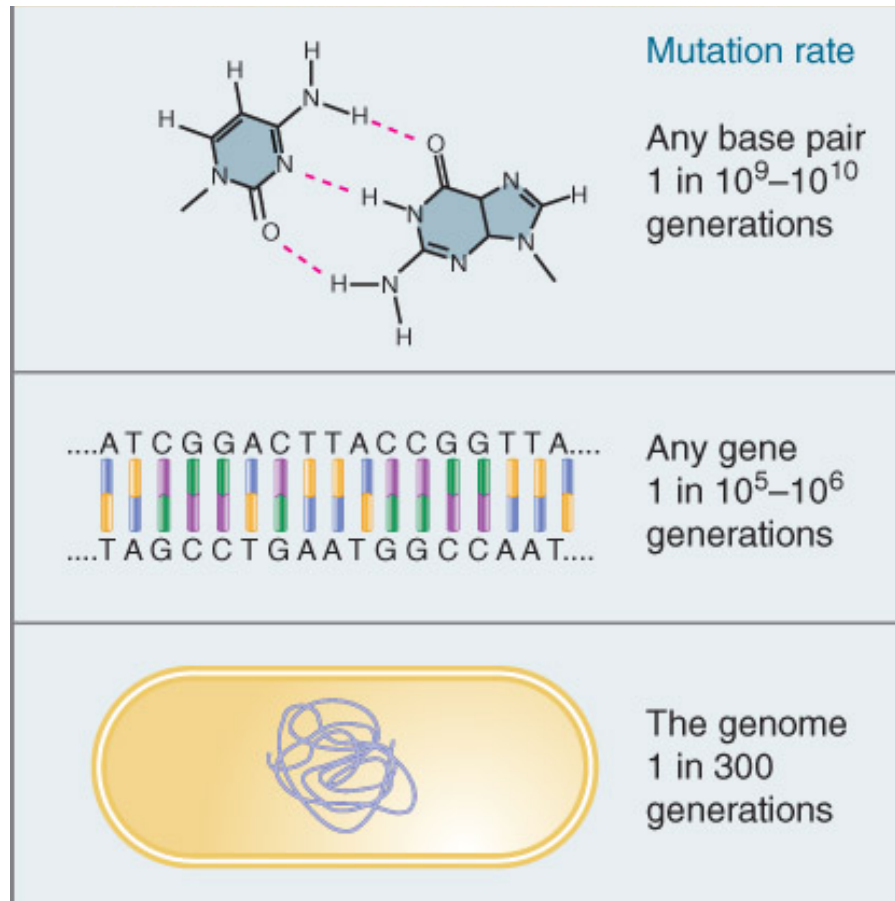
**Inducible mutations** (chemical modifications)

**Insertion of exogenous DNA** (viruses, transposons)

<http://education-portal.com/academy/lesson/mutagens-how-the-environment-affects-mutation-rates.html>

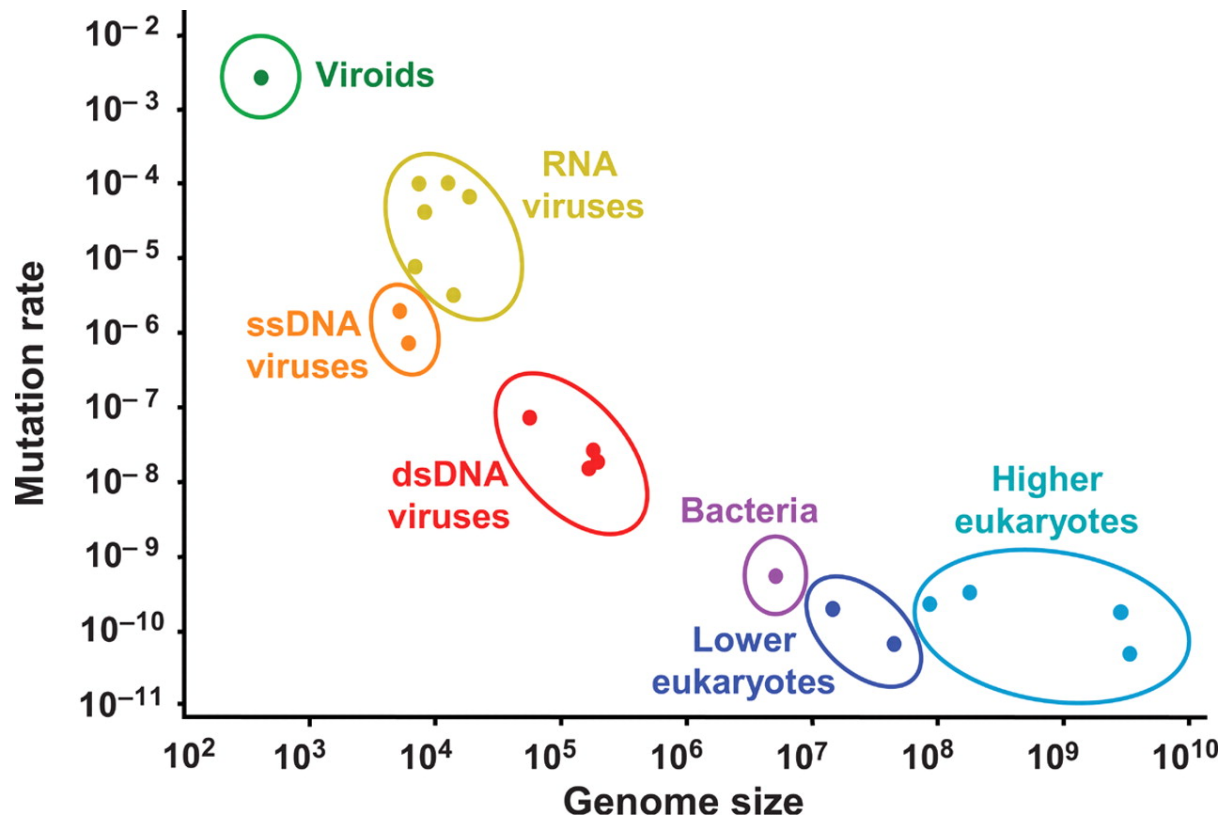
# IV. Mutations

## Spontaneous Mutations



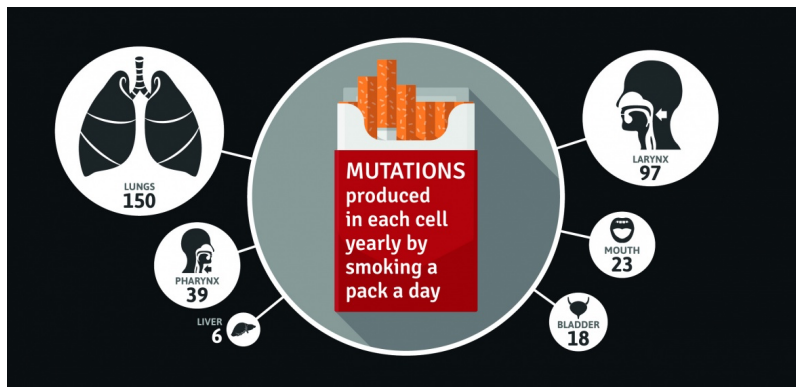
## IV. Mutations

Spontaneous Mutations : errors happening during the copy of the genome (replication)



# IV. Mutations

## Inducible Mutations and mutagens



(Science, Nov 2016)

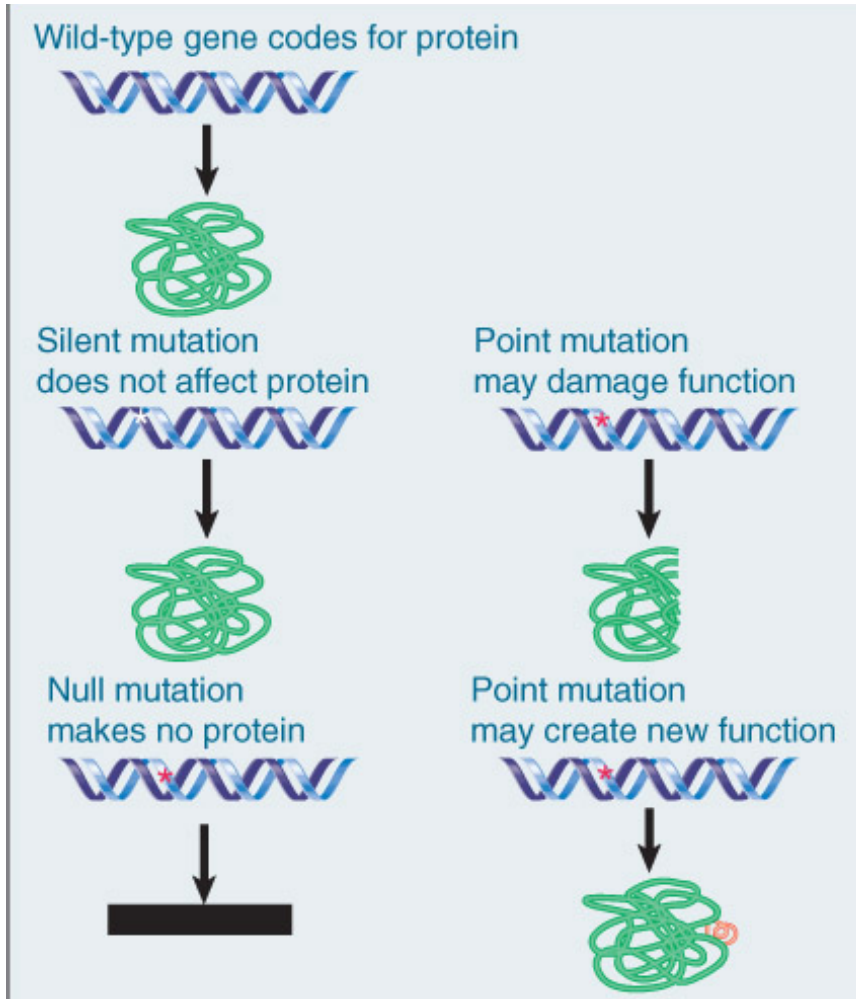
Table II. Partial list of chemicals evaluated with Mutatox and Ames Test for genotoxicity.

Compound	Mutatox	Ames
Aflatoxin B1	Positive	Positive
2-Aminoanthracene	Positive	Positive
2-Aminofluorene	Positive	Positive
9-Aminoacridine	Positive	Positive
Benzene*	Positive	Negative
Benzidine	Positive	Positive
Benzoin*	Negative	Negative
Benzo(a)pyrene	Positive	Positive
Captan	Positive	Positive
2-Chloroethanol*	Positive	Positive
Cyclophosphamide	Positive	Positive
1,2-Dichloropropane	Positive	Positive
1,3-Dichloropropene	Negative	Positive
Dioxane	Negative	Negative
Ethylene glycol	Negative	Negative
8-Hydroxyquinoline*	Positive	Positive
Lindane	Negative	Negative
Monuron*	Positive	Negative
3-methylcholanthrene	Positive	Positive
Nalidixic acid	Positive	Negative
Pyrene	Positive	Negative

\* Designated National Toxicology Program Chemical



## IV. Mutations



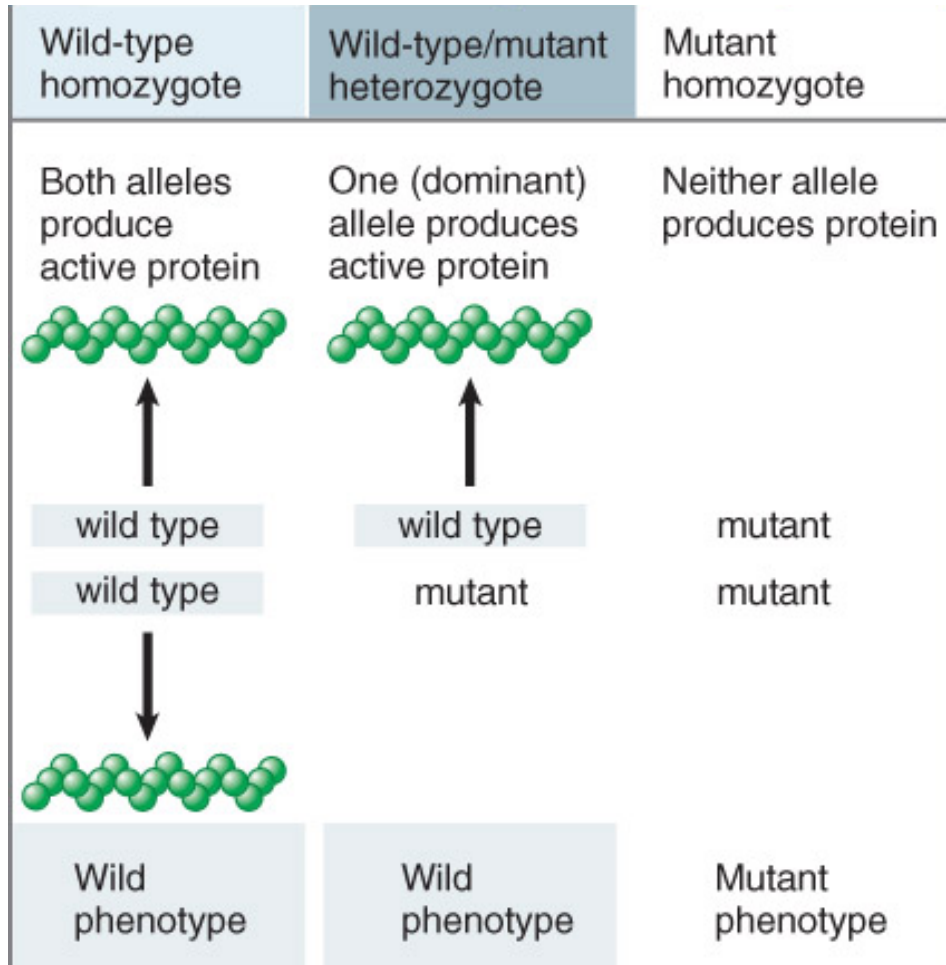
Mutations can be :

Silent (no effect)

Null (loss of function)

Gain of function (new function)

## IV. Mutations



- Mutations are in general recessive
- Recessive alleles produce inactive proteins

## IV. Mutations

1 : **Chromosomal mutations** : modifications of the structure or copy number of chromosomes

**n** (germinal cell, monoploid), **2n** (somatic cell, diploid) : normal euploidy

**3n, 4n,...8n** : abberent euploidy

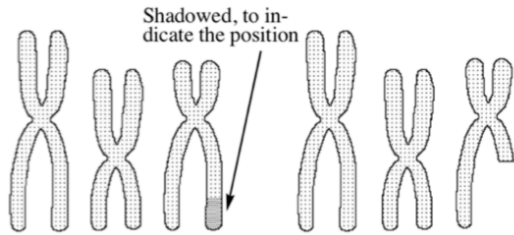
**2n-1, 2n+1** : aneuploidy

Name	Designation	Constitution	Number of chromosomes
<i>Euploids</i>			
Monoploid	$n$	A B C	3
Diploid	$2n$	AA BB CC	6
Triploid	$3n$	AAA BBB CCC	9
Tetraploid	$4n$	AAAA BBBB CCCC	12
<i>Aneuploids</i>			
Monosomic	$2n - 1$	A BB CC	5
		AA B CC	5
		AA BB C	5
Trisomic	$2n + 1$	AAA BB CC	7
		AA BBB CC	7
		AA BB CCC	7

# IV. Mutations

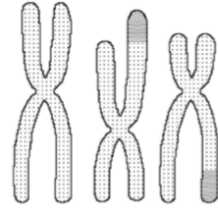
1 : **Chromosomal mutations** : modifications of the structure or copy number of chromosomes

## Chromosome mutations

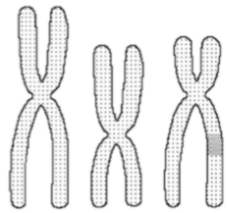


Normal subset of chromosomes

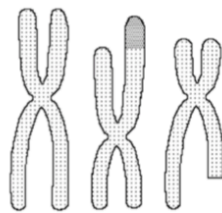
A deletion, a segment of a chromosome is lost



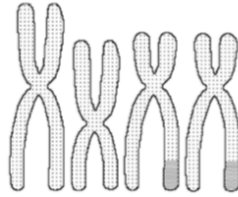
A duplication, a part is present more than once



An inversion, a segment is reversed



A translocation, a part has moved (within the chromosome or to another)

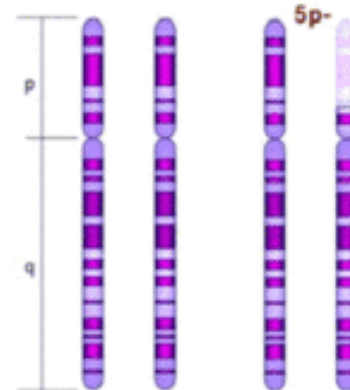


The number of chromosomes has changed

- Loss of DNA
- Move of DNA

➔ Serious for the cell

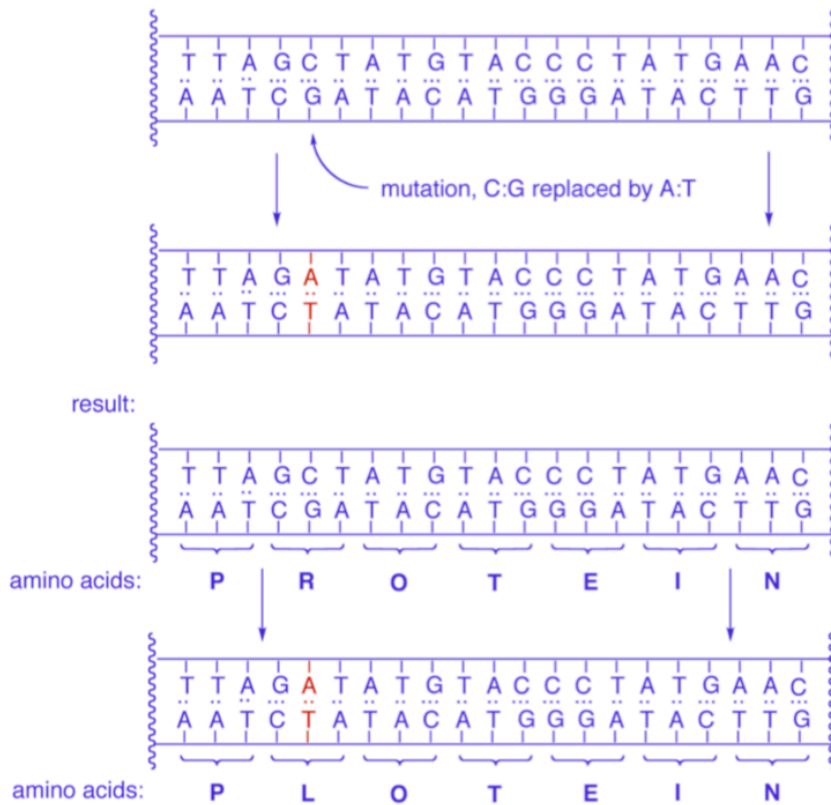
5p- syndrome = cri du chat syndrome



## IV. Mutations

### Substitutions in coding regions

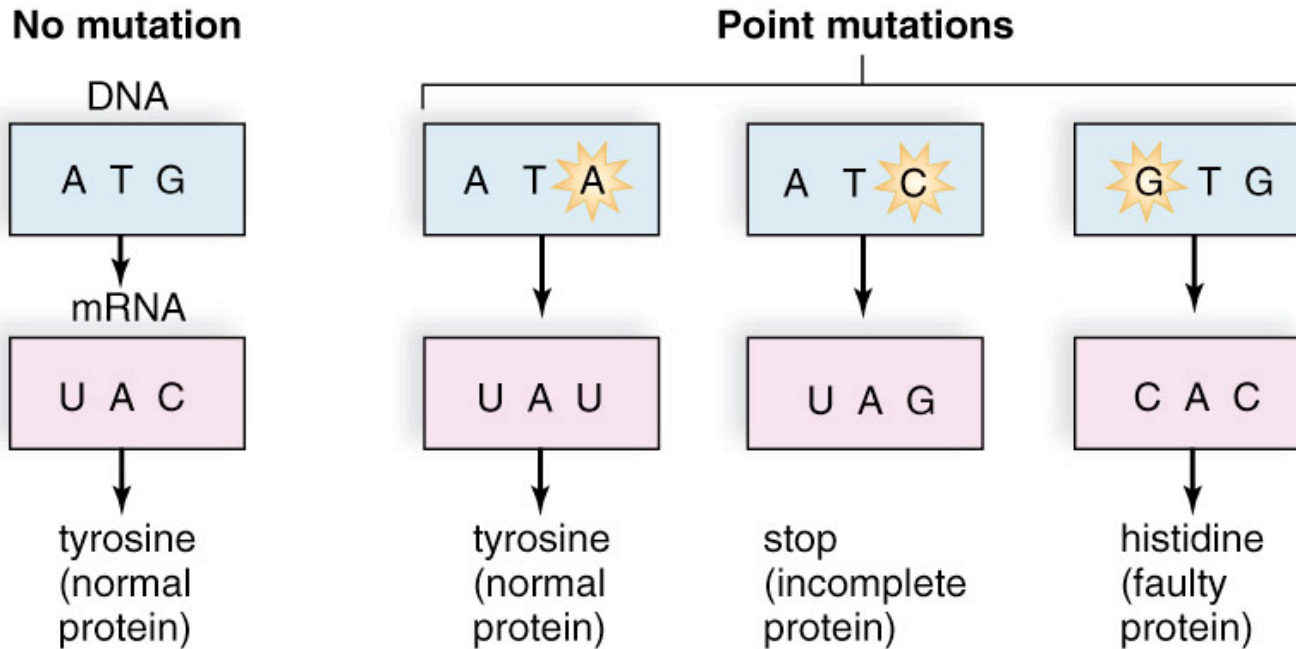
# Base pair substitution



a limited damage

## IV. Mutations

### Substitutions in coding regions

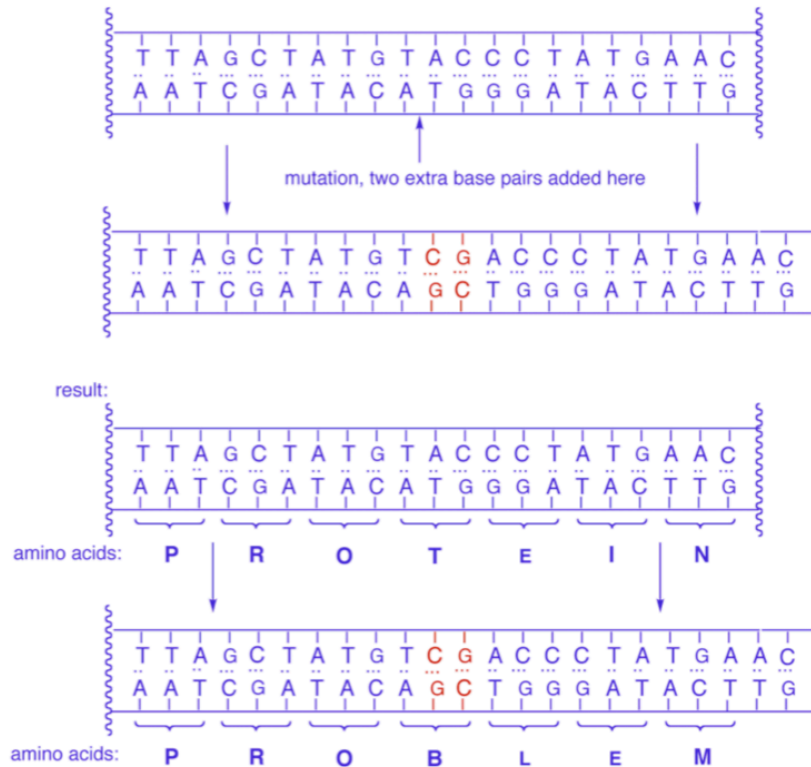


Substitutions may change the sequence of the final polypeptide

## IV. Mutations

### Insertions (deletions) in coding regions

# Frame shift mutation

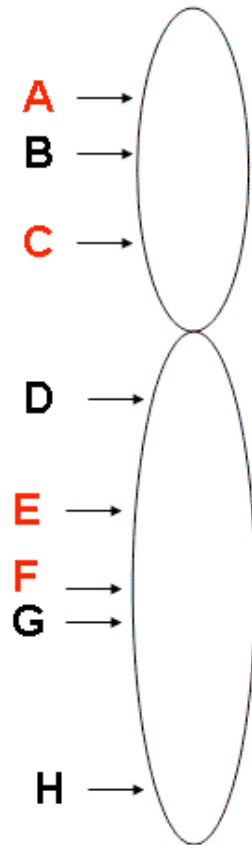


more  
serious

Insertions change the reading frame and are very likely to alter the sequence of the final polypeptide

## V. Decoding the genomes

### Genetic maps



### Genetic Maps

- Genes are shown in relative order and distance from each other based on pedigree studies.
- The chance of the chromosome breaking between A & C is higher than the chance of the chromosome breaking between A & B during meiosis.
- Similarly, the chance of the chromosome breaking between E & F is higher than the chance of the chromosome breaking between F & G.
- The closer two genes are, the more likely they are to be inherited together (co-occurrence).
- If pedigree studies show a high incidence of co-occurrence, those genes will be located close together on a genetic map.

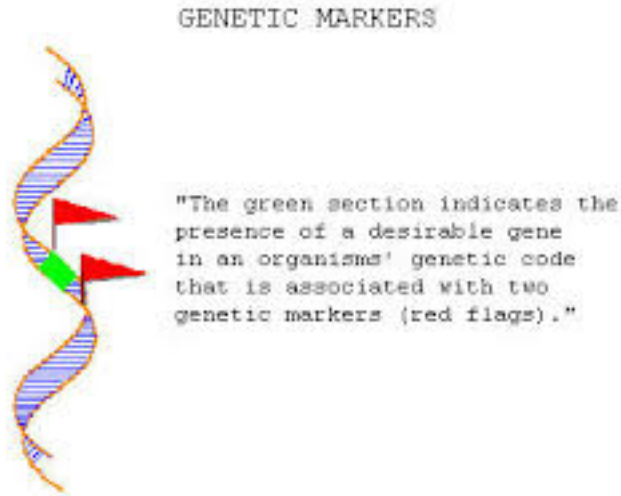


## V. Decoding the genomes

### The genetic/molecular markers :

Définition : fragment (sequence) of polymorphic DNA that is specifically identifiable in individuals

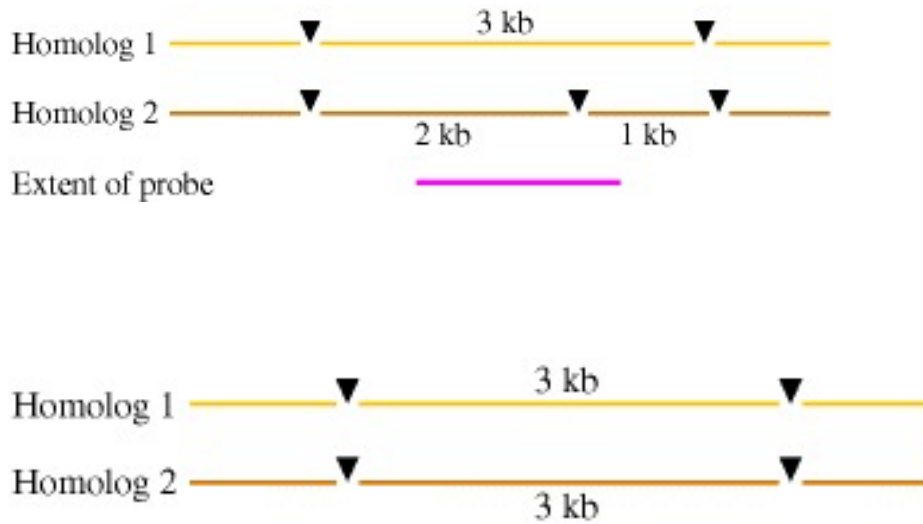
features: multiallelic (polymorphism), universal et inheritable



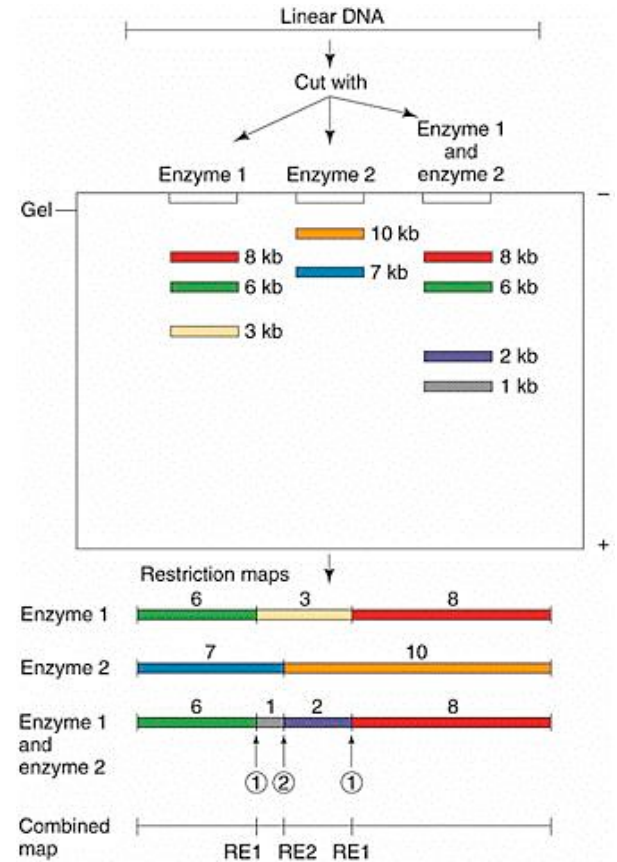
<http://www.youtube.com/watch?v=nrnJPC6e19c>

# V. Decoding the genomes

RFLP : Restriction length fragment polymorphism

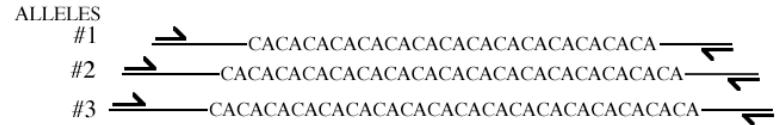


Gene coupling

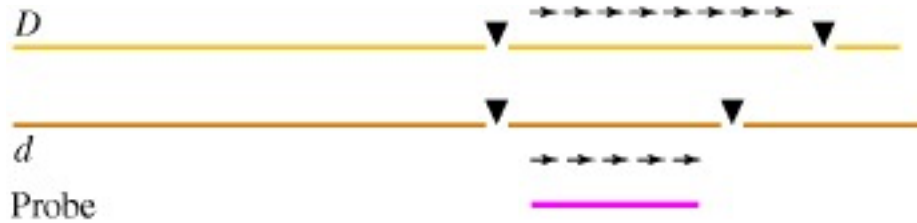


# V. Decoding the genomes

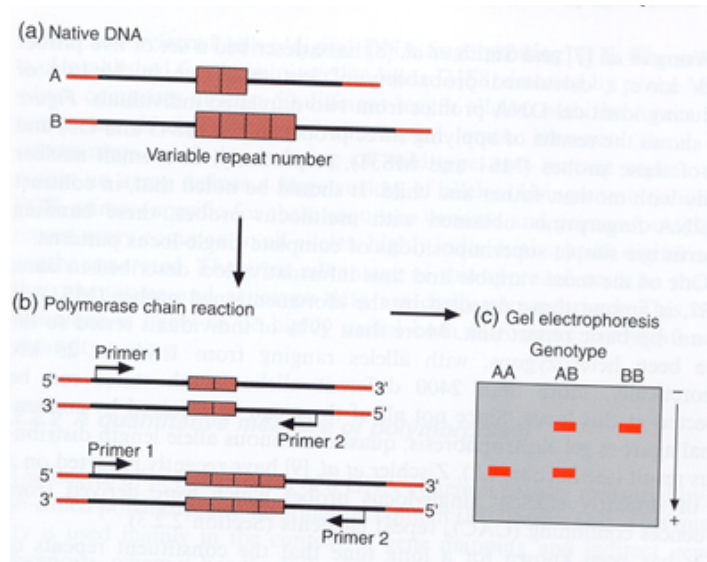
STRs : Short tandem repeats (VNTR)



Detected by RFLP :



Detected by AFLP :



<https://www.youtube.com/watch?v=DbR9xMXuK7c>

## V. Decoding the genomes : variant calling

Variant: Variation in a DNA sequence when comparing with a reference sequence

	Substitution	Insertion	Deletion
Wild-Type:	AACGGCC <b>T</b> GTAAC	AACGGCC <b>T</b> GTAAC	AACGGCC <b>T</b> GTAAC
Mutant:	AACGGCC <b>A</b> GTAAC	AACGGCC <b>AG</b> CTAAC	AACGGCC <b>-</b> GTAAC

### Substitution:

SNV : Single nucleotide variant : any change of a nucleotide with no criteria of frequency

SNP : Single nucleotide polymorphism : a SNV found in >1% of the population

Individual 1: AACGGCC**T**GTAAC  
Individual 2: AACGGCC**T**GTAAC  
Individual 3: AACGGCC**T**GTAAC  
Individual 4: AACGGCC**A**GTAAC  
Individual 5: AACGGCC**T**GTAAC  
Individual 6: AACGGCC**A**GTAAC

Individual 7: AACGGCC**T**GTAAC  
Individual 8: AACGGCC**T**GTAAC  
Individual 9: AACGGCC**T**GTAAC  
Individual 10: AACGGCC**A**GTAAC  
Individual 11: AACGGCC**T**GTAAC  
Individual 12: AACGGCC**A**GTAAC

### INDEL:

INsertion or DELetion of one or several nucleotides

MNV: Multi-Nucleotide Variant : multiple SNVs or INDELS in the same region

## V. Decoding the genomes : variant calling

Variant: Variation in a DNA sequence when comparing with a reference sequence

SV: Structural Variants : a region of DNA  $> 1$  kbp in which gross rearrangements have occurred



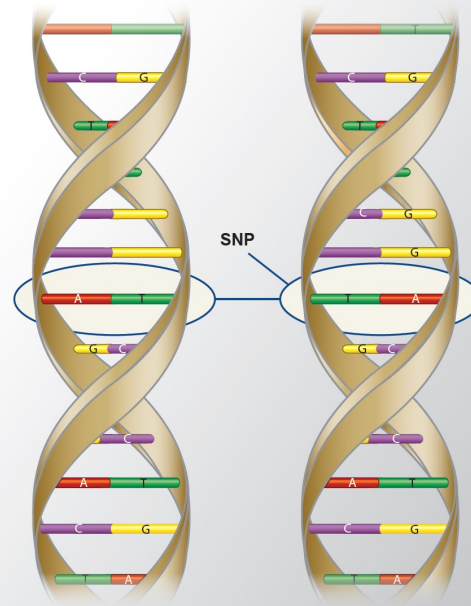
## V. Decoding the genomes : variant calling

SNP : Single nucleotide polymorphism (>1% of the population)

### What is a Single Nucleotide Polymorphism (SNP)?

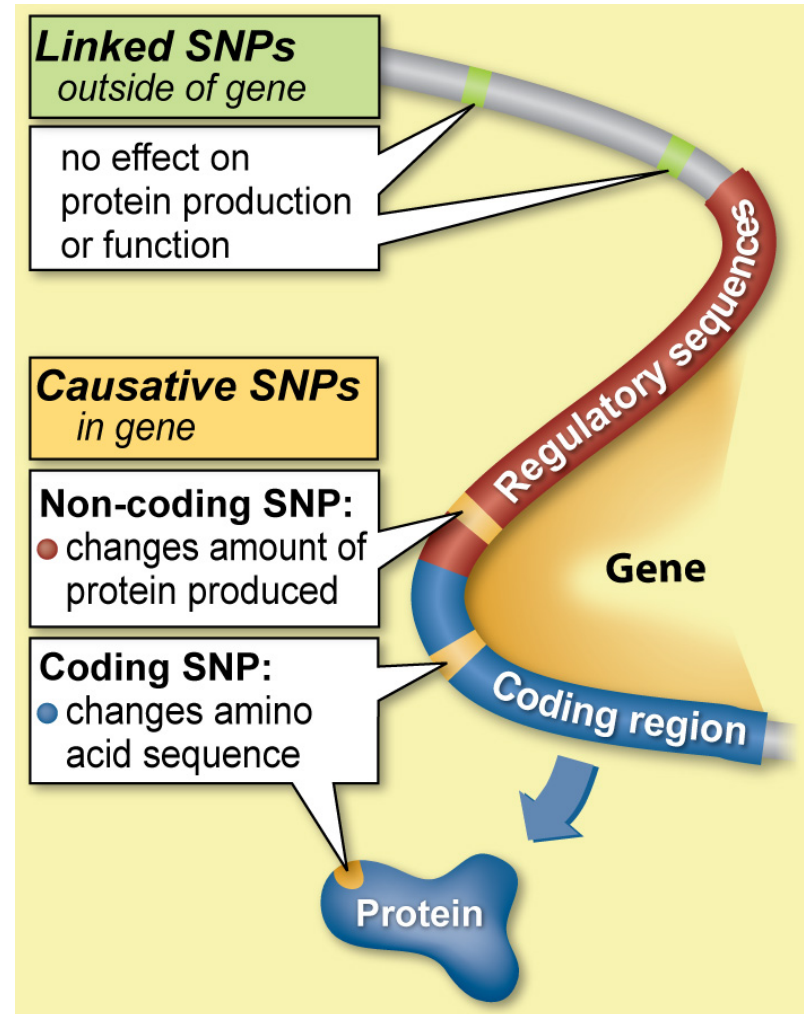
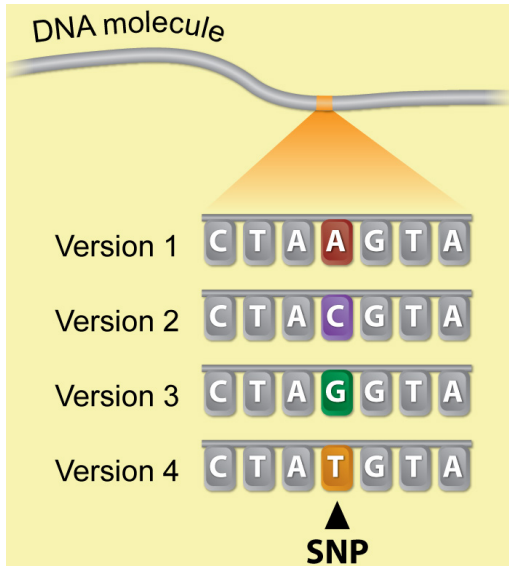
A SNP (pronounced "snip") is a DNA sequence variation that occurs when a single nucleotide (A, T, C, or G) in the genome sequence is modified.

SNPs do not necessarily cause disease, but they can help determine the likelihood that someone will develop a particular illness.



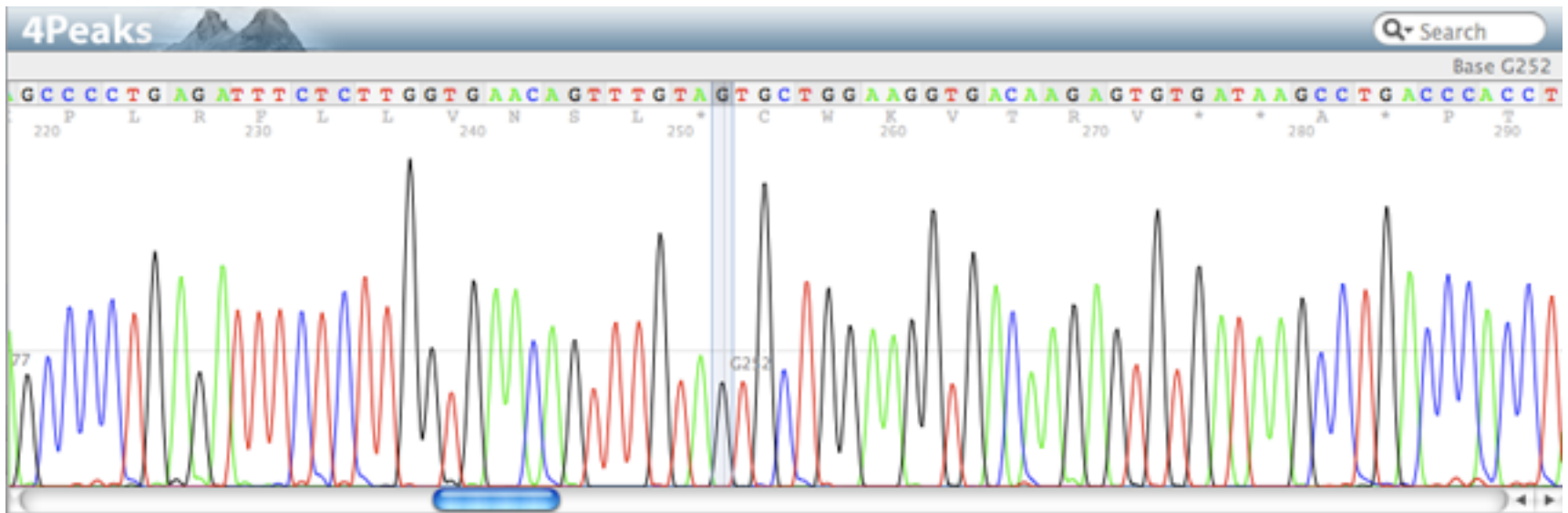
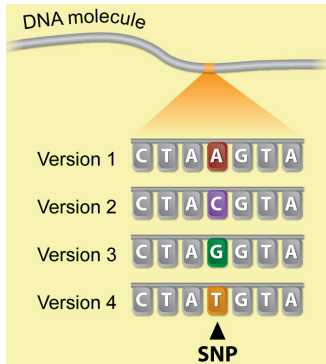
## V. Decoding the genomes

SNP : Single nucleotide polymorphism (>1% of the population)



## V. Decoding the genomes : variants

SNP : Single nucleotide polymorphism (>1% of the population)



[https://www.youtube.com/watch?v=DE9b1dxy\\_pE](https://www.youtube.com/watch?v=DE9b1dxy_pE)