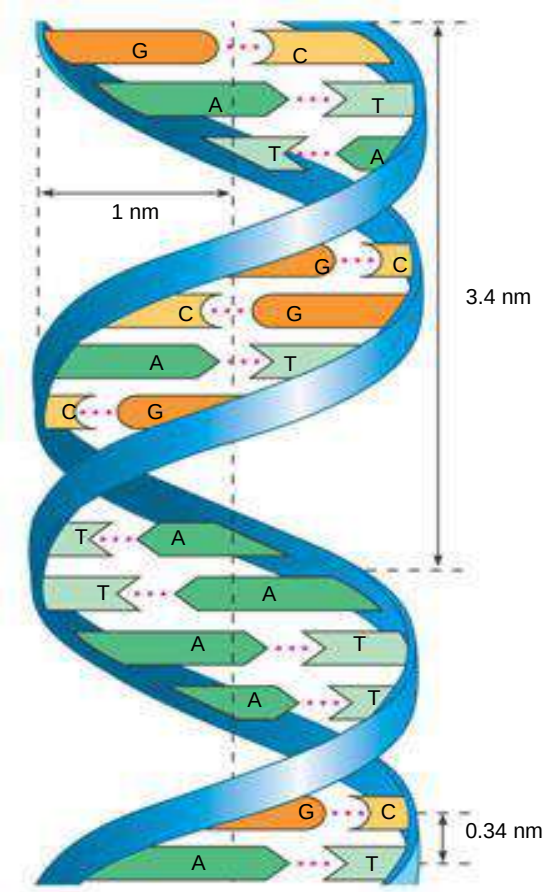
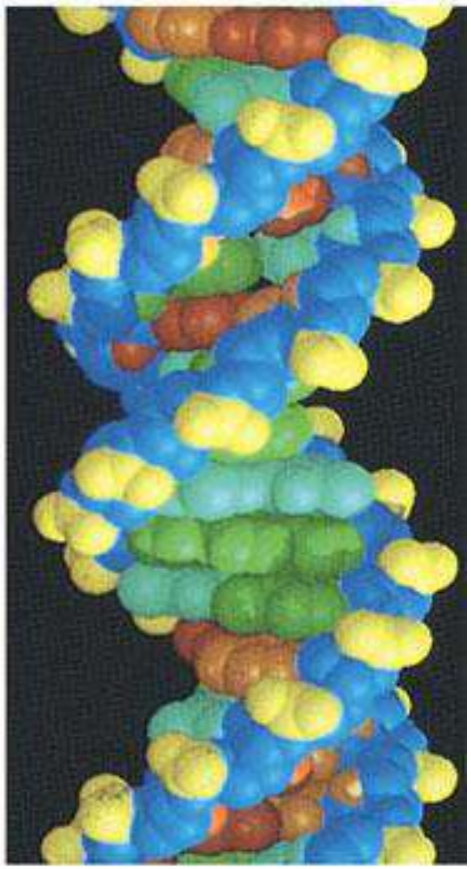
The Molecular Basis of Inheritance



(a) Key features of DNA structure



(c) Space-filling model

Figure 16.7a, c

DNA replication & Mutations

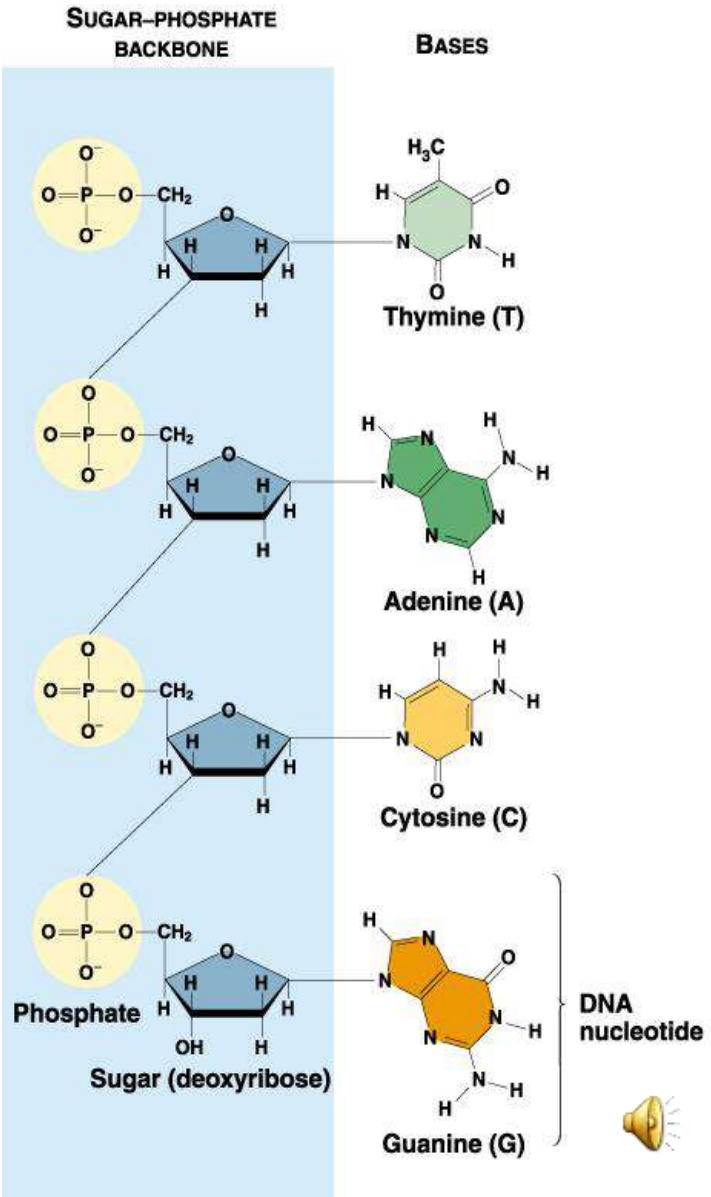
Genetics/th. Class

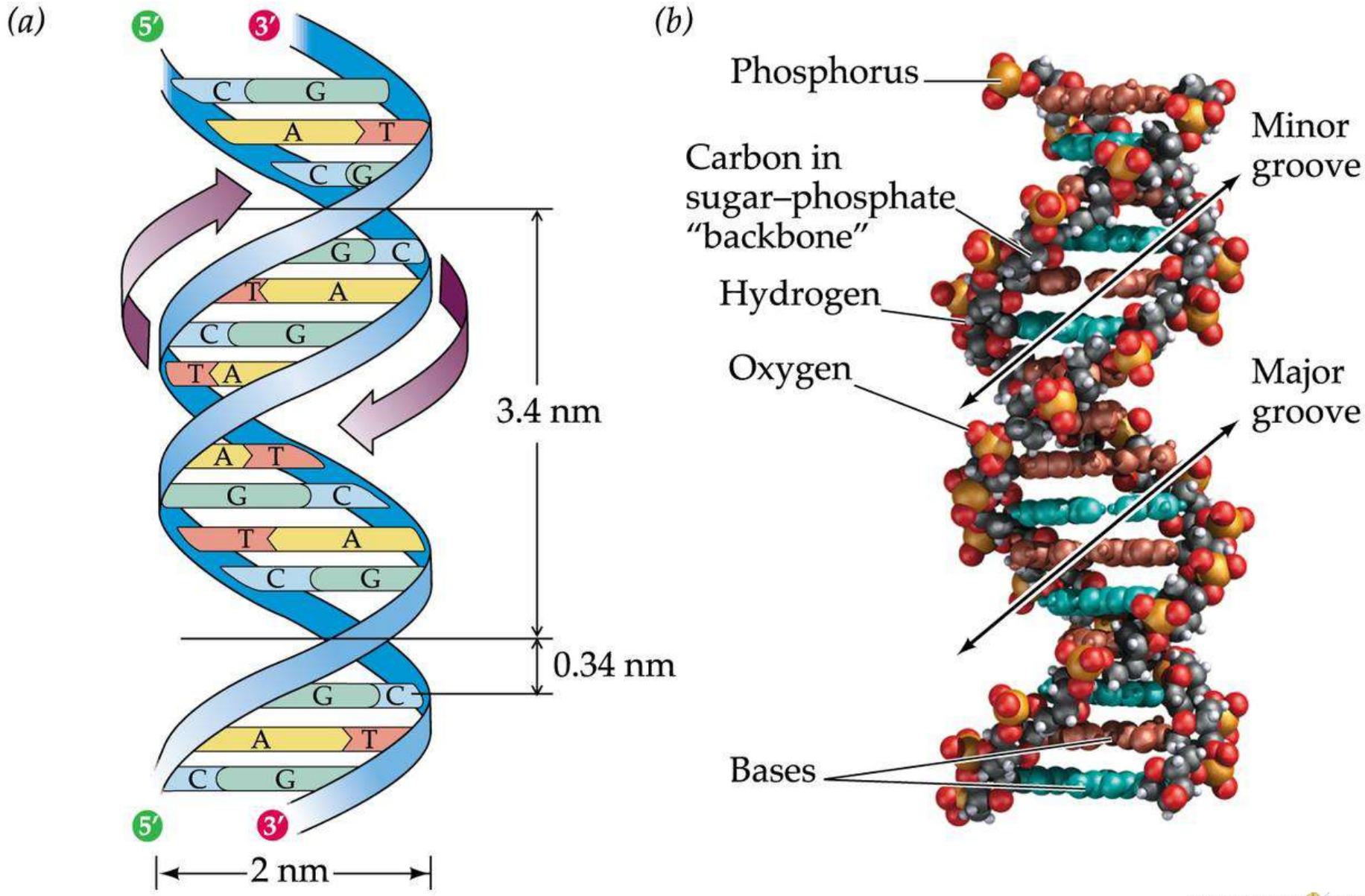
Lectures eight&nine&ten

Dr. Ibtesam B. H.

The Structure of DNA

- DNA is composed of four nucleotides, each containing: adenine, cytosine, thymine, or guanine.
- The amounts of A = T, G = C, and purines = pyrimidines [Chargaff's Rule].
- DNA is a double-stranded helix with antiparallel strands [Watson and Crick].
- Nucleotides in each strand are linked by 5'-3' phosphodiester bonds
- Bases on opposite strands are linked by hydrogen bonding: A with T, and G with C.





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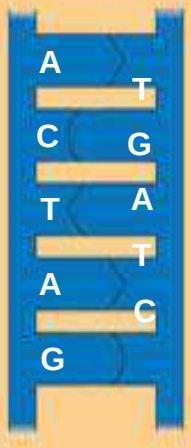
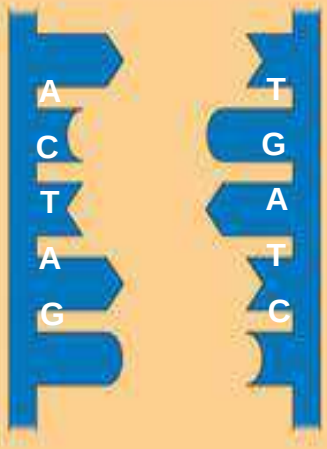
DNA replication

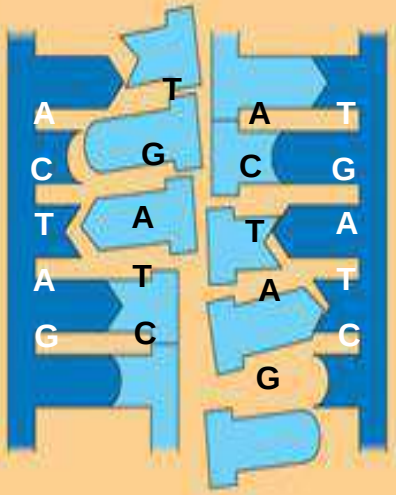
- The parent molecule unwinds, and two new daughter strands are built based on base-pairing rules



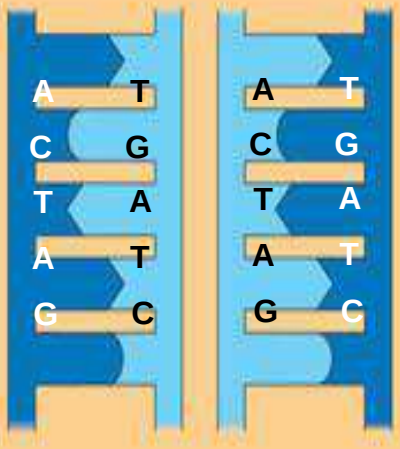
(a) The parent molecule has two complementary strands of DNA. Each base is paired by hydrogen bonding with its specific partner, A with T and G with C.



(b) The first step in replication is separation of the two DNA strands.



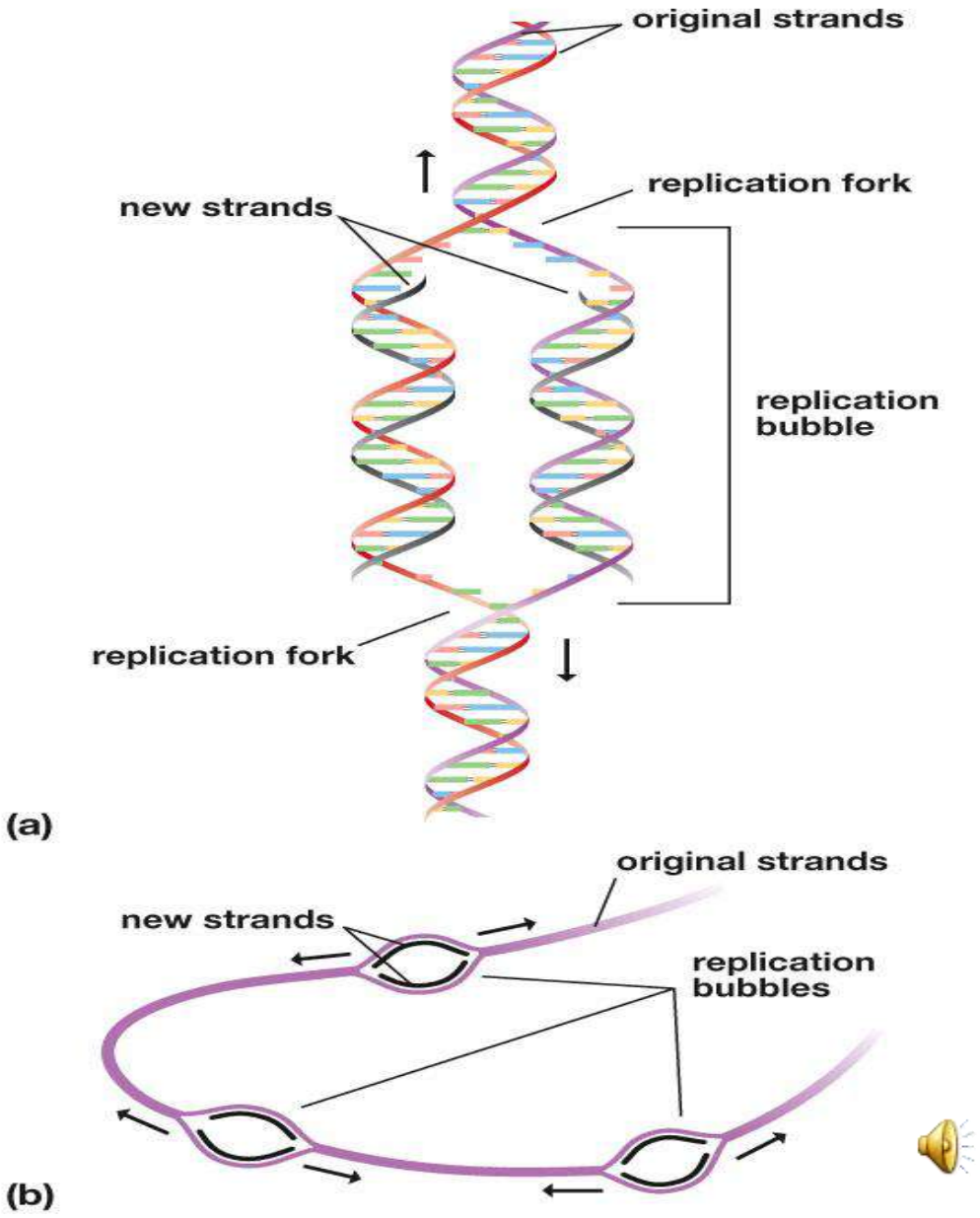
(c) Each parental strand now serves as a template that determines the order of nucleotides along a new, complementary strand.



(d) The nucleotides are connected to form the sugar-phosphate backbones of the new strands. Each "daughter" DNA molecule consists of one parental strand and one new strand.

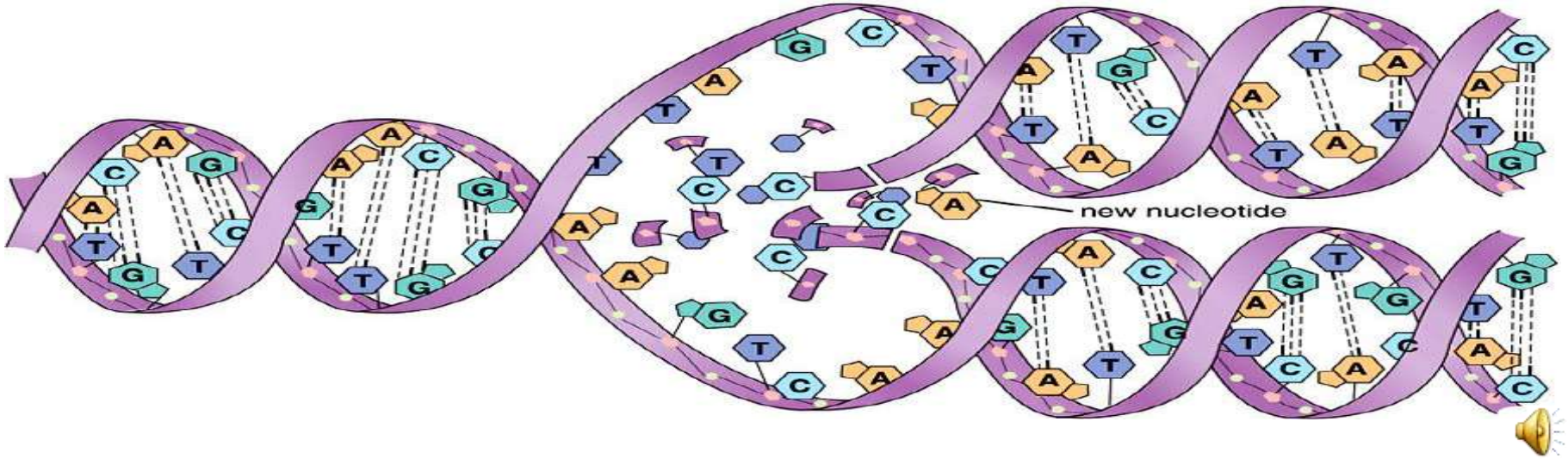
DNA Replication is "Semi-conservative"

- Each 2-stranded daughter molecule is only half new
- One original strand was used as a template to make the new strand



DNA Replication

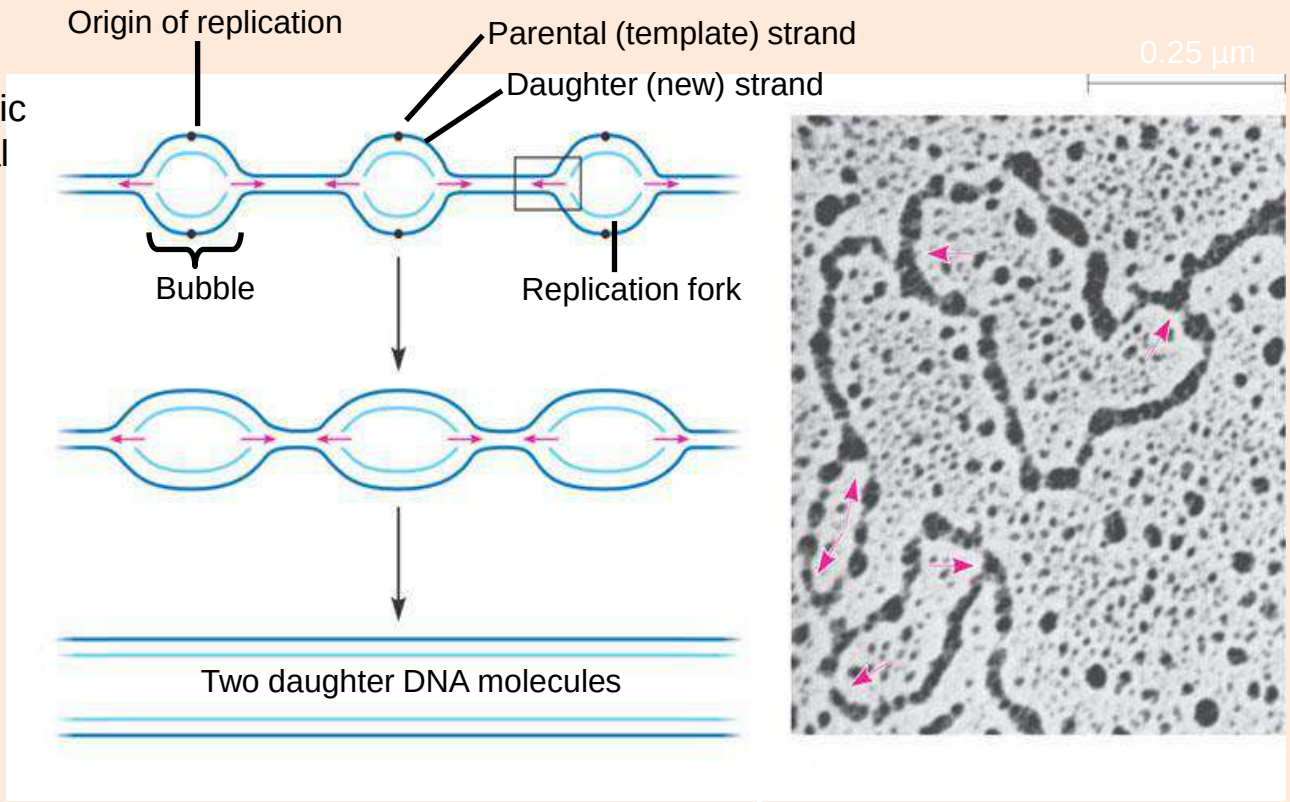
- The copying of DNA is remarkable in its speed and accuracy
- Involves unwinding the double helix and synthesizing two new strands.
- More than a dozen enzymes and other proteins participate in DNA replication
- The replication of a DNA molecule begins at special sites called **origins of replication**, where the two strands are separated



Origins of Replication

- **A eukaryotic chromosome may have hundreds or even thousands of replication origins**

1. Replication begins at specific sites where the two parental strands separate and form replication bubbles.
2. The bubbles expand laterally, as DNA replication proceeds in both directions.
3. Eventually, the replication bubbles fuse, and synthesis of the daughter strands is complete.

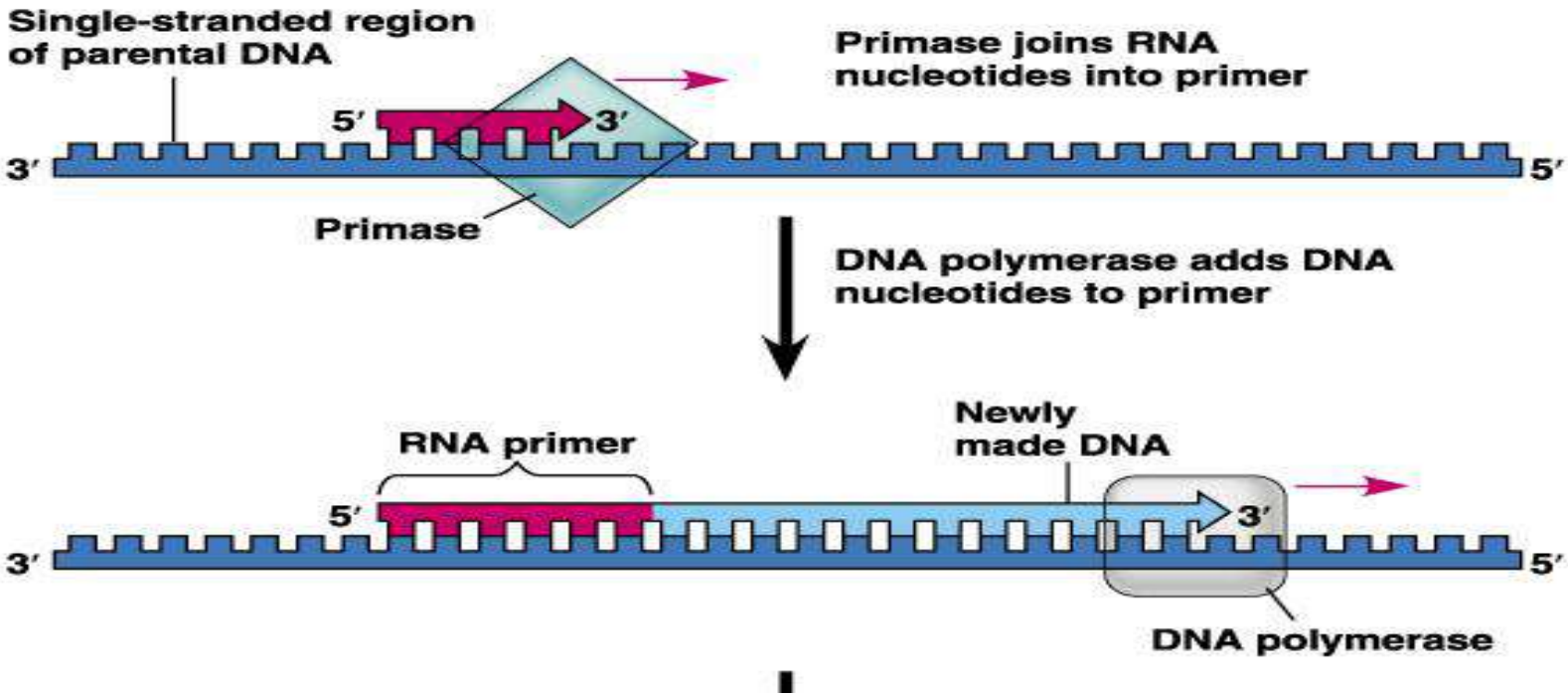


a) In eukaryotes, DNA replication begins at many sites along the giant DNA molecule of each chromosome

In this micrograph, three replication bubbles are visible along the DNA of a cultured Chinese hamster cell (TEM).

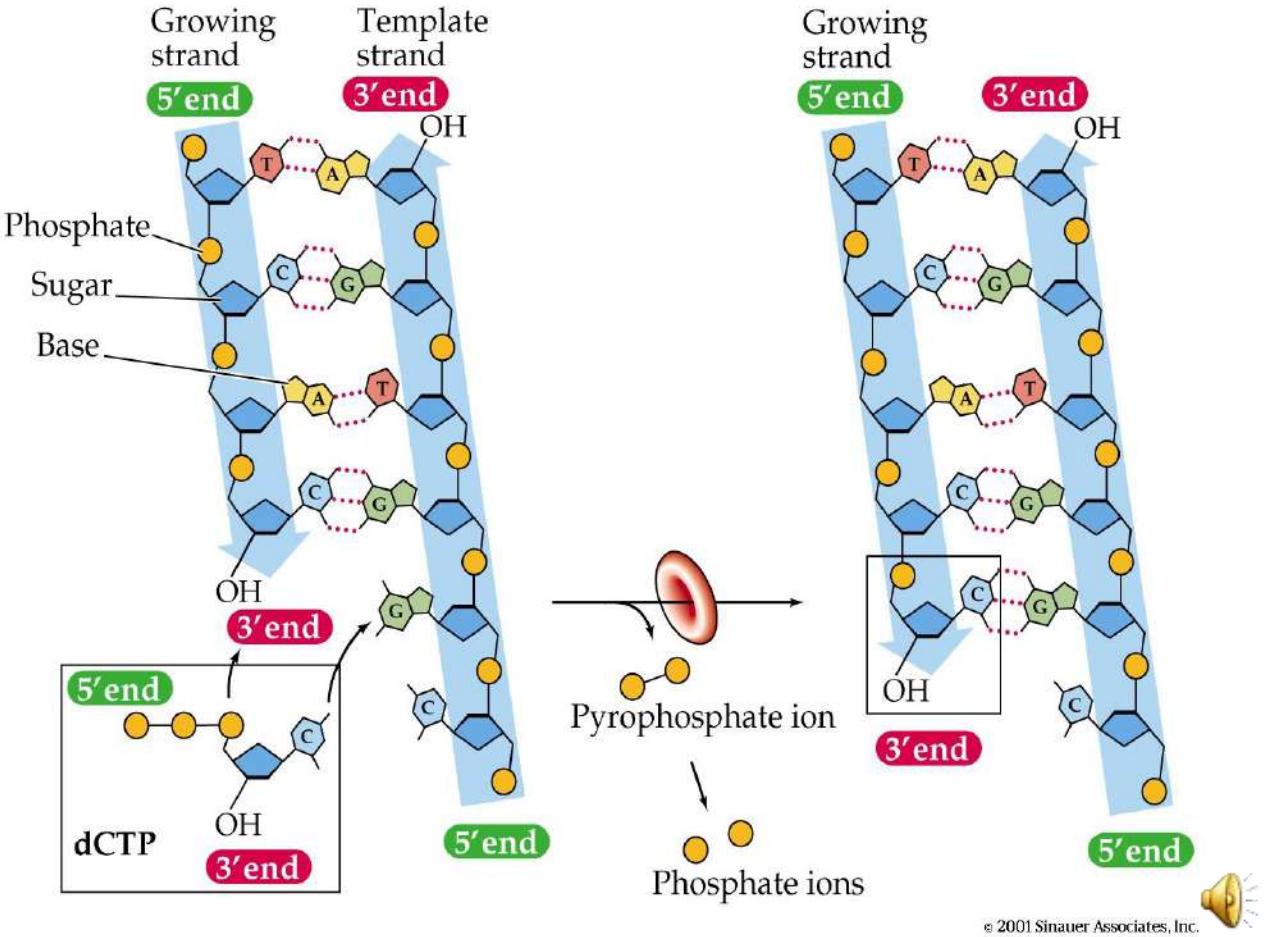
Mechanism of DNA Replication

- DNA replication is catalyzed by DNA polymerase which needs an RNA primer
- RNA primase synthesizes primer on DNA strand
- DNA polymerase adds nucleotides to the 3′ end of the growing strand



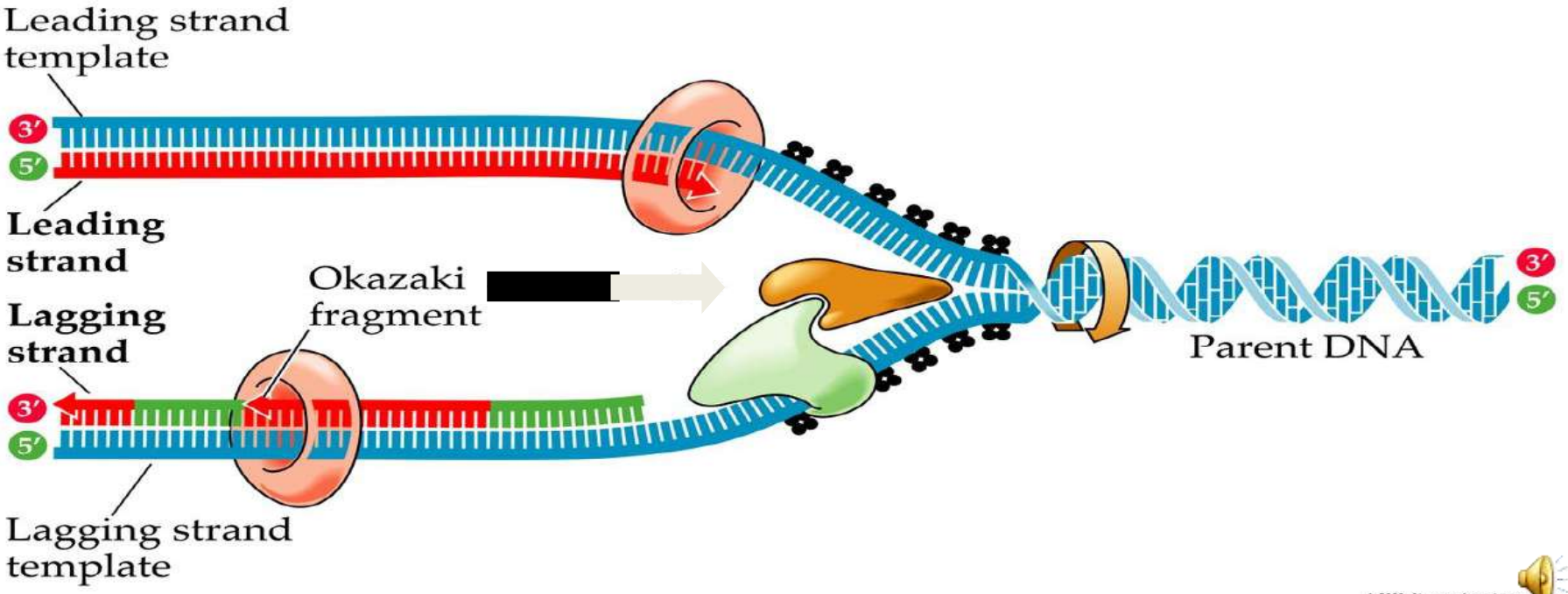
Mechanism of DNA Replication

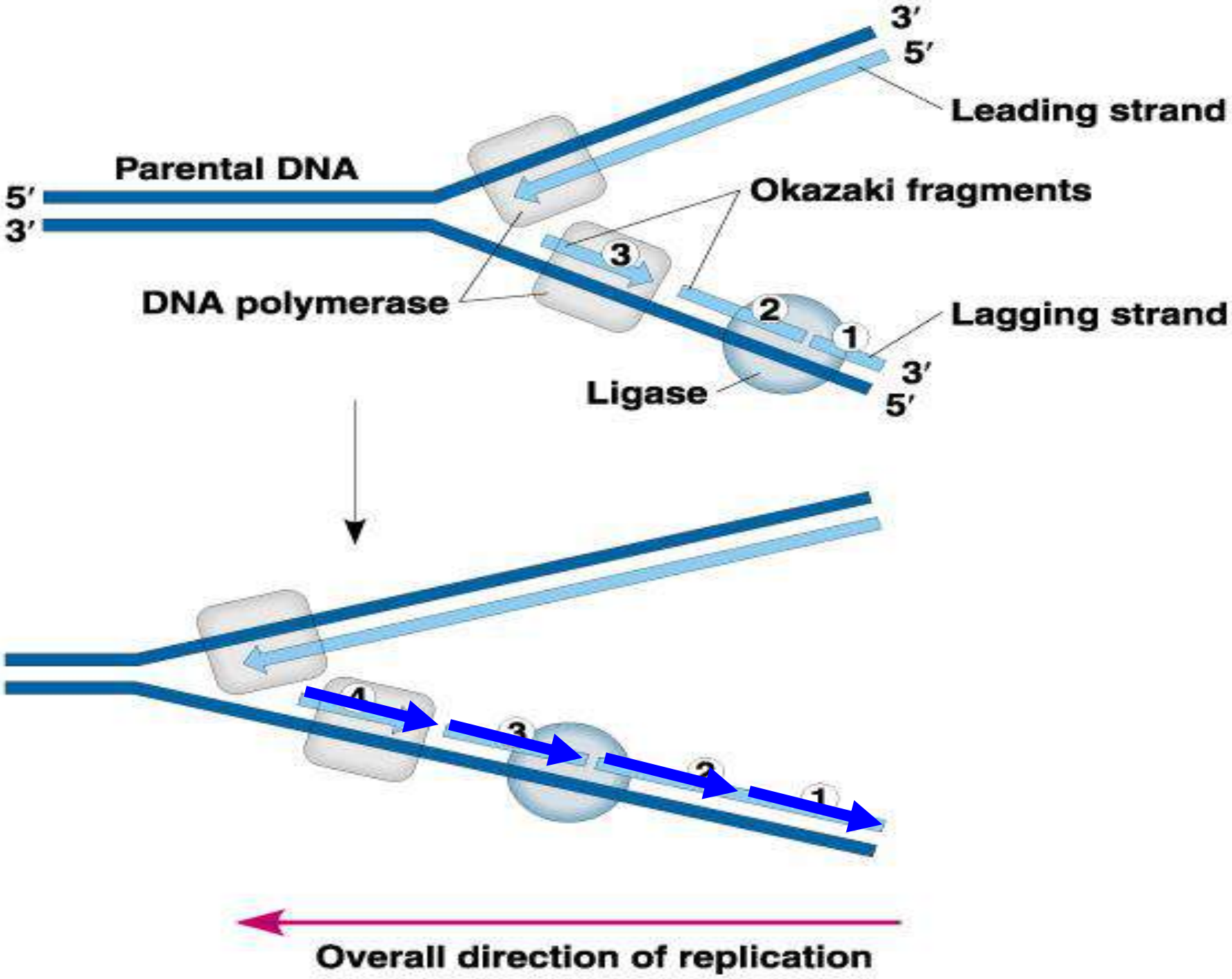
- Nucleotides are added by complementary base pairing with the template strand
- The substrates, deoxyribonucleoside triphosphates, are hydrolyzed as added, releasing energy for DNA synthesis.



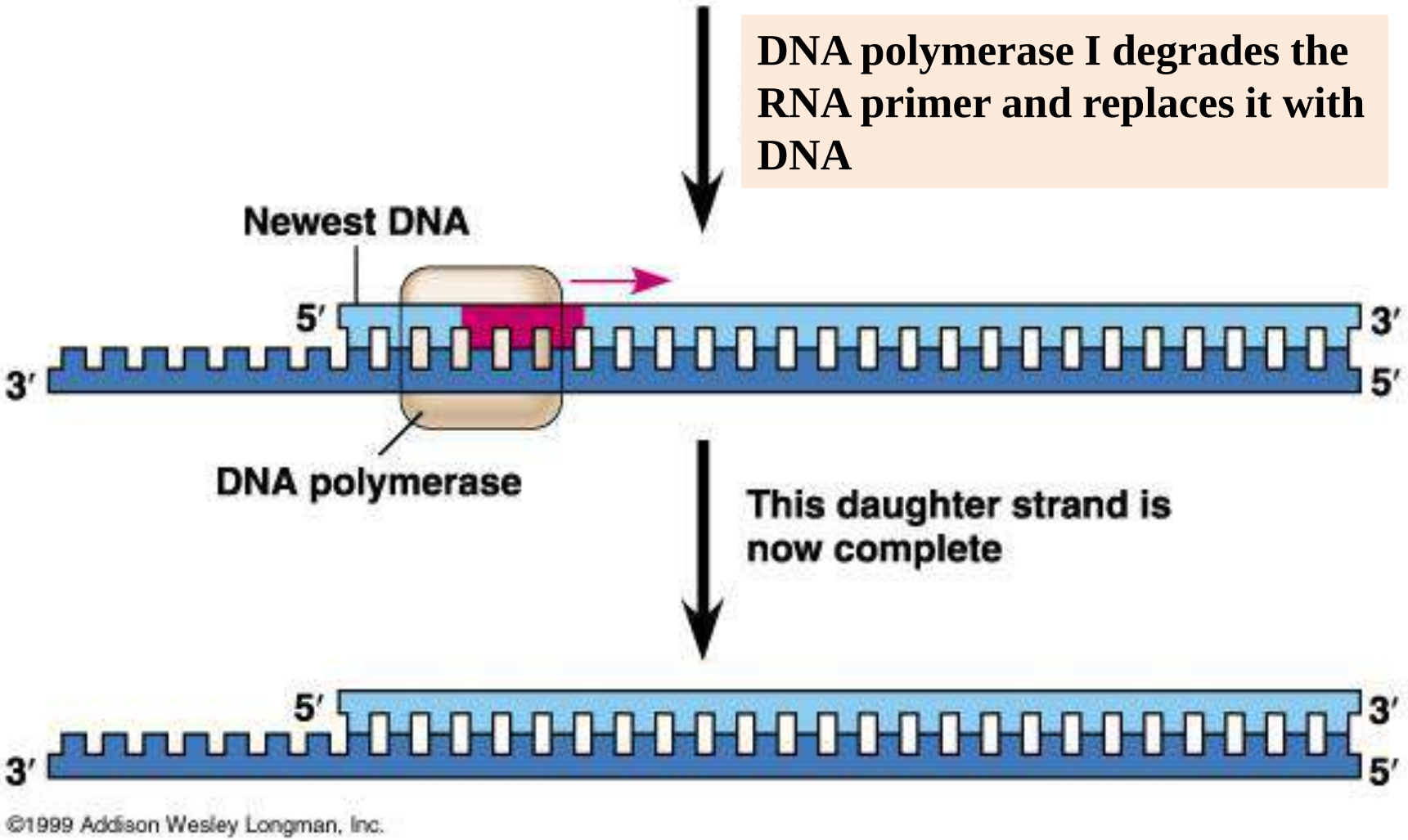
The Mechanism of DNA Replication

- DNA synthesis on the leading strand is continuous
- The lagging strand grows the same *general* direction as the leading strand (in the same direction as the Replication Fork). However, DNA is made in the 5′-to-3′ direction
- Therefore, DNA synthesis on the lagging strand is discontinuous
- DNA is added as short fragments (Okasaki fragments) that are subsequently ligated together




3′
5′
Leading strand
Parental DNA
5′
3′
Okazaki fragments
3
DNA polymerase
2
1
Lagging strand
3′
5′
Ligase
4
3
2
1
Overall direction of replication

DNA polymerase I degrades the RNA primer and replaces it with DNA



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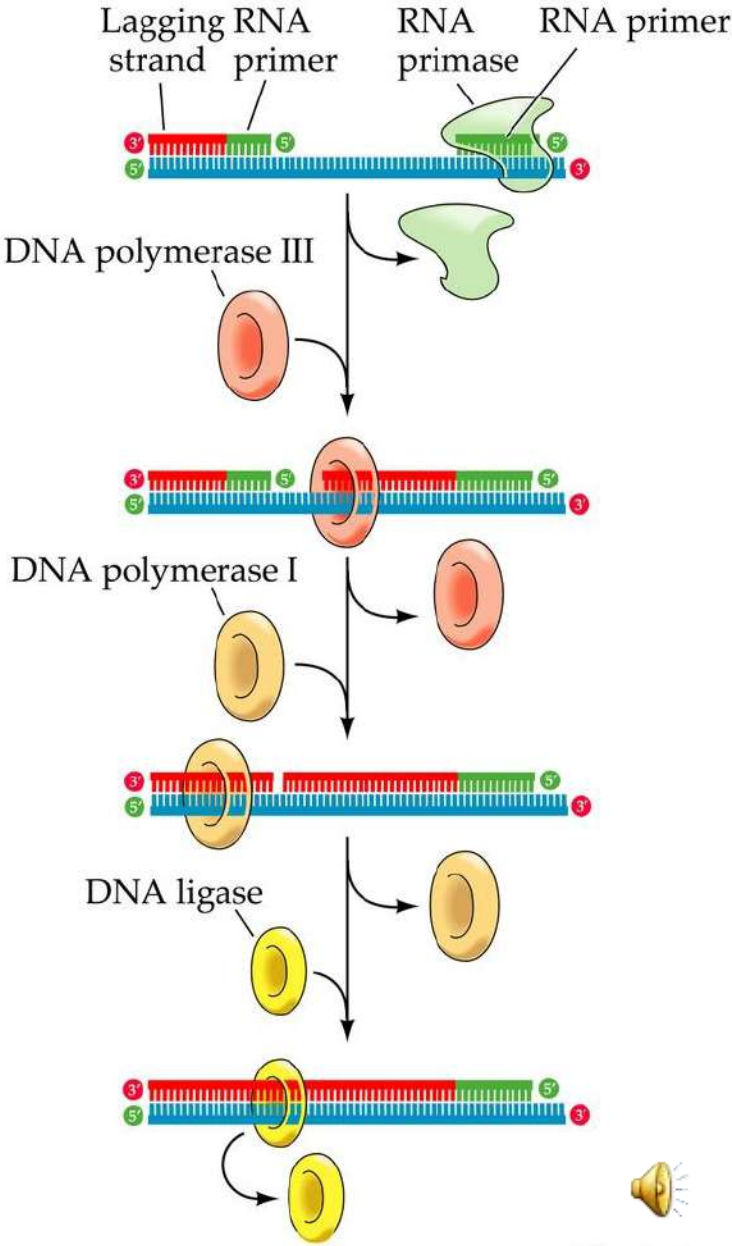
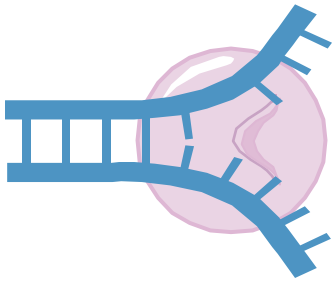
The Mechanism of DNA Replication

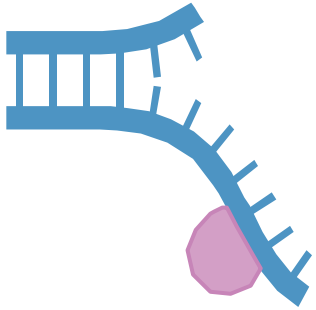
- Many proteins assist in DNA replication
- DNA helicases unwind the double helix, the template strands are stabilized by other proteins
- Single-stranded DNA binding proteins make the template available
- RNA primase catalyzes the synthesis of short RNA primers, to which nucleotides are added.
- DNA polymerase III extends the strand in the 5’-to-3’ direction
- DNA polymerase I degrades the RNA primer and replaces it with DNA
- DNA ligase joins the DNA fragments into a continuous daughter strand



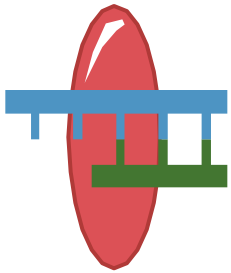
Enzymes in DNA replication



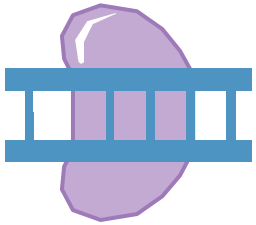
Helicase unwinds parental double helix



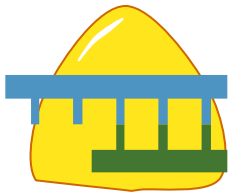
Binding proteins stabilize separate strands



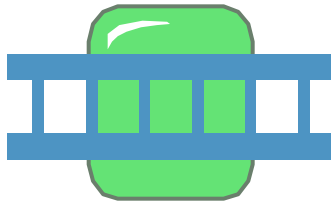
Primase adds short primer to template strand



DNA polymerase III binds nucleotides to form new strands

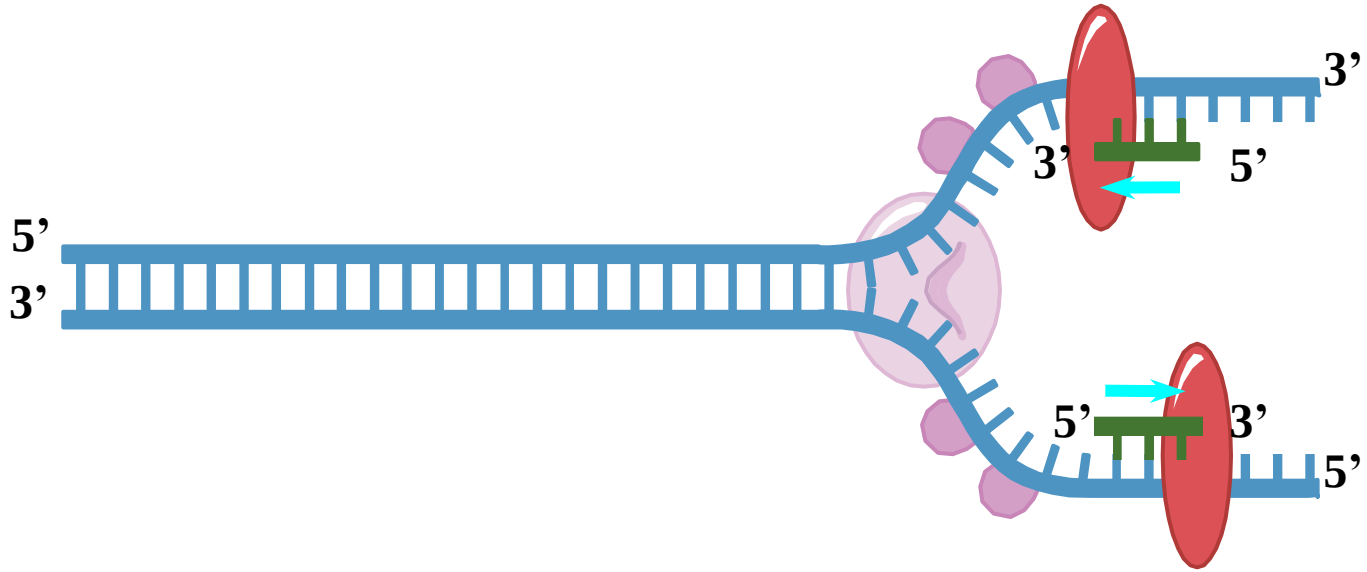


DNA polymerase I (Exonuclease) removes RNA primer and inserts the correct bases



Ligase joins Okazaki fragments and seals other nicks in sugar-phosphate backbone

Replication

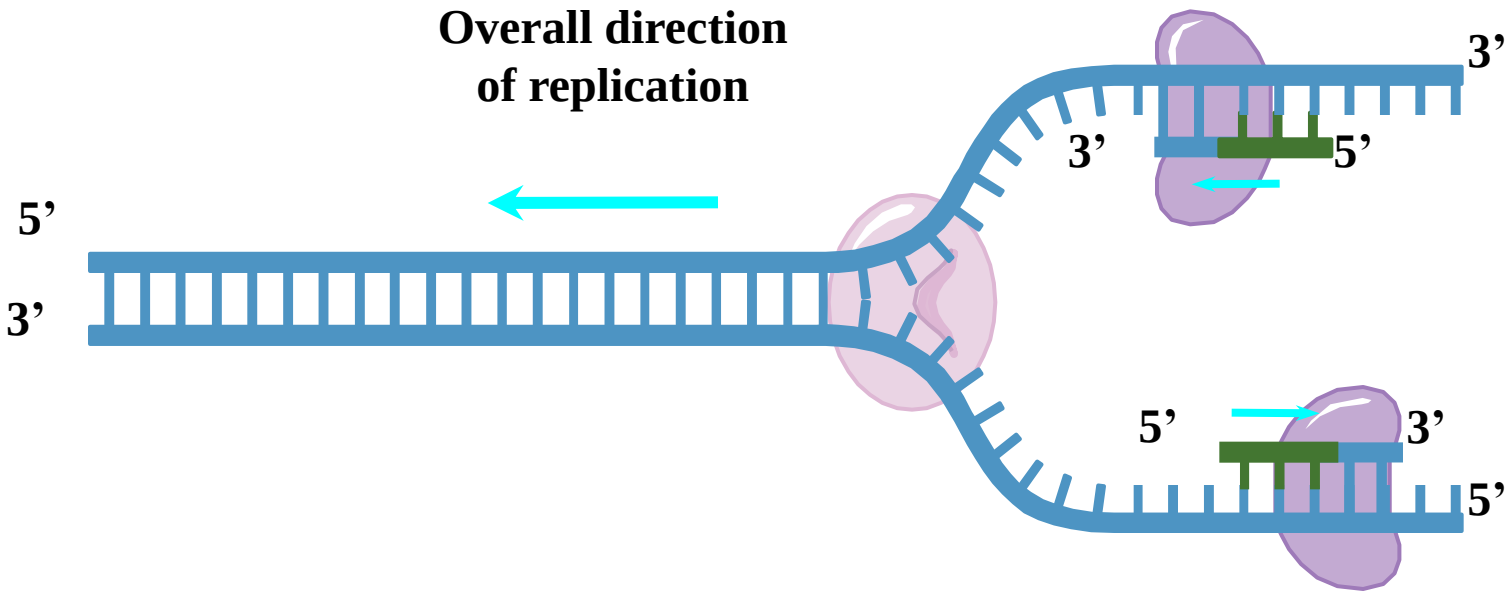


Helicase protein binds to DNA sequences called origins and unwinds DNA strands.

Binding proteins prevent single strands from rewinding.

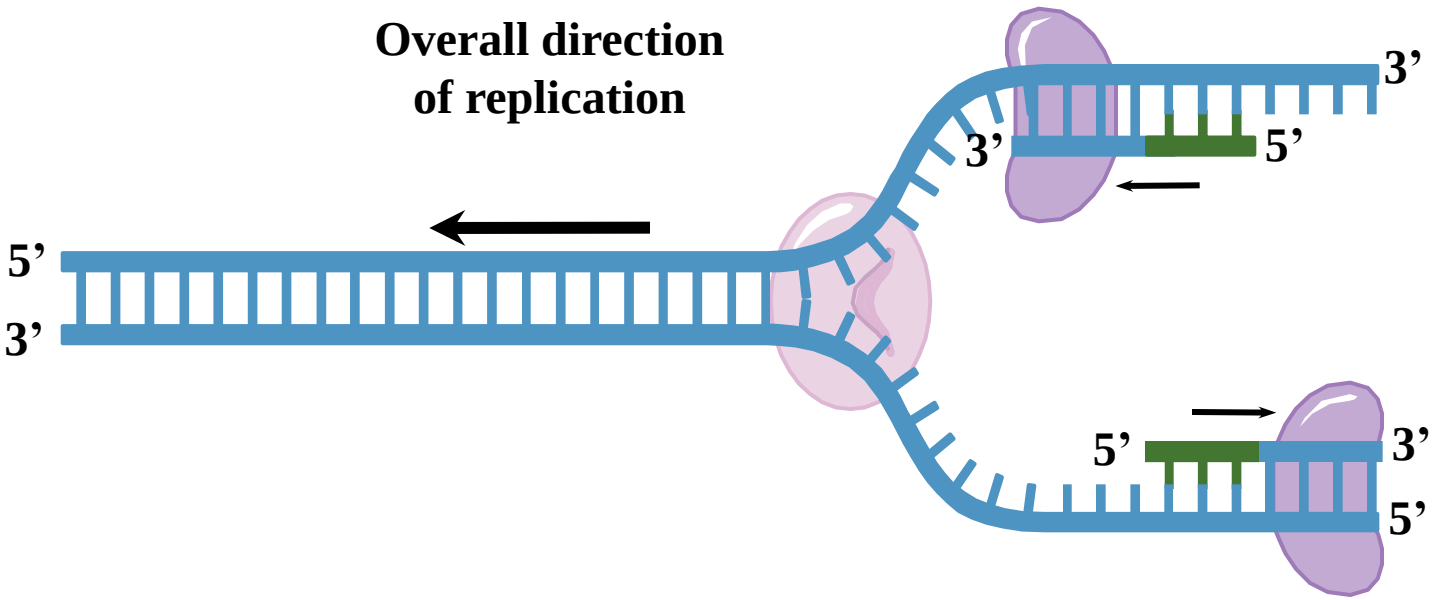
Primase protein makes a short segment of RNA complementary to the DNA, a primer.

Replication



DNA polymerase enzyme adds DNA nucleotides to the RNA primer.

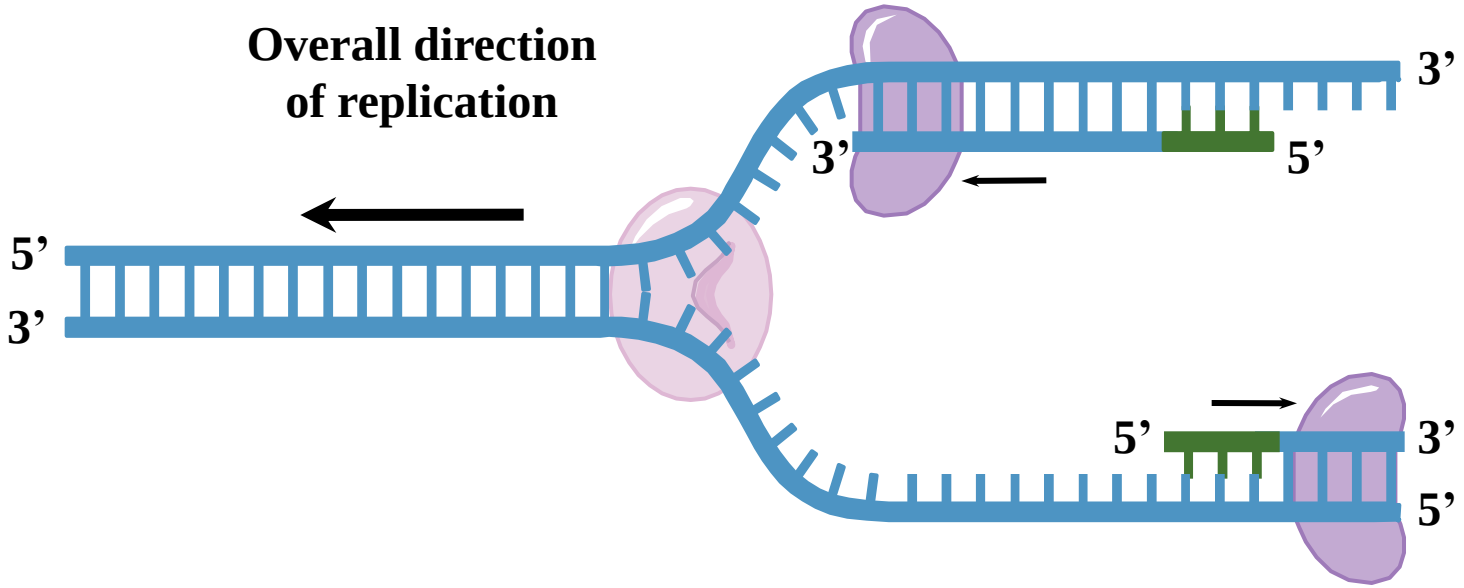
Replication



DNA polymerase enzyme adds DNA nucleotides to the RNA primer.

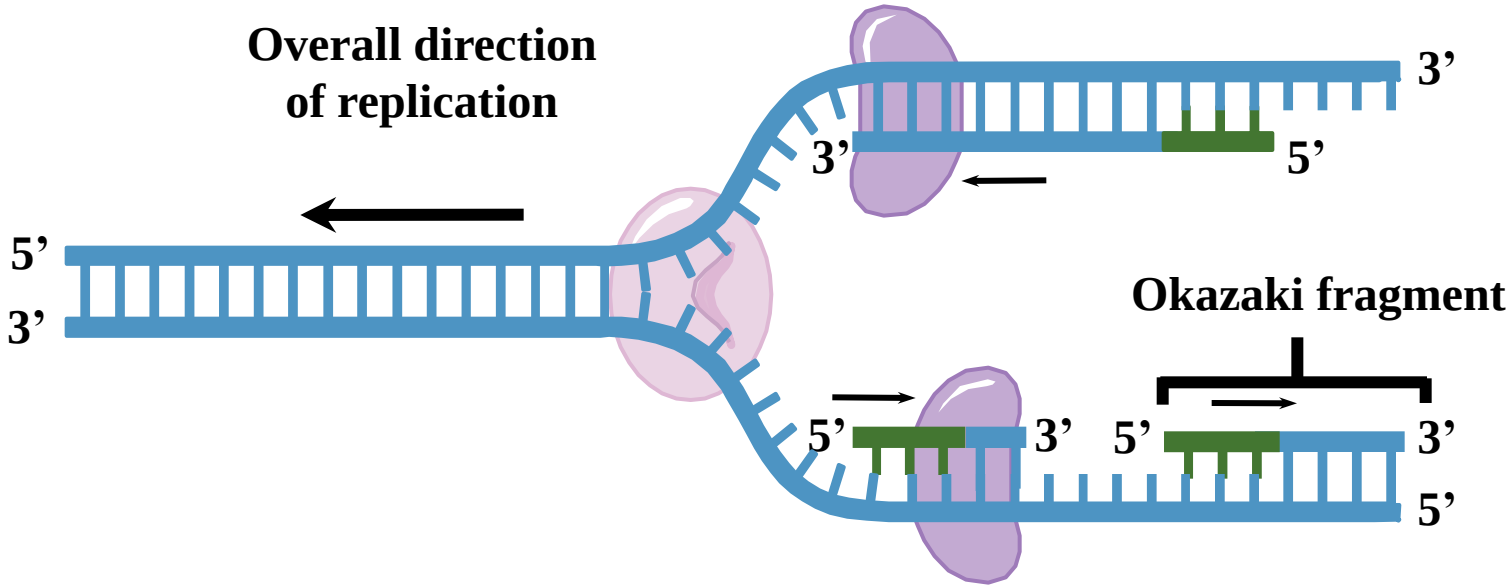
DNA polymerase proofreads bases added and replaces incorrect nucleotides.

Replication



Leading strand synthesis continues in a 5’ to 3’ direction.

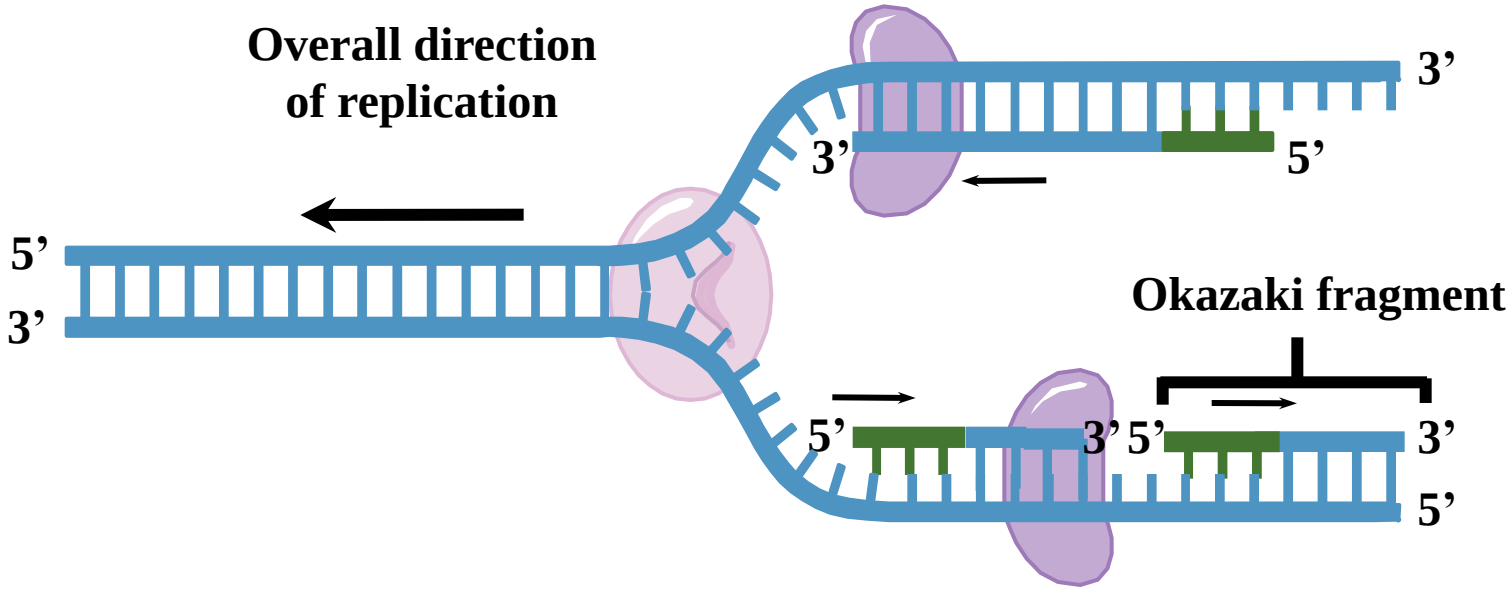
Replication



Leading strand synthesis continues in a 5’ to 3’ direction.

Discontinuous synthesis produces 5’ to 3’ DNA segments called Okazaki fragments.

Replication



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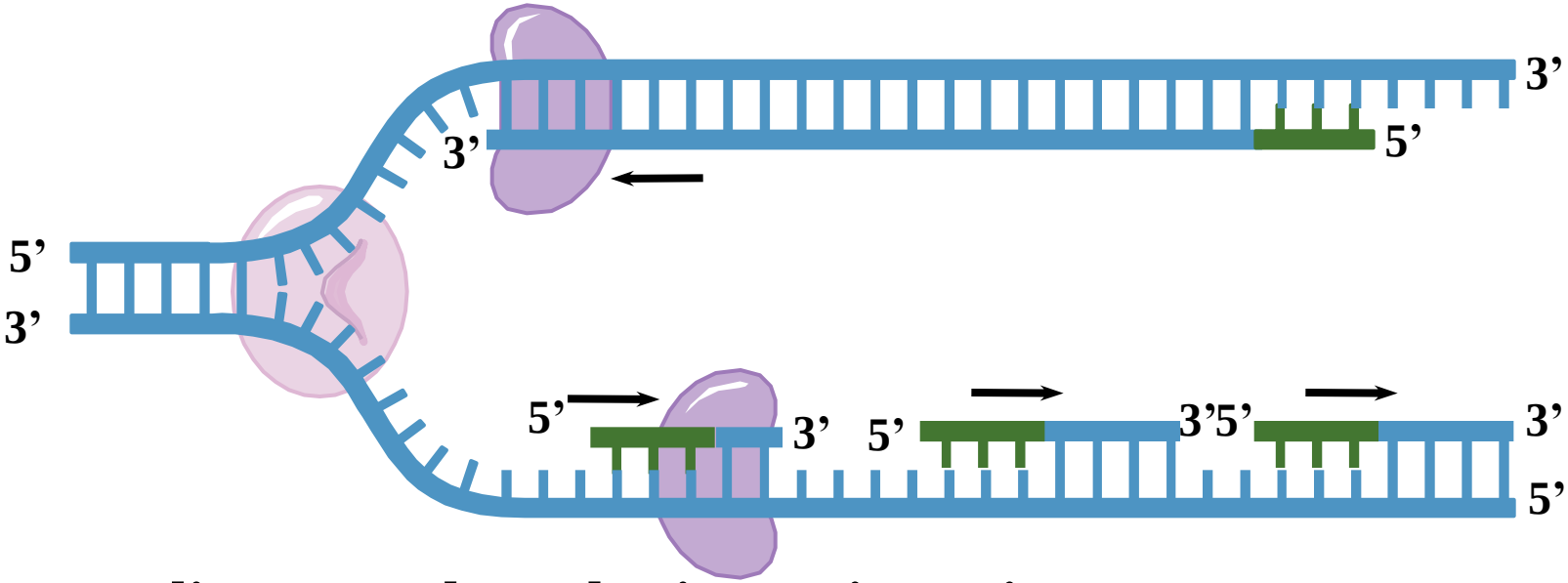

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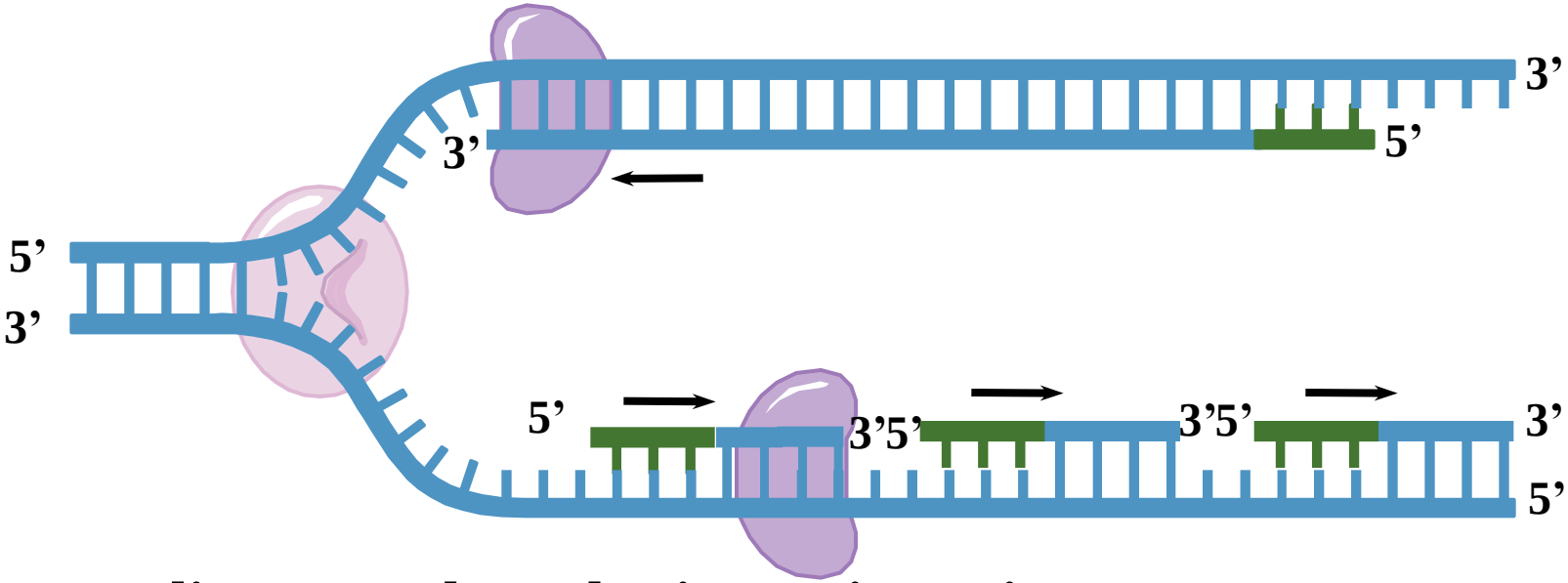
Replication



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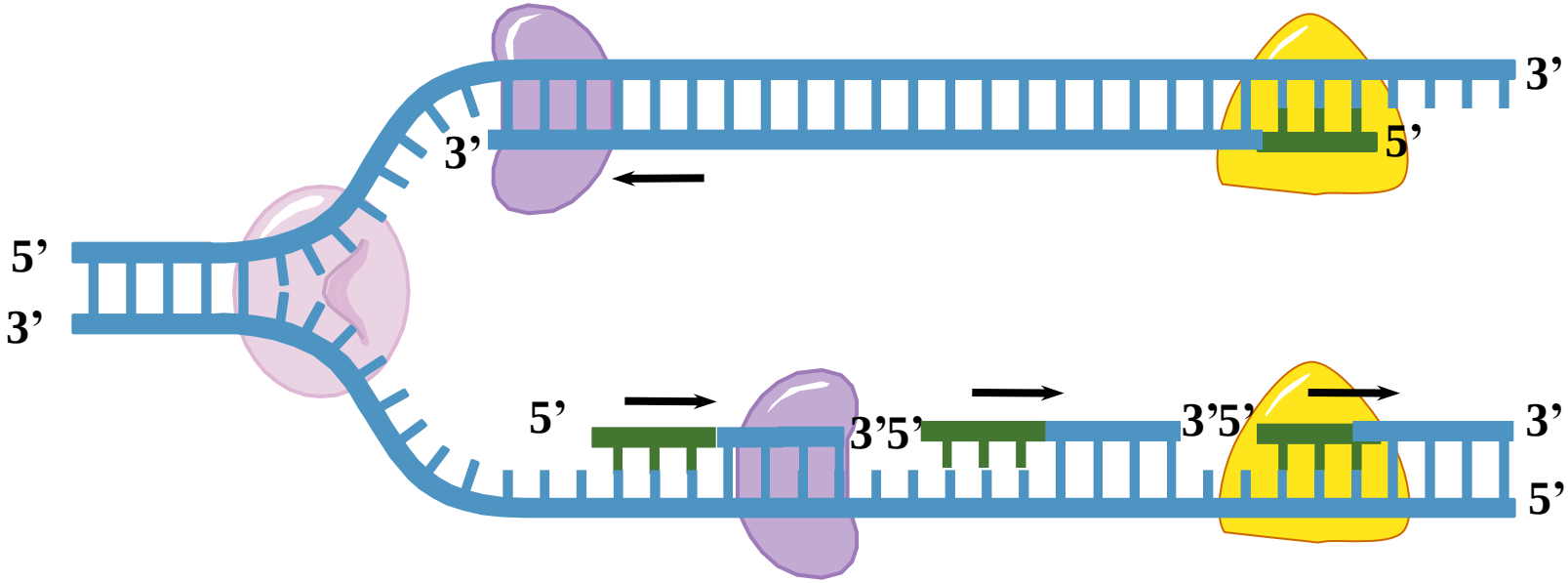
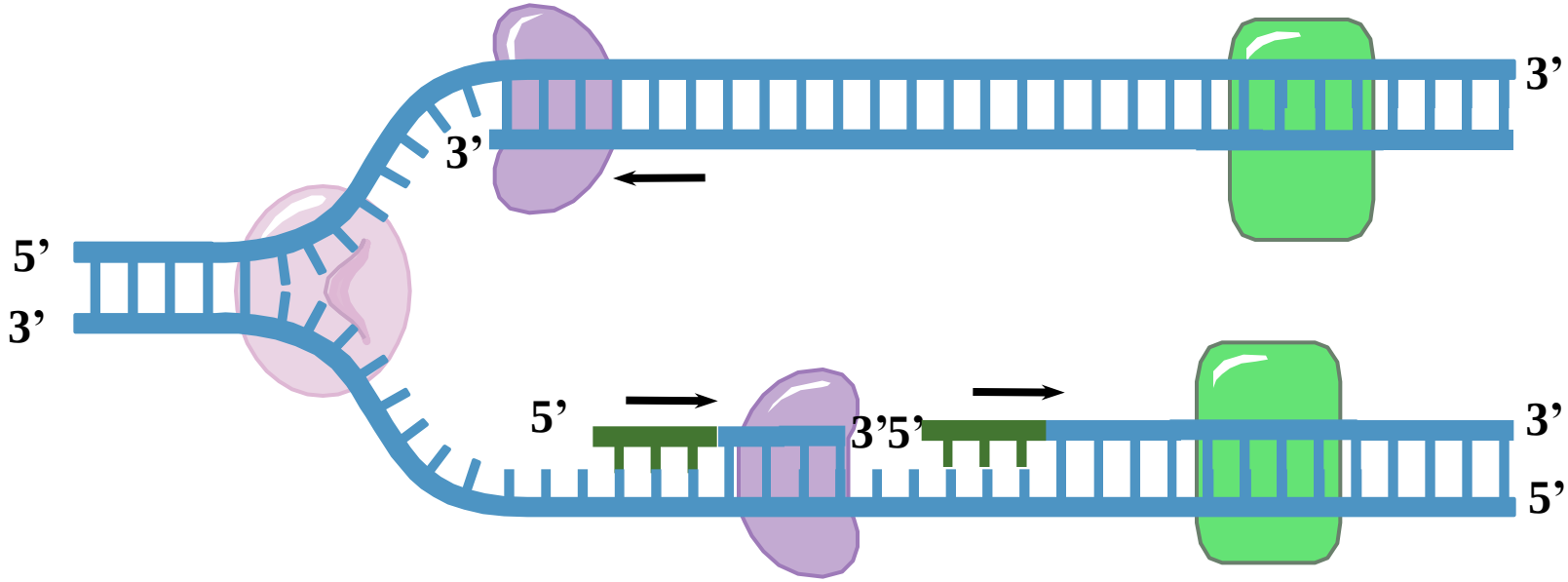
Replication



Exonuclease activity of DNA polymerase I removes RNA primers.

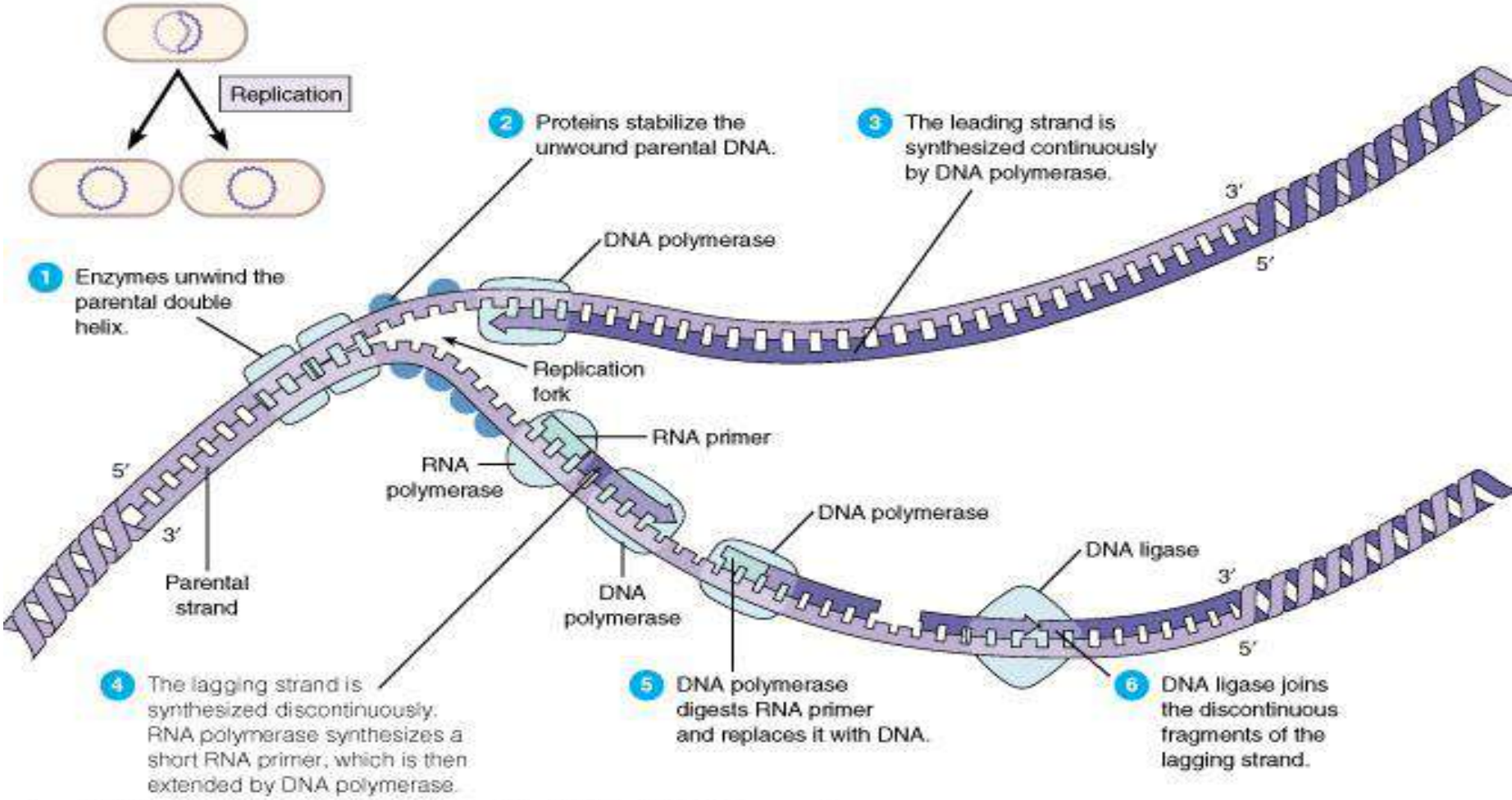
Replication



Polymerase activity of DNA polymerase I fills the gaps.

Ligase forms bonds between sugar-phosphate backbone.

Replication Fork Overview



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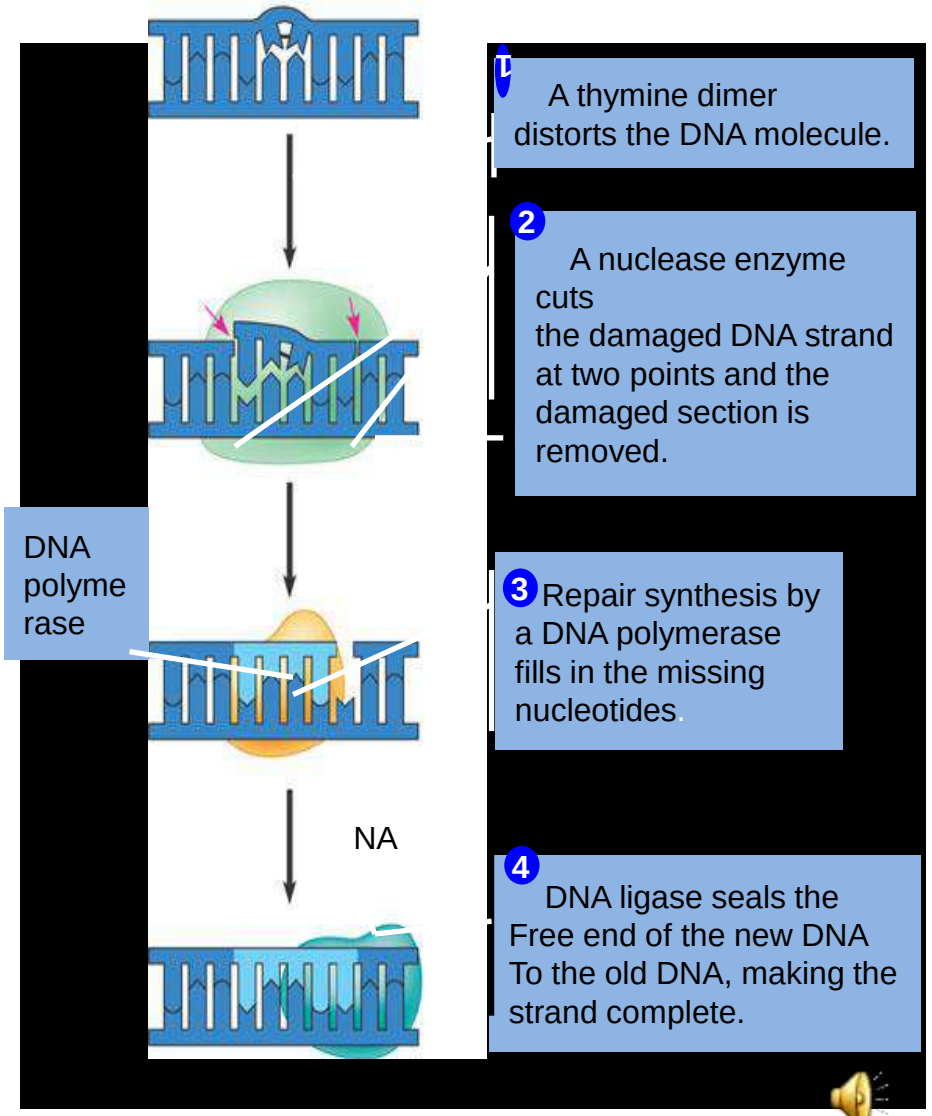
Proofreading

- DNA must be faithfully replicated…but mistakes occur
  - DNA polymerase (DNA pol) inserts the wrong nucleotide base in 1/10,000 bases
    - DNA pol has a proofreading capability and can correct errors
  - Mismatch repair: ‘wrong’ inserted base can be removed
  - Excision repair: DNA may be damaged by chemicals, radiation, etc. Mechanism to cut out and replace with correct bases

Proofreading and Repairing DNA

- DNA polymerases proofread newly made DNA, replacing any incorrect nucleotides
- In mismatch repair of DNA, repair enzymes correct errors in base pairing
- In nucleotide excision DNA repair nucleases cut out and replace damaged stretches of DNA



Accuracy of DNA Replication

- The chromosome of E. coli bacteria contains about 5 million bases pairs
  - Capable of copying this DNA in less than an hour
- The 46 chromosomes of a human cell contain about 6 BILLION base pairs of DNA!!
  - Printed one letter (A,C,T,G) at a time…would fill up over 900 volumes of Campbell.
  - Takes a cell a few hours to copy this DNA
  - With amazing accuracy – an average of 1 per billion nucleotides

Protein Synthesis

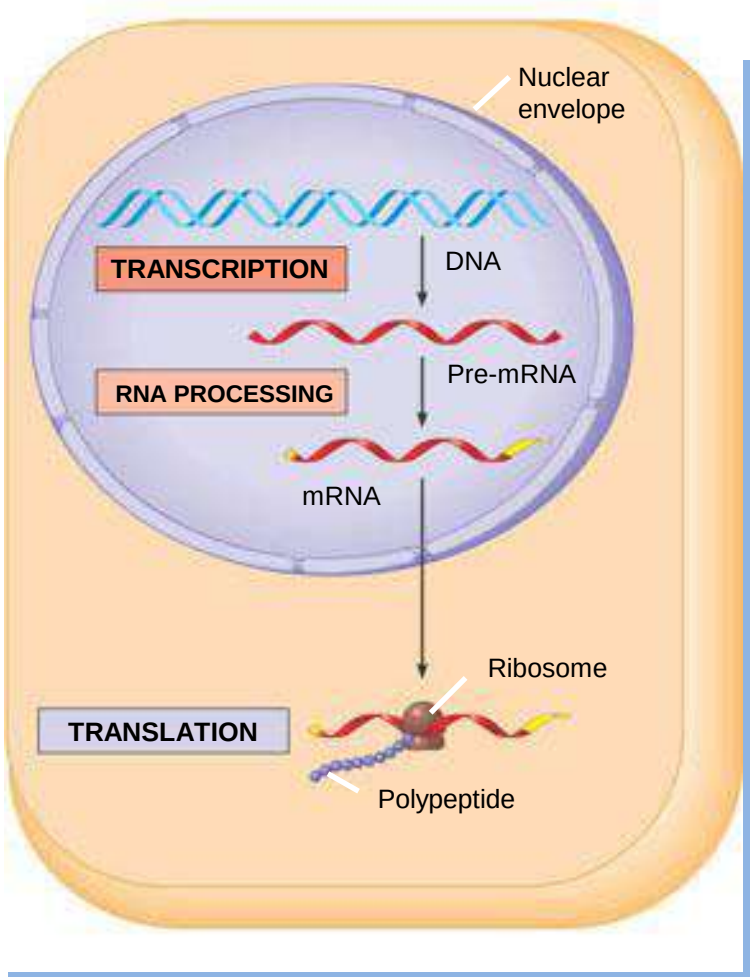
- The information content of DNA is in the form of specific sequences of nucleotides along the DNA strands
- The DNA inherited by an organism leads to specific traits by dictating the synthesis of proteins
- The process by which DNA directs protein synthesis, gene expression includes two stages, called transcription and translation

Transcription and Translation

- Cells are governed by a cellular chain of command
  - DNA $\rightarrow$ RNA $\rightarrow$ protein
- Transcription
  - Is the synthesis of RNA under the direction of DNA
  - Produces messenger RNA (mRNA)
- Translation
  - Is the actual synthesis of a polypeptide, which occurs under the direction of mRNA
  - Occurs on ribosomes

Transcription and Translation

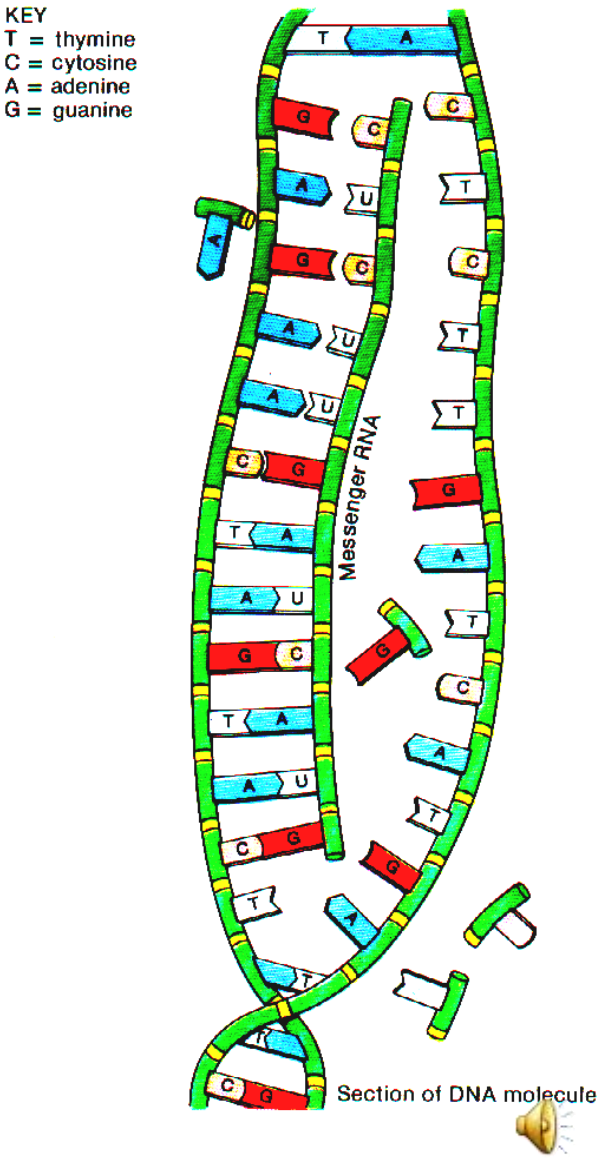
- In a eukaryotic cell the nuclear envelope separates transcription from translation
- Extensive RNA processing occurs in the nucleus



Eukaryotic cell. The nucleus provides a separate compartment for transcription. The original RNA transcript, called pre-mRNA, is processed in various ways before leaving the nucleus as mRNA.

Transcription

- Transcription is the DNA-directed synthesis of RNA
- RNA synthesis
  - Is catalyzed by RNA polymerase, which pries the DNA strands apart and hooks together the RNA nucleotides
  - Follows the same base-pairing rules as DNA, except that in RNA, uracil substitutes for thymine



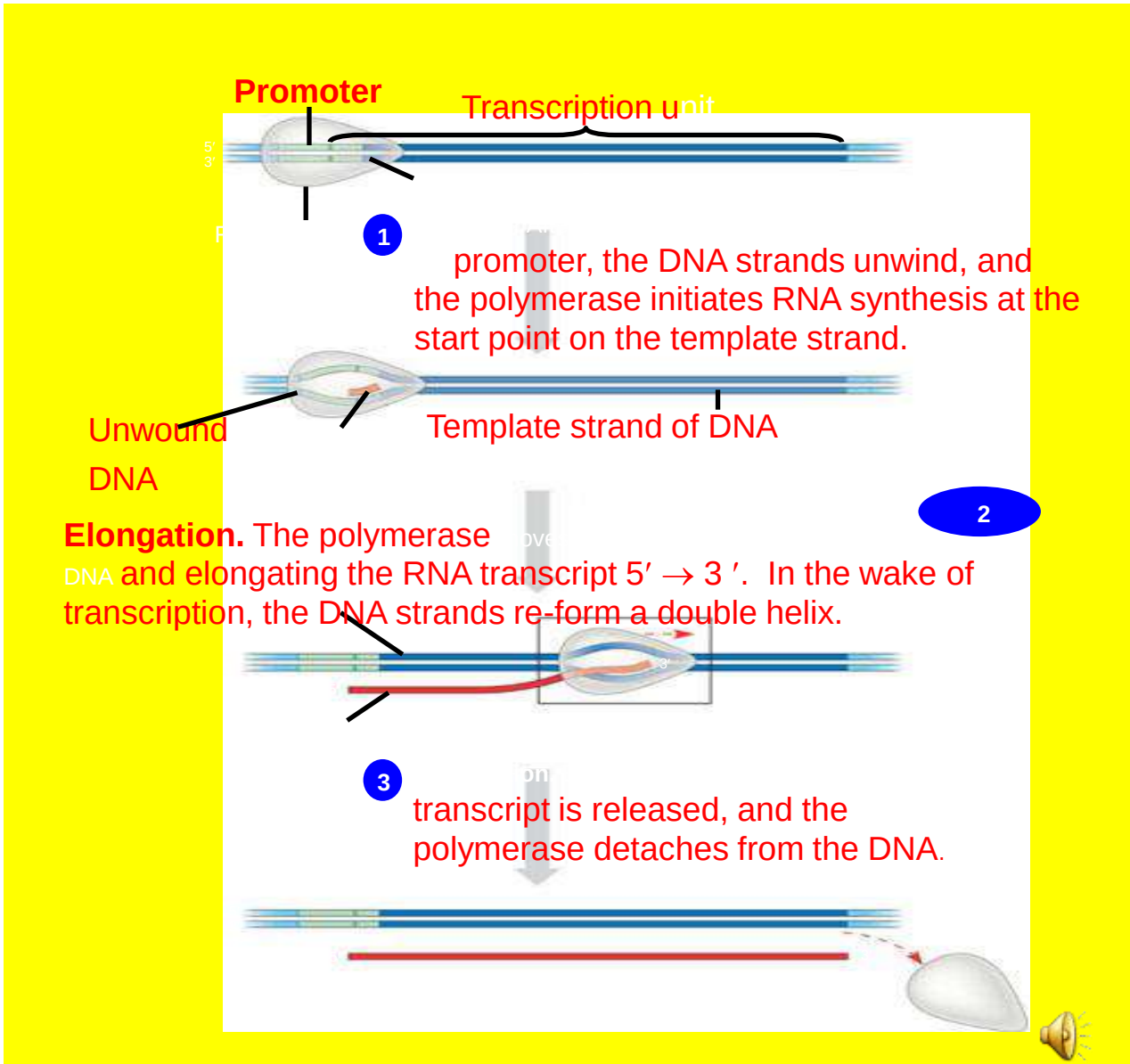
RNA

- RNA is single stranded, not double stranded like DNA
- RNA is short, only 1 gene long, where DNA is very long and contains many genes
- RNA uses the sugar ribose instead of deoxyribose in DNA
- RNA uses the base uracil (U) instead of thymine (T) in DNA.

Type of RNA	Functions
Messenger RNA (mRNA)	Carries information specifying amino acid sequences of proteins from DNA to ribosomes.
Transfer RNA (tRNA)	Serves as adapter molecule in protein synthesis; translates mRNA codons into amino acids.
Ribosomal RNA (rRNA)	Plays catalytic (ribozyme) roles and structural roles in ribosomes.
Primary transcript	Serves as a precursor to mRNA, rRNA, or tRNA, before being processed by splicing or cleavage. Some intron RNA acts as a ribozyme, catalyzing its own splicing.
Small nuclear RNA (snRNA)	Plays structural and catalytic roles in spliceosomes, the complexes of protein and RNA that splice pre-mRNA.

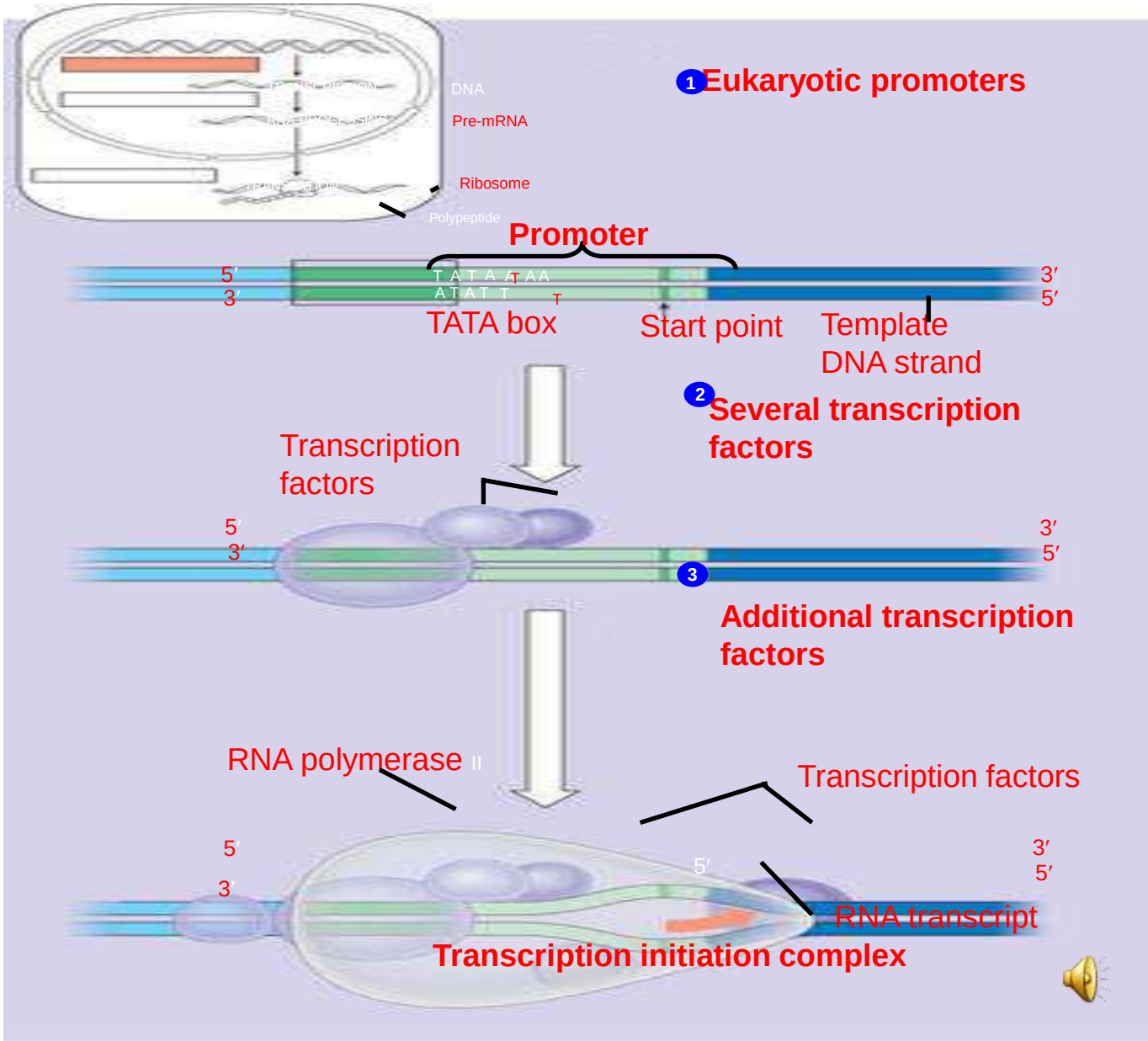
Synthesis of an RNA Transcript

- The stages of transcription are
  - Initiation
  - Elongation
  - Termination



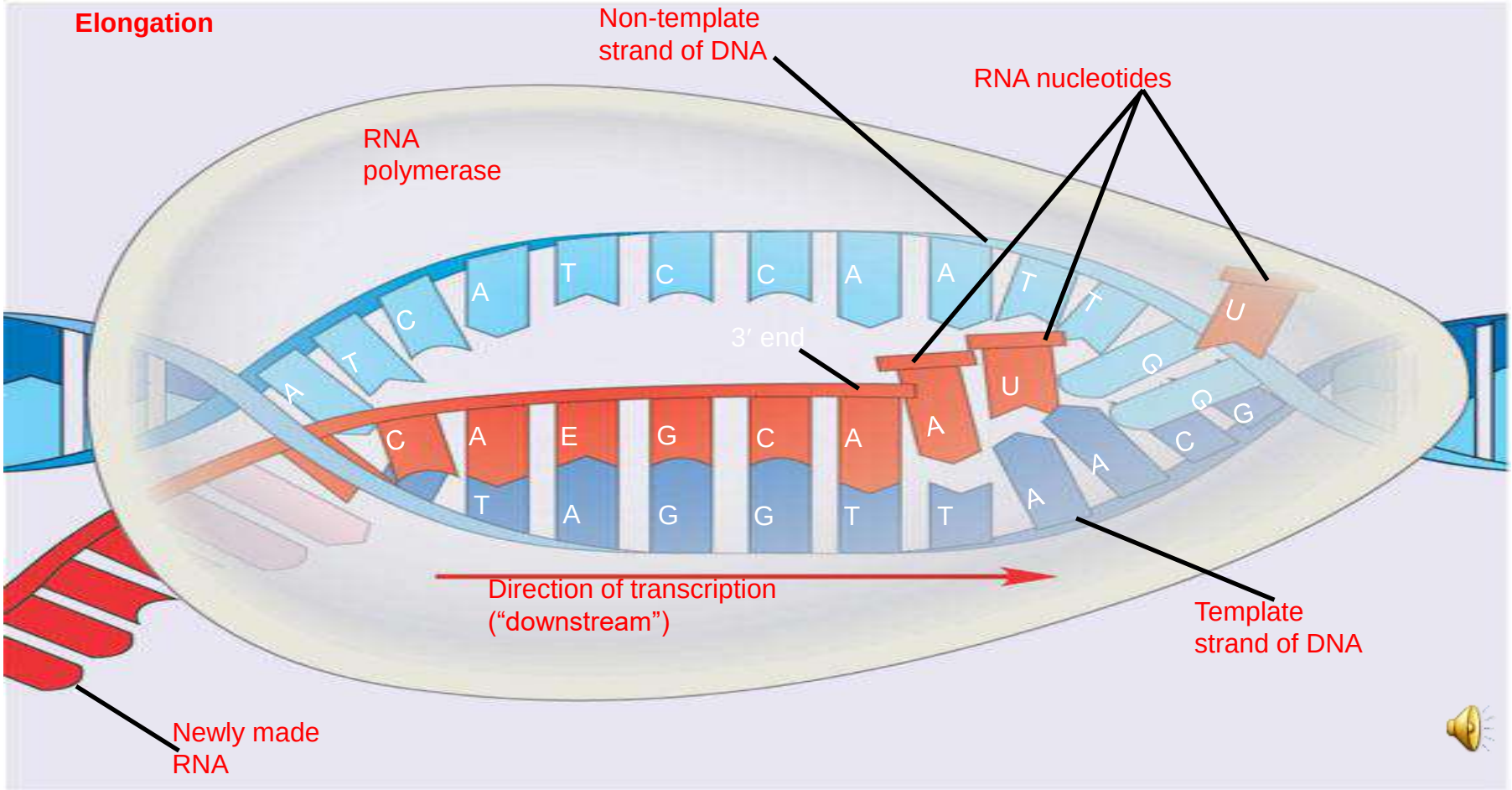
Synthesis of an RNA Transcript - Initiation

- Promoters signal the initiation of RNA synthesis
- Transcription factors help eukaryotic RNA polymerase recognize promoter



Synthesis of an RNA Transcript - Elongation

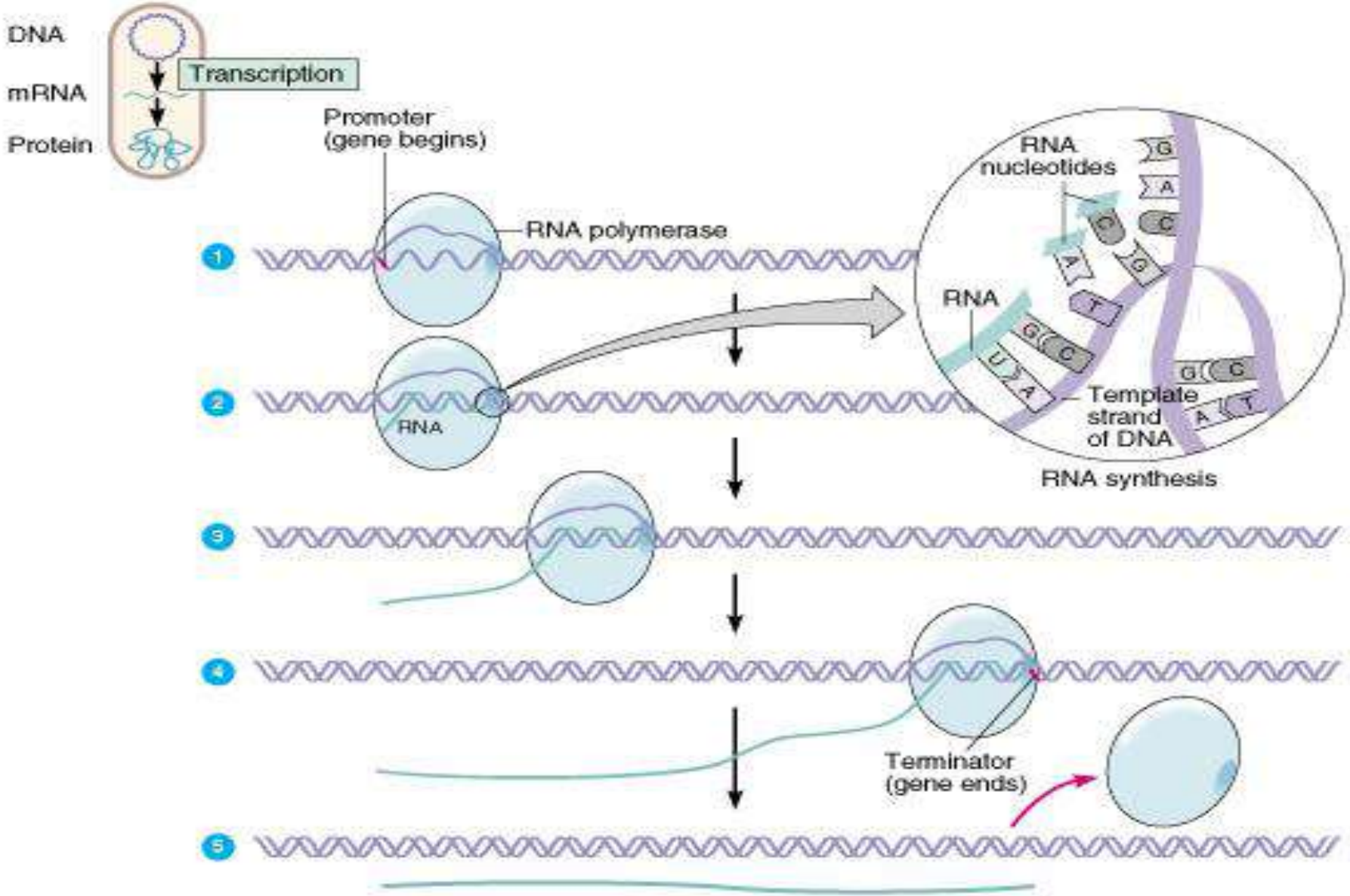
- **RNA polymerase synthesizes a single strand of RNA against the DNA template strand (anti-sense strand), adding nucleotides to the 3’ end of the RNA chain**
- **As RNA polymerase moves along the DNA it continues to untwist the double helix, exposing about 10 to 20 DNA bases at a time for pairing with RNA nucleotides**



Synthesis of an RNA Transcript - Termination

- Specific sequences in the DNA signal termination of transcription
- When one of these is encountered by the polymerase, the RNA transcript is released from the DNA and the double helix can zip up again.

Transcription Overview

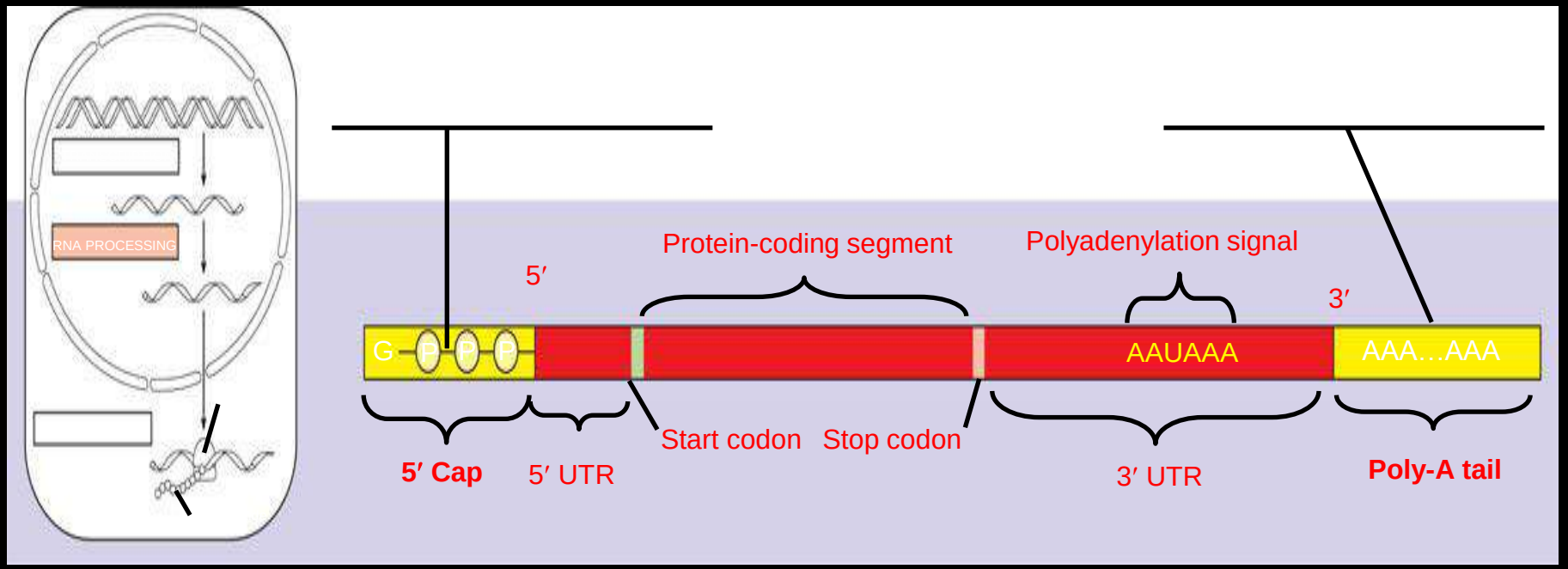


Post Termination RNA Processing

- Most eukaryotic mRNAs aren't ready to be translated into protein directly after being transcribed from DNA. mRNA requires processing.
- Transcription of RNA processing occur in the nucleus. After this, the messenger RNA moves to the cytoplasm for translation.
- The cell adds a protective cap to one end, and a tail of A's to the other end. These both function to protect the RNA from enzymes that would degrade
- Most of the genome consists of non-coding regions called introns
  - Non-coding regions may have specific chromosomal functions or have regulatory purposes
  - Introns also allow for alternative RNA splicing
- Thus, an RNA copy of a gene is converted into messenger RNA by doing 2 things:
  - Add protective bases to the ends
  - Cut out the introns

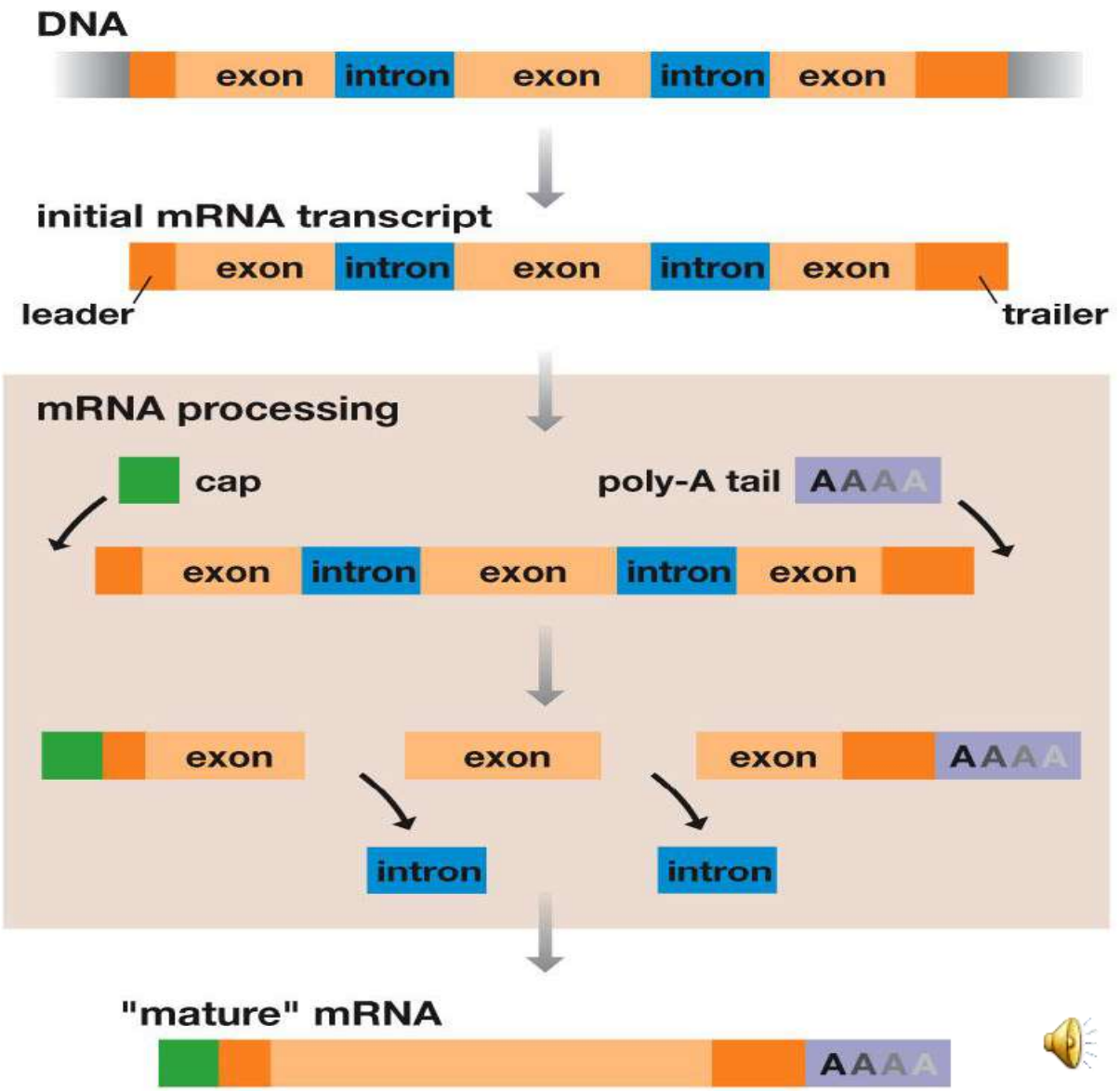
Alteration of mRNA Ends

- Each end of a pre-mRNA molecule is modified in a particular way
  - The 5′ end receives a modified nucleotide cap



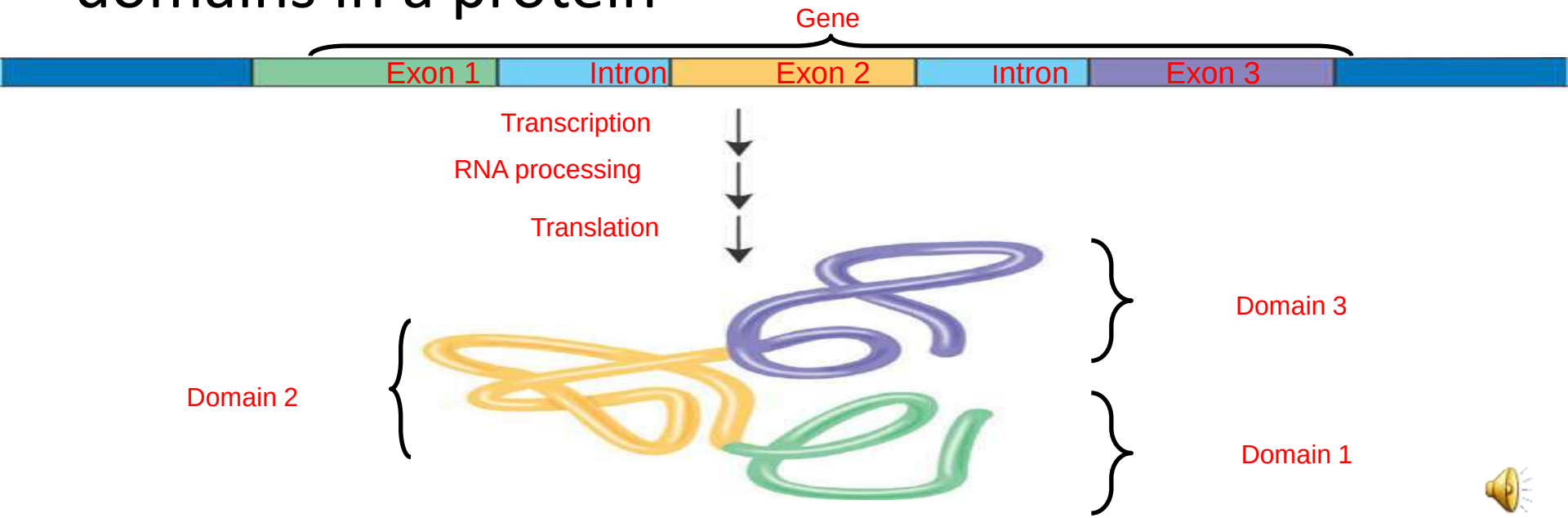
RNA Processing - Splicing

- The original transcript from the DNA is called pre-mRNA.
- It contains transcripts of both introns and exons.
- The introns are removed by a process called splicing to produce messenger RNA (mRNA)



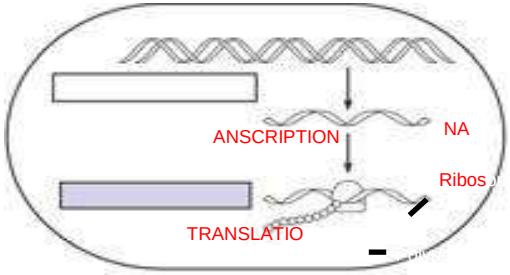
RNA Processing

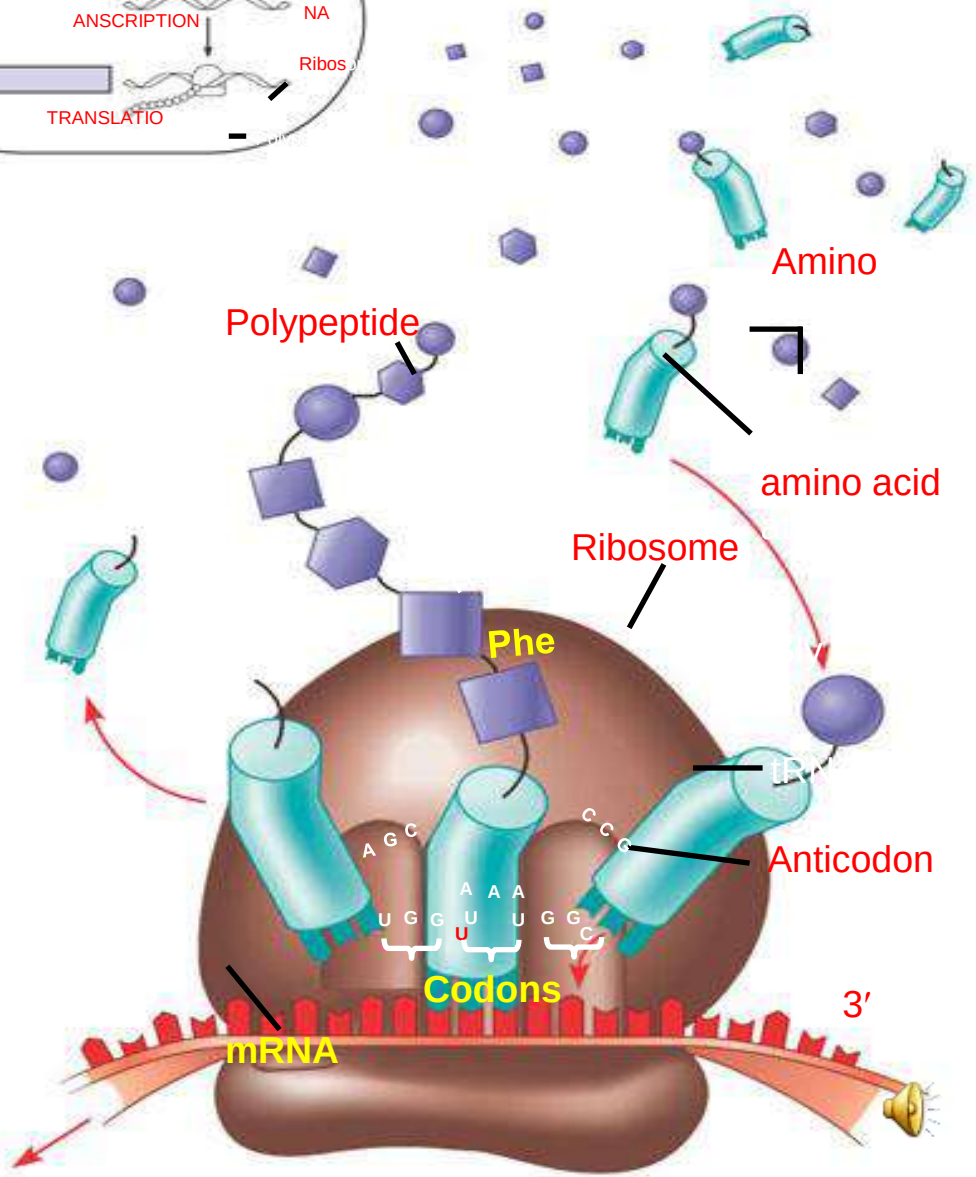
- Proteins often have a modular architecture consisting of discrete structural and functional regions called domains
- In many cases different exons code for the different domains in a protein



Translation

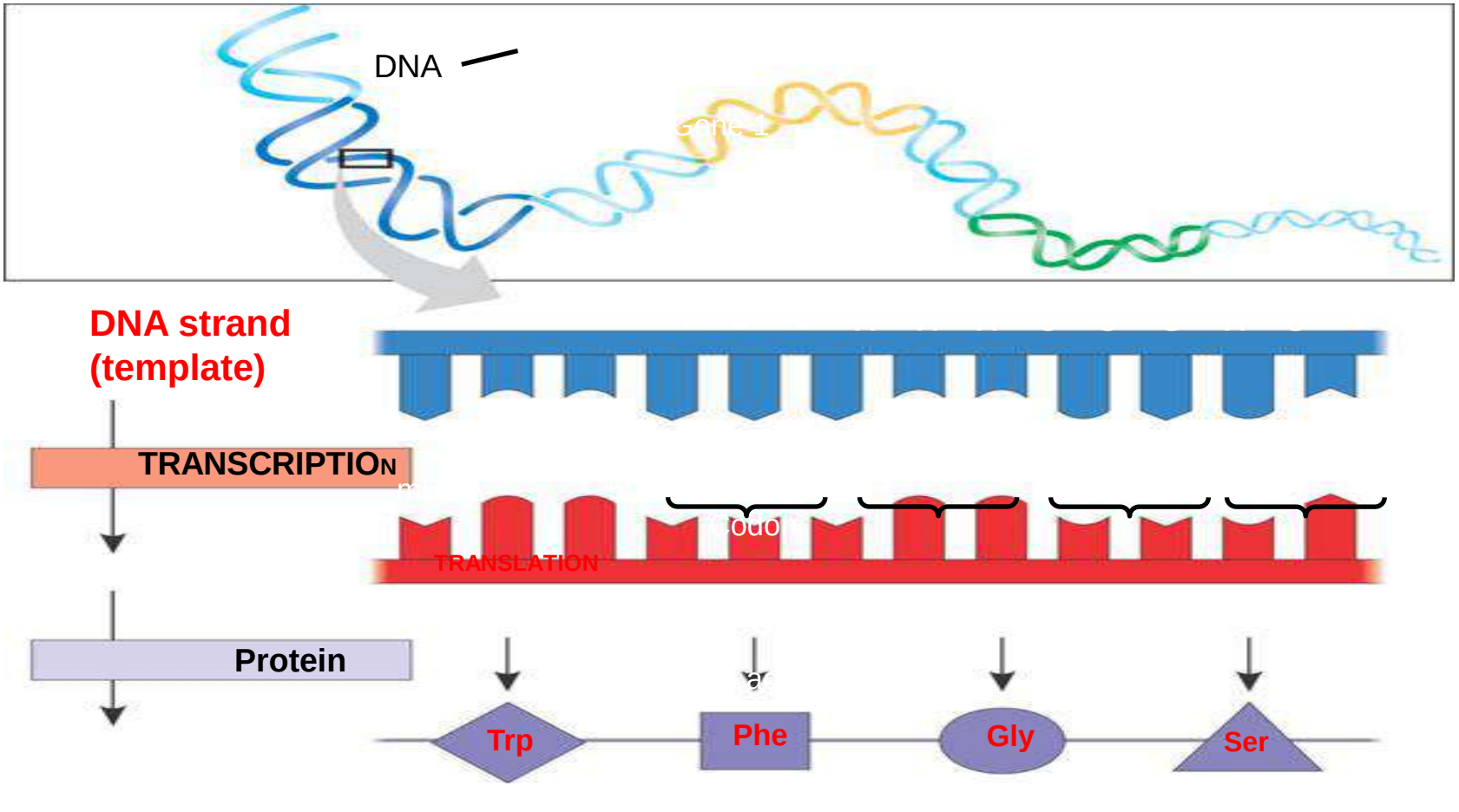
- Translation is the RNA-directed synthesis of a polypeptide
- Translation involves
  - mRNA
  - Ribosome's - Ribosomal RNA
  - Transfer RNA
  - Genetic coding - codons





The Genetic Code

- Genetic information is encoded as a sequence of no overlapping base triplets, or codons

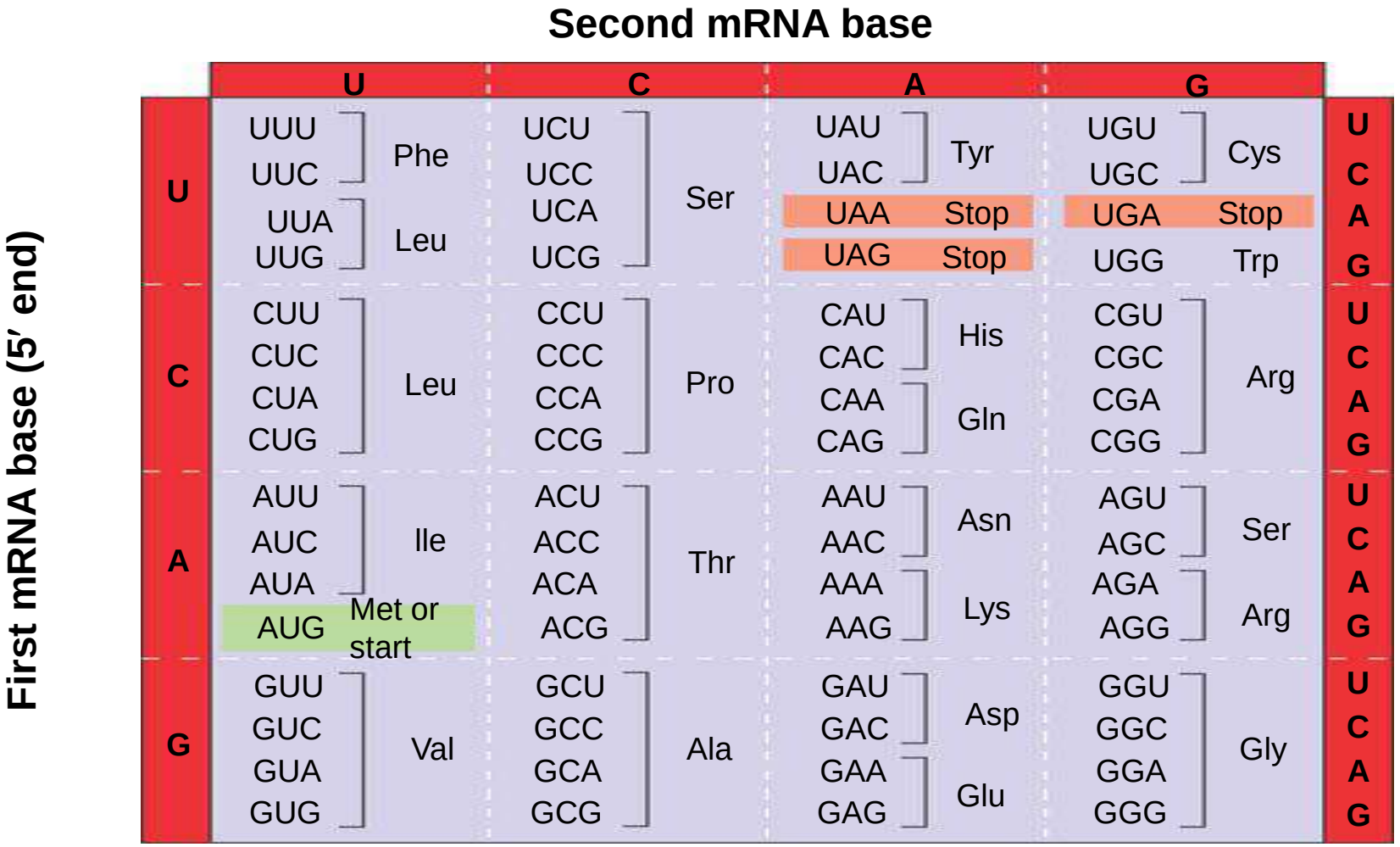


The Genetic Code

- Codons: 3 base code for the production of a specific amino acid, sequence of three of the four different nucleotides
- Since there are 4 bases and 3 positions in each codon, there are 4 x 4 x 4 = 64 possible codons
- 64 codons but only 20 amino acids, therefore most have more than 1 codon
- 3 of the 64 codons are used as STOP signals; they are found at the end of every gene and mark the end of the protein
- One codon is used as a START signal: it is at the start of every protein

The Genetic Code

- A codon in messenger RNA is either translated into an amino acid or serves as a translational start/stop signal

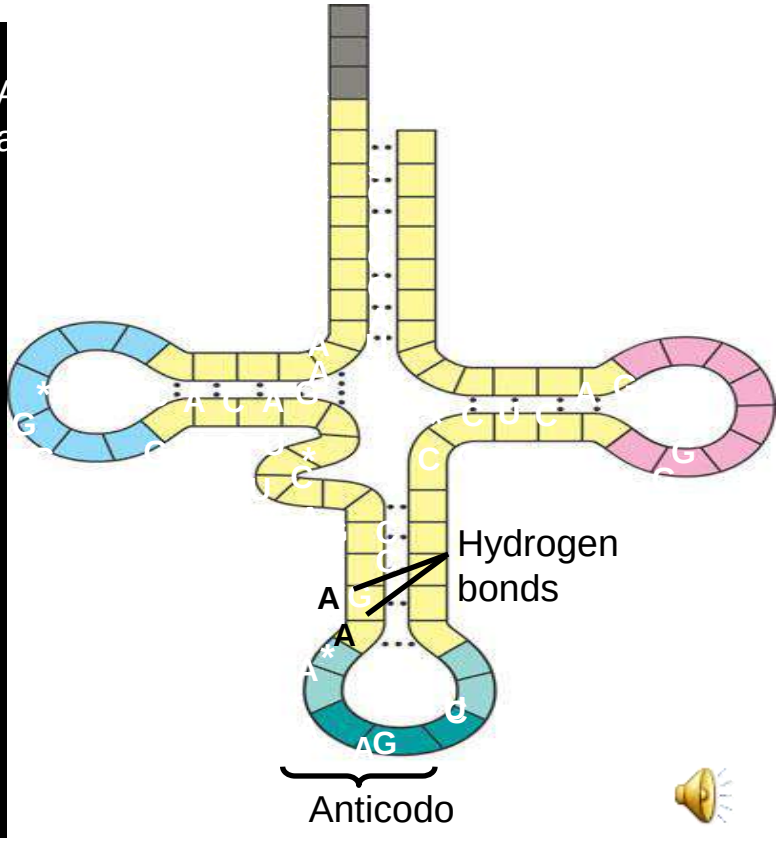


Transfer RNA

- Consists of a single RNA strand that is only about 80 nucleotides long
- Each carries a specific amino acid on one end and has an anticodon on the other end
- A special group of enzymes pairs up the proper tRNA molecules with their corresponding amino acids.
- tRNA brings the amino acids to the ribosomes,

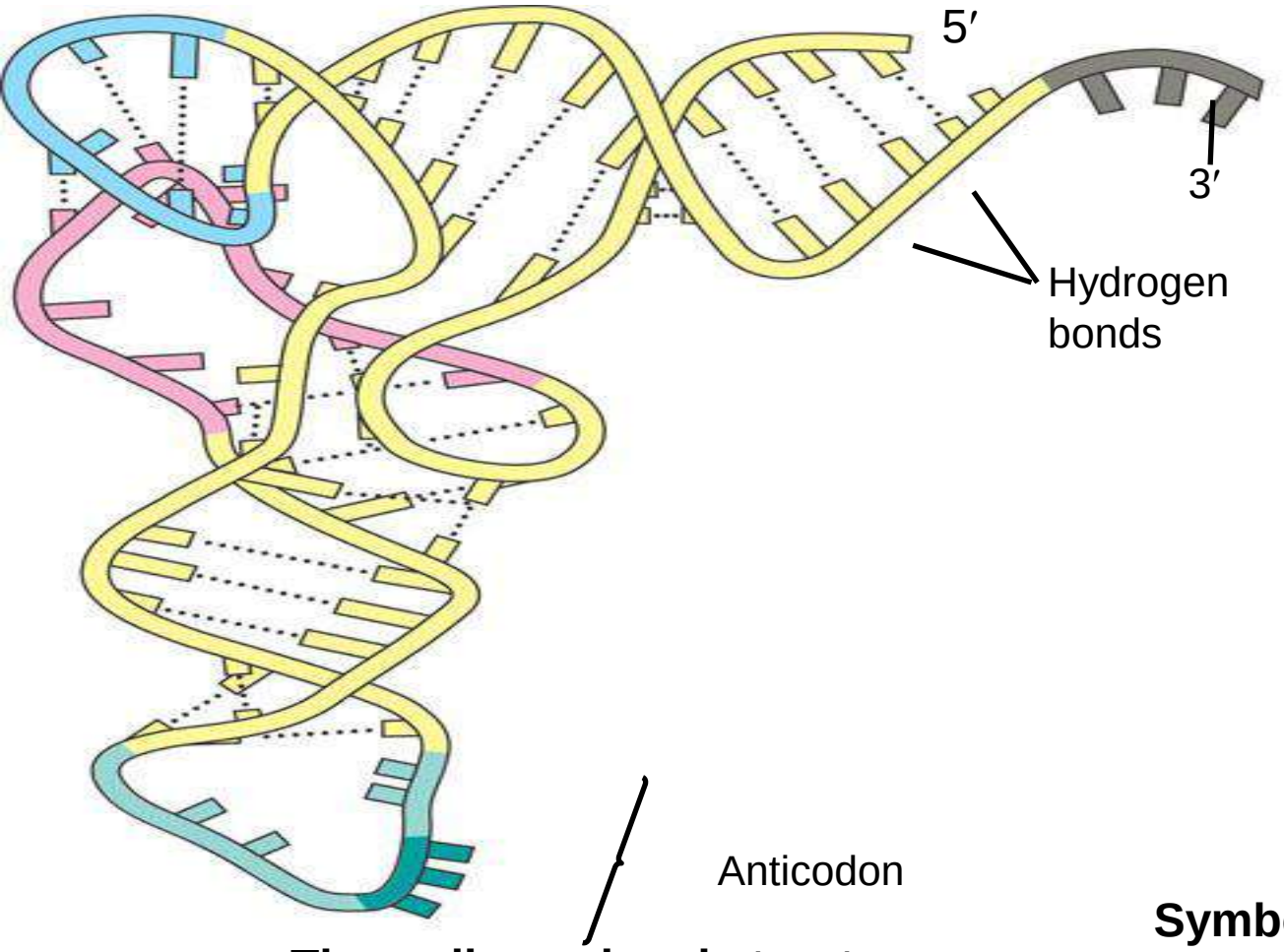
The "anticdon" is the 3 RNA bases that matches the 3 bases of the codon on the mRNA molecule

Two-dimensional structure. The four base-paired regions and three loops are characteristic of all tRNAs, as is the base sequence of the amino acid attachment site at the 3′ end. The anticodon triplet is unique to each tRNA type. (The asterisks mark bases that have been chemically modified, a characteristic of tRNA.)



Transfer RNA

- 3 dimensional tRNA molecule is roughly “L” shaped

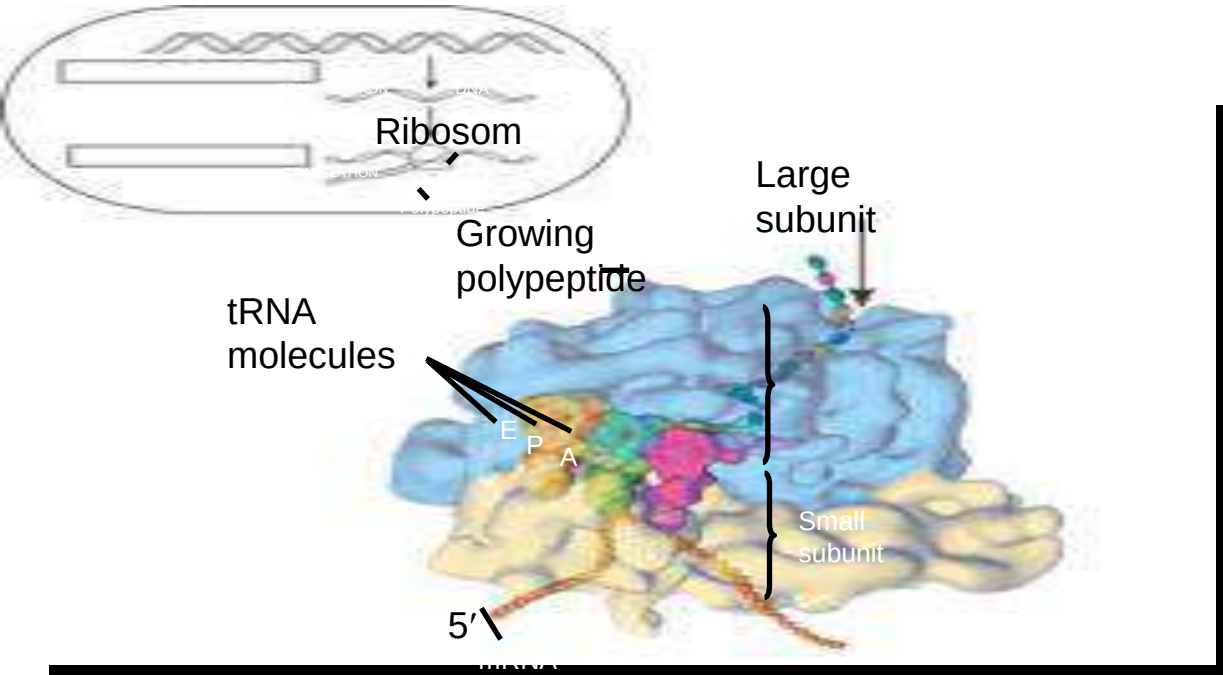


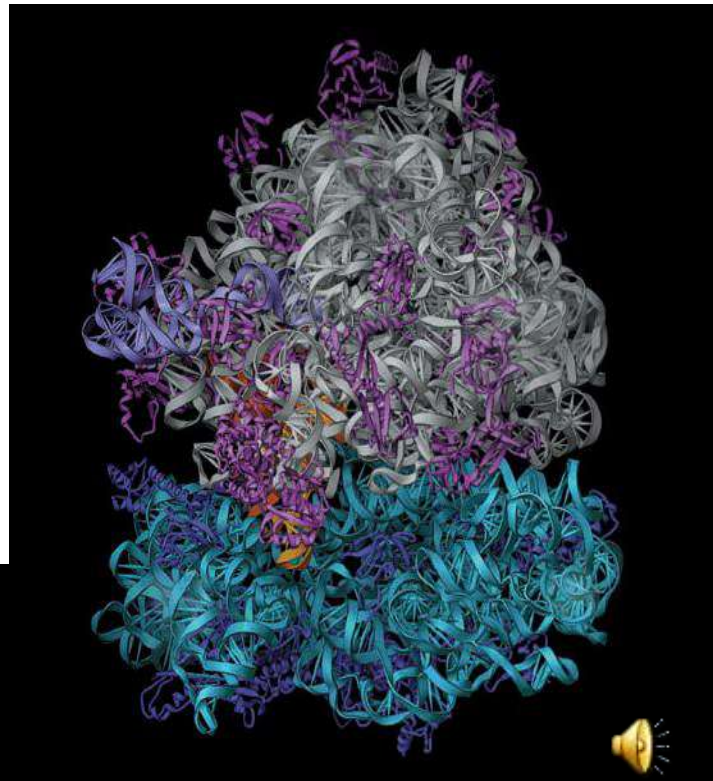
Three-dimensional structure

Symbol used

Ribosomes

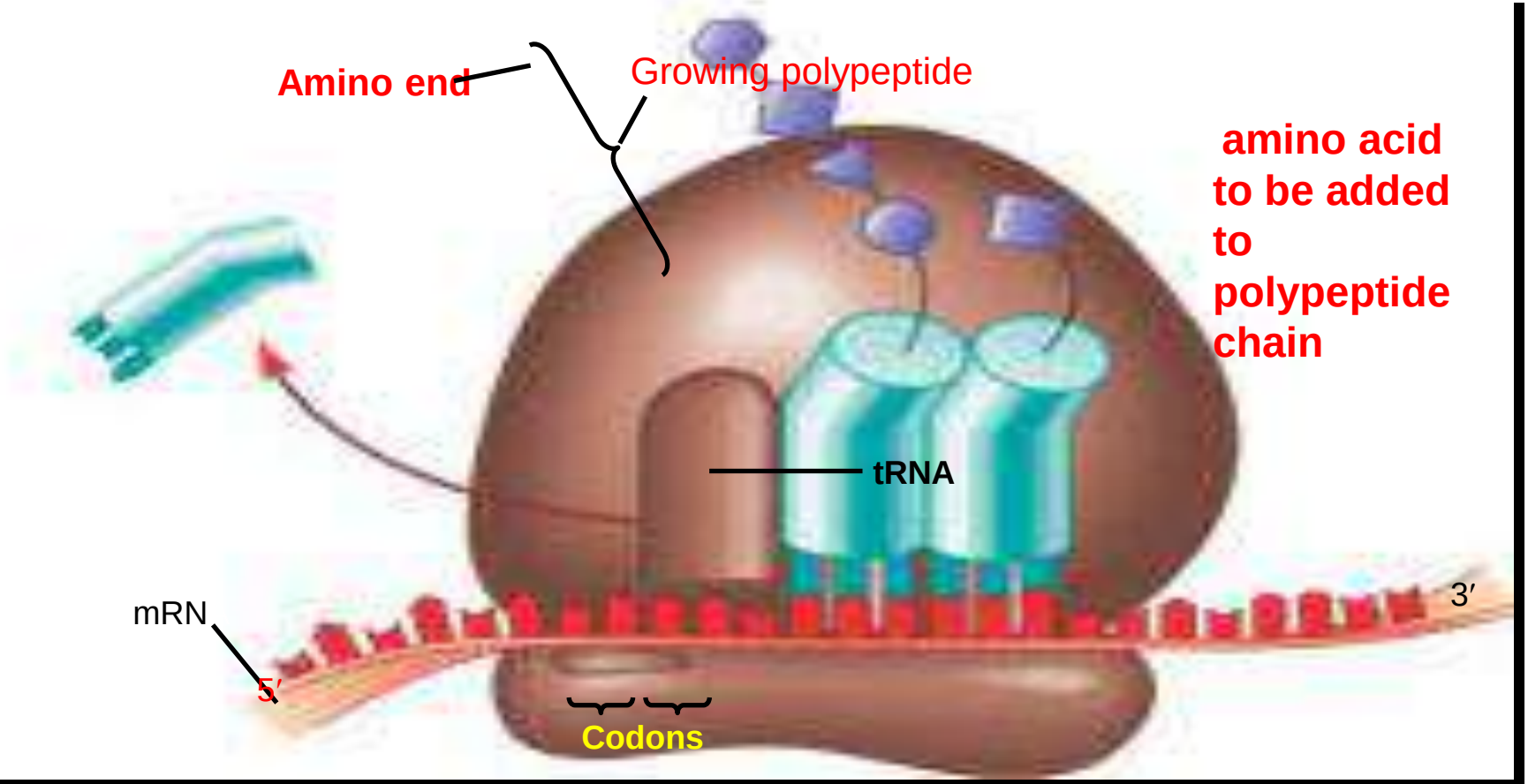
- Ribosomes facilitate the specific coupling of tRNA anticodons with mRNA codons during protein synthesis
- The 2 ribosomal subunits are constructed of proteins and RNA molecules named ribosomal RNA or rRNA





(a) Computer model of functioning ribosome. This is a model of a bacterial ribosome, showing its overall shape. The eukaryotic ribosome is roughly similar. A ribosomal subunit is an aggregate of ribosomal RNA molecules and proteins

Building a Polypeptide



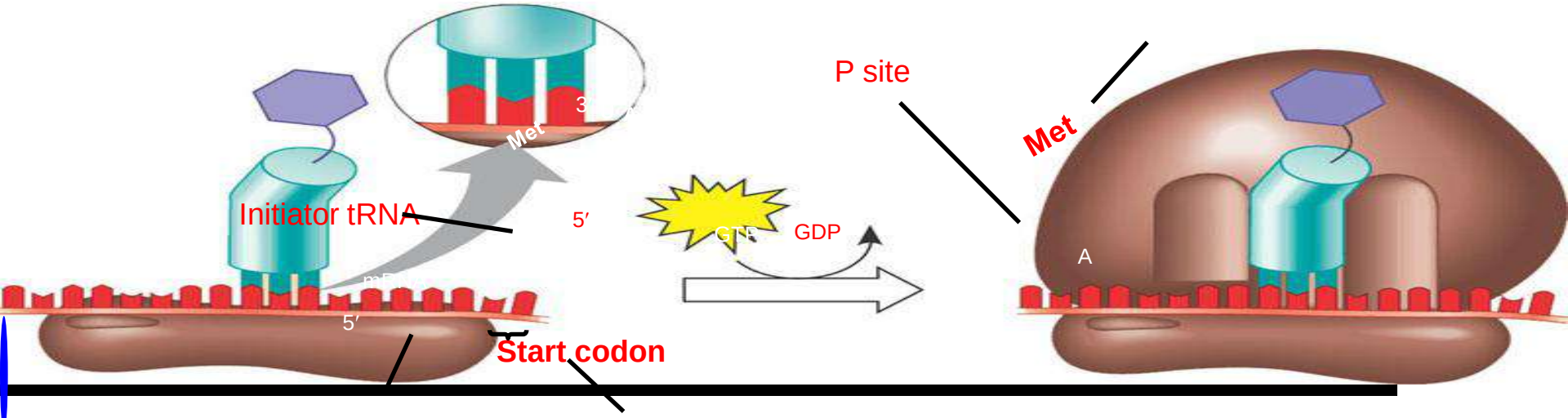
(c) **Schematic model with mRNA and tRNA. A tRNA fits into a binding site when its anticodon base-pairs with an mRNA codon. The P site holds the tRNA attached to the growing polypeptide. The A site holds the tRNA carrying the next amino acid to be added to the polypeptide chain. Discharged tRNA leaves via the E site.**

Building a Polypeptide

- We can divide translation into three stages
  - Initiation
  - Elongation
  - Termination
- The AUG start codon is recognized by methionyl-tRNA or Met
- Once the start codon has been identified, the ribosome incorporates amino acids into a polypeptide chain
- RNA is decoded by tRNA (transfer RNA) molecules, which each transport specific amino acids to the growing chain
- Translation ends when a stop codon (UAA, UAG,UGA) is reached

Initiation of Translation

- The initiation stage of translation brings together mRNA, tRNA bearing the first amino acid of the polypeptide, and two subunits of a ribosome

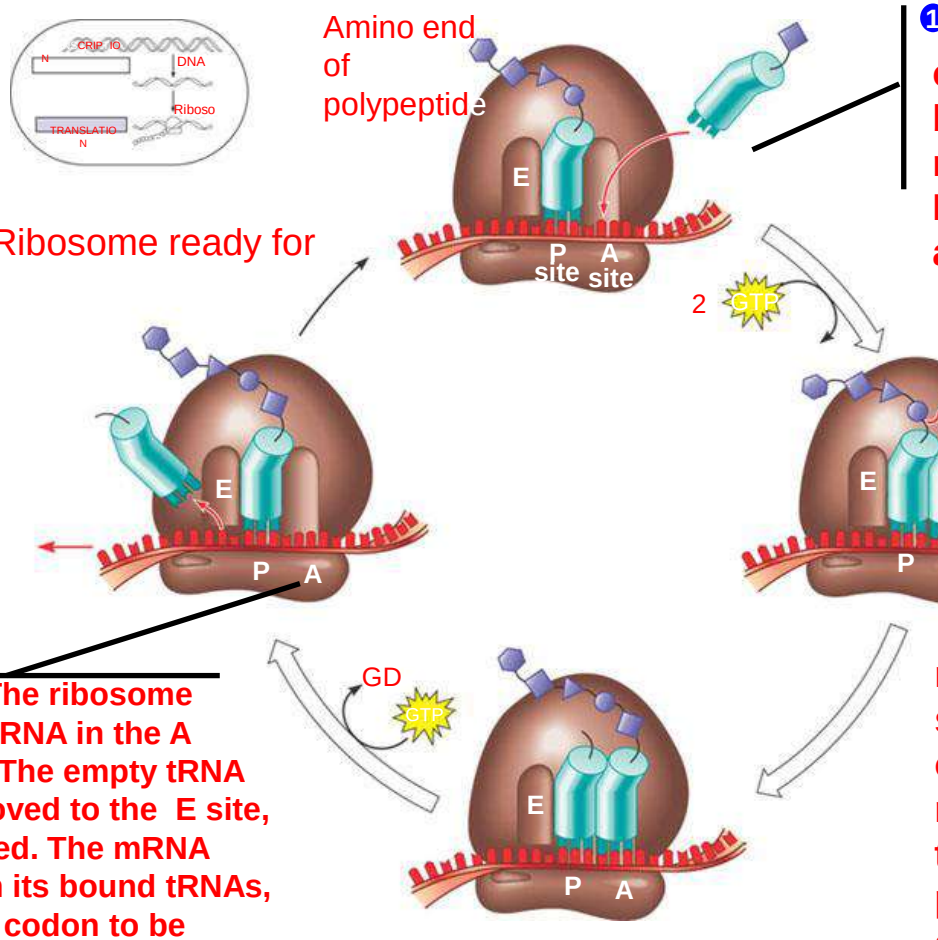


A small ribosomal subunit binds to a molecule of mRNA. In a prokaryotic cell, the mRNA binding site
on this subunit recognizes a specific nucleotide sequence on the mRNA just upstream of the start codon. An initiator tRNA, with the anticodon UAC, base-pairs with the start codon, AUG. This tRNA carries the amino acid methionine (Met).

The arrival of a large ribosomal subunit completes
the initiation complex. Proteins called initiation factors (not shown) are required to bring all the translation components together. GTP provides the energy for the assembly. The initiator tRNA is
in the P site; the A site is available to the tRNA bearing the next amino acid.

Elongation of the Polypeptide Chain

- **In the elongation stage, amino acids are added one by one to the preceding amino acid**



Ribosome ready for

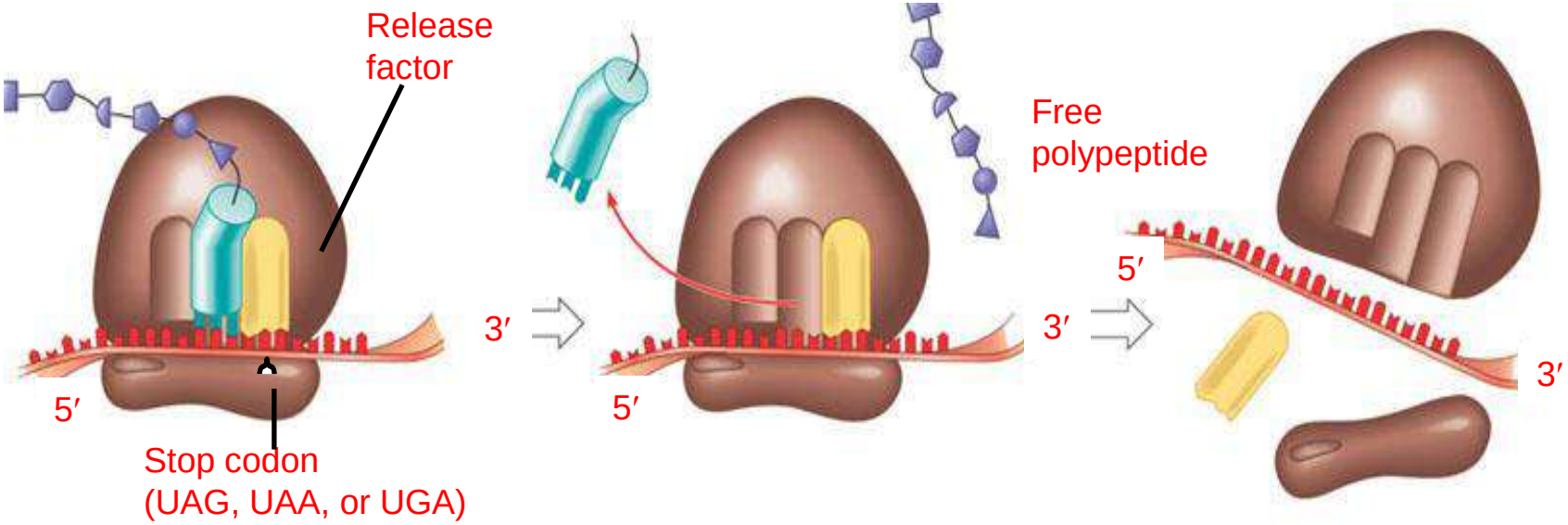
❶ **Codon recognition. The anticodon of an incoming aminoacyl tRNA base-pairs with the complementary mRNA codon in the A site. Hydrolysis of GTP increases the accurac and efficiency of this tep.**

❷ **Peptide bond formation. An rRNA molecule of the large subunit catalyzes the formation of a peptide bond between the new amino acid in the A site and the carboxyl end of the growing polypeptide in the P site. This step attaches the polypeptide to the tRNA in the A site**

❸ **Translocation. The ribosome translocates the tRNA in the A site to the P site. The empty tRNA in the P site is moved to the E site, where it is released. The mRNA moves along with its bound tRNAs, bringing the next codon to be translated into the A site**

Termination of Translation

- The final stage is termination when the ribosome reaches a stop codon in the mRNA



When a ribosome reaches a stop codon on mRNA, the A site of the ribosome accepts a protein called a release factor instead of tRNA.

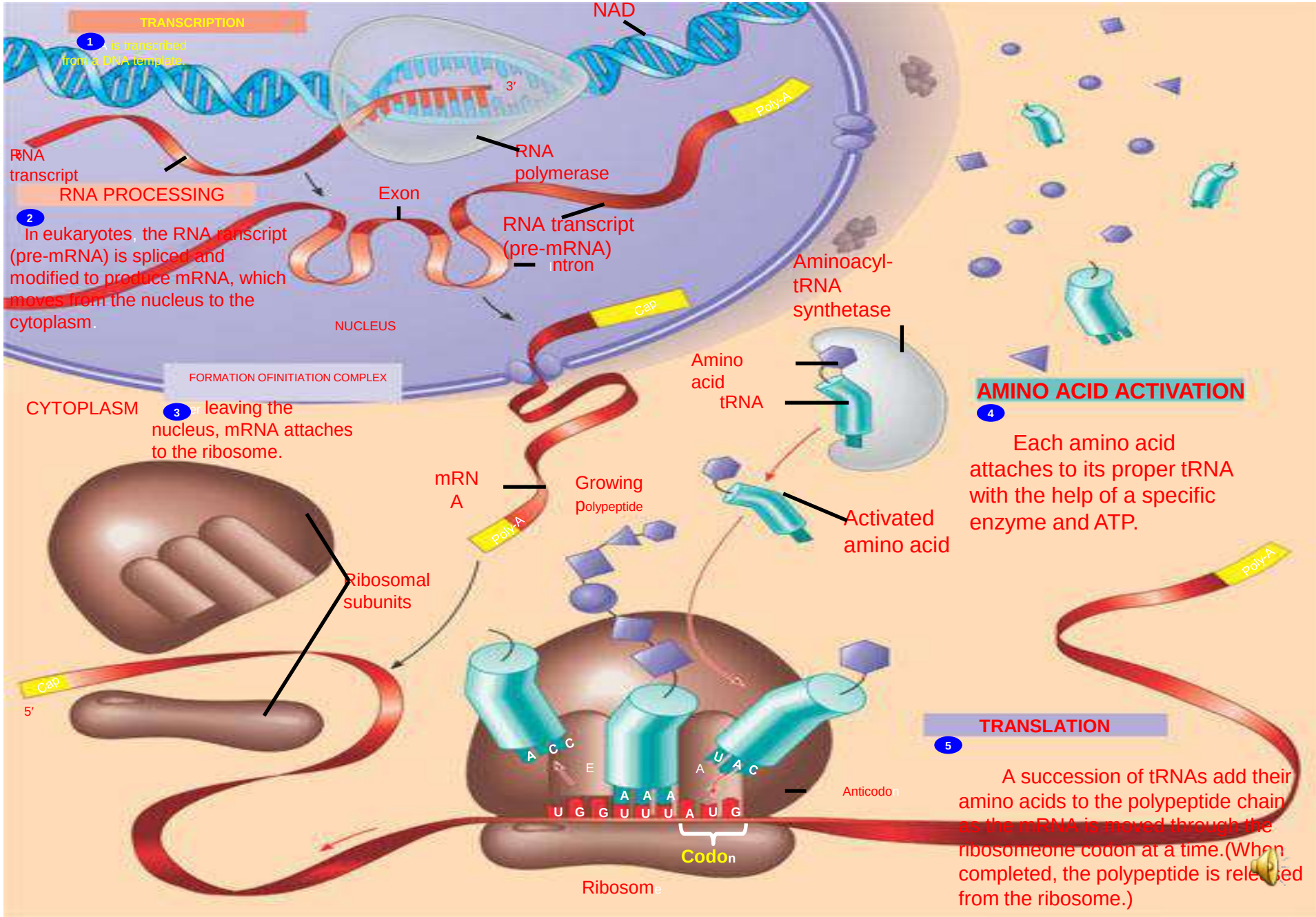
The release factor hydrolyzes the bond between the tRNA in the P site and the last amino acid of the polypeptide chain. The polypeptide is thus freed from the ribosome.

The two ribosomal subunits and the other components of the assembly dissociate.

Translation

- The final step in translation is termination. When the ribosome reaches a STOP codon, there is no corresponding transfer RNA.
- Instead, a small protein called a “release factor” attaches to the stop codon.
- The release factor causes the whole complex to fall apart: messenger RNA, the two ribosome subunits, the new polypeptide.
- The messenger RNA can be translated many times, to produce many protein copies.

A summary of transcription and translation in a eukaryotic cell



Post-translation

- The new polypeptide is now floating loose in the cytoplasm if translated by a free ribosome.
- It might also be inserted into a membrane, if translated by a ribosome bound to the endoplasmic reticulum.
- Polypeptides fold spontaneously into their active configuration, and they spontaneously join with other polypeptides to form the final proteins.
- Sometimes other molecules are also attached to the polypeptides: sugars, lipids, phosphates, etc. All of these have special purposes for protein function.

Mutations Genetics/th. class

Lecture s eleven

Dr.Ibtesam B.Hassan

Mutations

B. Gene mutation-involves changes in single base pairs

-Some mutations may not have any effect on the cell and may involve:

1. part of the sense strand of DNA which is not transcribed
2. part of the DNA that a cell does not use
3. changes in second or third bases of a codon (since the genetic code is degenerate the same base may still be coded for)

Mutations

B. Gene mutation-involves changes in single base pairs

Example: **Insertion or deletion of single organic bases**

-changes the DNA sequence that will be transcribed and translated

original DNA sequence: ATG-TCG-AAG-CCC

transcribed: UAC-AGC-UUC-GGG

translated: tyr-ser-phe-gly

addition of base A: AT**A-**GTC-GAA-GCC-C

transcribed: UA**U**-CAG-CUU-CGG

translated: thy-glu-leu-arg

Mutations: Base substitutions and sickle-cell anemia

A. Hemoglobin-protein that helps RBC carry oxygen

B. Hb is a gene that codes for hemoglobin

-made of 146 amino acids

C. In some cases one base is substituted for another

normal: (Hb^A)base substitution: (Hb^S)

CTC	CAC
GAG	GUG

-after transcription and translation Hb^A produces glutamic acid and Hb^S produces valine

Mutations

A. Chromosome mutations-involve large sections of chromosomes (or the whole thing)

   -Ex: Down's syndrome, Turner's syndrome

Mutagens

- **Mutagens** are chemical or physical agents that interact with DNA to cause mutations.
- Physical agents include high-energy radiation like X-rays and ultraviolet light
- Chemical mutagens fall into several categories.
  - Chemicals that are base analogues that may be substituted into DNA, but they pair incorrectly during DNA replication.
  - Interference with DNA replication by inserting into DNA and distorting the double helix.
  - Chemical changes in bases that change their pairing properties.
- Tests are often used as a preliminary screen of chemicals to identify those that may cause cancer
- Most carcinogens are mutagenic and most mutagens are carcinogenic.

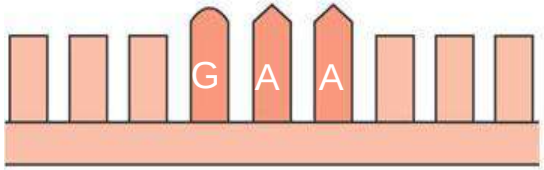
Point Mutation

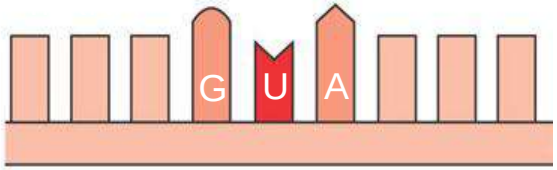
- The change of a single nucleotide in the DNA's template strand leads to the production of an abnormal protein

Wild-type hemoglobin DNA

Mutant hemoglobin DNA

In the DNA, the mutant template strand has an A where the wild-type template has a T.



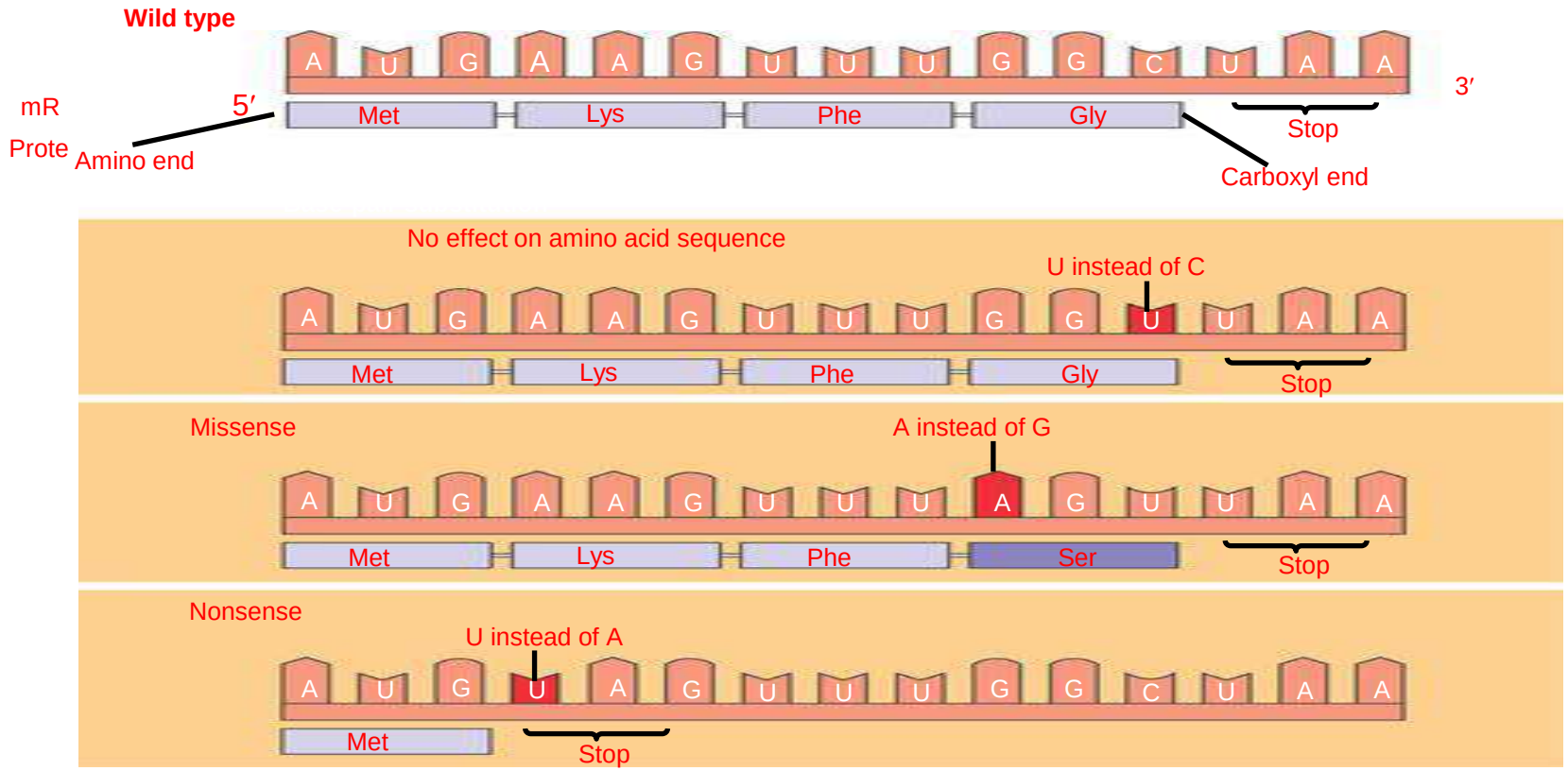


The mutant mRNA has a U instead of an A in one codon

The mutant (sickle-cell) hemoglobin has a valine (Val) instead of

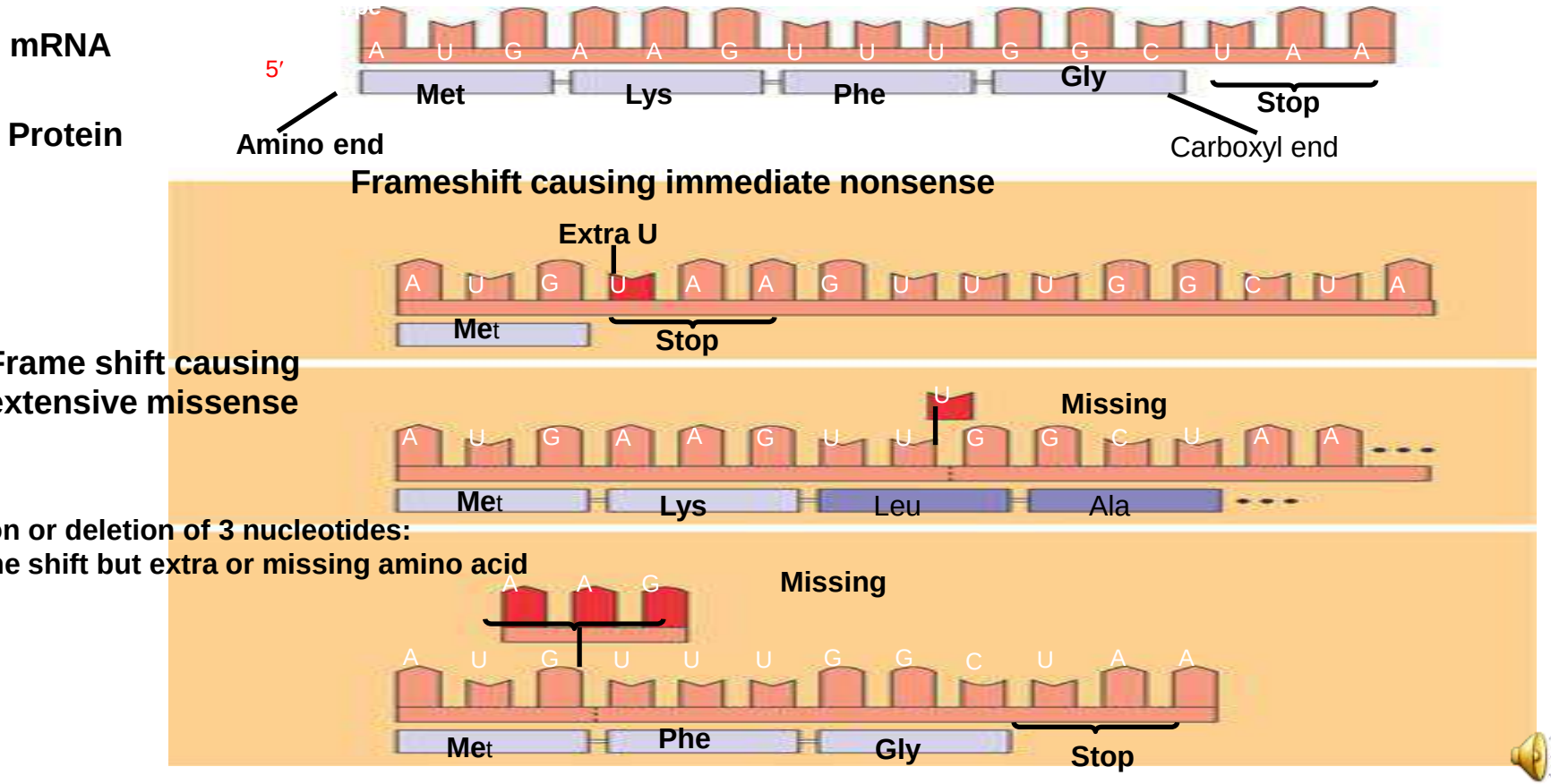
Substitutions

- A base-pair substitution is the replacement of one nucleotide and its partner with another pair of nucleotides
  - Silent - changes a codon but codes for the same amino acid
  - Missense - substitutions that change a codon for one amino acid into a codon for a different amino acid
  - Nonsense -substitutions that change a codon for one amino acid into a stop



Insertions and Deletions

- **Insertions and deletions**
  - **Are additions or losses of nucleotide pairs in a gene**
  - **May produce frame shift mutations that will change the reading frame of the gene, and alter all codons downstream from the mutation.**



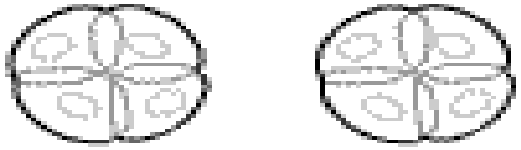
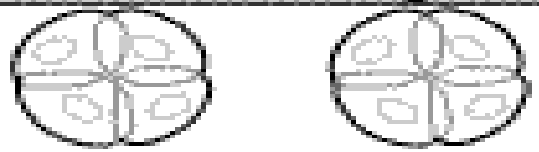
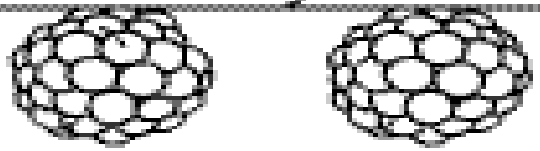
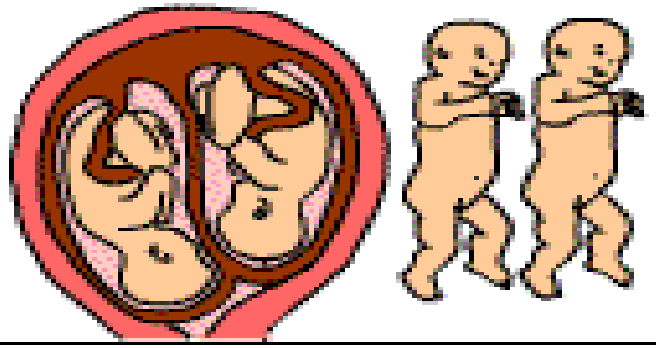
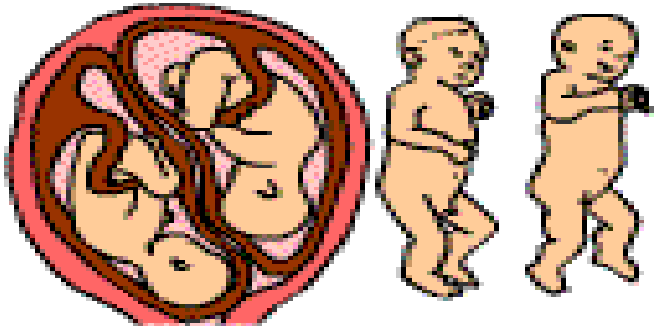
Twins Genetics/th. class

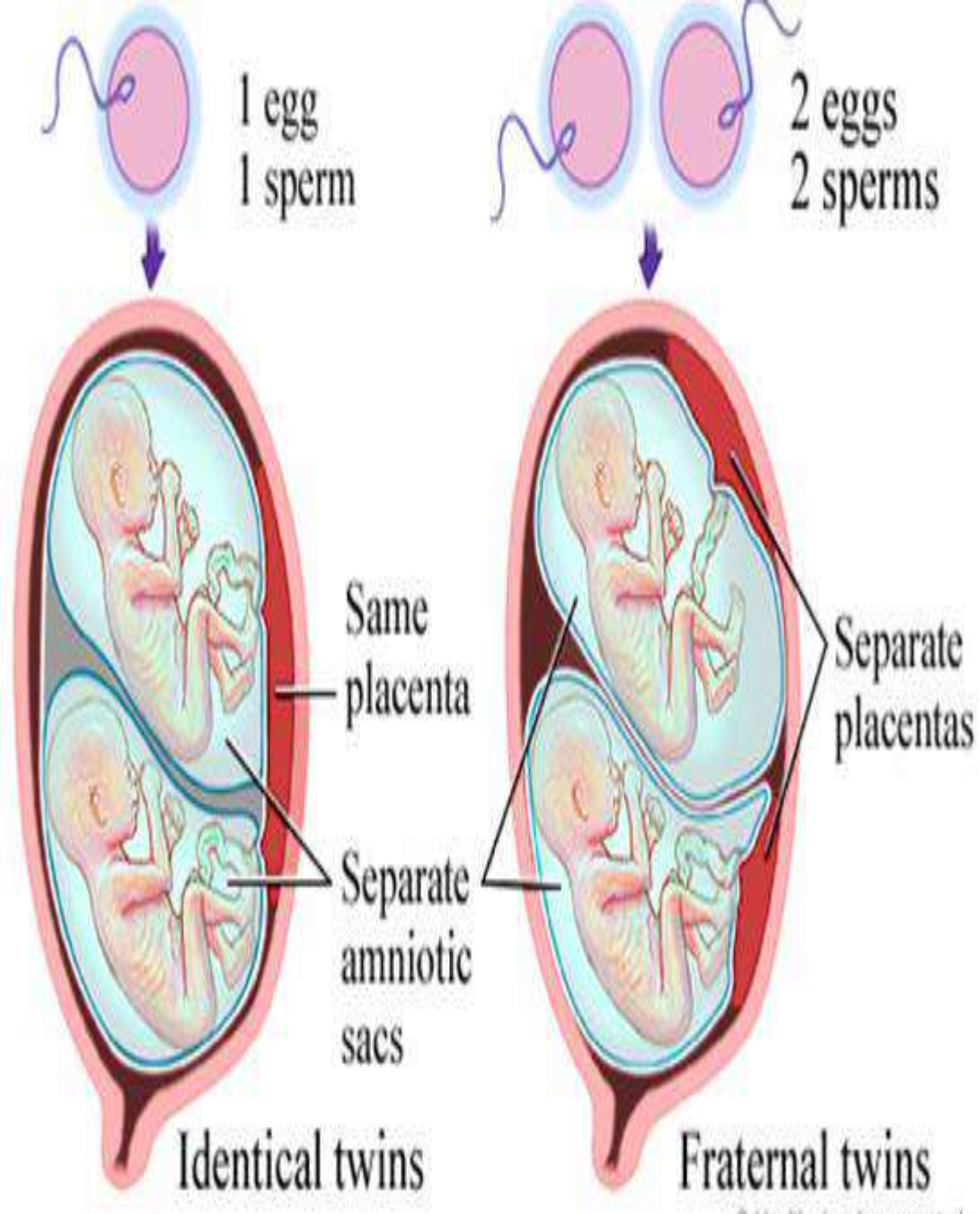
Lectures four

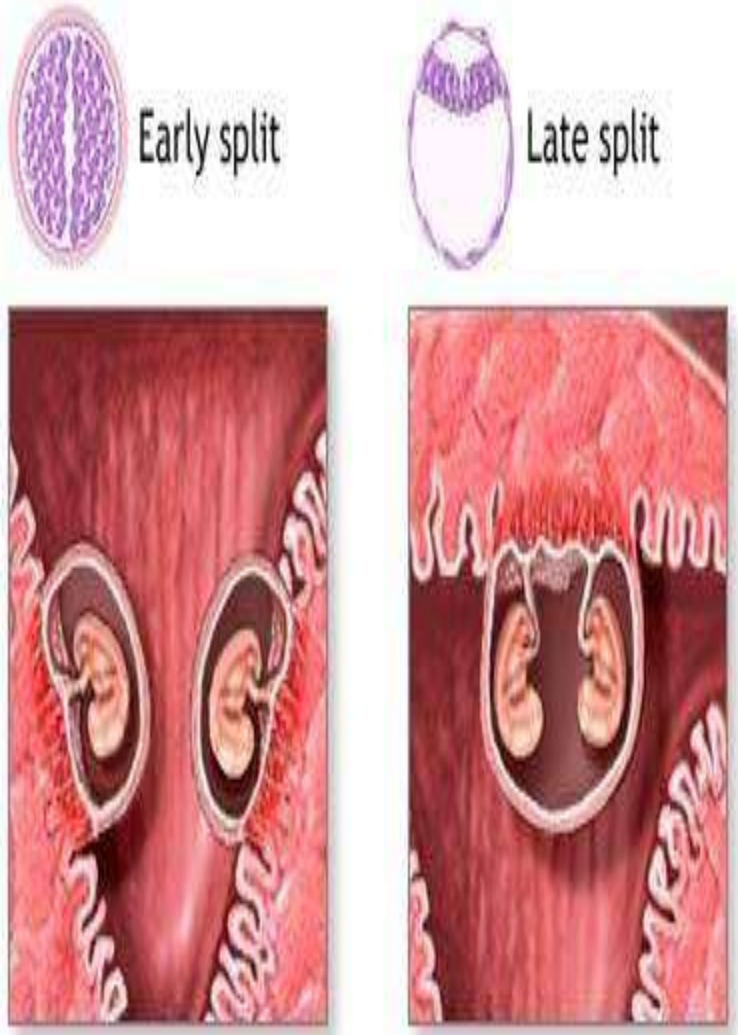
What are twins

- **(Non-identical) twins are formed when two egg cells are fertilized; each egg by a different sperm so that two embryos are formed. Fraternal twins can be of the same or opposite sex and they don't have to look at all alike.**

Identical twins are formed when one egg after being fertilized by one sperm, divides into two halves. The two halves are genetically identical. Identical twins are usually of the same sexes.

identical twins	ordinary twins (fraternal)
 1 egg ,1 sperm	each egg is fertilised by one sperm  2 eggs ,2 sperm
	the first cell divides for the first time 
	and divides again 
	after many divisions 
	





The earlier splitting of the single zygote occurs, the more independently the twins will develop

A.D.A.M.

Unusual twinning's, Degree of separation

The degree of separation of the twins in utero depends on if and when they split into two zygotes. Dizygotic twins were always two zygotes. Monozygotic twins split into two zygotes at some time very early in the pregnancy. The timing of this separation determines the chorionicity (the number of placentae) and amniocity (the number of sacs) of the pregnancy. Dichorionic twins either never divided (i.e.: were days. 4 dizygotic) or they divided within the first Monoamnionic twins divide after the first week

In very rare cases, twins become conjoined twins. Non-conjoined monozygotic twins form up to day 14 of embryonic development, but when twinning occurs after 14 days, the twins will likely be conjoined

Complications during pregnancy

1-Vanishing twins

fetus, which fails to develop and instead disintegrates and vanishes in the uterus. There are several reasons for the "vanishing" fetus, including it being embodied or absorbed by the other fetus, placenta or the mother. This is known as vanishing twin syndrome.

2-Craniopagus

Conjoined twins connected only at the head. They share bones of the skull and occasionally brain surface, separate trunks, four arms, four legs. About 2% of conjoined twins are craniopagus.

3-Ischiopagus

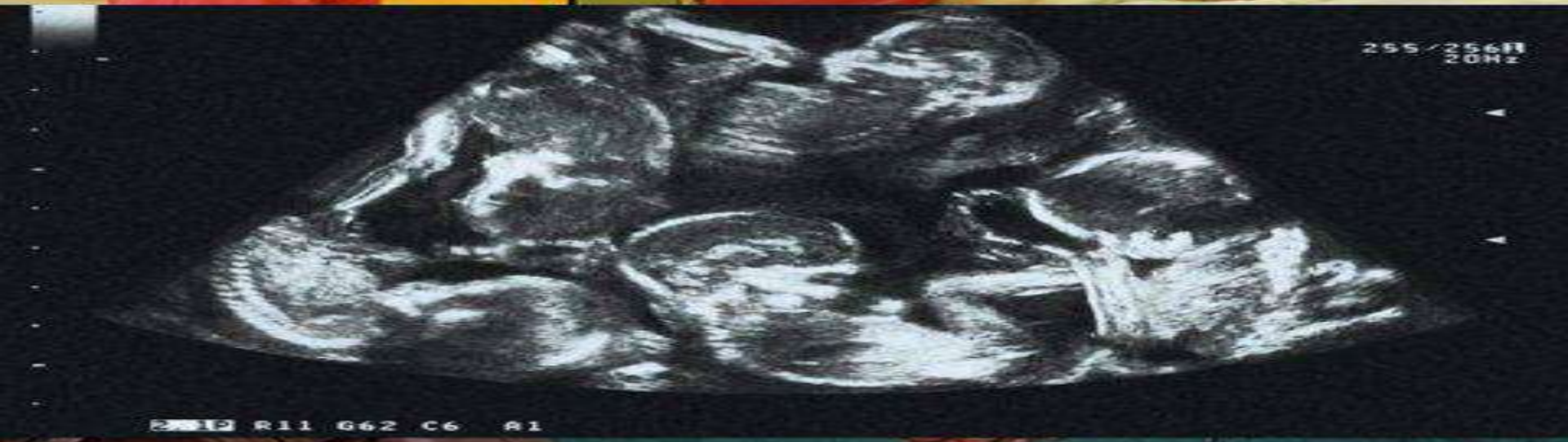
twins are joined at the pelvis. Many Ischiopagus share lower gastrointestinal tract, as well as the genital and urinary tract organs

4-Omphalopagus

Omphalopagus twins may share a liver, gastrointestinal or genitourinary functions, but rarely share a heart. Some Thorax

Multiples: When It's Twins, Triplets, or More

Multiple births occur when more than one embryo
grows in the uterus.
This process can occur naturally, or it can occur artificially during fertility
A pregnancy with three or more babies can be formed by more than one egg
being fertilized, a single fertilized egg splitting, or both processes occurring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R11 G62 C6 A1

Genetics/th. Class/ Gene mapping

Lectures five

Gene mapping

- **Gene mapping** describes the methods used to identify the locus of a gene and the distances between genes.
- Thomas Hunt Morgan's *Drosophila melanogaster* genetic linkage map. This was the first successful gene mapping work and provides important evidence for it Boveri–Sutton chromosome theory of inheritance.
- The map shows the relative positions of allelic characteristics on the second Drosophila chromosome.
- The distance between the genes (map units) are equal to the percentage of crossing-over events that occurs between different alleles.

للمساعدة في حماية خصوصيتك، قام PowerPoint بحظر التنزيل التلقائي لهذه الصورة.

Use of gene mapping

- Identification of genes is usually the first step in understanding a genome of a species; mapping of the gene is usually the first step of identification of the gene. Gene mapping is usually the starting point of many important downstream studies.

Disease association

- The process to identify a genetic element that is responsible for a disease is also referred to as "mapping". If the locus in which the search is performed is already considerably constrained, the search is called the *fine mapping* of a gene. This information is derived from the investigation of disease manifestations in large families (genetic linkage) or from populations-based genetic association studies.

Genetics/th. Class/ Chromosomes

Lectures six

Chromosomes

- Each cell contains 23 pairs of matched chromosomes for a total of 46 chromosomes per cell.
- One chromosome from each pair is inherited from each parent.
- There are 22 pairs of autosomes, which control most traits in the body, and one pair of sex chromosomes, which determine gender and other traits.

- Some genes are dominant and their characteristics are expressed even if only on one chromosome.

- Some genes are recessive and their characteristics will be expressed only if they are carried by both chromosomes in a pair.

Autosomal Dominant

- Trait appears in every generation (does not skip)
- Both males and females are affected
- Each pregnancy of an affected person has a 50% chance of producing an affected offspring
- Autosomal Dominant Disorders
  - Huntington's Disease
  - Retinitis Pigmentosa
  - Polycystic Kidney Disease
  - Achodroplasia
  - Marfan Syndrome

Marfan Syndrome

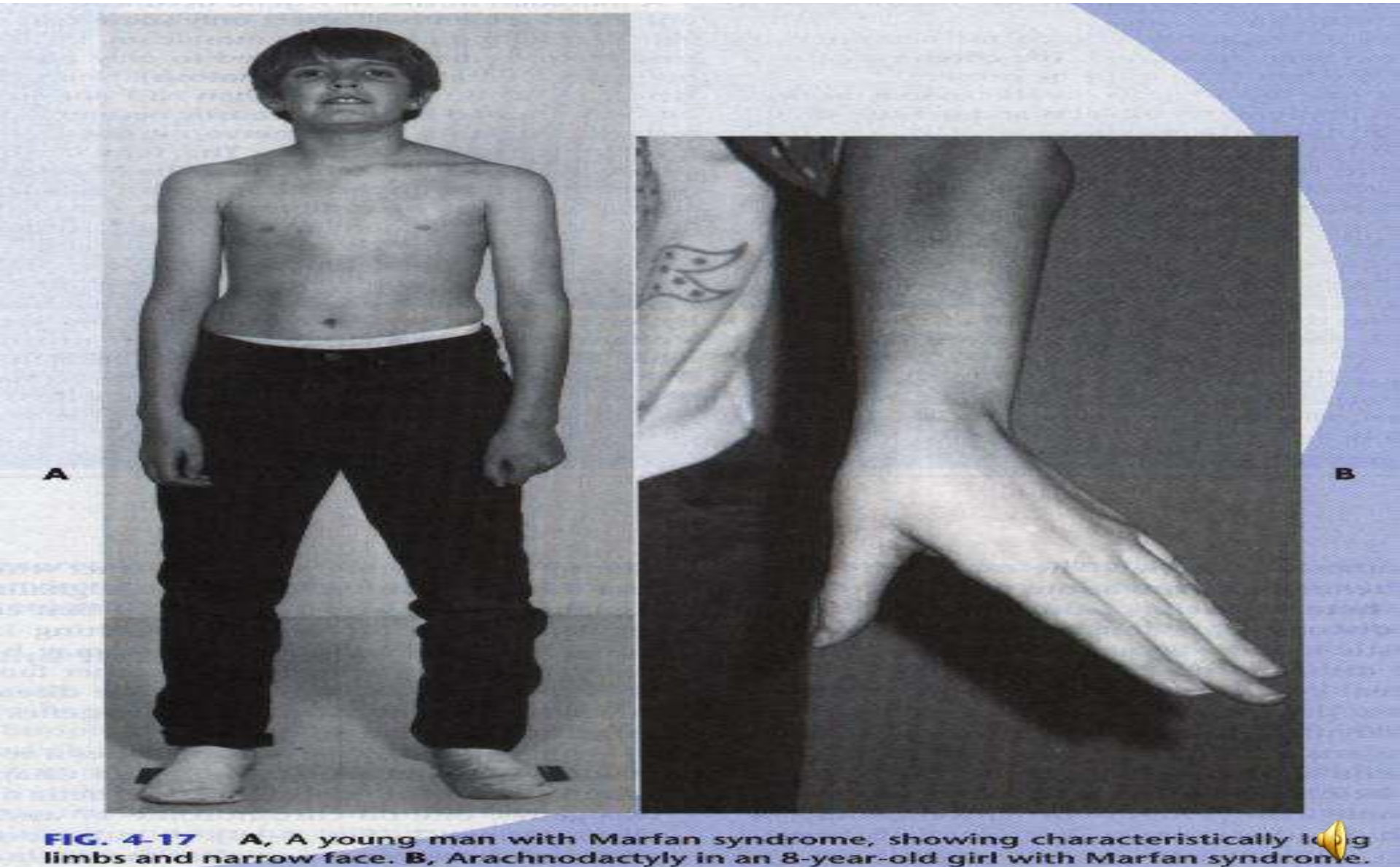
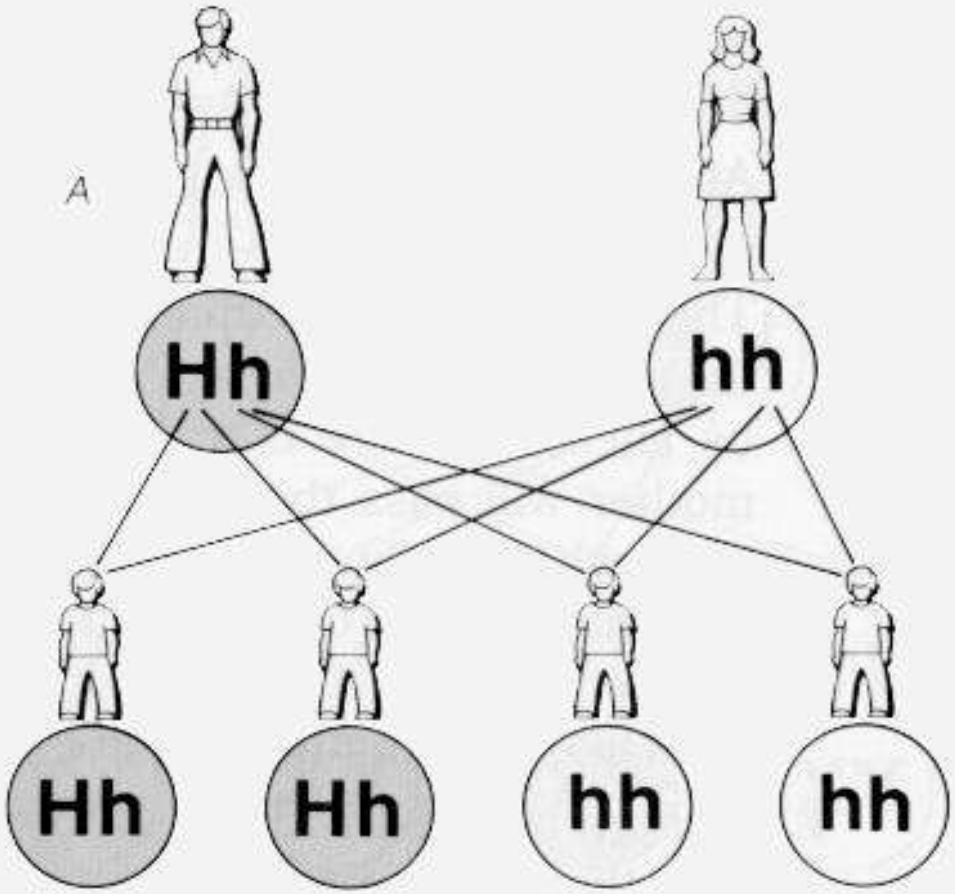
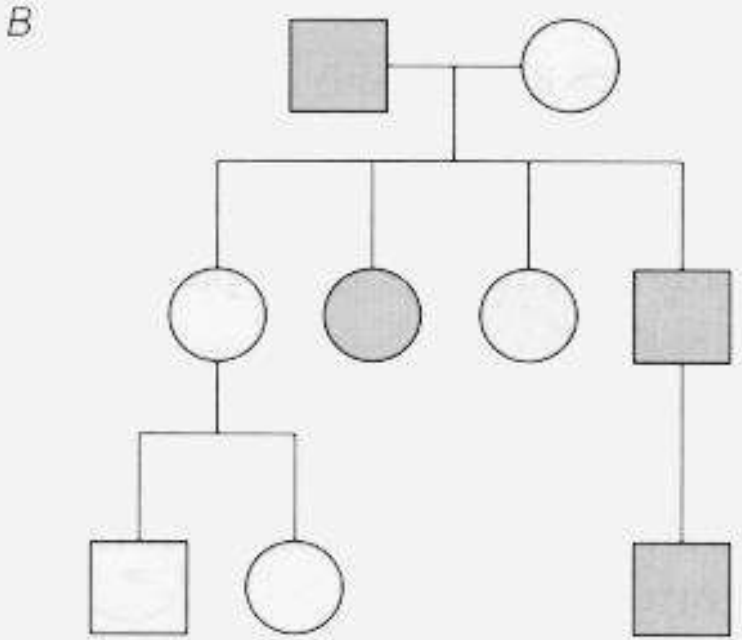


FIG. 4-17 A, A young man with Marfan syndrome, showing characteristically long limbs and narrow face. B, Arachnodactyly in an 8-year-old girl with Marfan syndrome.

Autosomal Dominant Inheritance



H = Gene for Huntington's chorea
h = Normal allele
Hh = Affected individual
hh = Nonaffected individual



= Affected male
= Affected female

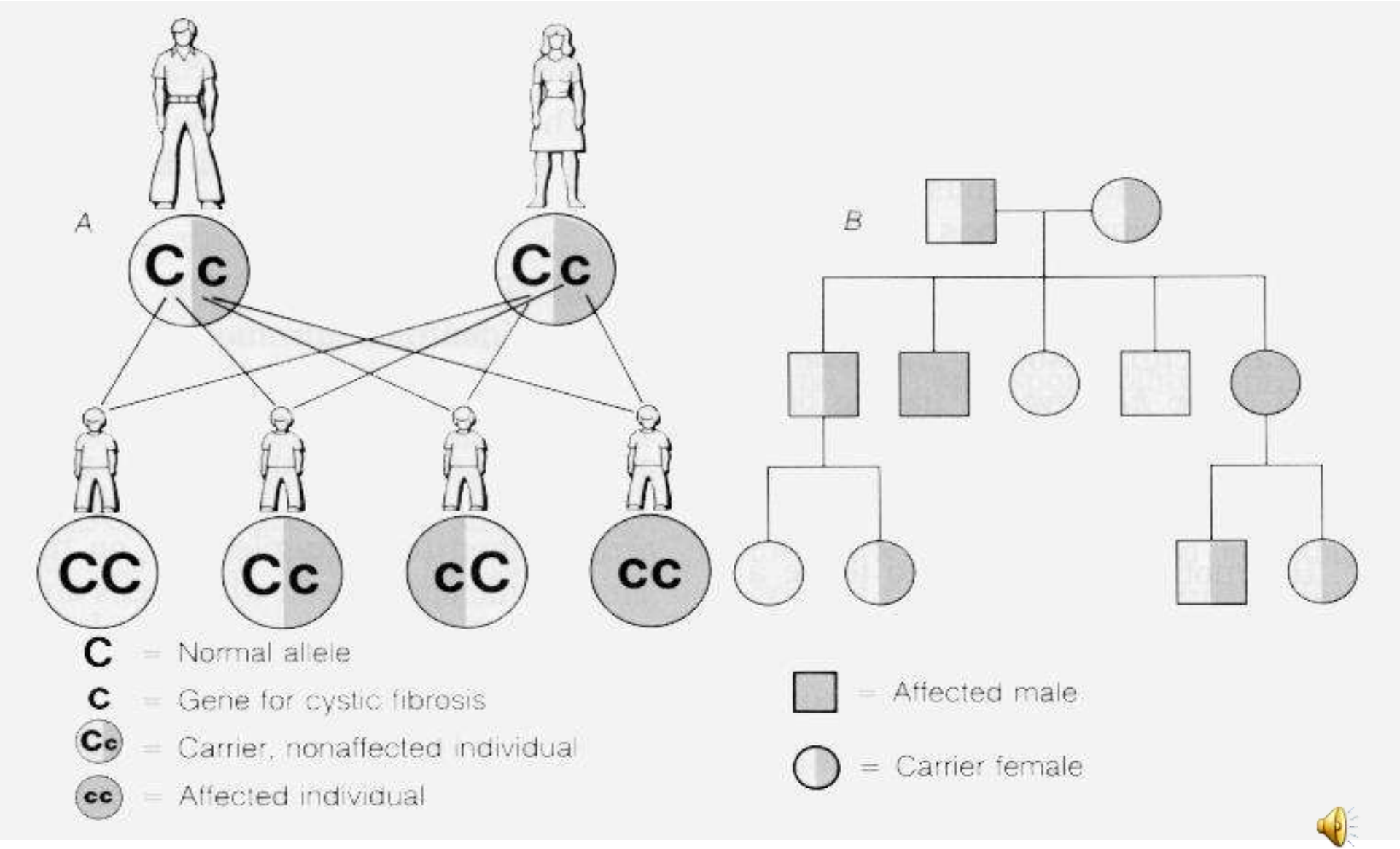
Autosomal Recessive

- Both parents are usually unaffected, but are carriers
- Trait first appears only in siblings rather than in parents
- Trait found equally in males and females
- 25% risk when both parents are carriers
- Increased incidence with consanguinity

Autosomal Recessive

- **Disorders**
  - –Phenylketonuria
  - –Fanconi's Anemia
  - –Tay Sachs Disease
  - –Sickle Cell Anemia
  - –Cystic Fibrosis

Autosomal Recessive Inheritance



X-linked Inheritance

- Sex-Modified Traits - Dominant genes are expressed in both males & females but at differing frequencies
  - Ex: Baldness - expressed as dominant in males, but recessive in females, never as severe in females
- Very rare
- Often lethal in males therefore few males present in the pedigree
- Multiple miscarriages may be present
- No carrier status, all individuals with the gene are affected
- Trait appears in every generation

X-linked Dominant

- Female children of affected males will all be affected (100% risk); no male to male transmission.
- Homozygous females (both X chromosomes are affected) have a 100% chance of having an affected child of either sex.
- Heterozygous females (only one X affected) have a 50% of having an affected child with each pregnancy.
- Disorders :Hypophosphatemic Rickets
- Fragile X Syndrome

Fragile X Syndrome

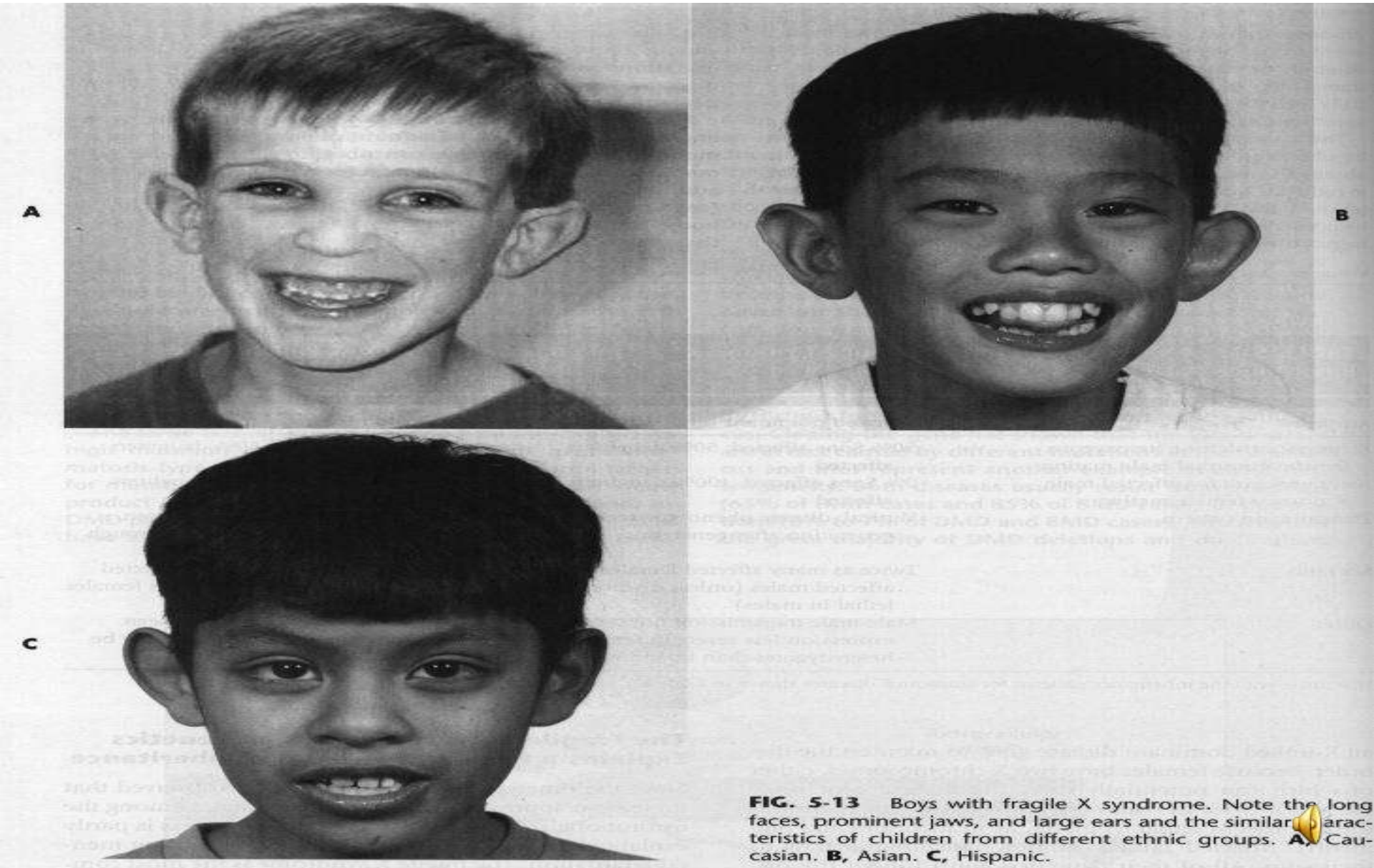


FIG. 5-13 Boys with fragile X syndrome. Note the long faces, prominent jaws, and large ears and the similar characteristics of children from different ethnic groups. **A,** Caucasian. **B,** Asian. **C,** Hispanic.

X-linked Recessive

- Incidence of trait much higher among males in a kinship than among females
- Trait cannot be transmitted from father to son
- An affected male will pass the carrier status to all his daughters
- Female carriers have a 50% risk of transmitting the gene to their offspring with each pregnancy

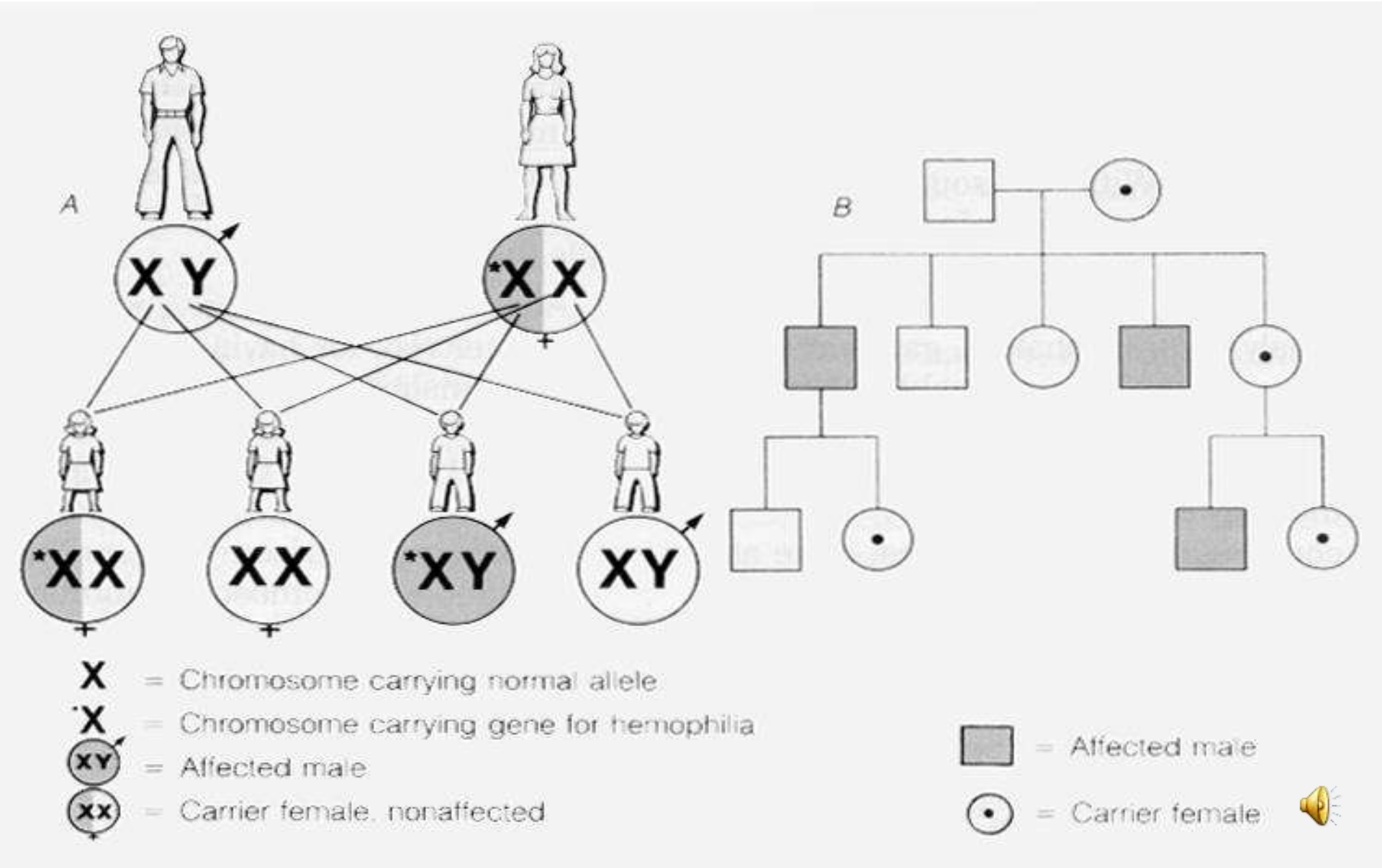
X-linked Recessive

- Disorders
  - Hemophilia A
  - Duchenne's Muscular Dystrophy
  - Color-Blindness

Duscenne's Muscular Dystrophy

FIG. 5-10 A patient with late-stage Duchenne muscular dystrophy, showing severe muscle loss.

X-Linked Recessive Inheritance



modification

- Traits can be environmentally modified
  - type 2 diabetes
  - PKU
- Traits can be medically modified
  - Sickle cell disease (bone marrow transplant)
  - Polycystic kidney disease (kidney transplant)
- However, genotype stays the same so next generation are not saved from condition

Karyotypes

- Karyotypes
  - The arranged representation of the chromosomal make-up of a cell nucleus

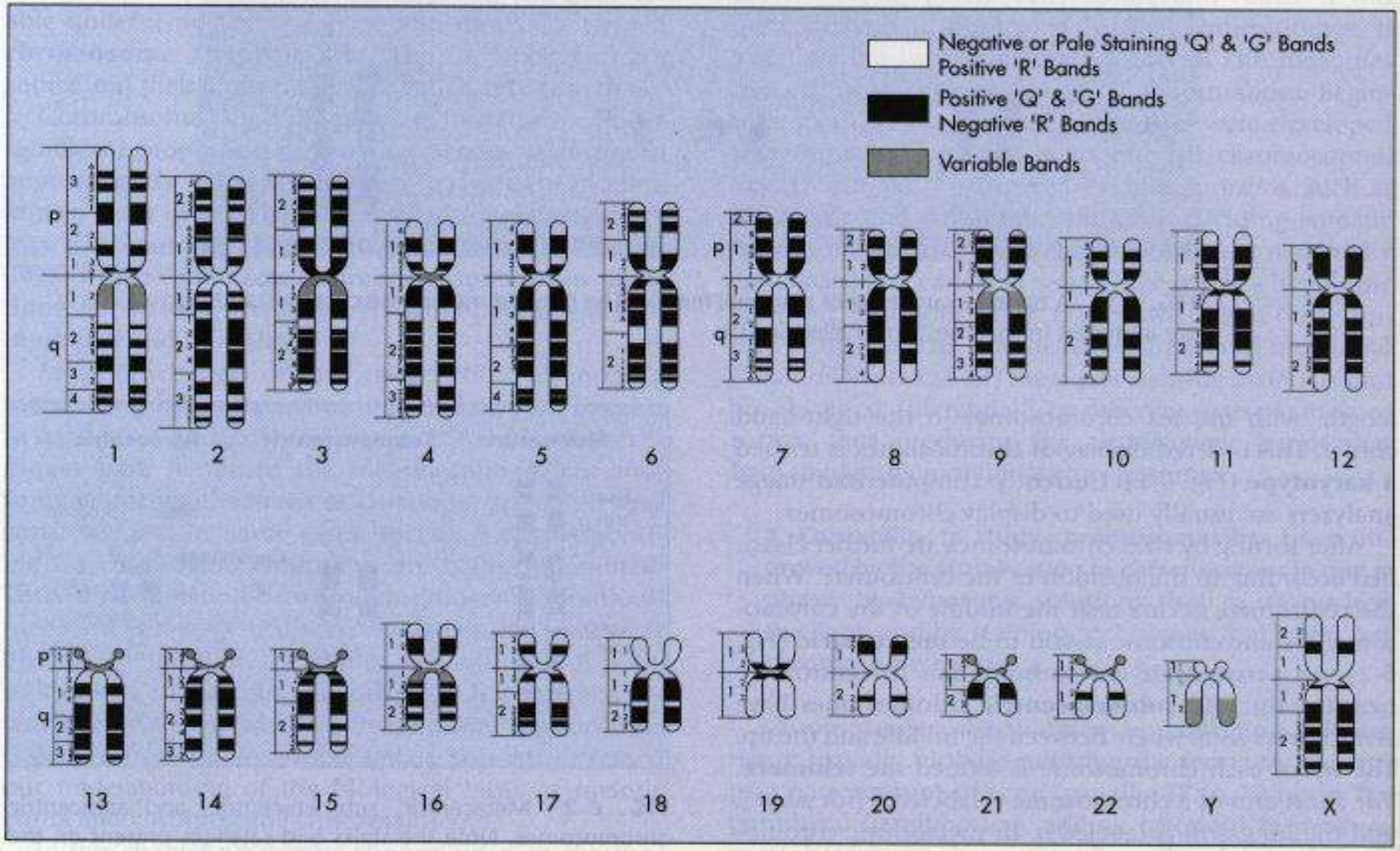


FIG. 6-3 A schematic representation of the banding pattern of a G-banded karyotype. 300 bands are represented in this ideogram. The short and long arms of the chromosomes are designated, and the segments are numbered according to the standard nomenclature adopted at the Paris conference, 1971. In this illustration, both sister chromatids are shown for each chromosome.

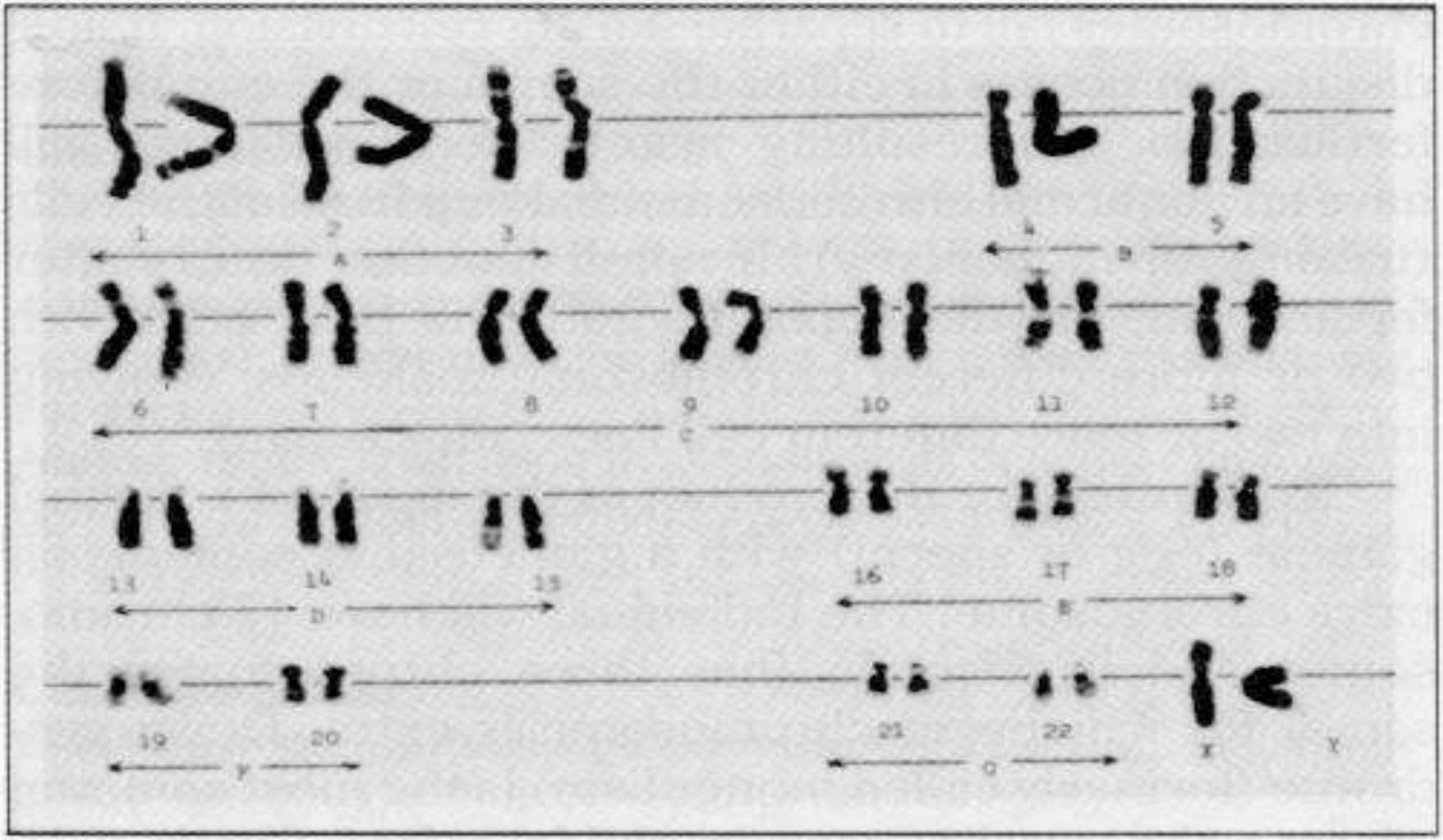


FIGURE 4.6 Normal female karyotype. (Courtesy Dr Arthur Robinson, National Jewish Hospital and Research Center.)

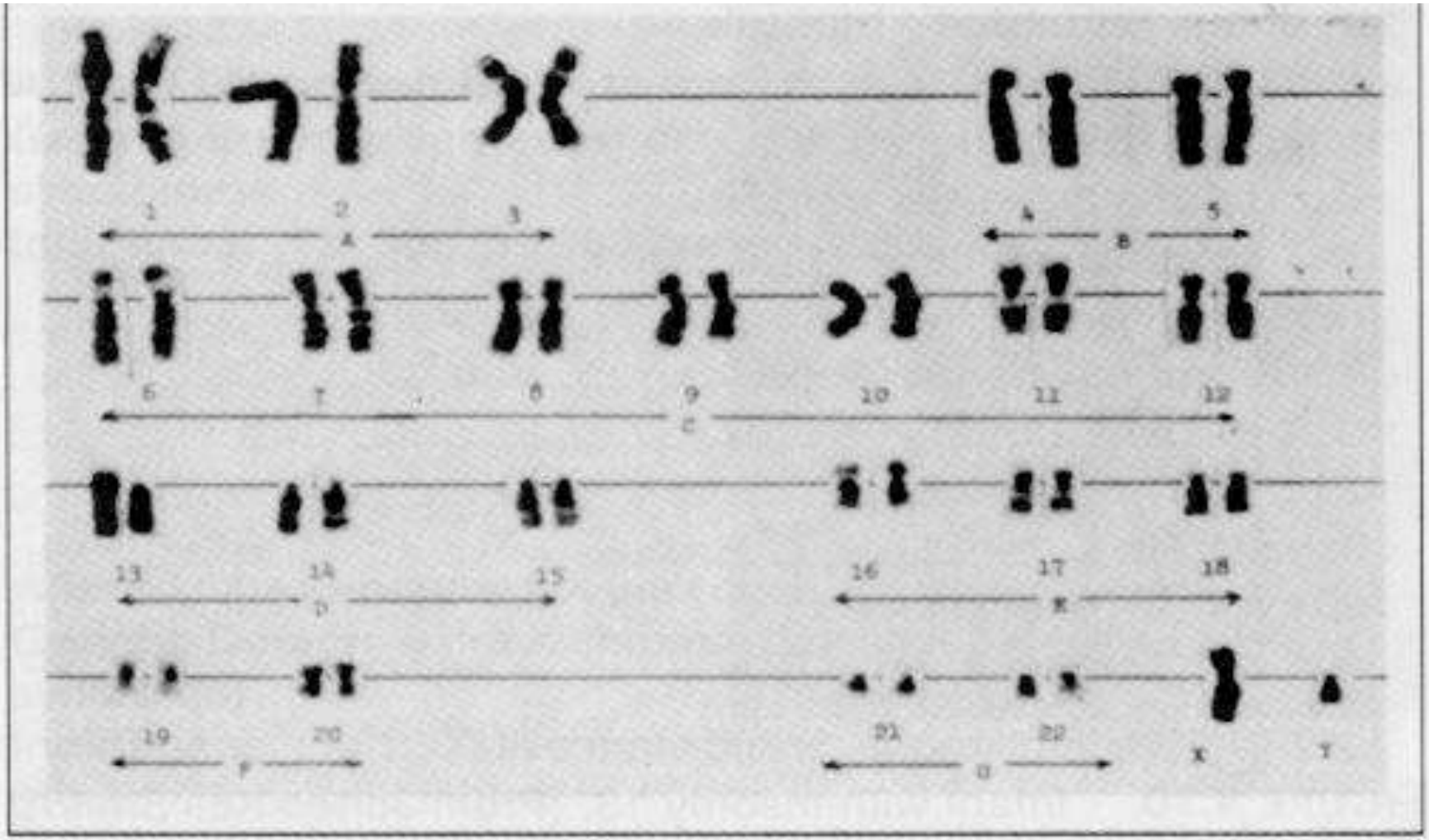


FIGURE 4.5 Normal male karyotype. (Courtesy Dr Arthur Robinson, National Jewish Hospital and Research Center.)

Chromosomal Abnormalities

- Abnormalities in number of chromosomes
  - Caused by nondisjunction: failure of homologous chromosomes or sister chromatids to separate properly into different progeny cells
  - Monosomy - condition in which one chromosome of a pair is missing from a somatic cell

Monosomy X - Turners Syndrome

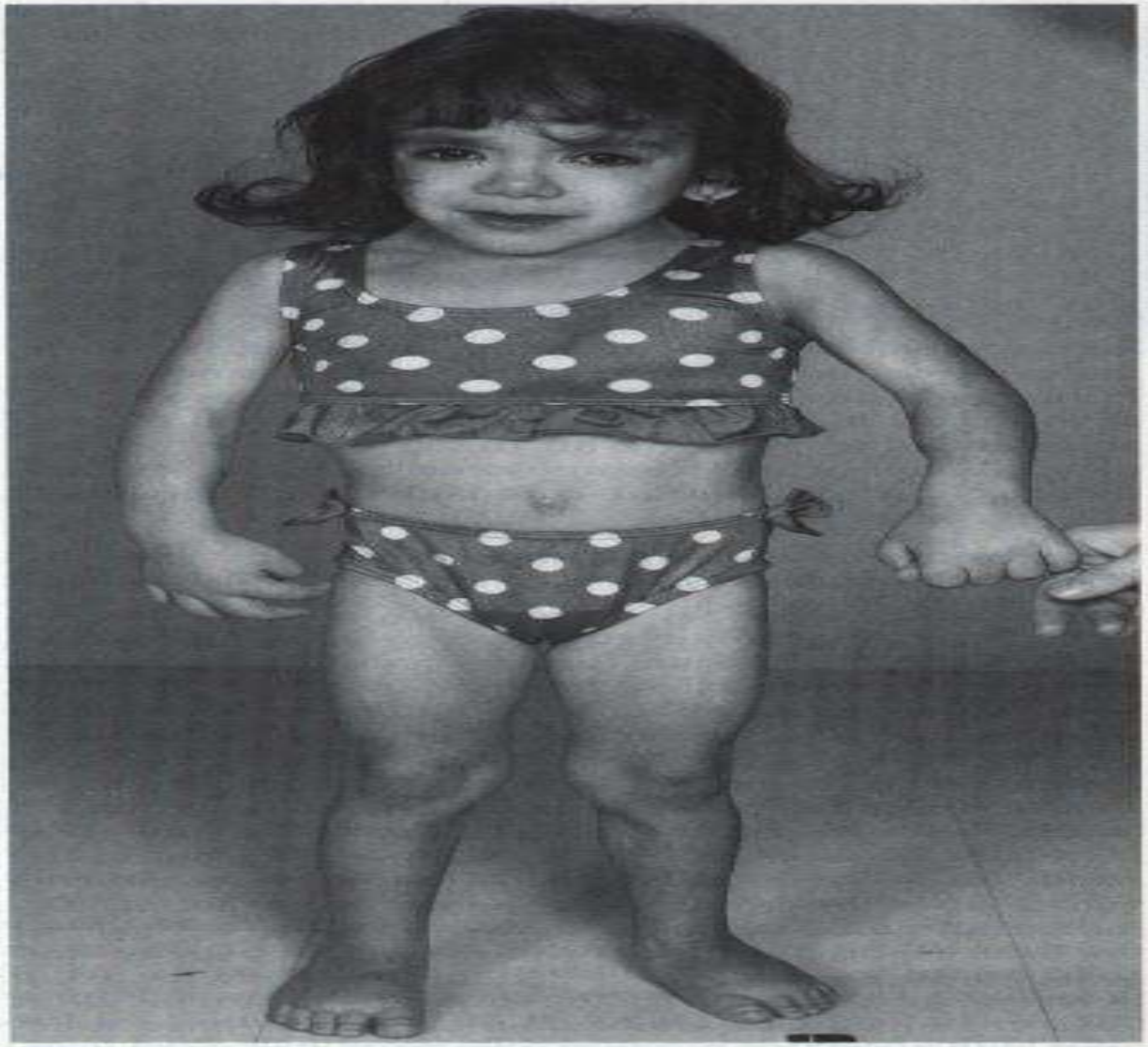
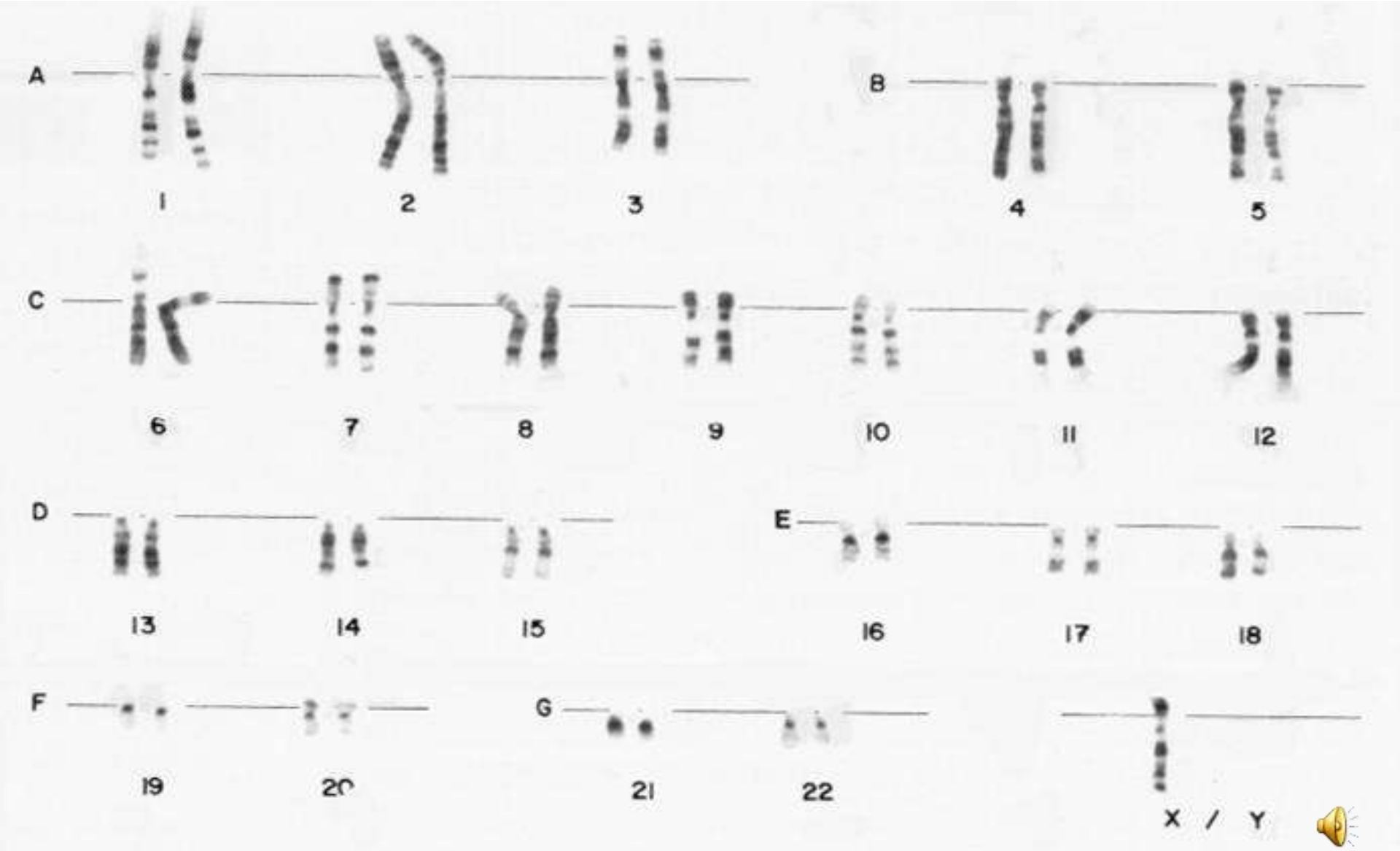


FIG. 6-11 A female with Turner syndrome (45,X). Note the characteristically broad, "webbed" neck. Stature is reduced, and swelling (i.e., lymphedema) is seen in the ankles and wrists.

Monosomy--Turner's Syndrome



- Trisomy - condition in which one chromosome in the pair is present in three copies in a somatic cell
- Down Syndrome (21), Trisomy 13 or 18
- Klinefelter's Syndrome – XXY
- Deletions - absence of normal chromosomal material; can be terminal or interstitial
- Duplications - presence of an extra copy of a chromosomal segment
- Inversions - Intrachromosomal re-arrangement such that the rearranged section is inverted
- Ring Chromosome - Fusion of the ends of a chromosome that forms a circle or ring

- Translocations - Interchromosomal rearrangement; can be balanced (all chromosomal material is present) or unbalanced (chromosomal material has been gained or lost); can be reciprocal or Robertsonian

Structural Abnormalities

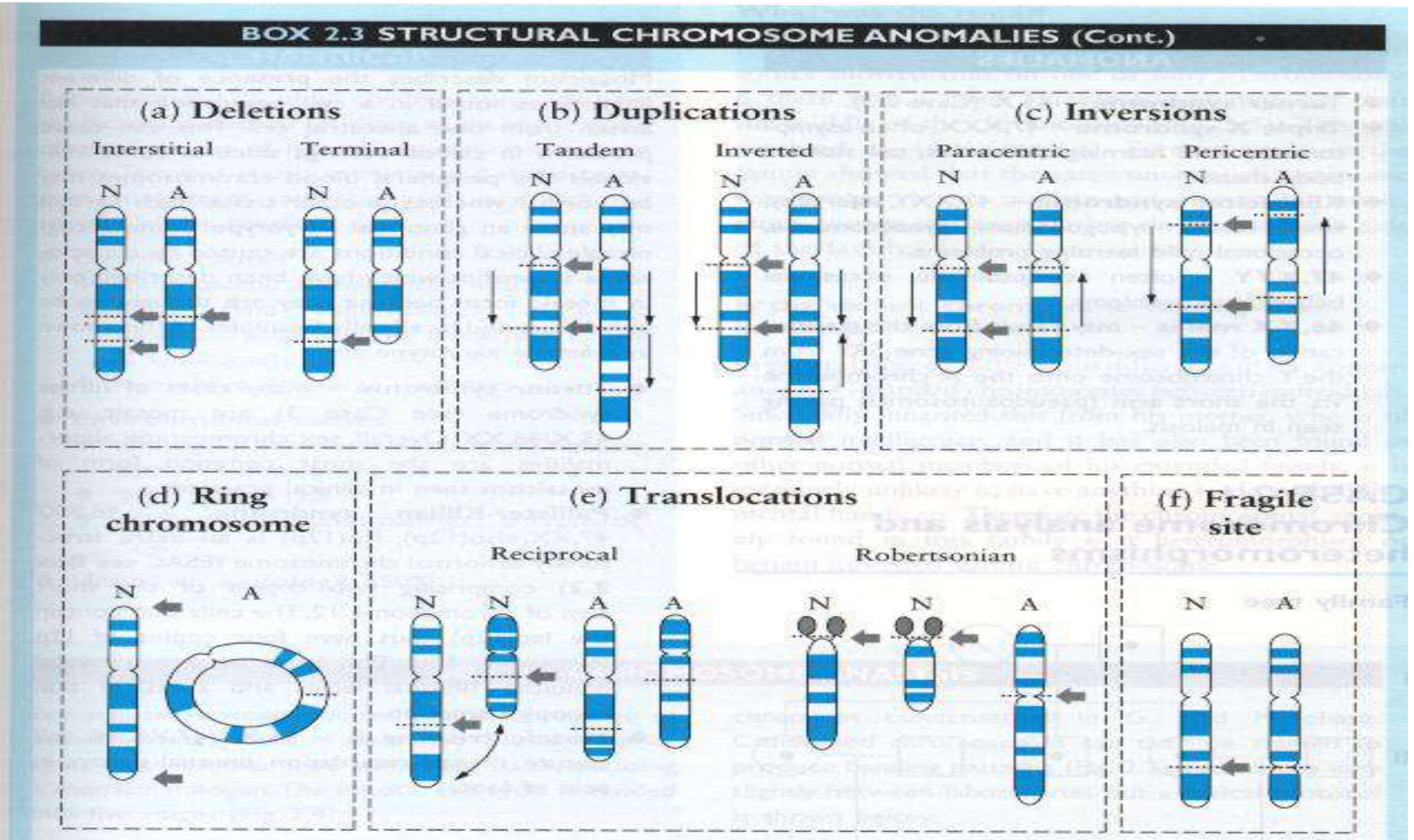
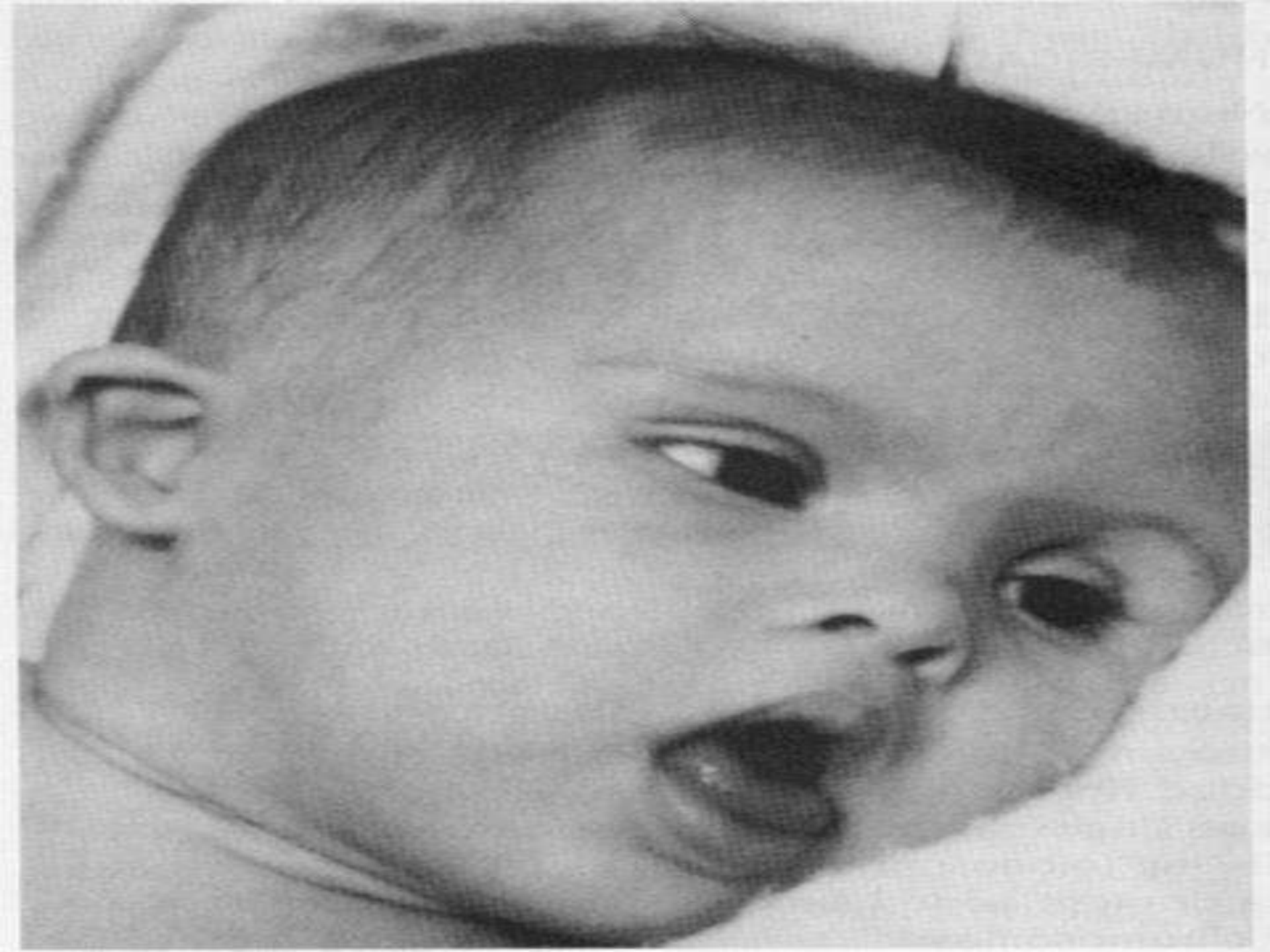


Fig. 2.3 An idealized chromosomal ideogram used to give examples of each structural chromosomal problem mentioned in the text: deletions (a), duplications (b), inversions (c), ring chromosomes (d), translocations (e) and fragile sites (f). N, normal chromosome; A, abnormal chromosome and grey arrow indicate breakpoint.



Genetics/th. Class

MENDELIAN GENETICS

Lecture One

Gregor Mendel

Gregor Johann Mendel

- Austrian monk
- Studied the inheritance of traits in pea plants
- Developed the laws of inheritance
- Mendel's work was not recognized until the
- Between 1856 and 1863, Mendel cultivated and tested some 28,000 pea plants
- He found that the plants' offspring retained traits of the parents
- Called the “Father of Genetics"
- turn of the 20th century

Mendel was the first biologist to use Mathematics – to explain his results quantitatively.

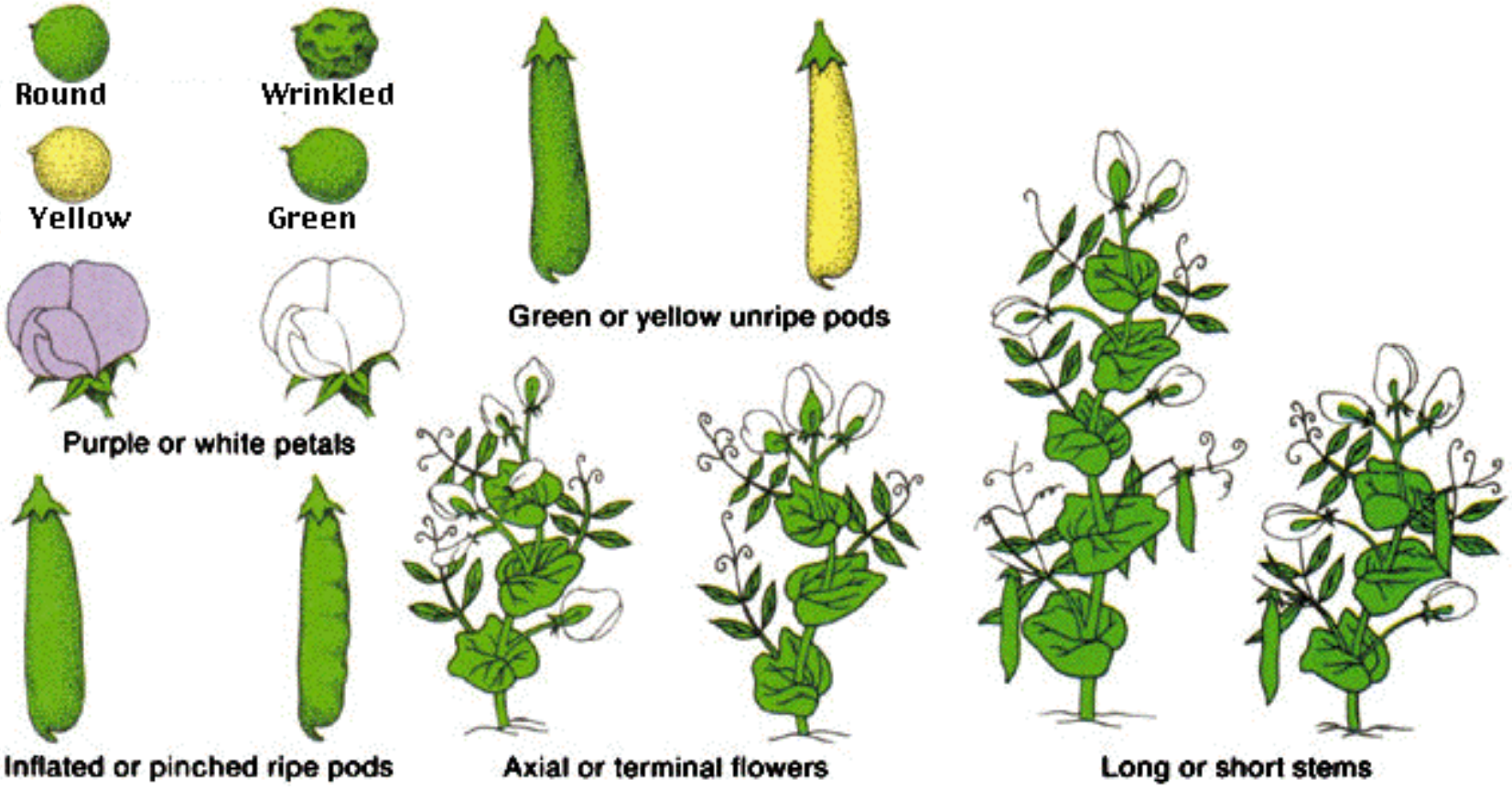
Mendel predicted

The concept of genes

That genes occur in pairs

That one gene of each pair is present in the gametes

Mendel looked at seven traits or characteristics of pea plants:



Homozygous – having identical genes (one from each parent) for a particular characteristic.
Heterozygous – having two different genes for a particular characteristic.

Dominant – the allele of a gene that masks or suppresses the expression of an alternate allele; the trait appears in the heterozygous condition.
Recessive – an allele that is masked by a dominant allele; does not appear in the heterozygous condition, only in homozygous.

Genotype – the genetic makeup of an organisms

Phenotype – the physical appearance of an organism (Genotype + environment)

Monohybrid cross: a genetic cross involving a single pair of genes (one trait); parents differ by a single trait.

P = Parental generation

$\mathbf{F_1}$ = First filial generation; offspring from a genetic cross.

$\mathbf{F_2}$ = Second filial generation of a genetic cross

7 Characteristics in Peas

Trait	Stem length	Pod shape	Seed shape	Seed color	Flower position	Flower color	Pod color
Characteristics	 Tall	 Inflated	 Smooth	 Yellow	 Lateral	 Purple	 Green
	 Dwarf	 Constricted	 Wrinkled	 Green	 Terminal	 White	 Yellow

Mendel hand-pollinated flowers using a paintbrush

He could snip the stamens to prevent self-pollination

Covered each flower with a cloth bag

He traced traits through the several generations

Generation "Gap"

Parental P_1 Generation = the parental generation in a breeding experiment.

F_1 generation = the first-generation offspring in a breeding experiment. **(1st filial generation)**

From breeding individuals from the P_1 generation

F_2 generation = the second-generation offspring in a breeding experiment.

(2nd filial generation)

From breeding individuals from the F_1 generation

Mendel's two Laws

1. Law of segregation

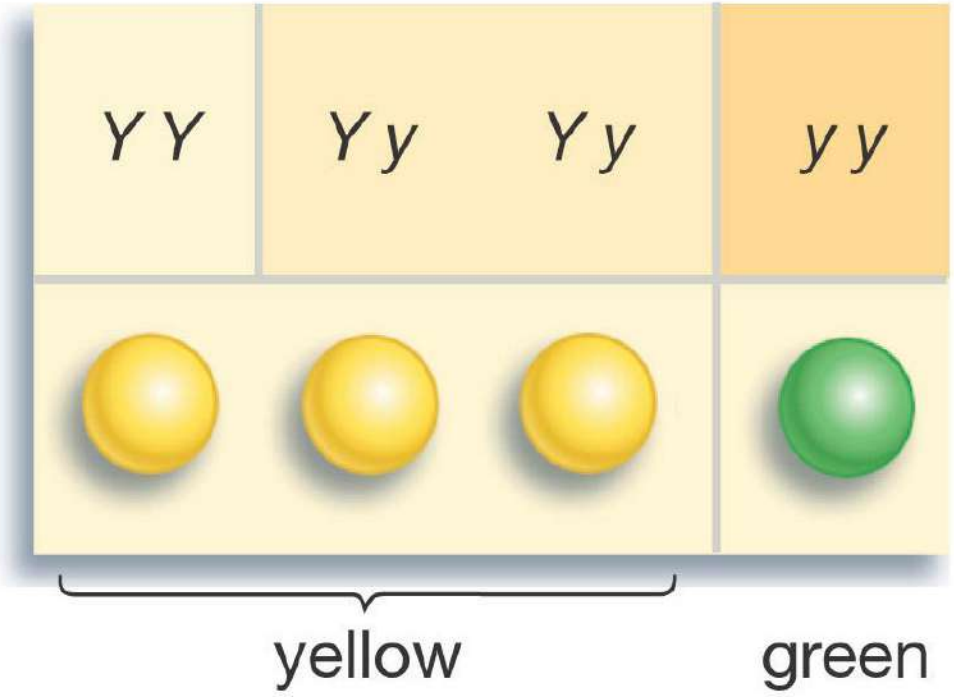
The two alleles for a trait segregate during gamete formation and **only one allele for a trait is carried in a gamete**. The gametes combine at random

(In other words:A cell contains two copies of a particular gene, they separate when a gamete is made).

2. Law of Independent Assortment

Alleles from one trait behave independently from alleles for another trait. Traits are inherited independently from one another

Law of Dominance



Three genotypes yield . . .

two phenotypes.

Monohybrid cross

Parents differ by a single trait.
Crossing two pea plants that differ in stem size, one tall one short
T = allele for Tall
t = allele for dwarf

TT = homozygous tall plant
t t = homozygous dwarf plant

T T × t t

P = parentals true breeding, homozygous plants

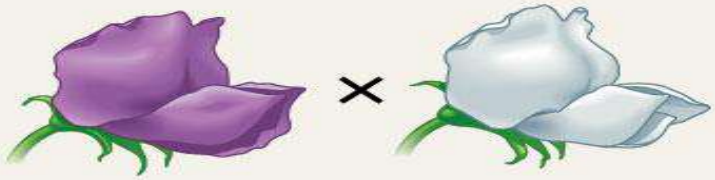
$$T\,T \times t\,t$$

(tall) (dwarf)

$$T\,t$$

F_1 = generation is heterozygous

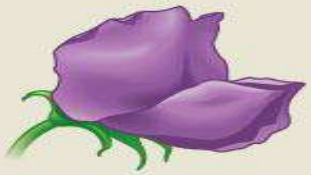
(all tall plants)



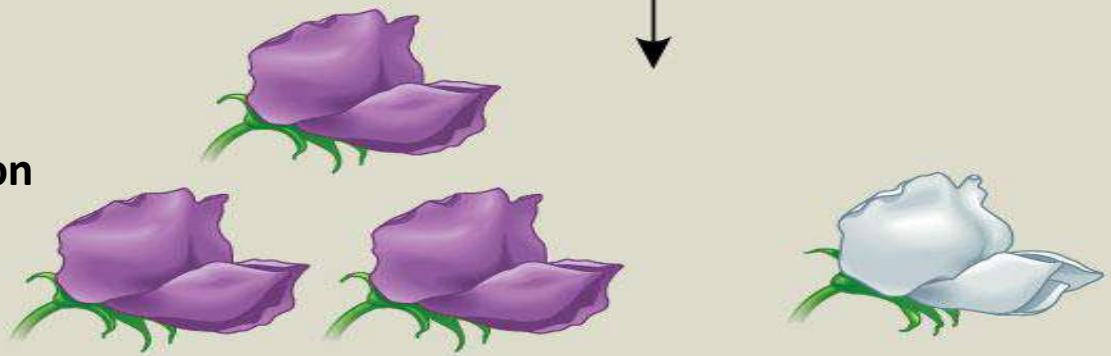
Purple flowers

White flowers

F_1 Generation



F2 Generation



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A Dihybrid Cross - F_1 Results

AABB X ***aabb***

AB ***AB*** ***ab*** ***ab***

AaBb

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Test Cross

You cross an individual that shows the dominant phenotype with an individual with recessive phenotype (one who is homozygous recessive for that trait)

Examining offspring allows you to determine the genotype of the dominant individual

Trait: Seed Shape

r – Wrinkled Alleles: R – Round

Cross: Wrinkled seeds x Hybrid

Rr x Round seeds = rr

Genotype: Rr, rr

Phenotype: Round & Wrinkled

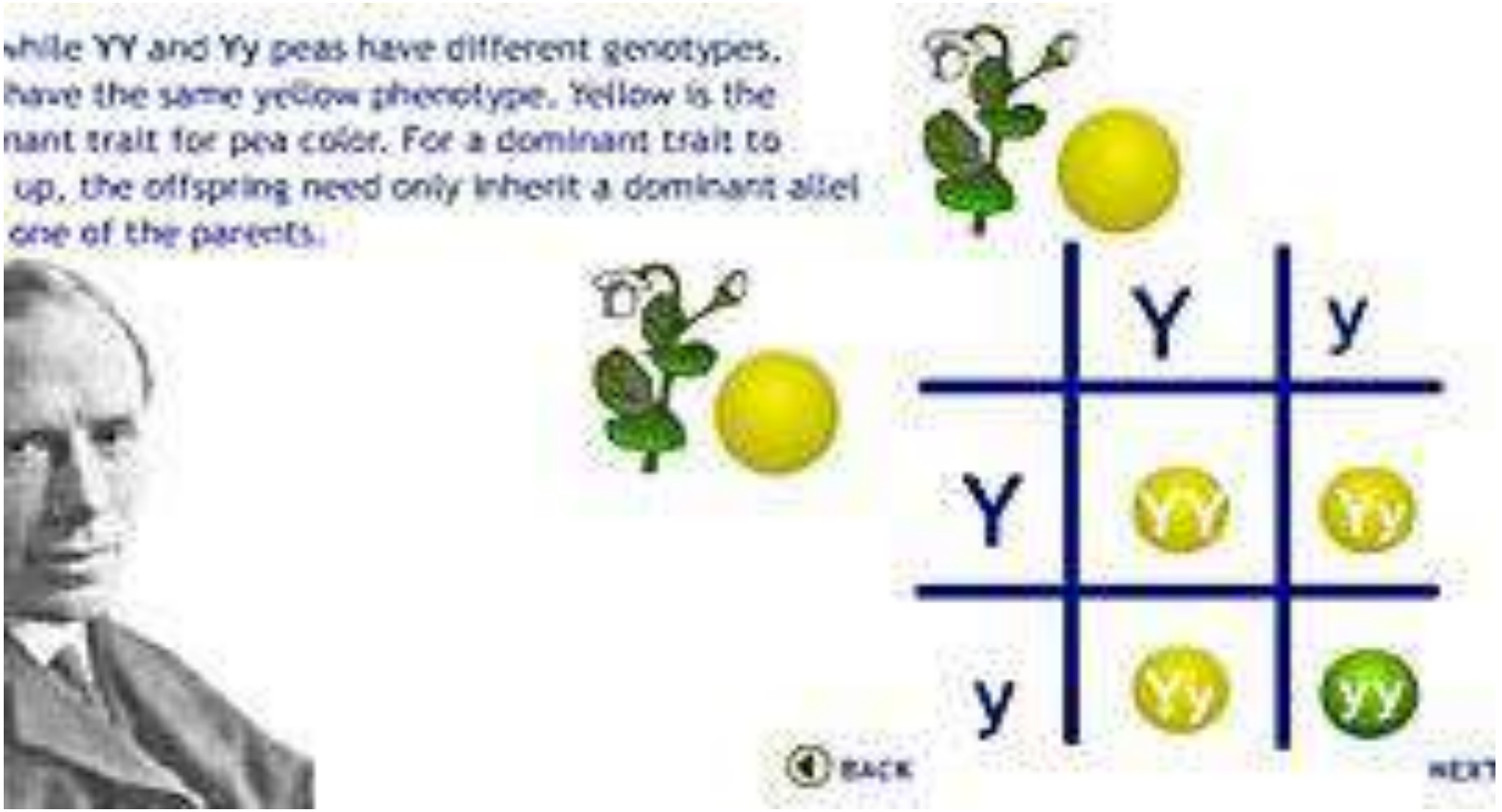
G. Ratio: 1:1

P.Ratio: 1:1

F_2 Monohybrid Cross Review

- Homozygous x heterozygous(hybrid)
- Offspring:
- 50% Homozygous RR or rr
- 50% Heterozygous Rr
- Phenotypic Ratio is 1:1
- Called Test Cross because the offspring have SAME genotype as parents

مربع بانیت


while YY and Yy peas have different genotypes,
have the same yellow phenotype. Yellow is the
nant trait for pea color. For a dominant trait to
up, the offspring need only inherit a dominant allel
one of the parents.
Y
y
Y
y
BACK

Genetics/th. Class

Lecture Tow &Three

NON MENDELIAN GENETICS

Mendel's Laws Not Perfect:

Shortly people began to notice that not all traits are "Mendelian"
This means, they do NOT follow Mendel's laws
Was he just plain wrong?

Truth is, his laws are correct and did explain how genetics works
Real life is just more complicated than peas!

Altering Mendel's Ratios

Two different types of complications:

1. Genotypic ratios follow Mendel's laws, but phenotypes do not
   - Somehow the underlying genotypic ratios are hidden
2. Mendel's laws do not apply
   - Both genotypes and phenotypes are not following Mendel's laws

Type 1 – Laws in effect:

1. Lethal genotypes
2. Allelic Heterogeneity
3. Incomplete dominance
4. Epitasis
5. Penetrance
6. Expressivity
7. Pleiotropy
8. Phenocopies
9. Genetic Heterogeneity

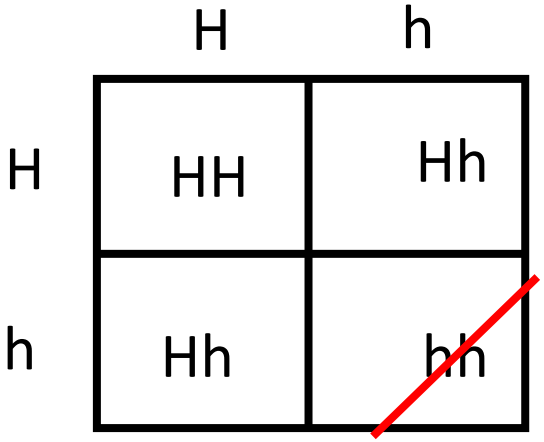
1. Lethal Genotypes

If a certain genotype (combination of alleles) causes death

Every genotype causes death if you wait long enough…

Usually stillbirth or miscarriage

Don't ever see the phenotype



Expect to see 3:1 ratio

Instead see 100% dominant

2. Allelic Heterogeneity or multiple Alleles

More than two alleles of the same gene

ex: Cystic Fibrosis has hundreds of alleles possible on the same gene

Causes differences in phenotype depending on which two alleles a person inherits

Still follow Mendel's laws within one cross

Individual can only have two alleles (only have two chromosomes)

One inherited from mother, one from father

3. Incomplete Dominance

One allele is not completely dominant over the other

Causing the heterozygote to have a third, different phenotype

ex: Blending in flowers

Homo Dominant = red flowers

Homo recessive = white flowers

Heterozygotes = pink flowers

P1 ,F1,F2 Generation

Phenotype: Pink Genotype: Rr

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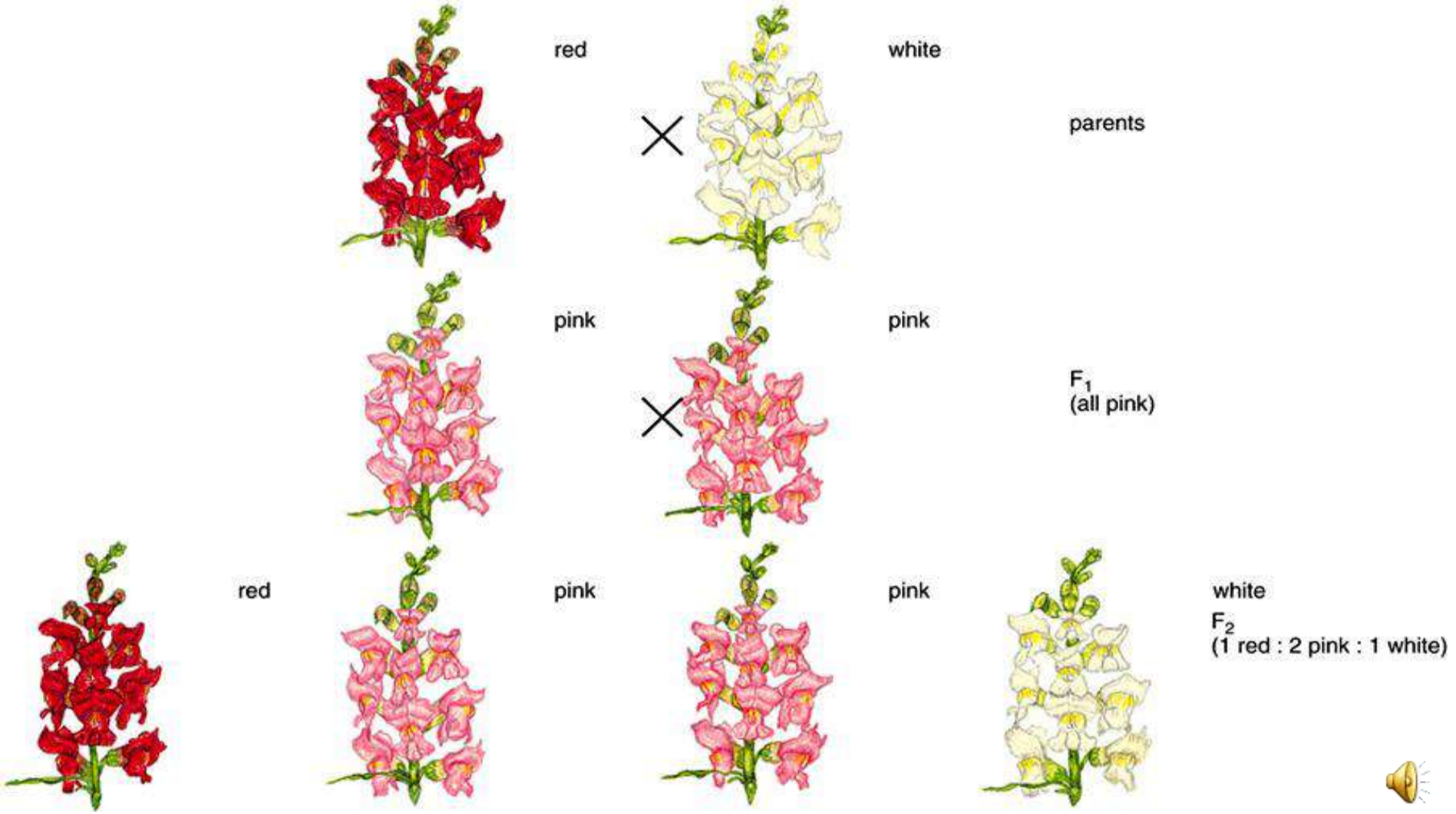


3. Incomplete Dominance

ex: Blood Types
Type A = AA or Ao
Type B = BB or Bo
Type AB = AB (heterozygote)
Type O = oo (homozygous recessive)

Still following Mendel's laws:
Two alleles per cross
1:2:1 genotypic ratios
Just not showing 3:1 phenotypic ratios

Definition

Two nonidentical alleles of a pair express two different phenotype in the heterozygote.

Example

1) Blood groups are controlled by three alleles (multiple allele system).

a) I^A, I^B, i

2) Possible Outcomes

a) ii = O blood group

b) I^AI^A or I^Ai = A blood group

c) I^BI^B or I^Bi = B blood group

d) I^AI^B = AB blood group (Codominance)

4. Epistasis

Two genes interacting to affect phenotype
Therefore Mendel's law about the one gene, is changed by the second gene

ex: Gene C controls the color of a person's eyes

However gene A causes albinism (lack of any pigment anywhere in body)

Therefore if a person is carrying gene A it will not matter which genotype for gene C is carried (eyes will be red)

Black	Brown	Yellow
BBEE		
BbEE	bbEE	BBee
BBEe	bbEe	Bbee
BbEe		bbee

4. Epistasis

One gene effecting or masking another gene
or
Two genes controlling same phenotype

Mendel's Laws are still working for each individual gene, but phenotype is not determined by that single gene's genotype alone

5. Penetrance

Sometimes the same genotype will not produce the phenotype in all individuals

Penetrance = the percent of individuals who have a certain genotype and show the expected phenotype

Mendel traits penetrance = 100 %

Some traits penetrance is less than 100%

5. Penetrance

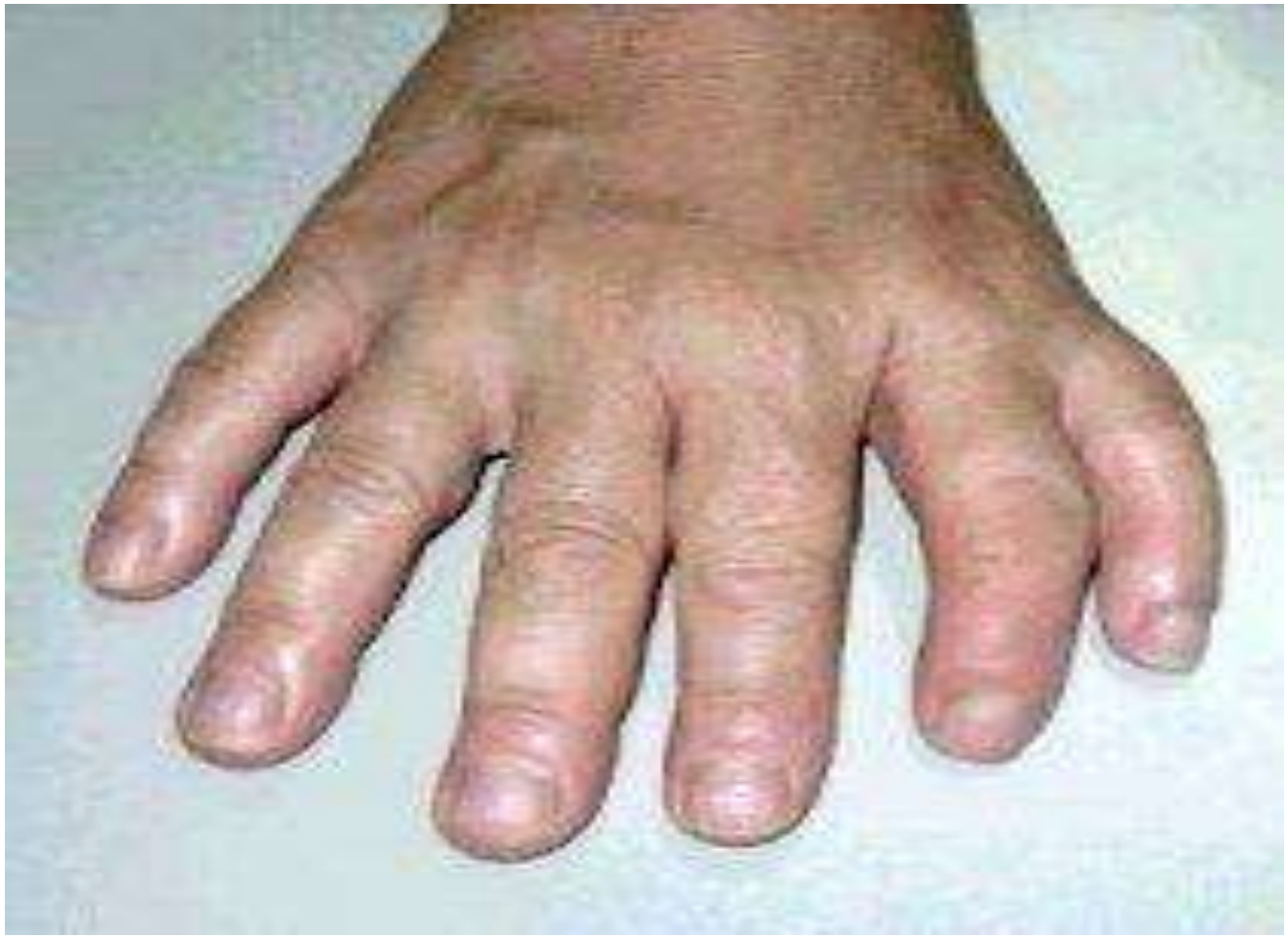
Decreased penetrance or “low penetrance” means that some people inherit genotype and yet do not show the phenotype

Penetrance is calculated as:

Number of individuals who have genotype and expected phenotype Total number of individuals who have genotype (any phenotype)

Usually decrease caused by interaction of additional genes or environment

Penetrance (Expressivity)



6. Expressivity

Sometimes the same genotype will produce different “degrees” of phenotype in individuals

Expressivity = the severity or extent of the phenotype an individual shows

ex: Hypercholesterolemia

Some individuals have extremely high cholesterol from birth, others can control with diet and exercise and lead normal lives

Penetrance vs. Expressivity

Both follow Mendel's laws
Genotypic ratio is still 1:2:1
Phenotypic ratio is affected
Both have to do with "amount" phenotype is present
Penetrance – is all or none, person is affected with disease or not
Expressivity – is the severity of the phenotype

7. Pleiotropy

One gene causes more than one phenotype

Pleiotropy occurs when one gene controls more than one pathway or is expressed in more than one body part

ex: One gene makes connective tissue Needed for lens of eye

Heart Muscle

Needed for lens of eye
Heart Muscle

Therefore a mutation in this one gene will cause defects in eye sight, heart attacks, and weakness in muscles and limbs

8. Phenocopies

Trait is not genetic at all
An environmentally caused trait that appears to be genetic/inherited
or
An environmentally caused phenotype that is the same as an inherited phenotype
Not breaking any of Mendel's laws because it's not genetic!

Polygenic Inheritance

Definition

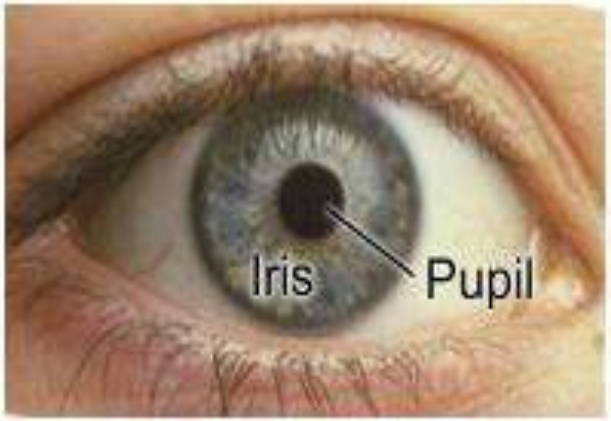
Continuous range of small differences in a given trait among all the individuals of a population due to inheritance of multiple alleles that affect the same trait.

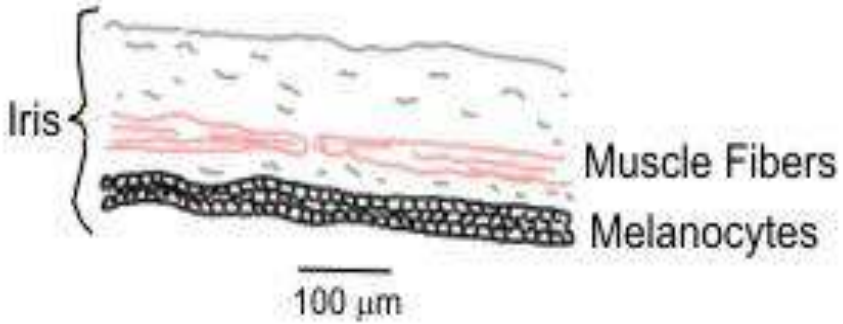
Examples

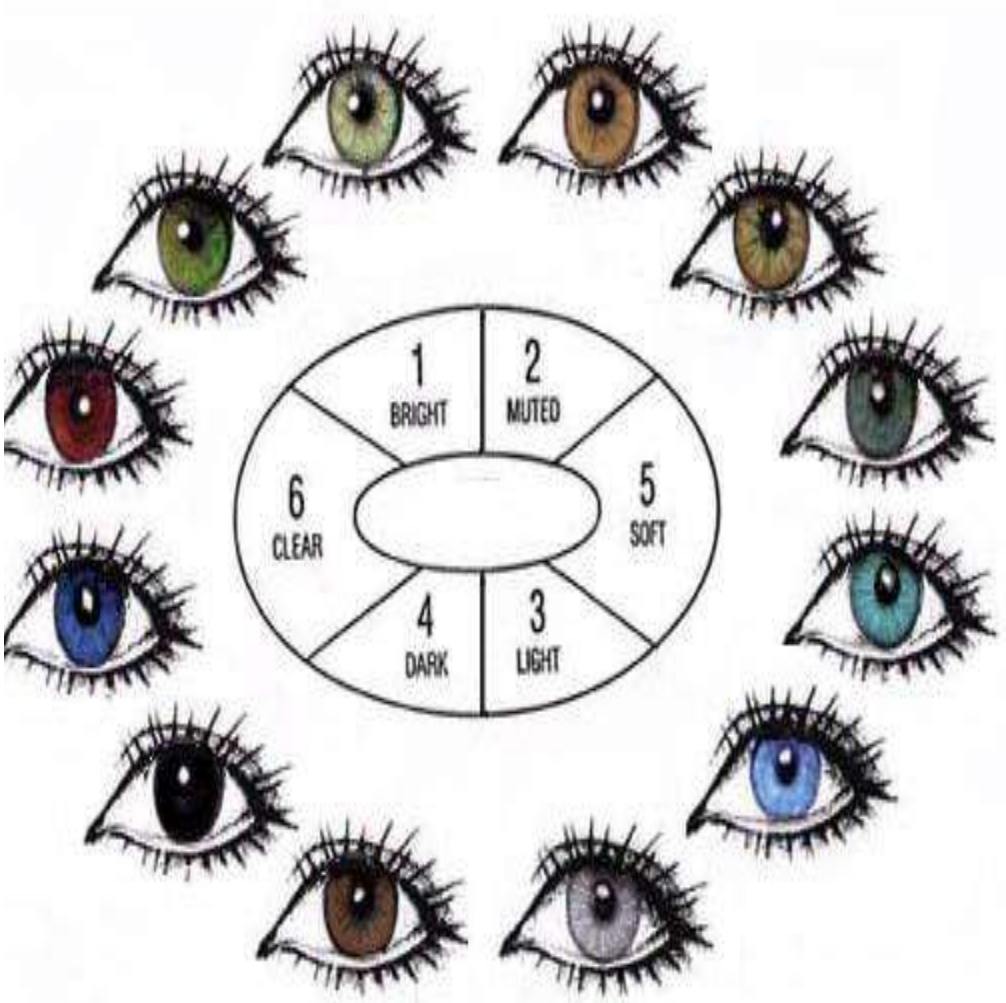
Height 1)

(4 Genes and 8 Alleles) Eye color 2)

EYE COLOR







Blue Light

Yellow Light

Polygenic Inheritance

Eye Color	*Alleles*	*Alleles*
Light Blue	aabbccdd	0
Medium Blue	aabbccDd	1
Dark Blue	aabbCcDd	2
Gray	aaBbCcDd	3
Green	AaBbCcDd	4
Hazel	AaBbCcDD	5
Light Brown	AaBbCCDD	6
Medium Brown	AaBBCCDD	7
Dark Brown	AABBCCDD	8

Environmental Effects

Definition

The environment can affect the expression of a gene.

1) Example

Himalayan rabbits

a) Homozygous for c^h allele coding for tyrosinase expressing melanin production

b) Tyrosinase is not active above 33° C

c) Hair appears light due to lack of melanin

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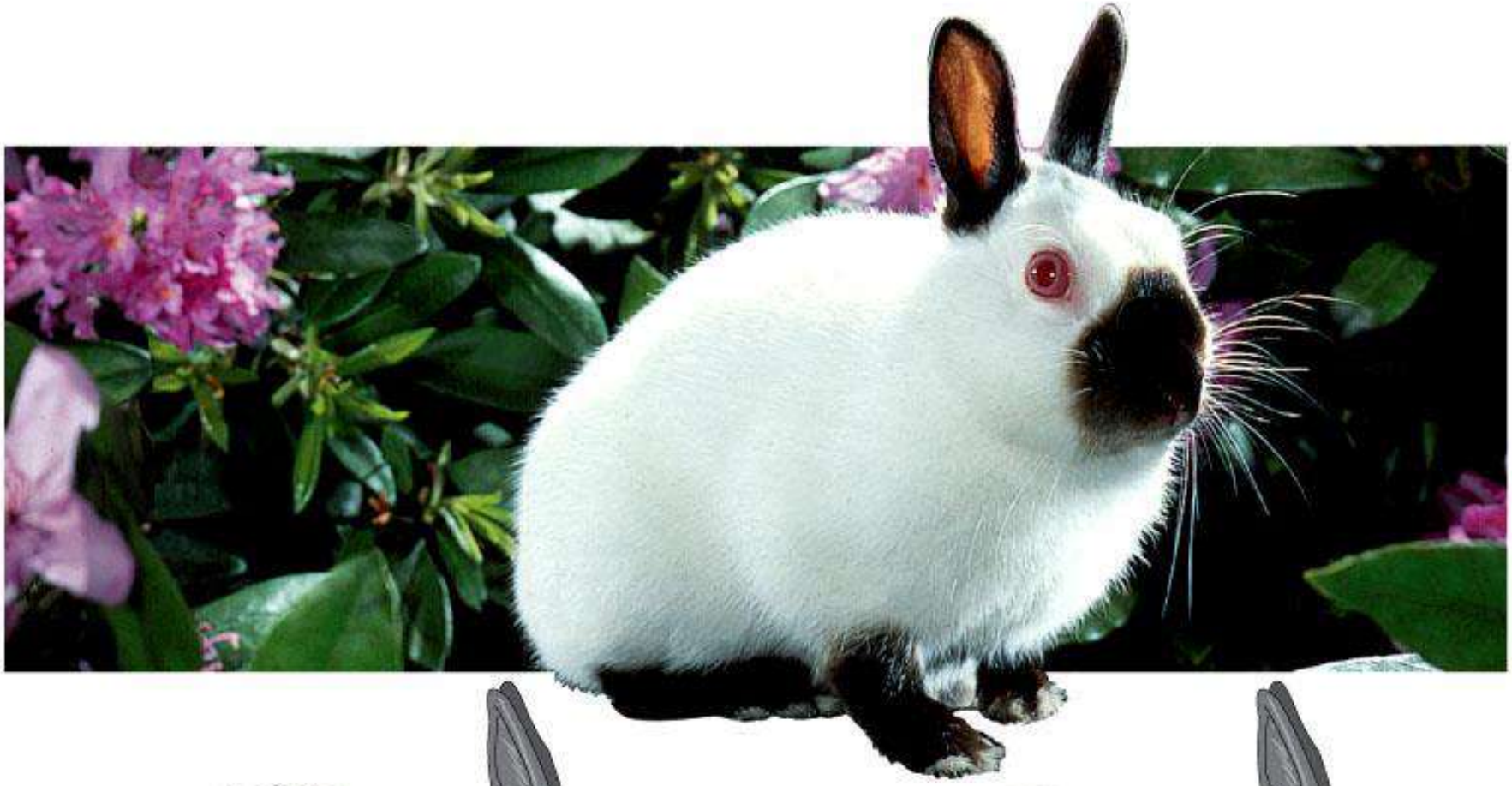
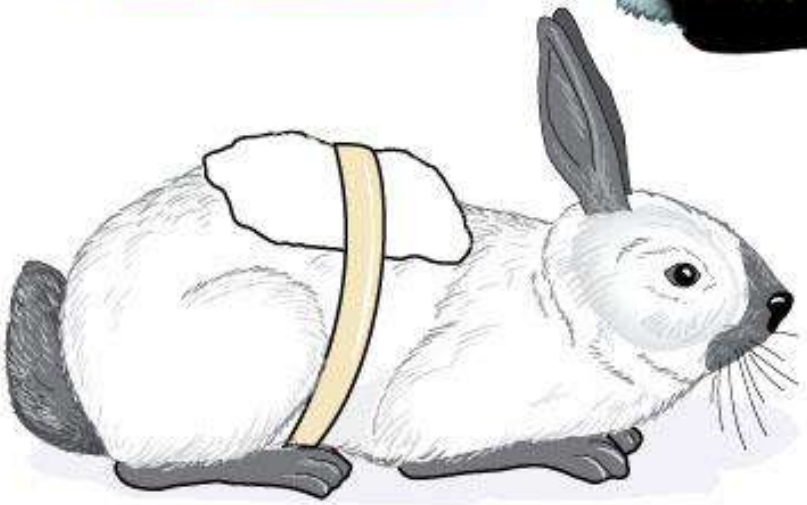
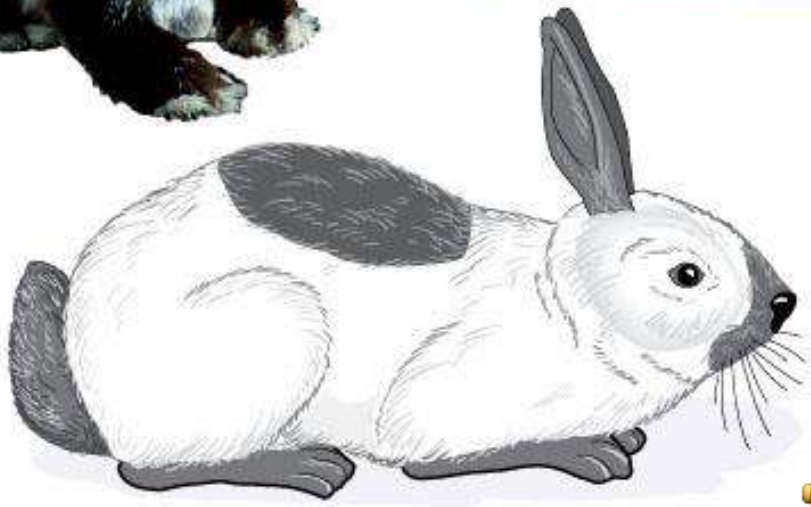






Type 2 – Mendel's Laws No Longer Apply

1. Mitochondrial Inheritance
   - Mitochondria have their own DNA, which is solely maternally inherited
2. Linkage
   - Two genes that are close together physically
3. Linkage Disequilibrium
   - Two alleles that are not inherited separately

DNA Structure and Function

Genetics/th. Class

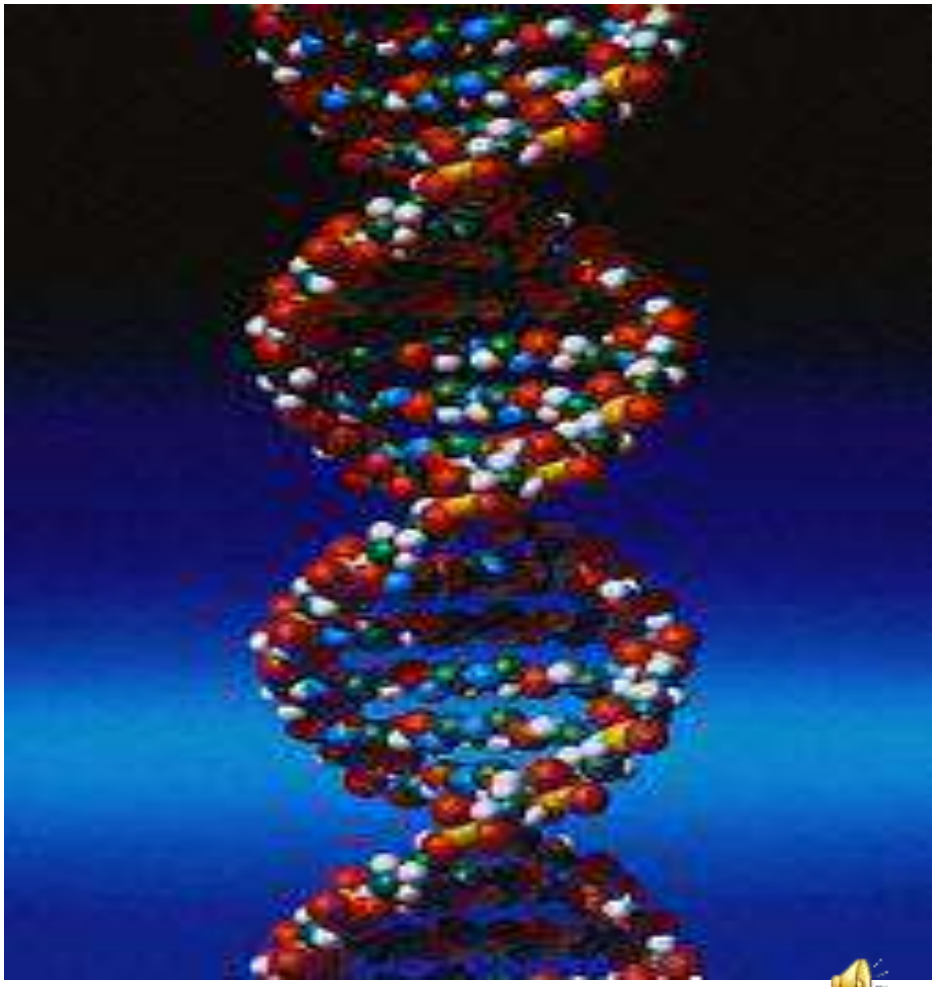
Lectures sevene

Dr. Ibtesam B. H.

Why do we study **DNA**?

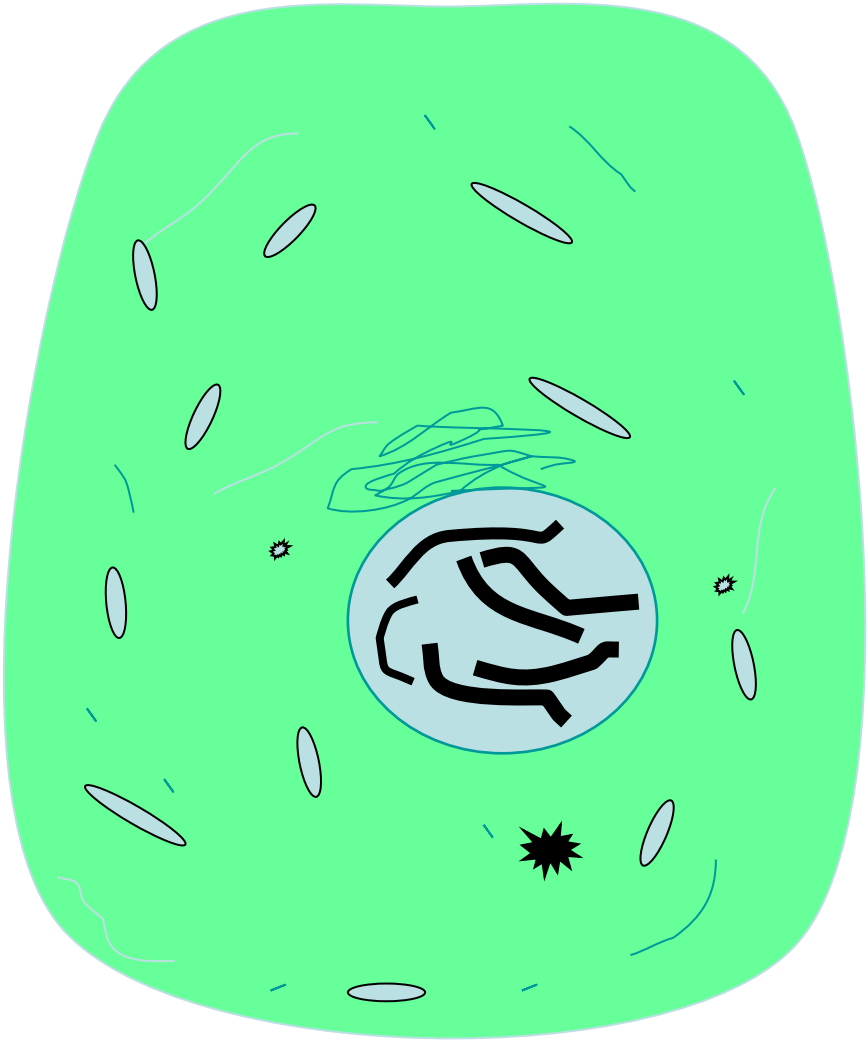
We study DNA for many reasons, e.g.,

1. **its central importance to all life on Earth,**
2. **medical benefits such as cures for diseases,**
3. **better food crops**.



Chromosomes and DNA

Our genes are on our chromosomes. Chromosomes are made up of a chemical called DNA.



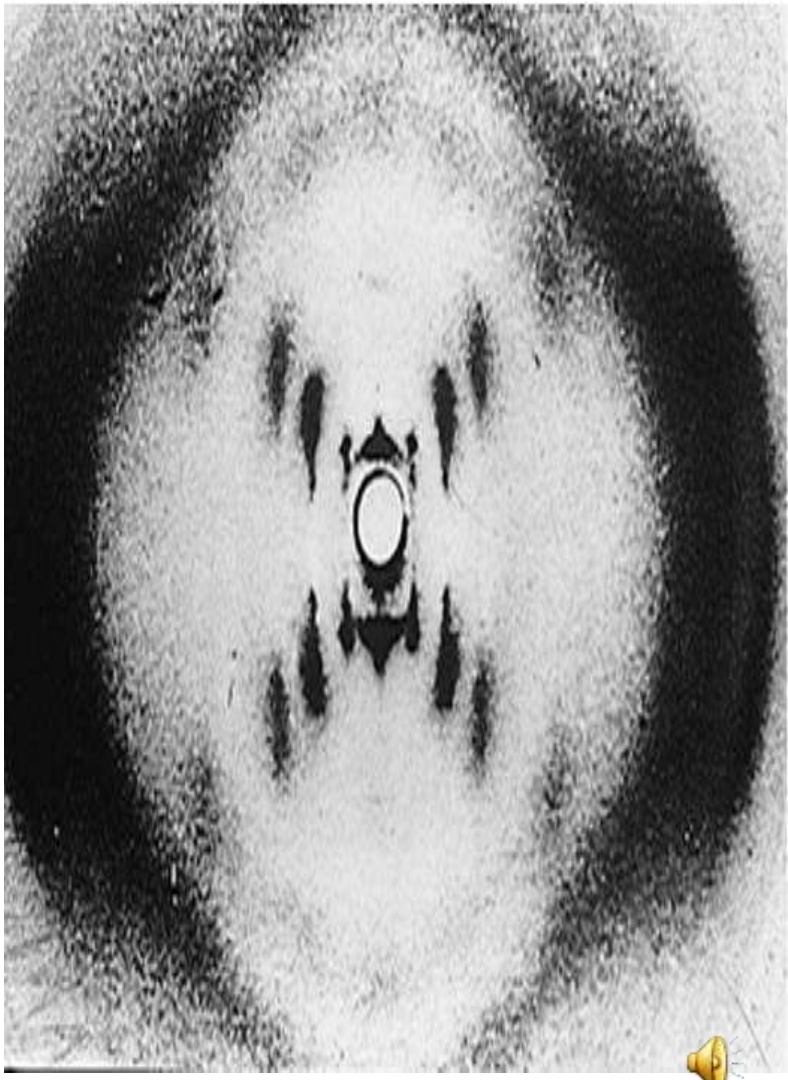
Rosalind Franklin

Fig. 13.8, p. 220

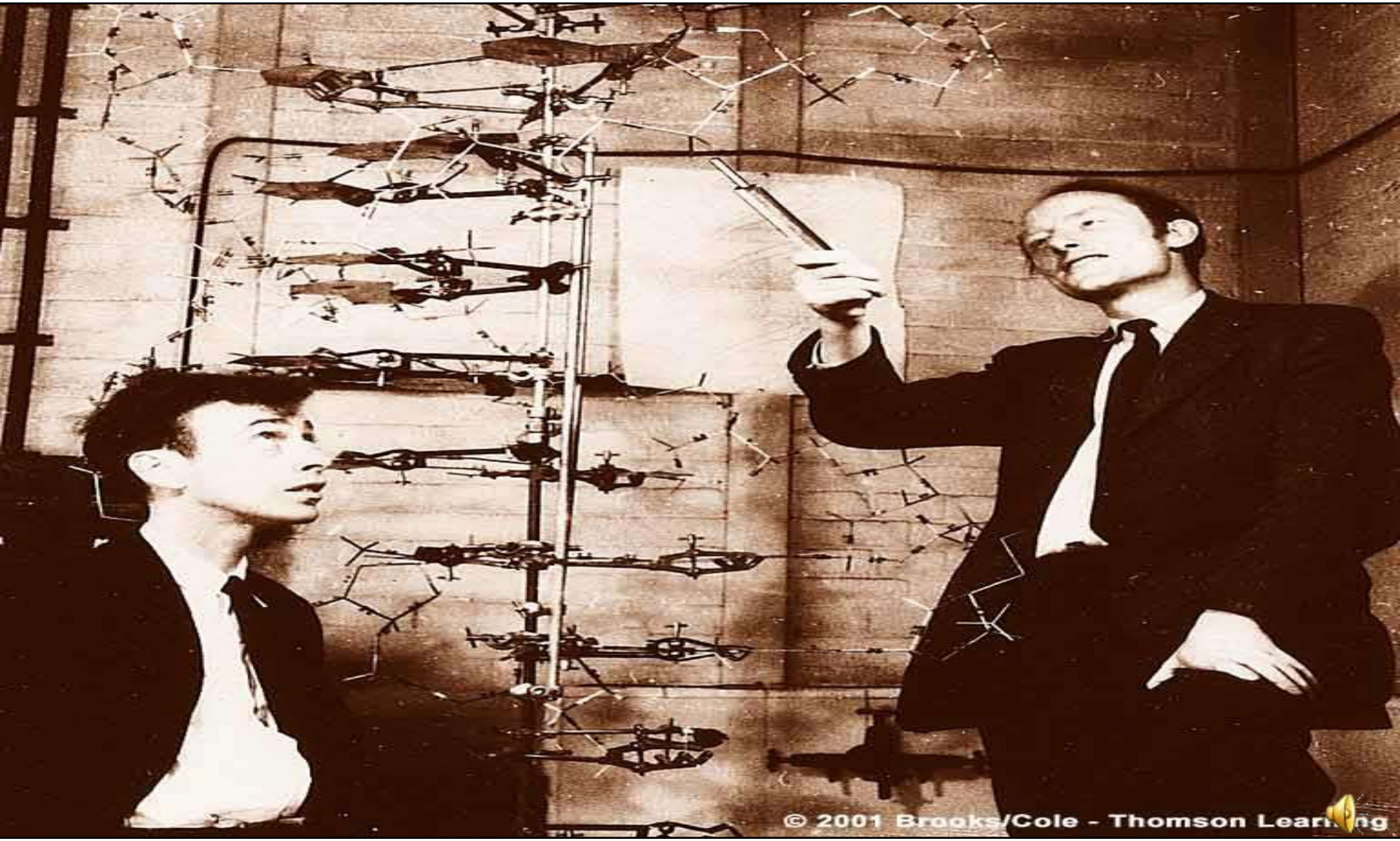
Rosalind Franklin

1953

- Crystallized DNA and X-ray diffraction
- From picture it was clear that DNA was in a helix
- With symmetrically organized bases in center



James Watson and Francis Crick



DNA Structure

- **Nucleotides**
  - **Deoxyribose**
  - **Phosphate Group**
  - **Nitrogen base**
    - **Adenine A**
    - **Guanine G**
    - **Thymine T**
    - **Cytosine C**

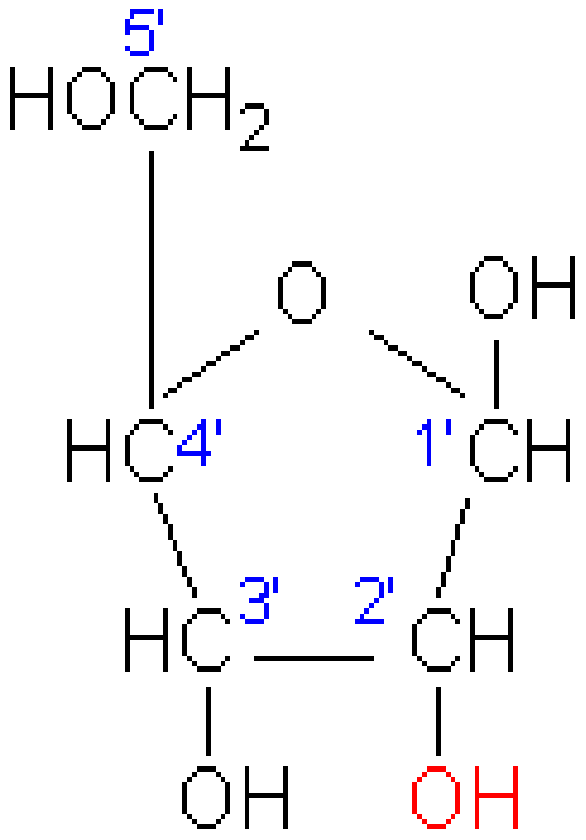
- **Pairing Arrangement**
  - **A - T**
  - **C – G**

Amount of A=T and C=G

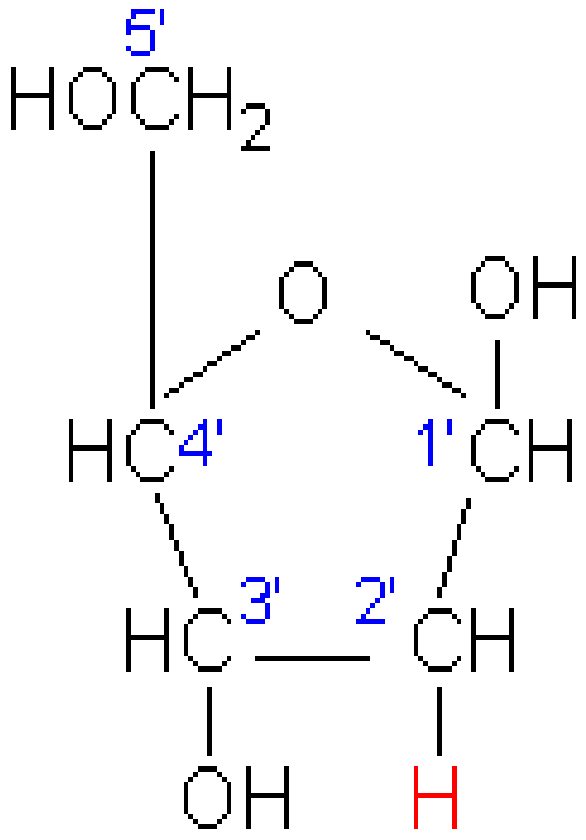
NUCLEIC ACIDS

- Nucleic acids are polymers
- Monomer---nucleotides
  - Nitrogenous bases
    - Purines
    - Pyrimidines
  - Sugar
    - Ribose
    - Deoxyribose
  - Phosphates +nucleoside=nucleotide

The Sugars

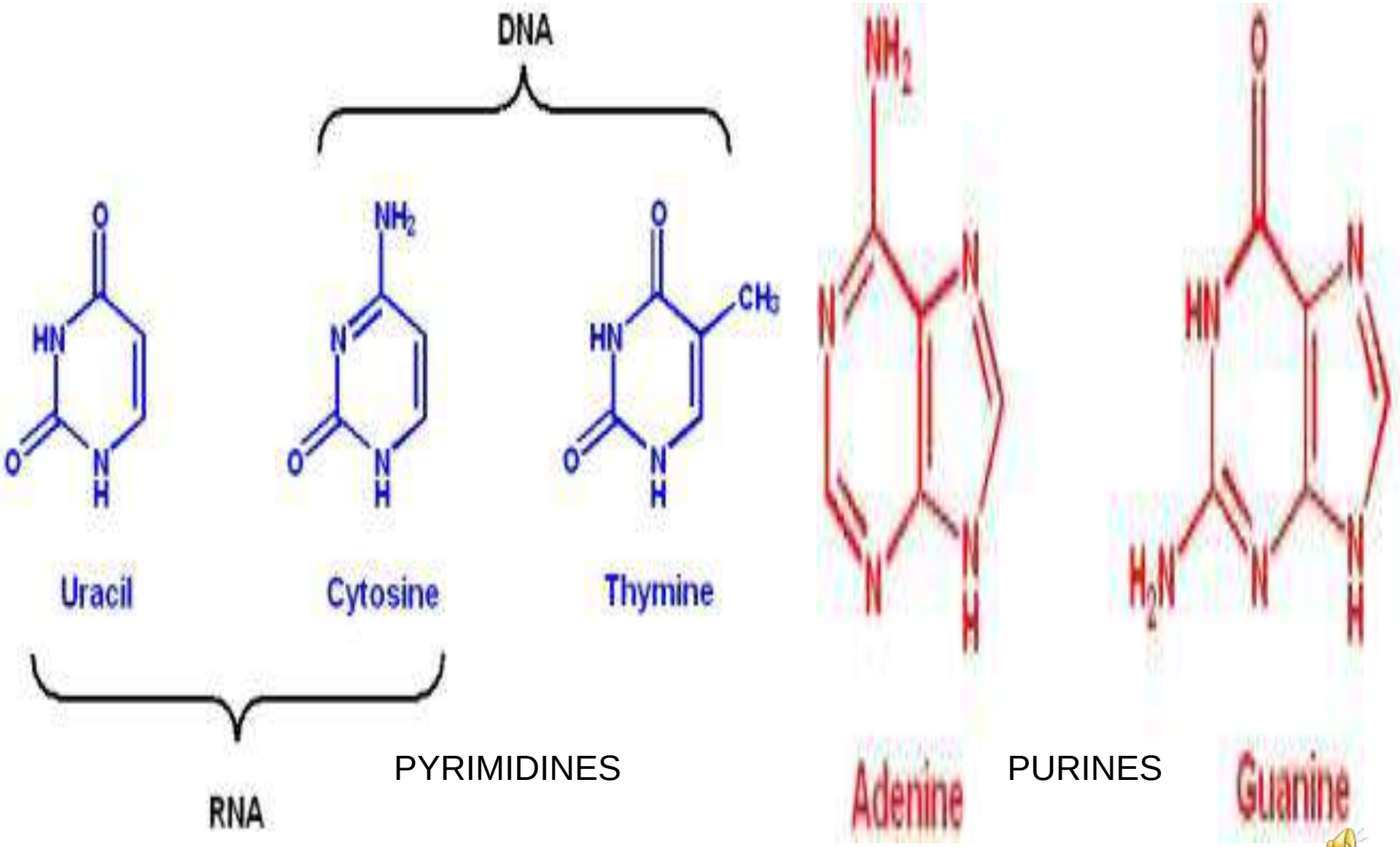


Ribose
(in RNA)



2'-Deoxyribose
(in DNA)

The Bases


DNA
Uracil
Cytosine
Thymine
RNA
PYRIMIDINES
Adenine
PURINES
Guanine

DNA Stabilization– Complementary Base Pairing

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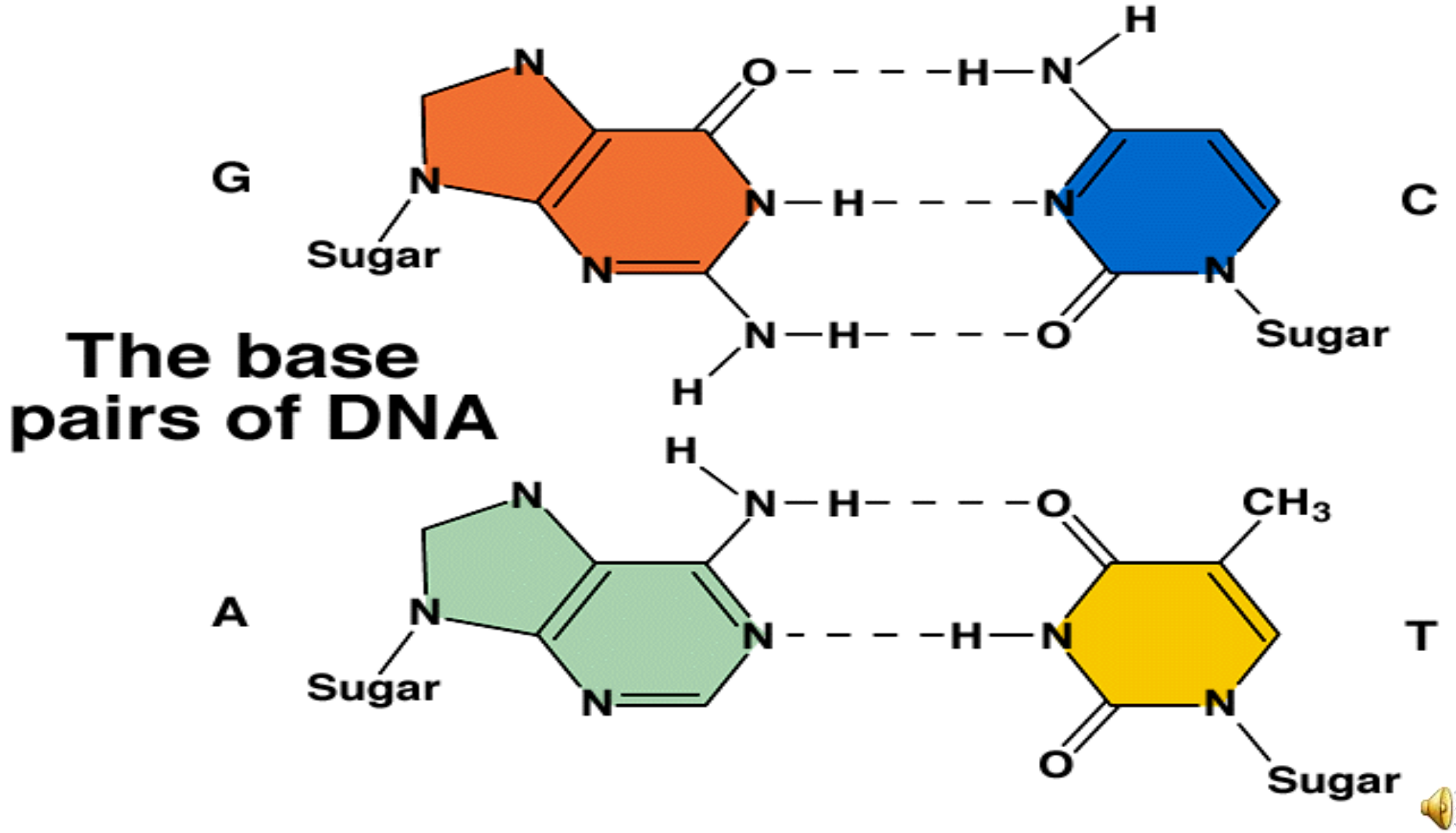

Structure of DNA

- **DNA consists of two strands of nucleotides held together at bases by hydrogen bonds**
  - **A=T and C=G**
- **The two strands twist into a double helix.**
- **The two strands run in opposite directions (anti-parallel)**
  - **Each strand runs in a 5’ to 3’ direction**

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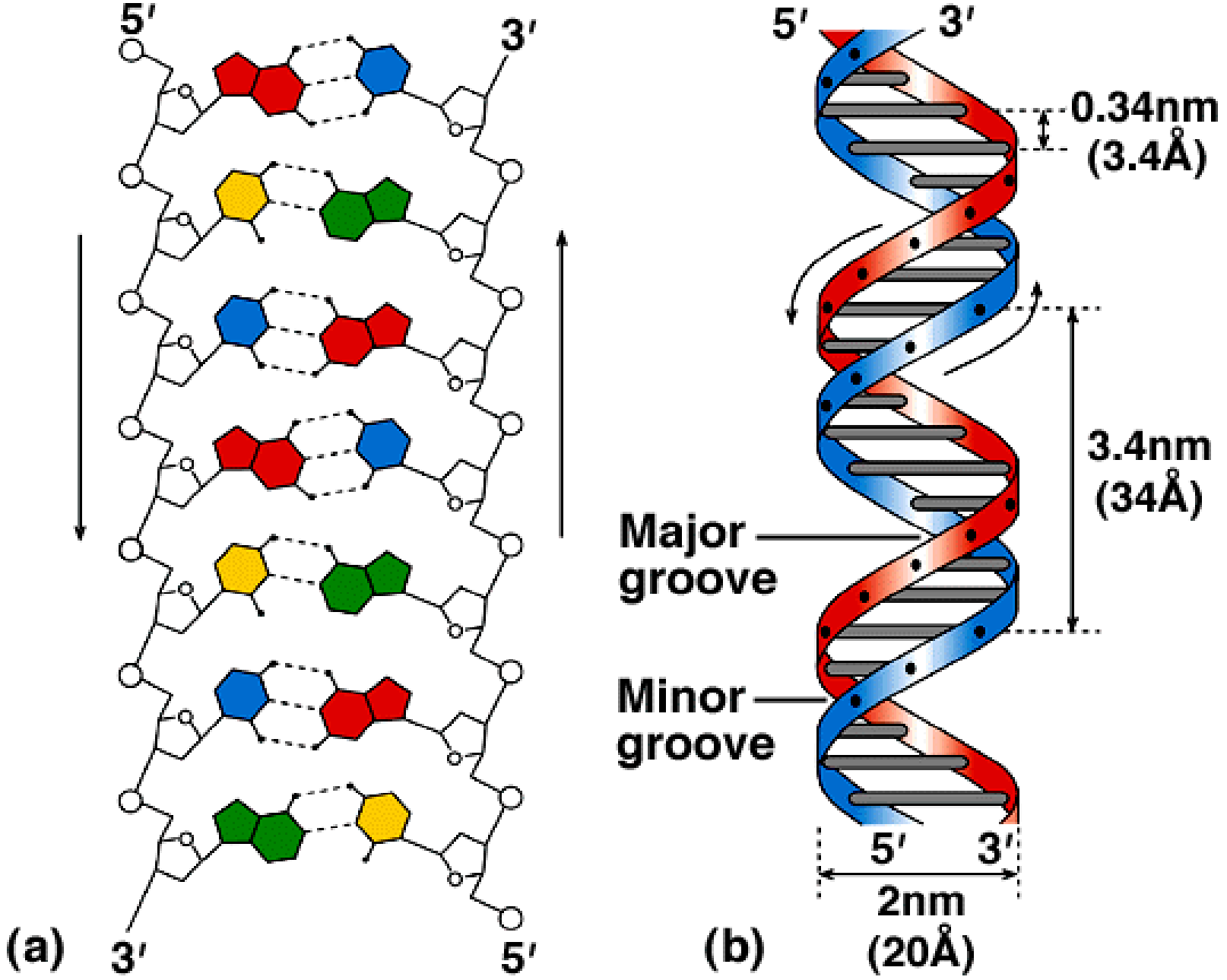
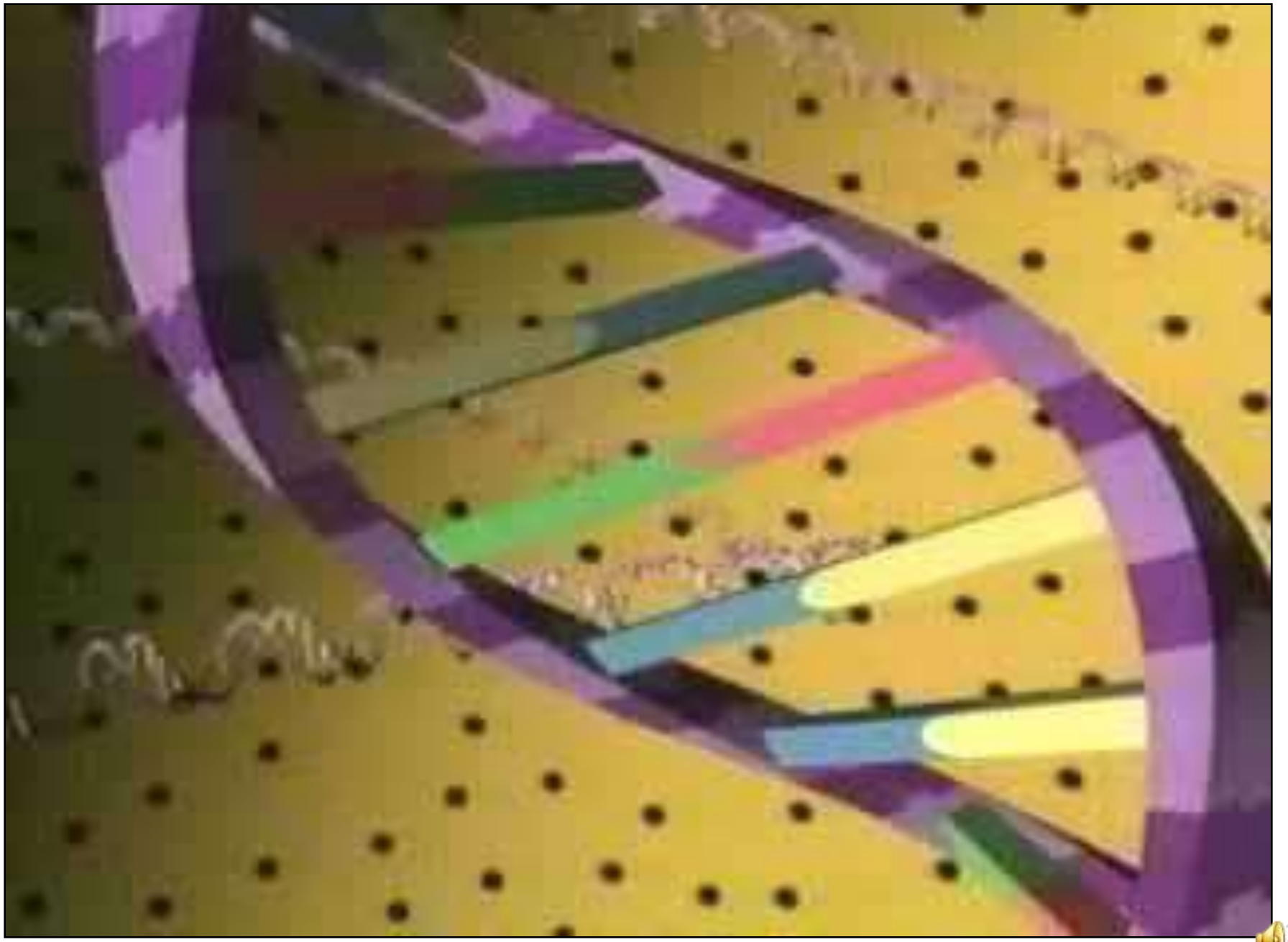
Three models of DNA structure



Semi-conservative Replication

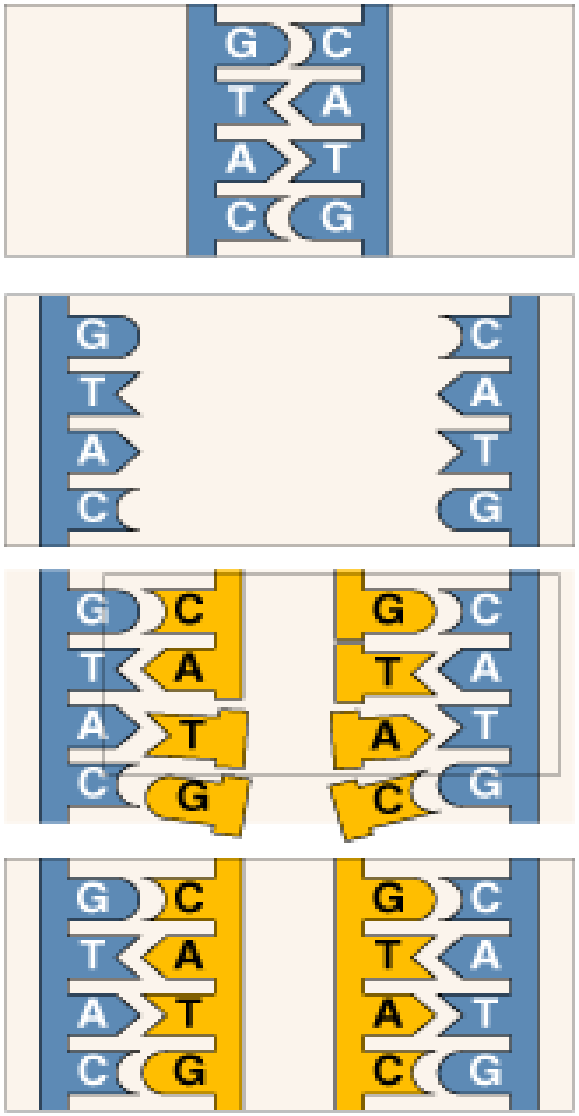
- DNA Replication is semi-conservative

- There are 3 enzymes that are used for replicating a new strand of DNA
  - Helicase
  - DNA polymerase
  - Ligase



DNA Replication and Repair

- **Enzyme regulated**
  - **Hydrogen bonds break**
  - **Attachment of nucleotides to new strands**
  - **DNA polymerases DNA ligases**
  - **New strand is half old, half new**



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Detailed Look at Replication

- **Nucleotides can only be added in the 5’ to 3’ direction**
- **Leading Strand assembly is continuous**
- **Lagging strand discontinuous**

Creating Clones

- **Dolly the sheep was first mammal to be cloned from a differentiated cell**
  - **Nucleus from sheep udder cell was transferred into enucleated unfertilized egg**
  - **Egg grew into sheep by mitotic divisions**
- **Mice and cows have now also been cloned from adult cells**

In Conclusion

- **Hereditary information is located in DNA**
- **DNA consists of nucleotides**
- **DNA molecule consists of two nucleotide strands twisted into a double helix**
- **The bases of DNA strands pair in a constant fashion**
- **DNA of one species has specific nucleotide sequences**

Population Genetics

Matthew B Hamilton

WILEY-BLACKWELL

Genetics/th. Class

Population Genetics

Lectures 15,16

Dr. Ibtesam B. Hassan

Population Genetics

- Mendelian genetics predicts the outcome of specific matings between individuals
- What about the genetics of an entire population?
  - Population = all individuals of one species living in a given area
- Population genetics works with the entire **gene pool**
  - or all the alleles present in the whole population

Genetics of Populations

- Population
  - a localized group of individuals belonging to same species
  - The definition of a species not always clear
- Gene pool = The total genes in a population
- Evolution on the smallest scale occurs when the relative frequency of alleles in a population changes over a succession of generations = *microevolution*

Population: a group of individuals of the same species **that live** in the same area and interbreed (interbreeding causes production of fertile offspring)

freepptbackground.com

Species

- **Species** = a group of populations whose individuals have the potential to interbreed and produce fertile offspring in nature

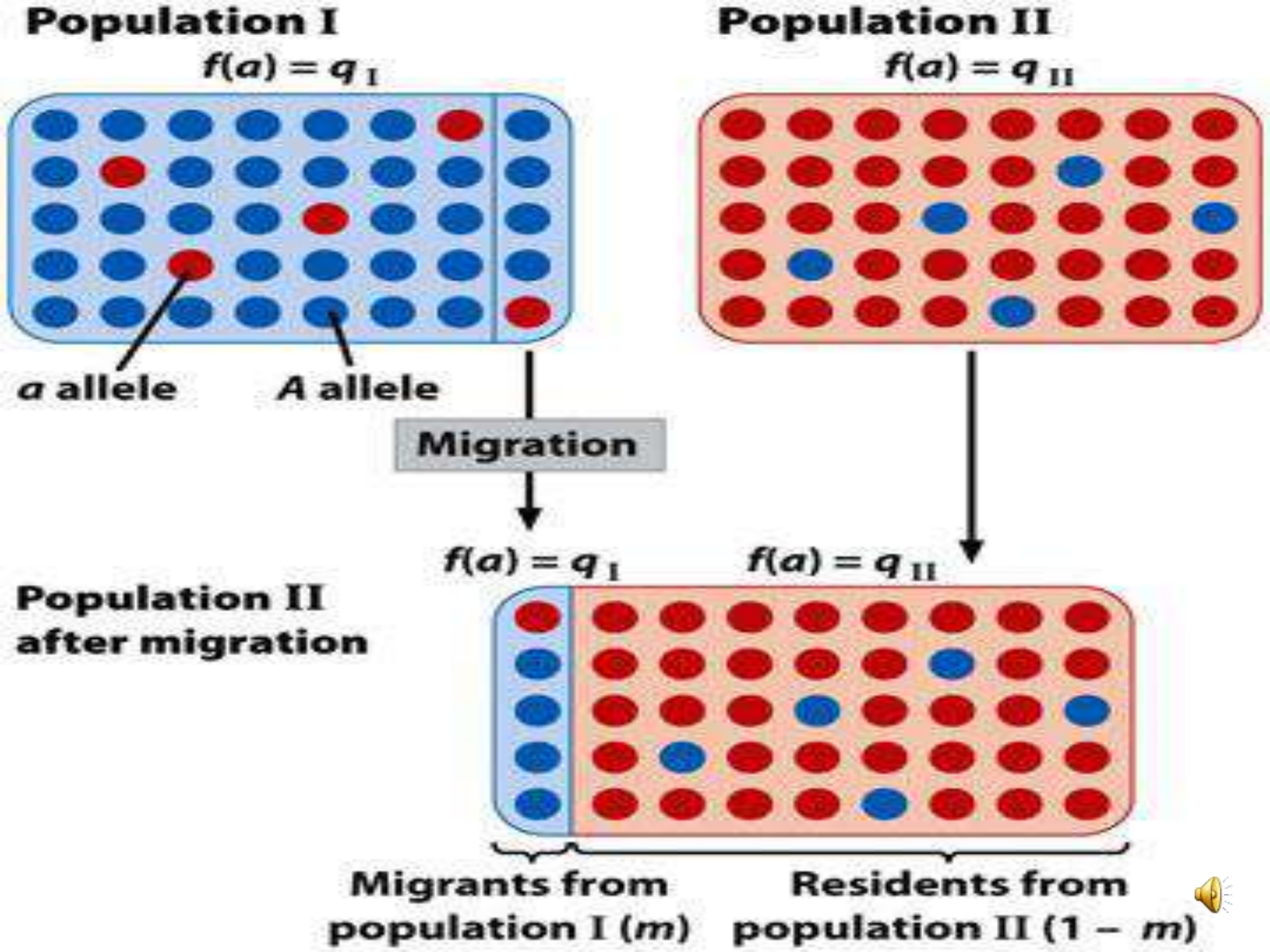
- Members of a population are more likely to breed within the population, so genes tend to stay in the **same population** for generations

Phenotypic Evolution: Process

Factors Changing Population Genetics

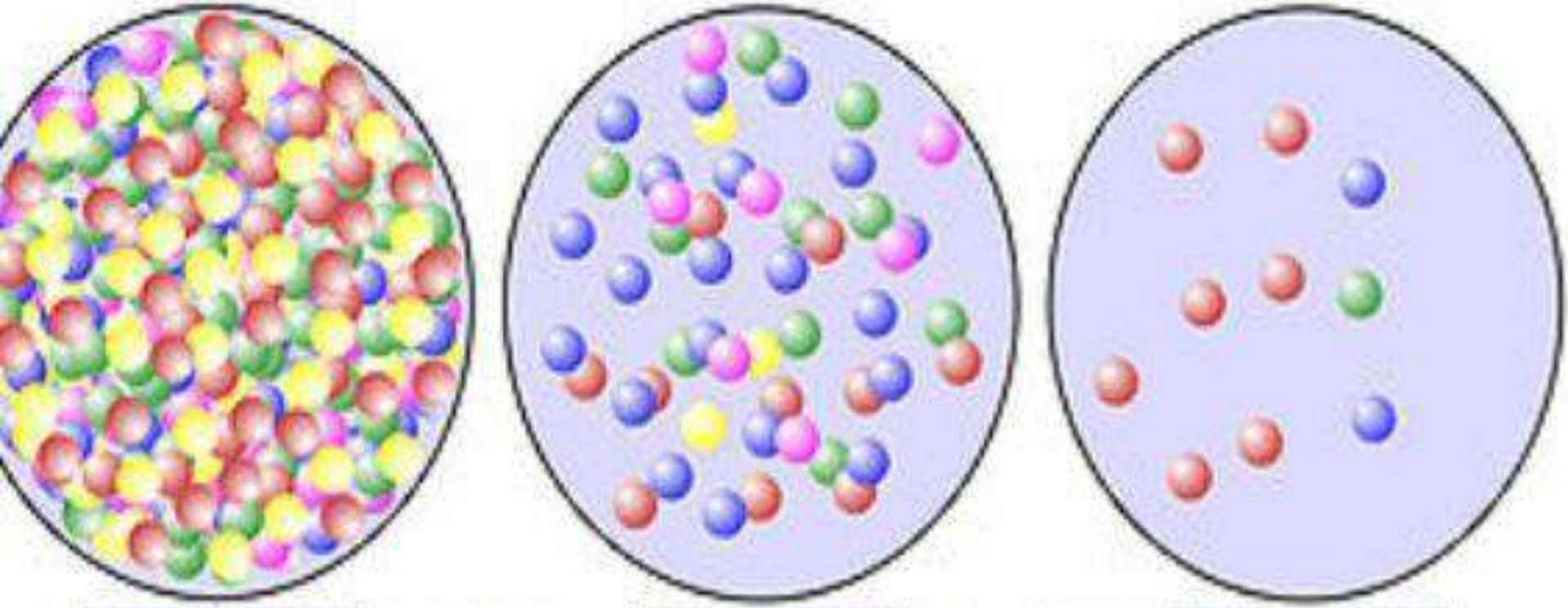
1-Migration (gene flow)

The phenomenon of migration, or so-called gene flow, is also a factor in changing the static, which contributes to the transition of the cells from static to other, which contributes to change. This phenomenon also contributes to the reduction of genetic differences between distant populations.


Population I
$f(a) = q_I$
Population II
$f(a) = q_{II}$
a allele
A allele
Migration
$f(a) = q_I$
$f(a) = q_{II}$
Population II
after migration
Migrants from
population I (m)
Residents from
population II (1 – m)

2-Natural selection

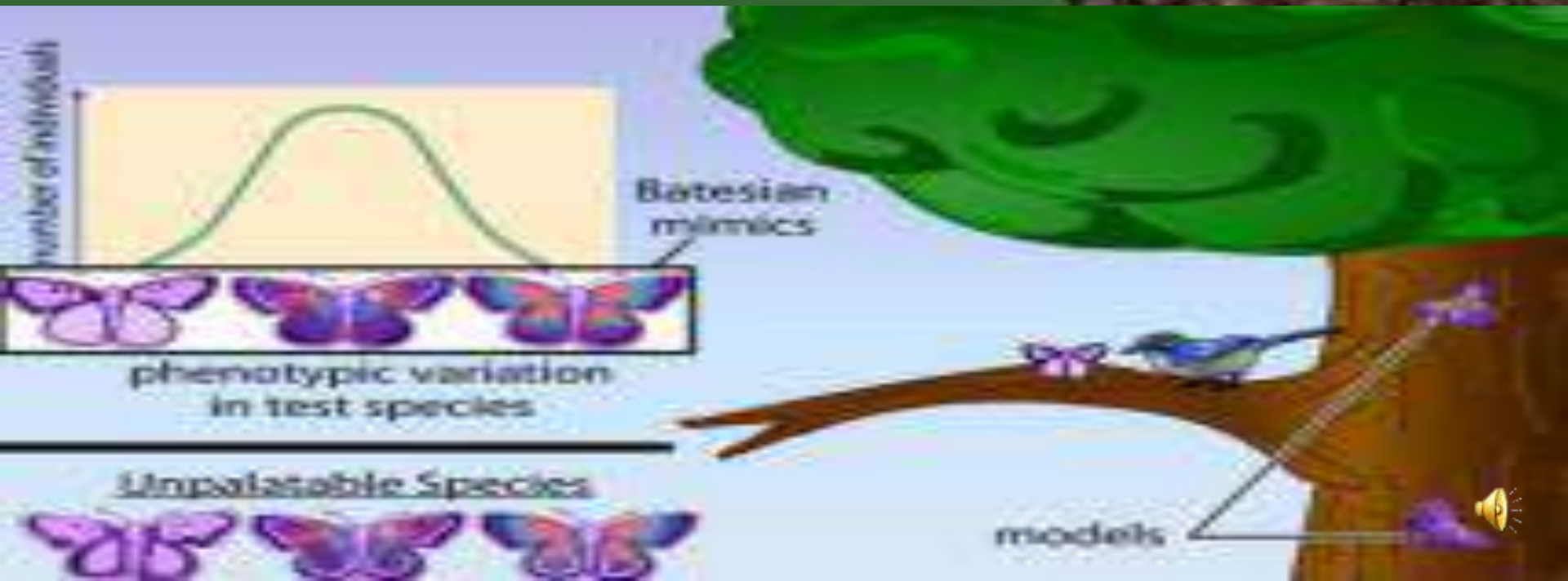
An important factor contributing to the change of population is the phenomenon of natural selection, since not all members of a given population have the same qualifications to survive, nor do they have the same ability to procreate and give a successor capable of living.



Initial frequency distribution	
	0.20
	0.20
	0.20
	0.20
	0.20

5th generation frequency distribution	
	0.40
	0.06
	0.20
	0.14
	0.20

10th generation frequency distribution	
	0.20
	0.00
	0.10
	0.00
	0.70


Batesian mimics
phenotypic variation in test species
Unpalatable Species
models

3- Genetic drift

Gene drift is another manifestation of population change. The number of real inhabitants is not always infinite, making the frequency of alleles fluctuating randomly, especially in low-income populations. This is caused by random fluctuation, the stabilization of alleles, and the deletion of other deer.

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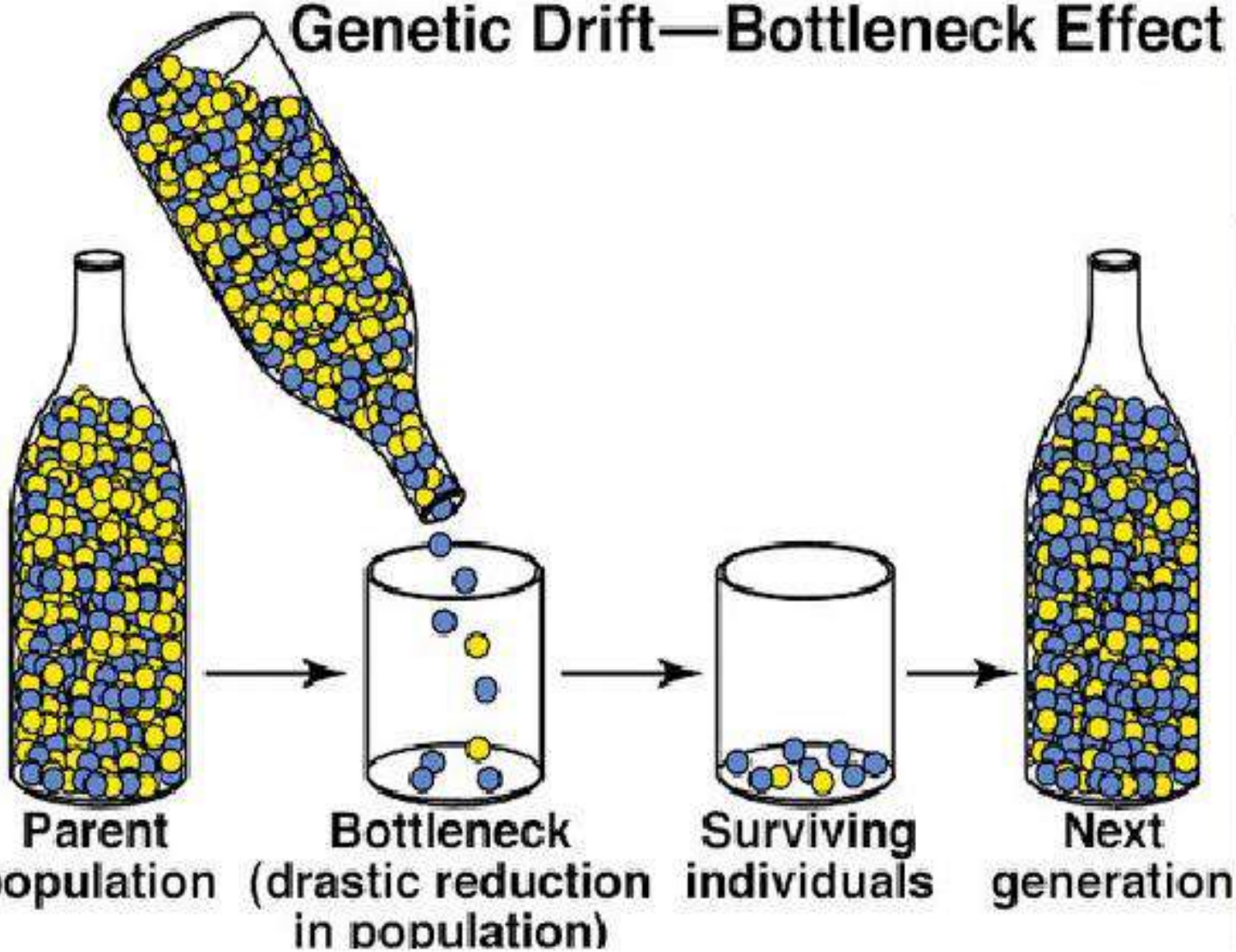
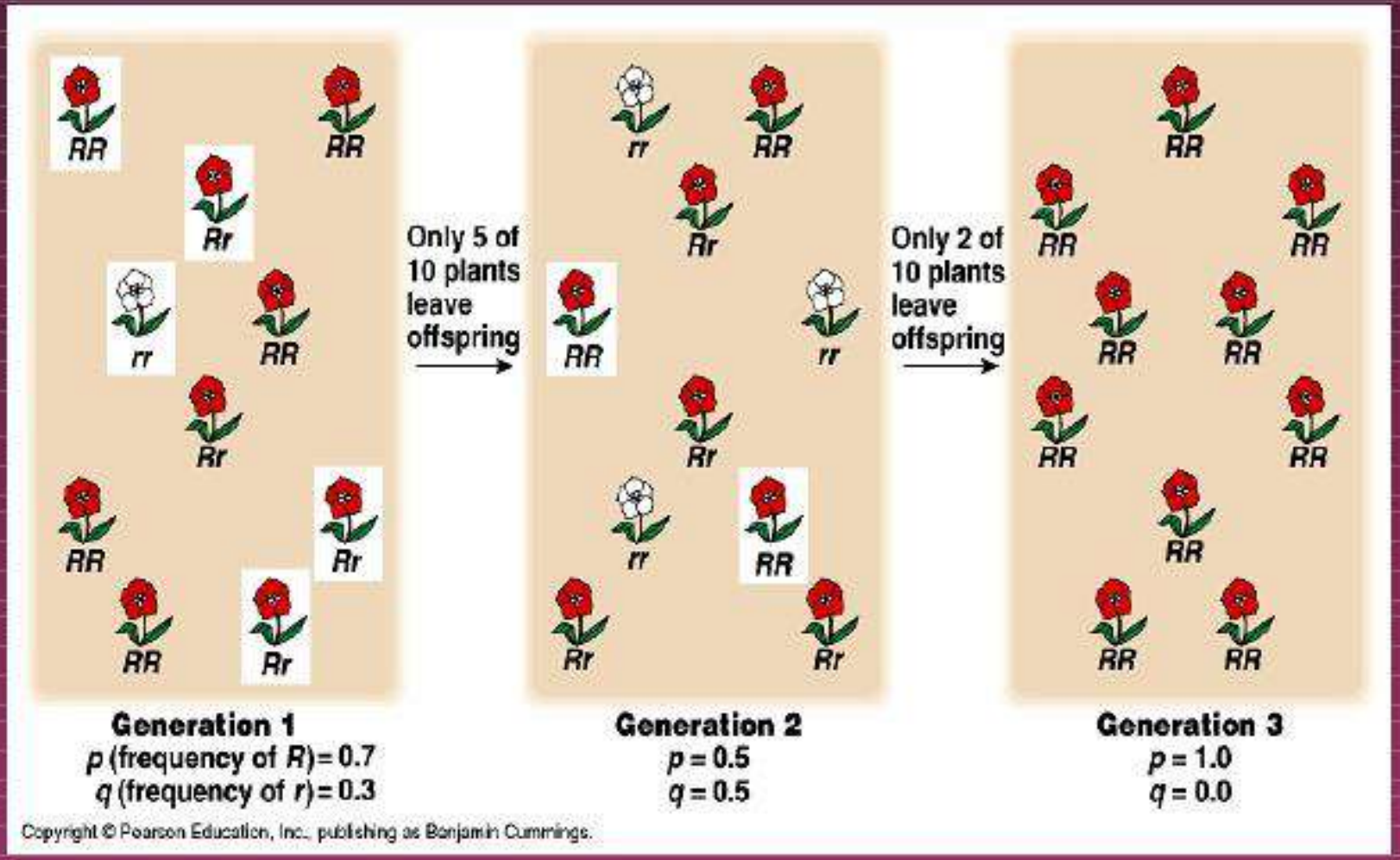
Genetic Drift—Bottleneck Effect



Illustrating Genetic Drift



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Population 1 : Allelic Frequencies

$$f(a) = q = f(aa) + \frac{1}{2} f(Aa)$$

$$q = \frac{8}{20} + \frac{1}{2}\left(\frac{8}{20}\right)$$

$$q = 0.4 + 0.2 = 0.6$$

Population 2 : Allelic Frequencies

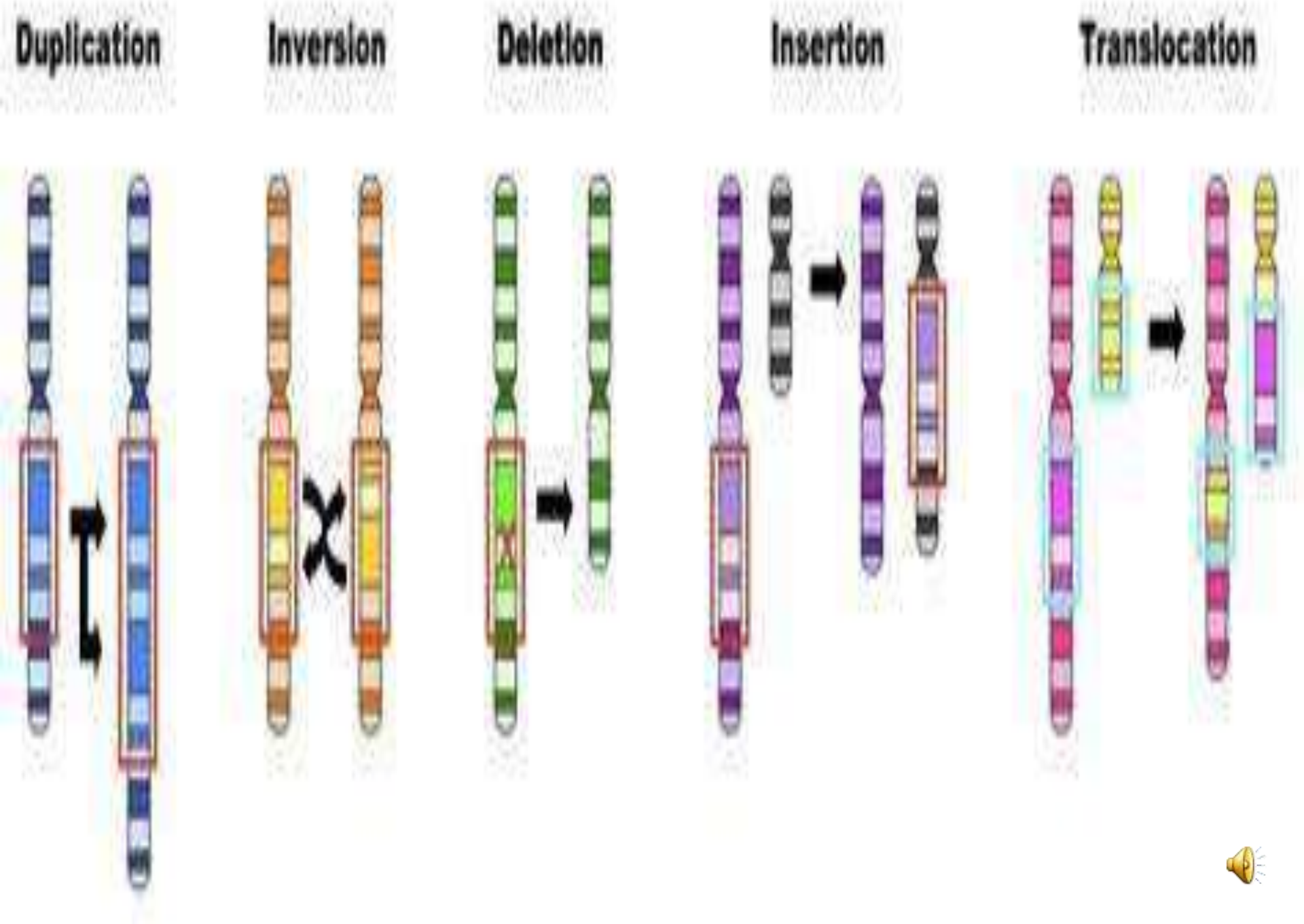
$$f(a) = q = f(aa) + \frac{1}{2} f(Aa)$$

$$q = \frac{6}{20} + \frac{1}{2}\left(\frac{12}{20}\right)$$

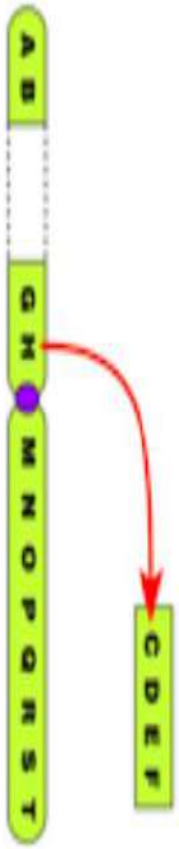
$$q = 0.3 + 0.3 = 0.6$$

4-Mutations

Mutation is a sudden change occurring at the level of the gene, in its chemical composition or position, and is characterized by spontaneity and scarcity. When mutations affect the host cells (the mother cells of the gametes), they are hereditary. Mutations are also characterized by diversity, with point mutations and chromosomal mutations.


Duplication
Inversion
Deletion
Insertion
Translocation

Deletions

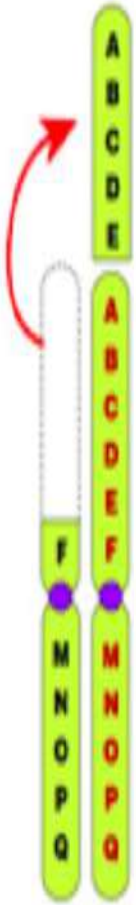


Chromosme Segment Lost

Translocation

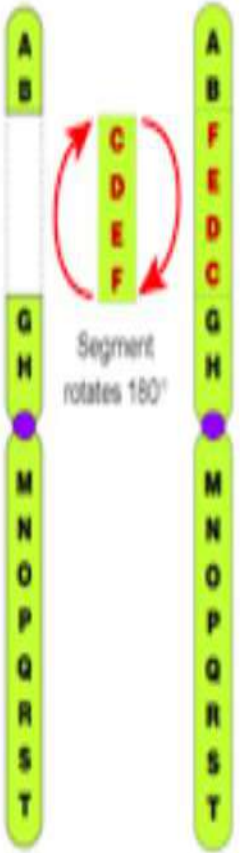
A segment from chromosome is transferred to another

Duplication



A segment from one chromosme is transferred to its homologous chromosme, giving it a duplicate of some genes

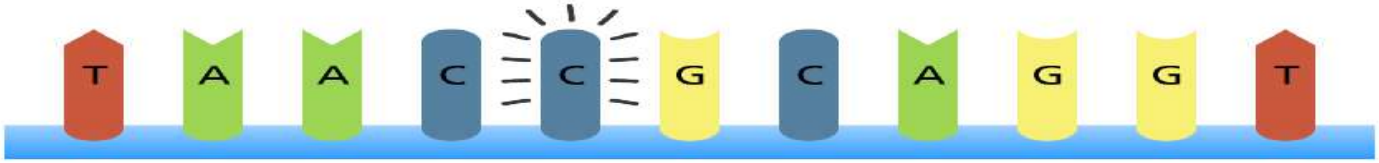
Inversion



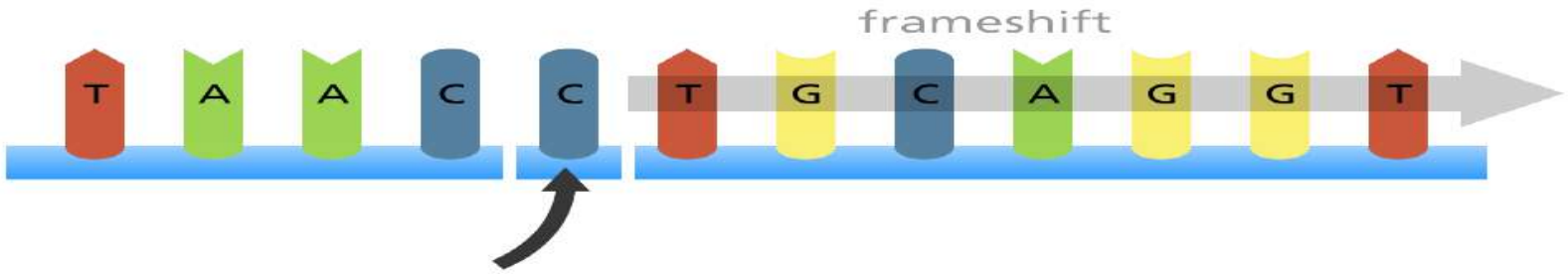
A segment of a chromosme arm is inverted

Original sequence

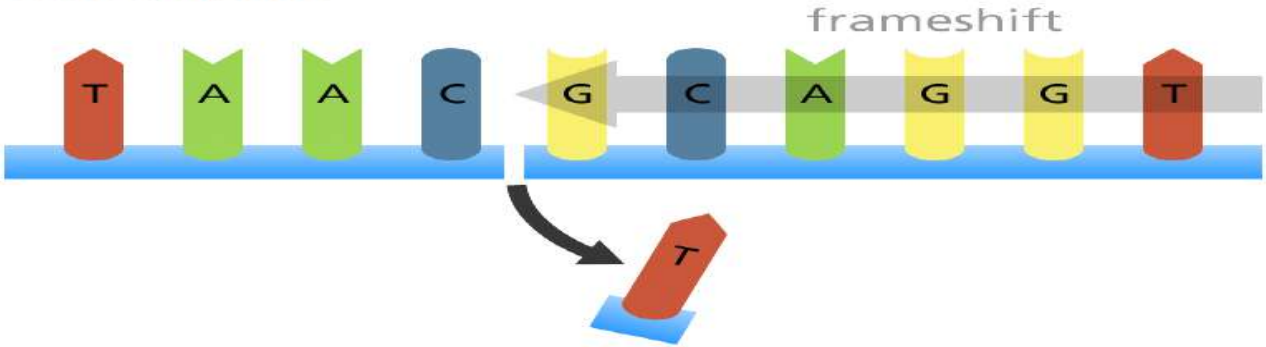
Base substitution



Base addition



Base deletion



Hardy-Weinberg equilibrium (1908)

Frequency of alleles and genotypes in a population will remain constant from generation to generation if the population is stable and in genetic equilibrium

Five conditions

1. A large breeding population
2. Random mating
3. No mutation
4. No immigration or emigration
5. No natural selection

Conditions necessary for HW equilibrium:

1. Large population
2. Random mating
3. No genetic drift
4. No gene flow - migration
5. No natural selection
6. No mutations

Animation of gene frequencies changing

http://zoology.okstate.edu/zoo_lrc/biol1114/tutorials/Flash/life4e_15-6-OSU.swf

Hardy-Weinberg equations

- Allele frequency:
  - Let p = frequency of the dominant allele
  - Let q = frequency of the recessive allele
  - Then, $p + q = 1$
- Genotype frequency:
  - p^2 = frequency of homozygous dominant genotype
  - q^2 = frequency of homozygous recessive genotype
  - $2pq$ = frequency of heterozygous genotype
  - $p^2 + 2pq + q^2 = 1$

The Hardy-Weinberg Principle

frequency of homozygous dominant genotype

frequency of homozygous recessive genotype

$$p^2 + 2pq + q^2 = 1$$

frequency of heterozygous genotype

Epigenetics Genetics/th. Class

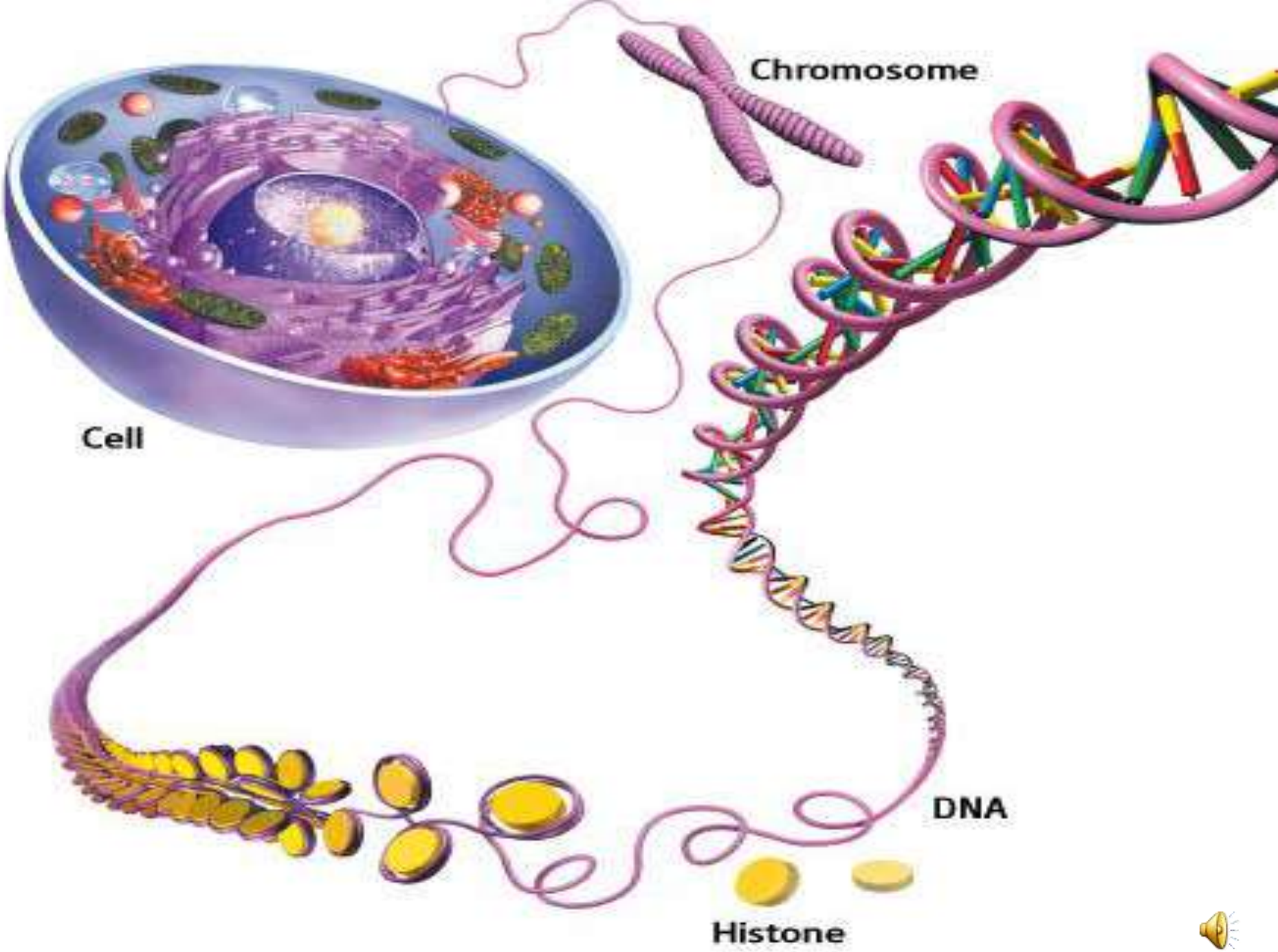
Lectures thirteen & fourteen

Dr. Ibtesam B. Hassan

What is Epigenetics?

- Epigenetics is the study of inherited changes in phenotype (appearance) or gene expression caused by mechanisms other than changes in the underlying DNA sequence.
-
- These changes may remain through cell divisions for the remainder of the cell's life and may also last for multiple generations.

- Changes in gene expression that do not involve alterations in DNA base sequence


Chromosome
Cell
DNA
Histone

Genetics vs. Epigenetics

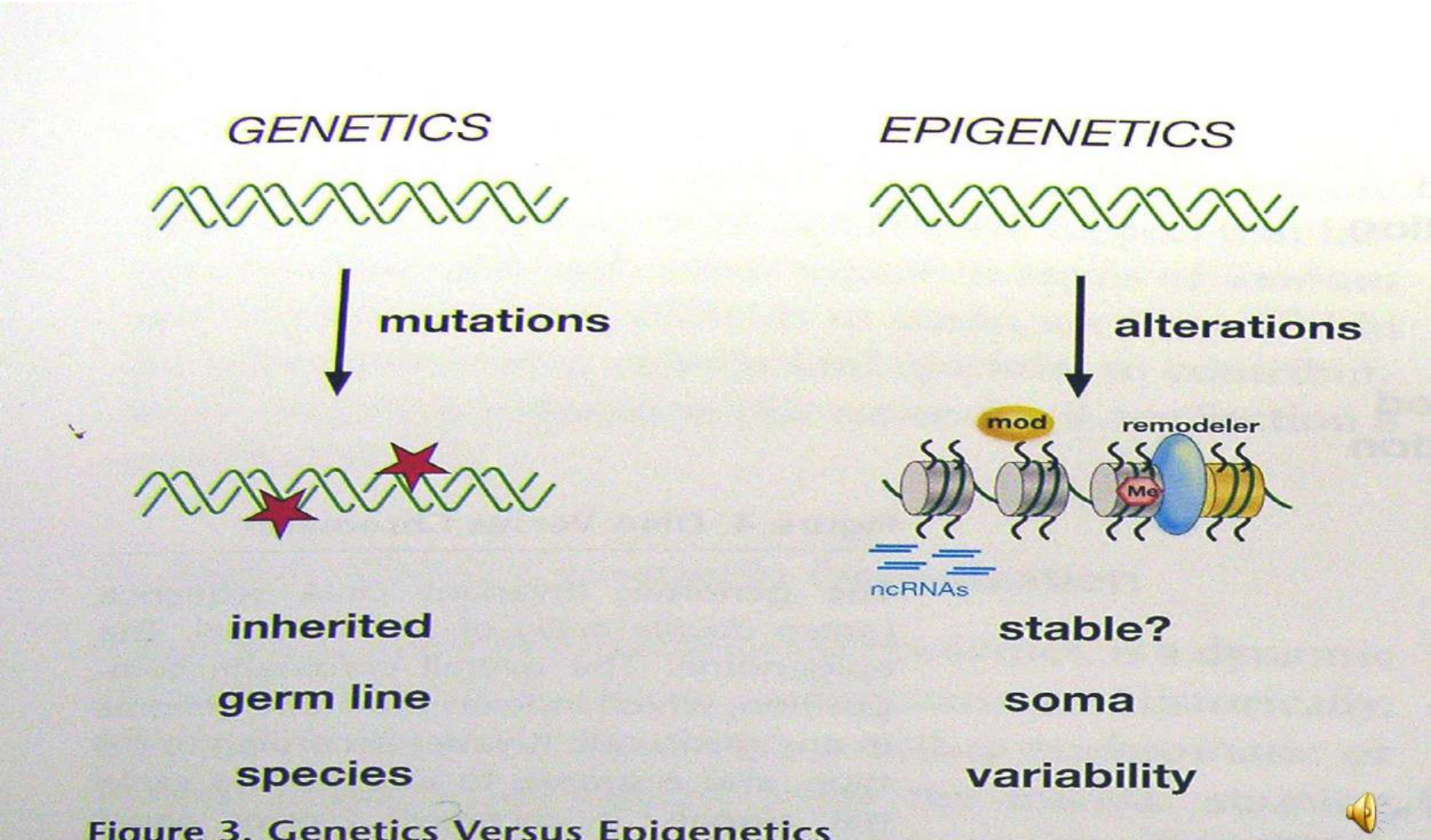


Figure 3. Genetics Versus Epigenetics

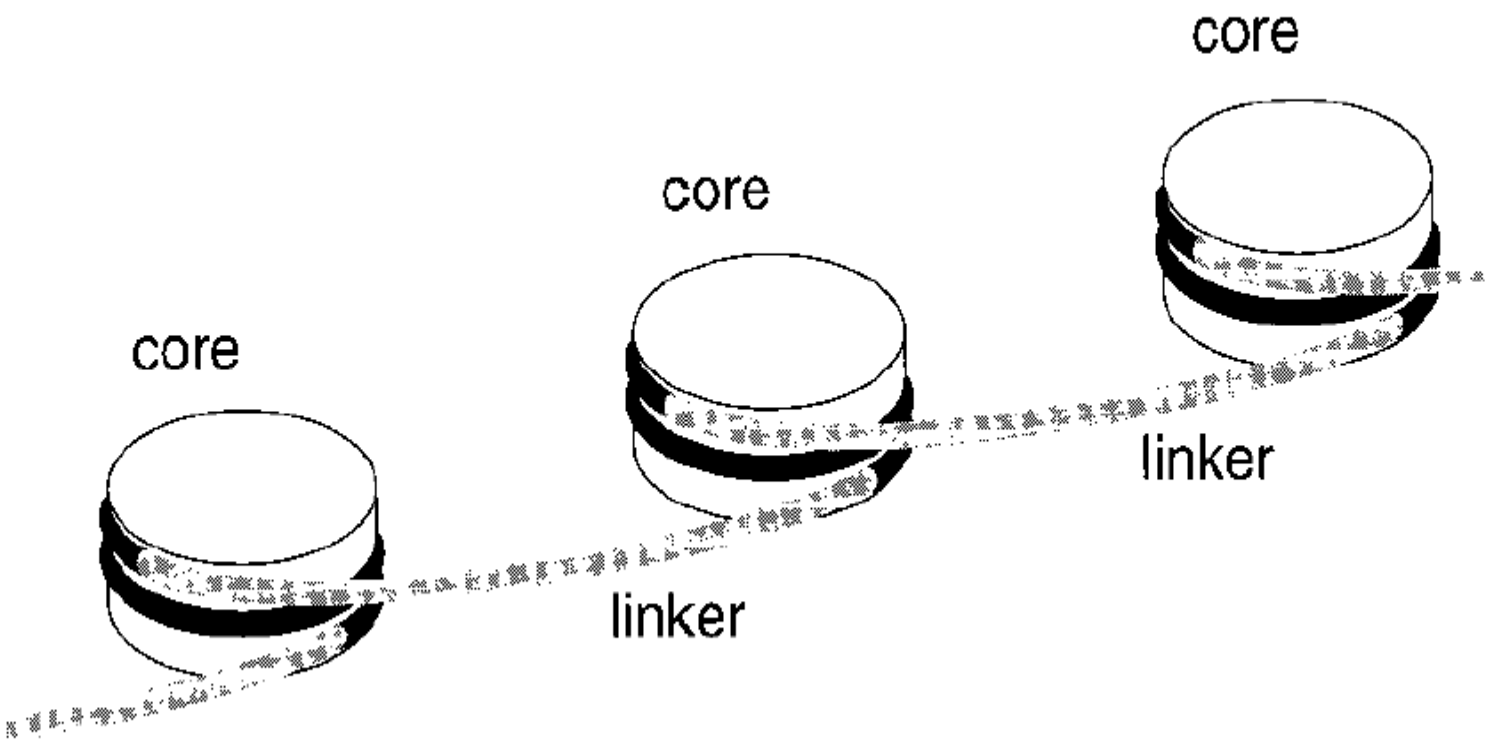
Epigenetic Modifications

DNA Methylation

Histone Modification (e.g. Acetylation, methylation)

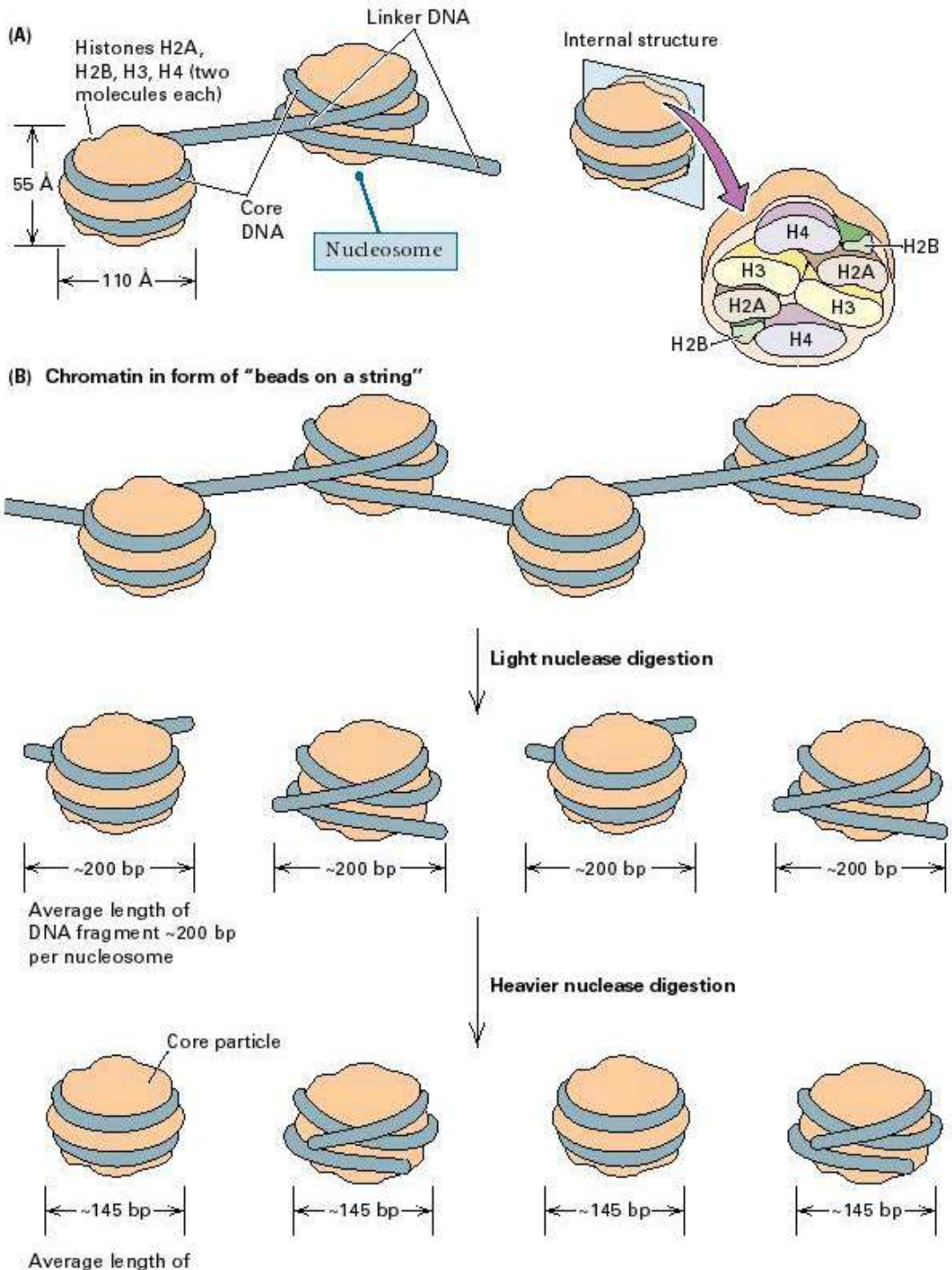
Non-coding RNAs (e.g. microRNA)

All Regulate Gene Expression

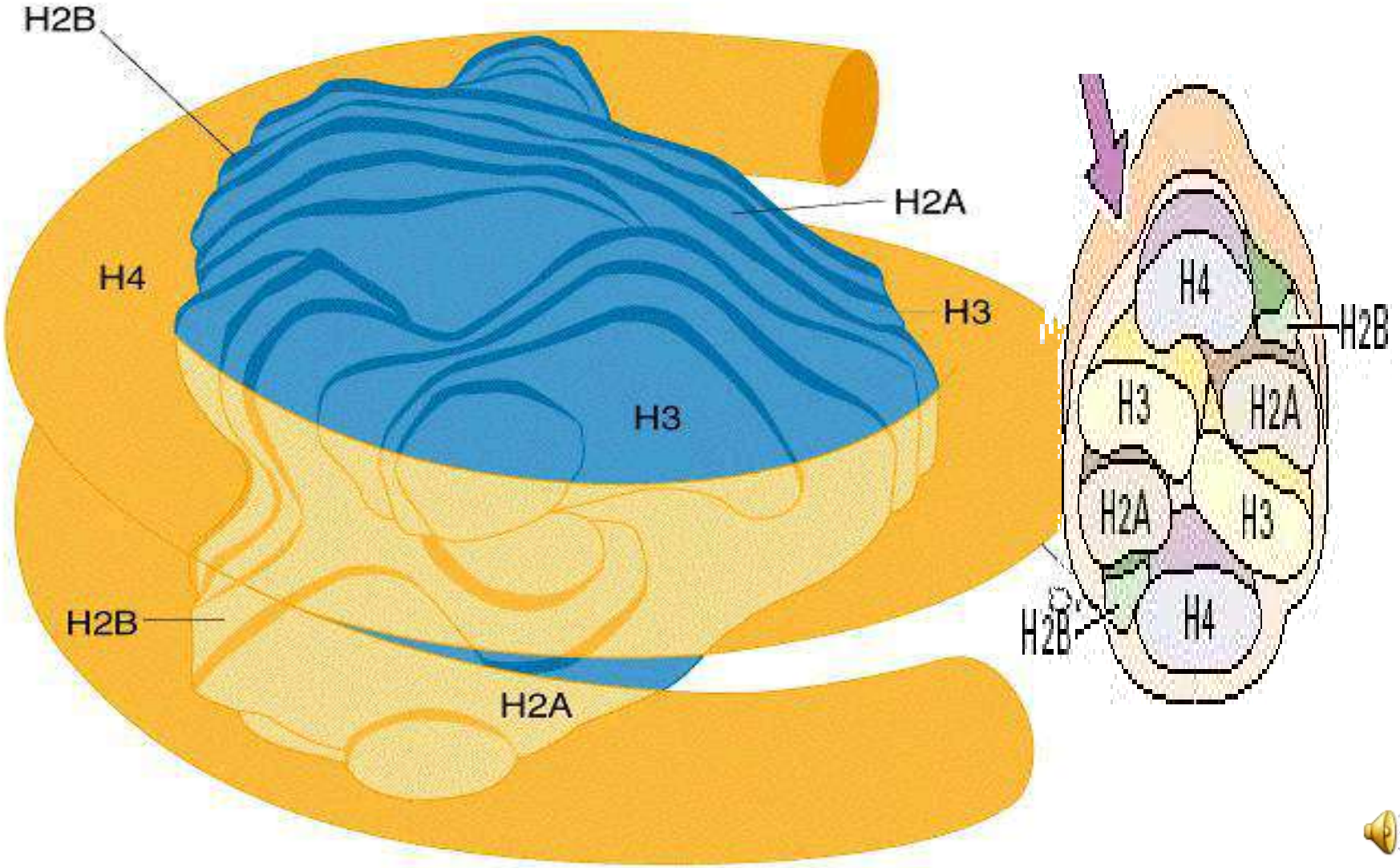


Twenty-Five Years of the Nucleosome,
Fundamental Particle of the Eukaryote Chromosome
Roger D. Kornberg and Yahli Lorch; Cell, 1999.

Nucleosome:
147 bp of DNA
Histone octamer
= 1.7 turns



The nucleosome: histones plus DNA

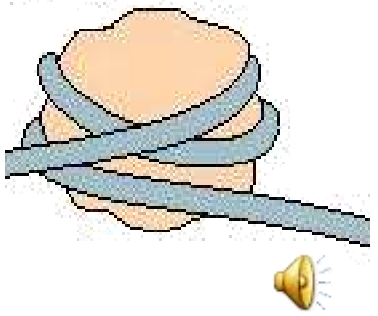


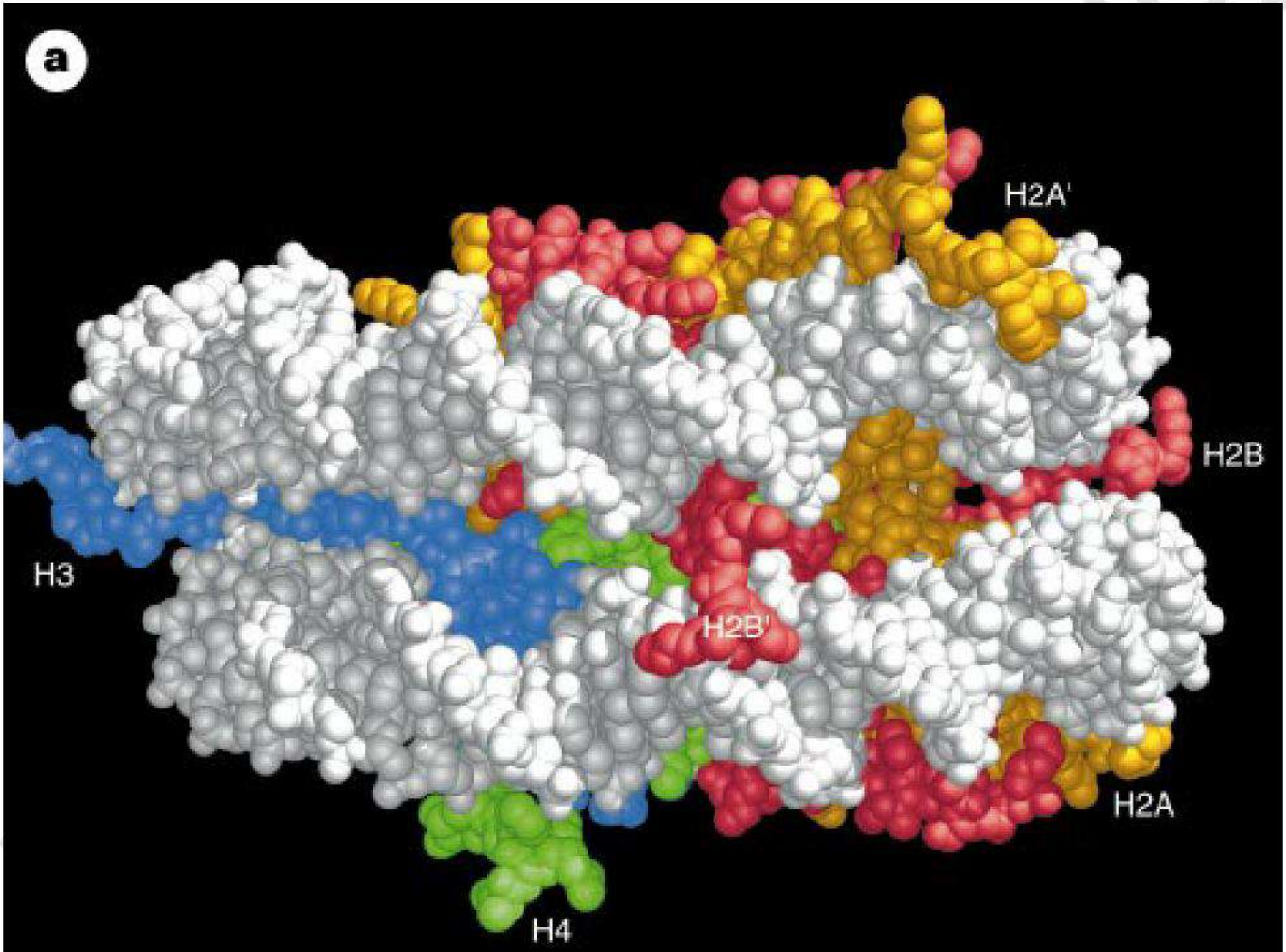
Chromatin: nucleosomal arrays

Nucleosome: DNA plus histone octamer

DNA wound around the histone octamer: core DNA

DNA between nucleosomes: linker DNA




a
H2A'
H2B
H3
H2B'
H2A
H4

Two classes of histones (canonical)

Core Histones

H2A conserved

H2B conserved

H3 highly conserved

H4 very highly conserved

Linker Histones

H1 not conserved

Small proteins, ca. 10 kD, very basic

Three domains

A. Histone fold

B. Histone fold extension

C. Extended N (and C)-termini

Euchromatin

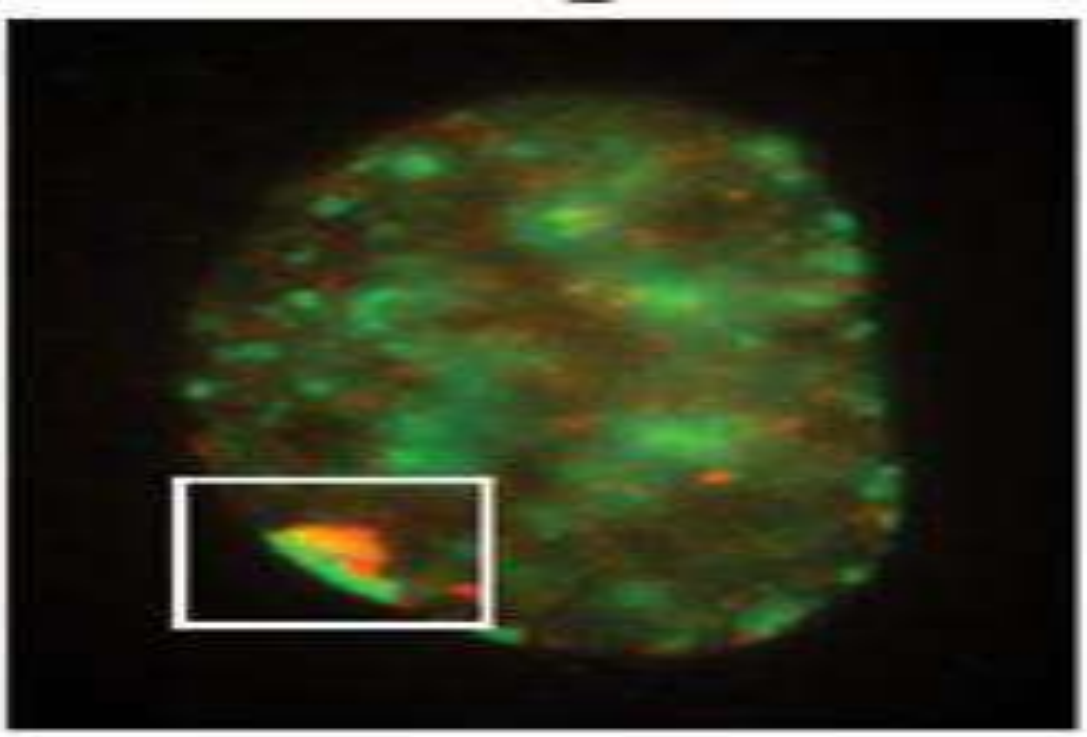
Transcriptionally active, less compacted

Heterochromatin

Less transcriptionally active, very compacted

a) constitutive heterochromatin
centromeres, telomeres

b) facultative heterochromatin
rDNA, transposons, inactive X chromosome



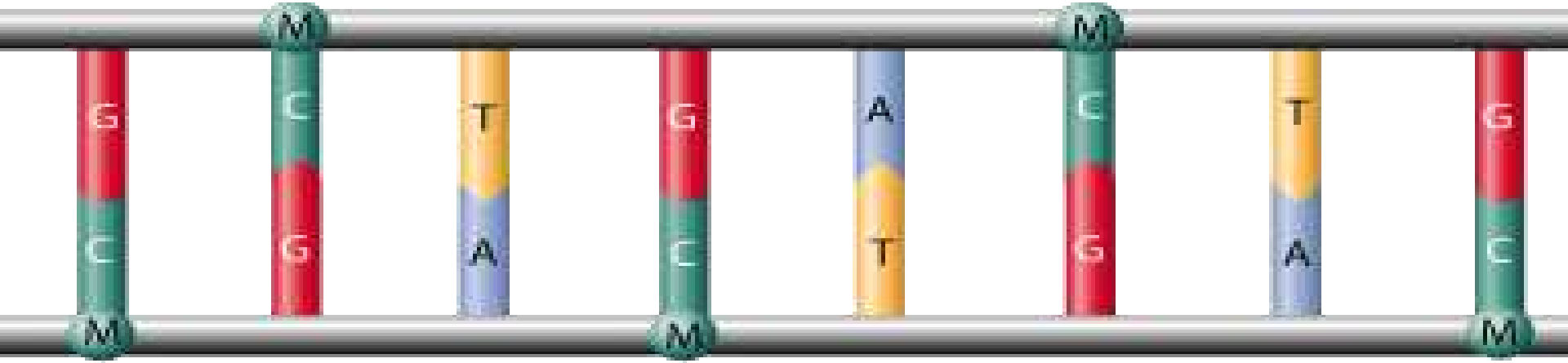
Barr Body Region

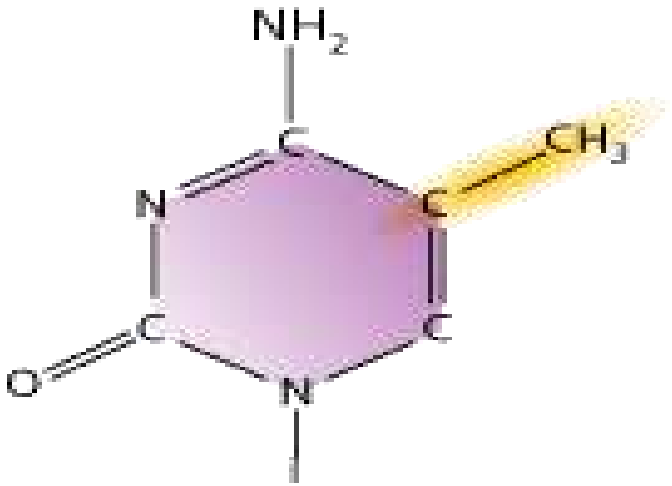
* Immunofluorescent straining of the human interphase nucleus.

* The white box indicates the Barr body region where the inactive X chromosome resides during interphase.

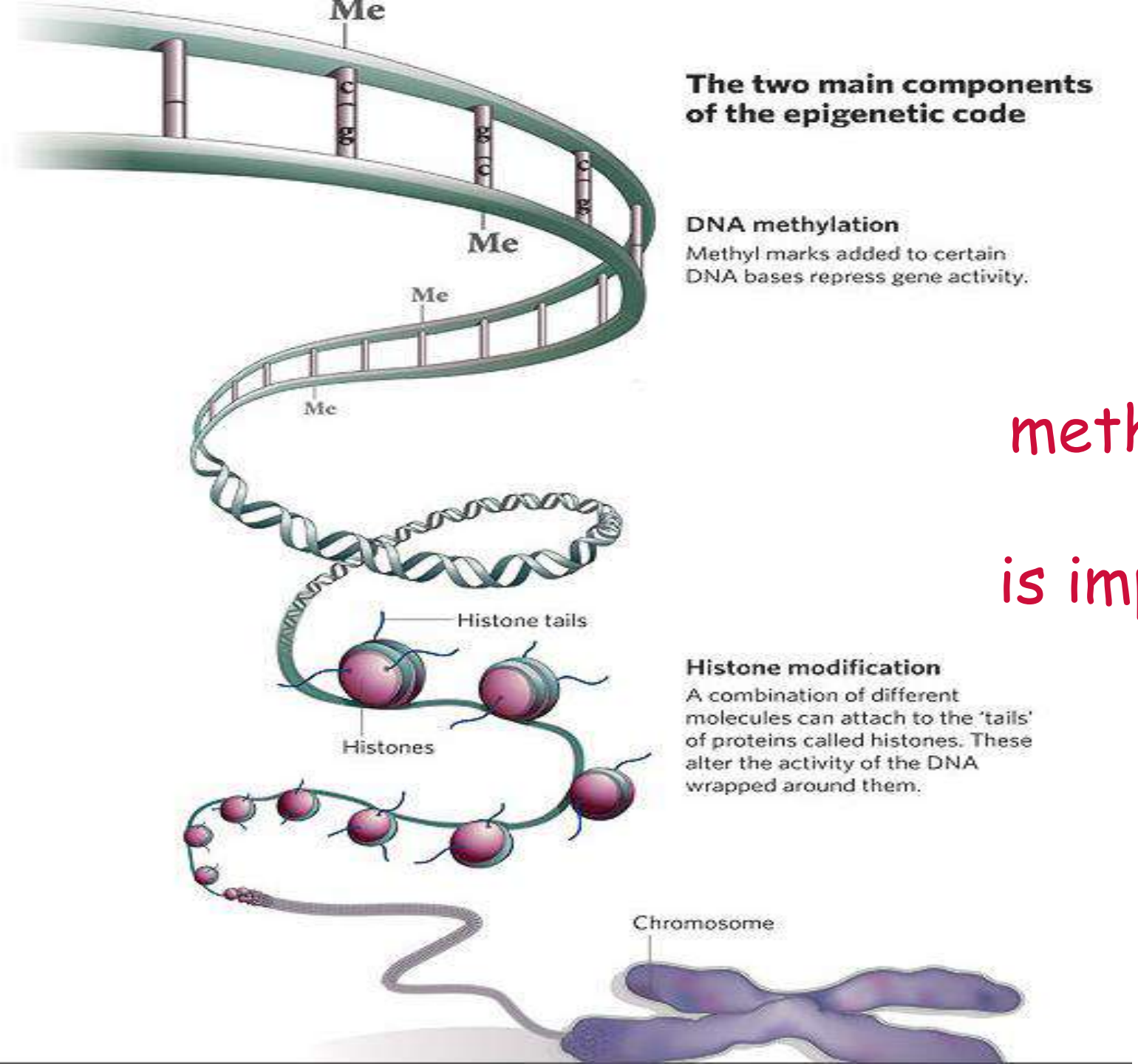
Chadwick and Willard (2004) PNAS

DNA methylation is the addition of a methyl group to the carbon-5 position of cytosine residues.



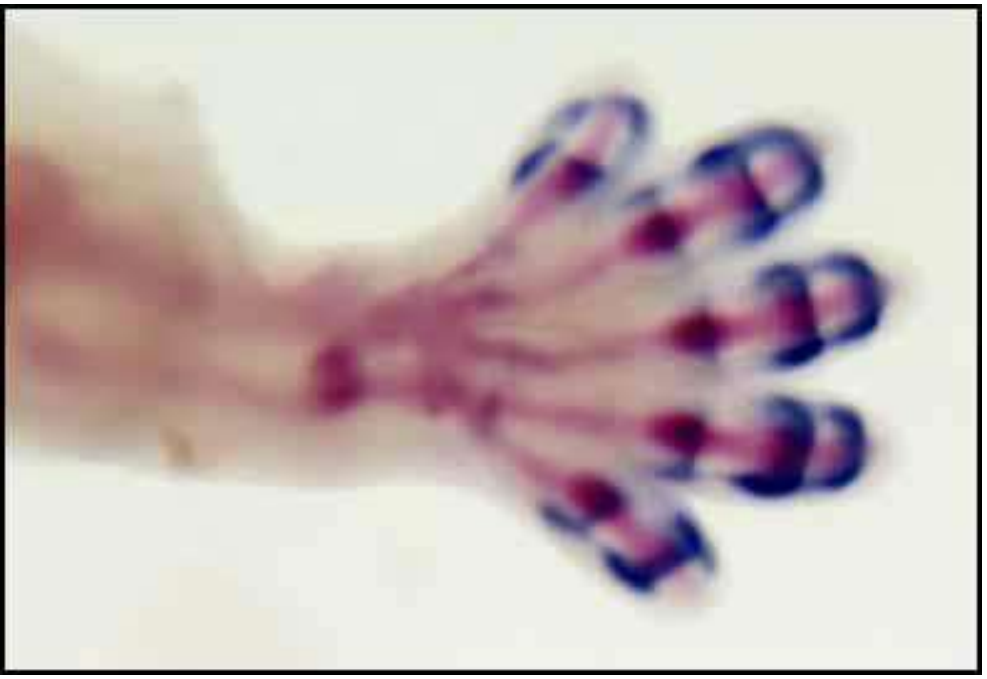


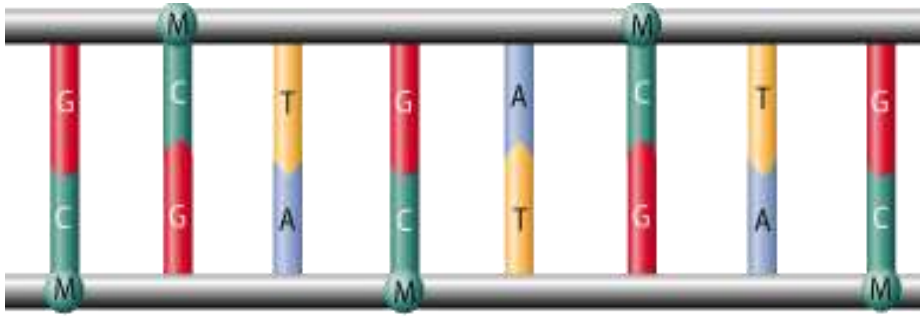
DNA methylation is the addition of a methyl group (M) to the DNA base cytosine (C).

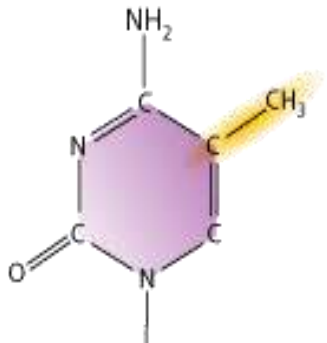


DNA methylation status is important

aims to identify, catalogue and interpret genome-wide DNA methylation patterns of all human genes in all major tissues.
Methylation is tissue specific and is of major importance in the regulation of gene expression during development.







DNA methylation is the addition of a methyl group (M) to the DNA base cytosine (C).

All levels of chromatin condensation have been implicated in controlling accessibility of the genomic DNA

effect on:
replication, recombination, repair, and transcription

Mechanism exist to "condense" chromatin

- Histone modifying enzymes
- alter histone tail modifications

- DNA methylases,

- Recruitment of chromatin binding proteins
- Polycomb proteins
- Heterochromatin Protein

Can alter gene activity without change in DNA

Epigenetic/chromatin phenomena

- Chromatin-based restriction of genome accessibility during
- differentiation
- Selective activation of genome after perception of stimulus
- (influence of environment/stress)

- Mitotic maintenance of cell identity (or loss there of in cancer)
- Dosage compensation in the male versus female genome
- (X inactivation in mammals)
- Memory, Behavior, Aging

cancer

- The human body is prone to developing cancer, from a very early stage of life, until the end of life.
- The human genome has several built in tumour suppressor genes, whose protein products suppress the formation of tumours. It is important for these genes to continue expressing their tumour suppressor proteins as long as the person lives.
- One way these genes can lose their ability to make protective proteins is through methylation.

Epigenetics and The Environment

- Epigenetic changes can be inherited mitotically in somatic cells
- Pre-natal and early post-natal exposures can result in changes in risk of developing disease
  - Nutrition
  - Xenobiotic chemicals
  - Behavioural Factors
  - Reproductive Factors, Hormonal Exposures

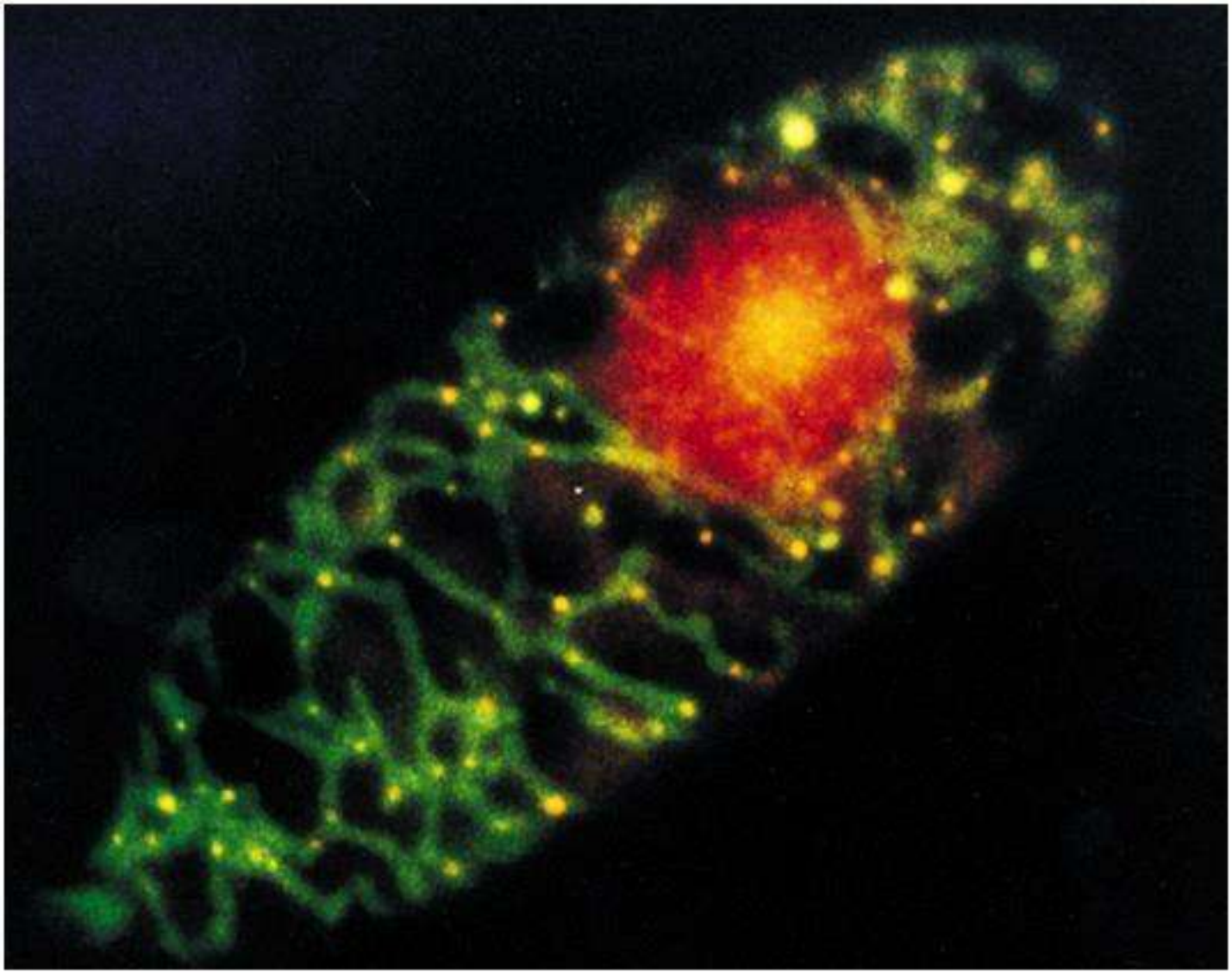
  Epigenetic alterations may also be inherited transgenerationally (developmental origins of adult-onset disease)

Genetics/th. Class

Mitochondrial DNA

Lec. 12

Dr. Ibtesam B. Hassan



Mitochondrial DNA

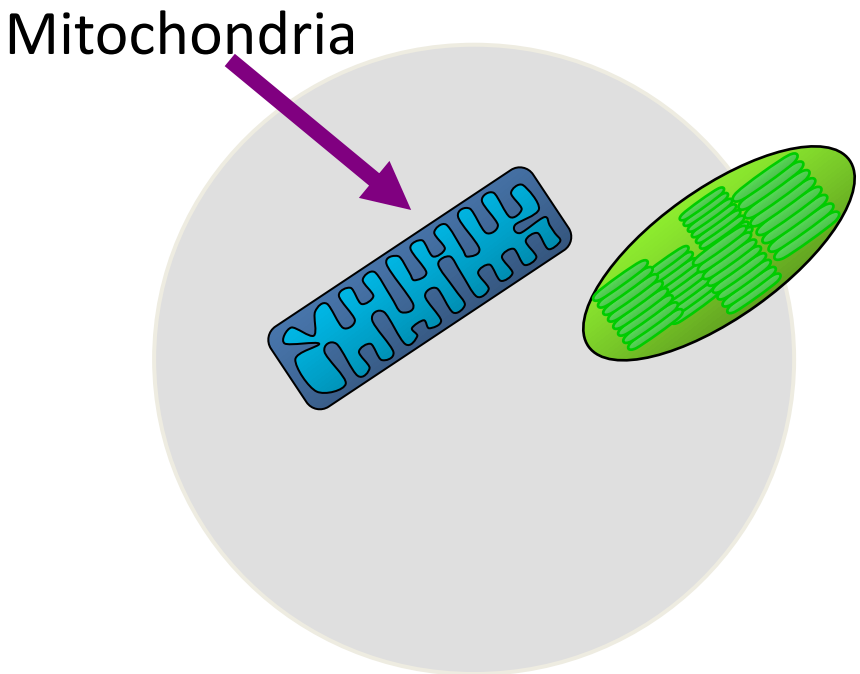
- Another type of DNA used for individual characterization is mitochondrial DNA.
- Mitochondrial DNA (mDNA) is located outside the cell's nucleus and is inherited from the mother.
- Mitochondria are structures found in all our cells used to provide energy that our bodies need to function.

- Mitochondria and chloroplasts have their own DNA
- This extra nuclear DNA exhibits non-Mendelian inheritance
- Extra nuclear DNA may also be called cytoplasmic DNA
- Generally mtDNA and ctDNA is circular and contains genes for multimeric proteins, some portion of which are also coded for in the nucleus
- Extranuclear DNA has a rate of mutation that is independent of nuclear DNA
- Generally, but not always, all the RNAs needed for transcription and translation are found in mtDNA and ctDNA, but only some of the protein genes

Origin of Eukaryotes

Two popular theories presupposing naturalism seek to explain the origin of membrane bound organelles:

1. **Endosymbiosis** to explain the origin of mitochondria and chloroplasts (popularized by Lynn Margulis in 1981)
2. **Invagination** of the plasma membrane to form the endomembrane system



Mitochondrial genome

- Human mtDNA
  - 16,751 nucleotides
  - 37 genes: 22 for tRNA
    2 for rRNA (12S, 16S)
    13 for oxidative phosphorylation enzymes
  - No introns

Human mtDNA mutations

- Mutations in human mtDNA cause diseases called mitochondrial cytopathies
- Affect organs with highest energy demand

(muscles, nerves)

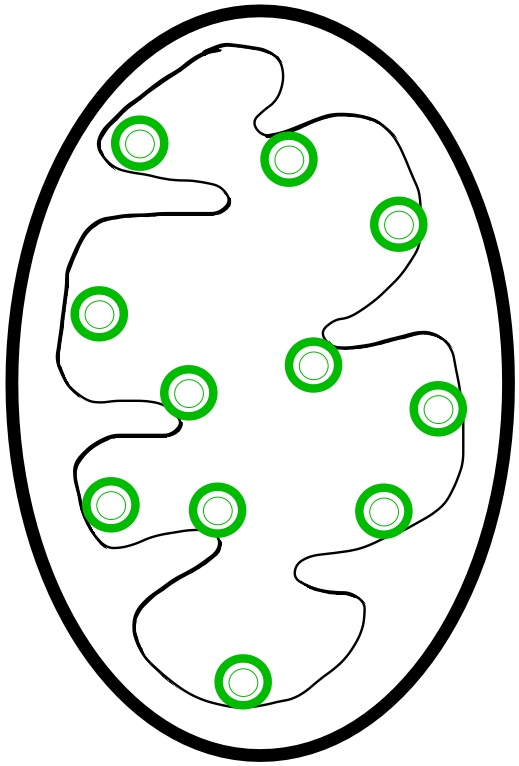
- MERRF
  - Myoclonic epilepsy and ragged red fibers
  - Muscle disease
  - G8344A point mutation
- Kearns-Sayre syndrome
  - Neuromuscular disorder
  - 5 kb mtDNA deletion (crossover between 13 bp repeats)

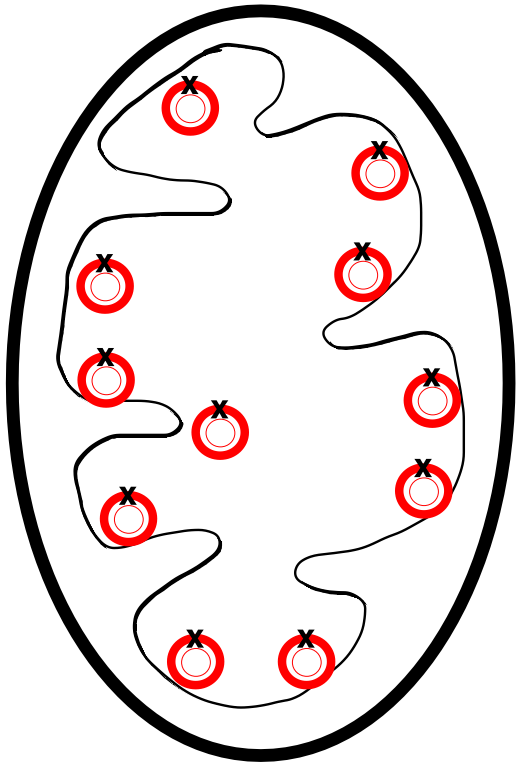
Homoplasmic

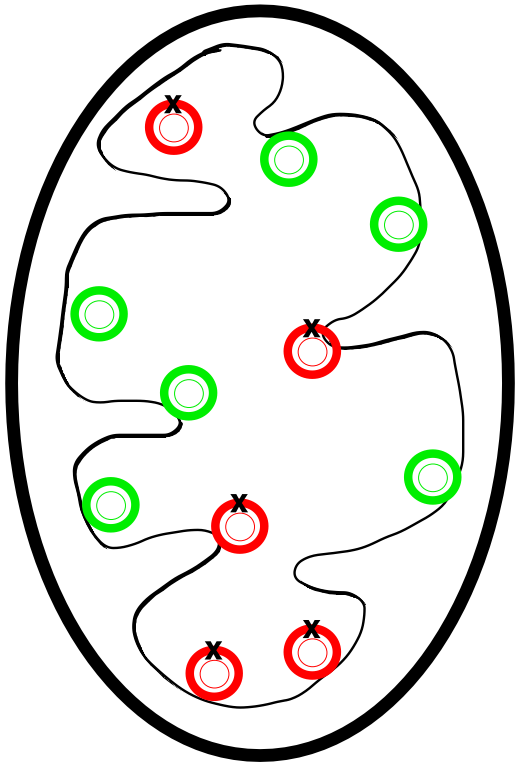
Heteroplasmic

wild type

mutant



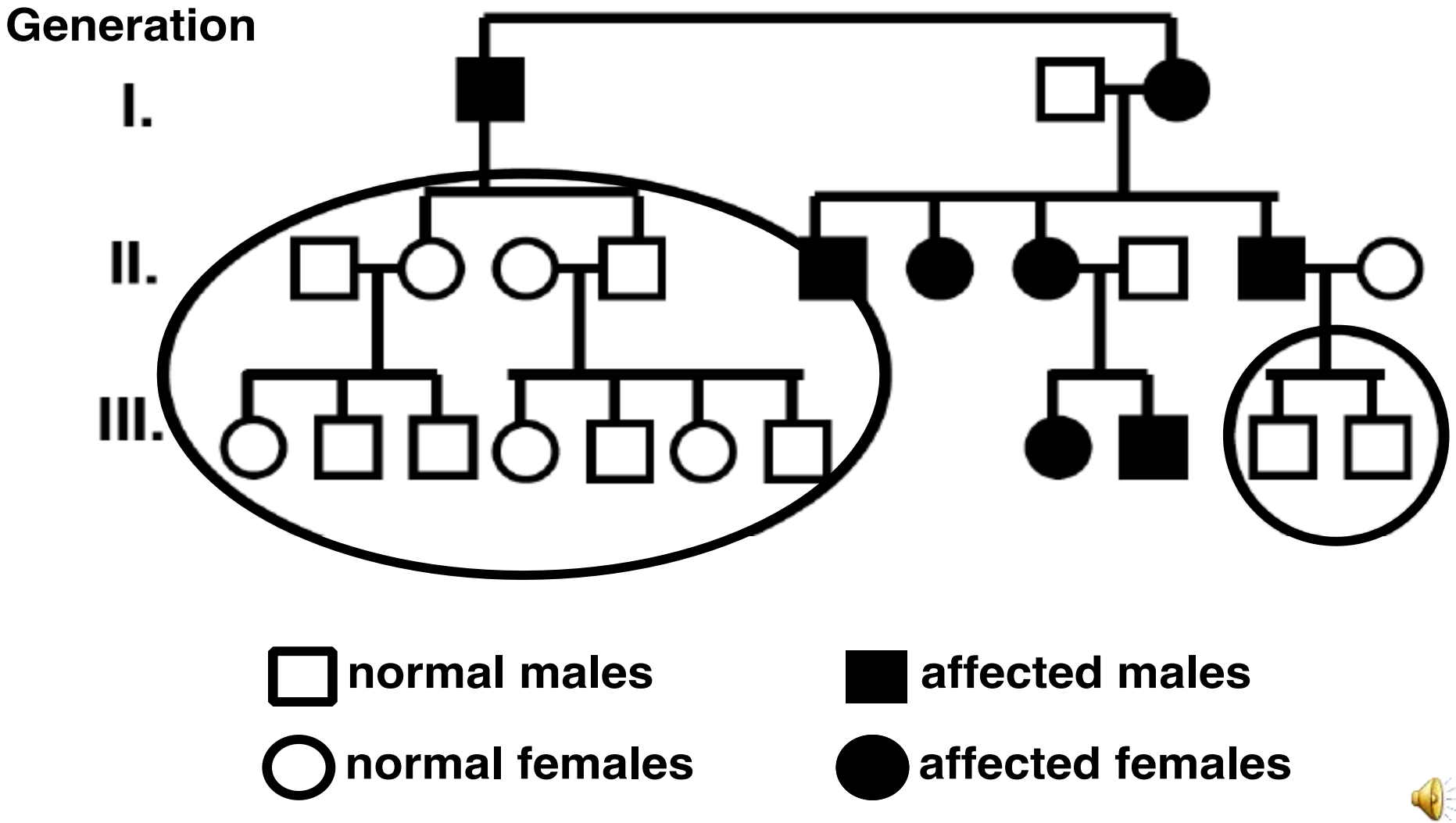


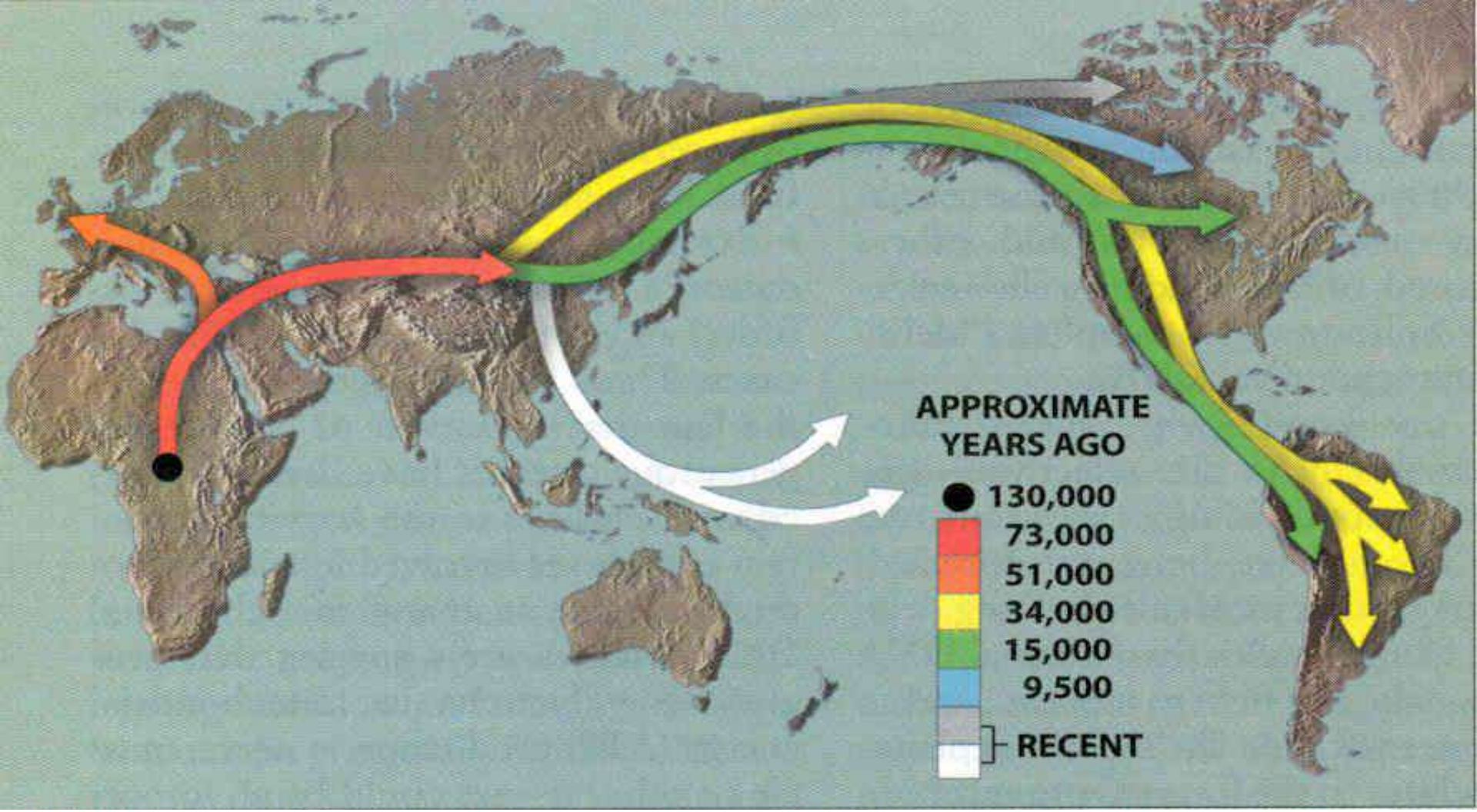


wild type mtDNA

mutant mtDNA

Maternal inheritance pedigree





All humans descend from a small group of Africans

This group originated in central Africa ~200,000 years ago

The founding group was small (10^2-10^4 people)

Descendants of this group replaced all other hominids everywhere in the world

What is Mitochondrial disease?

- Range of symptoms (can be late onset) – extreme tiredness, heart problems, diabetes, difficulties with mobility/ balance, deafness, epilepsy, myopathy, MERRF, MELAS, KSS, PEO
- Mitochondrial disease can be due to mutations in nuclear DNA or mitochondrial DNA
- Diseases caused by mutations in mitochondrial DNA are inherited through the maternal line.

HOW THE EMBRYOS ARE MADE