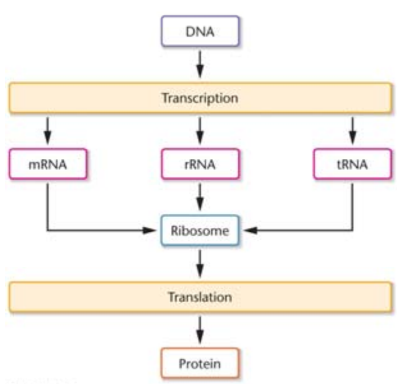
MOLECULAR ANATOMY OF CHROMOSOMES, GENES AND GENOMES

Threshold Concepts

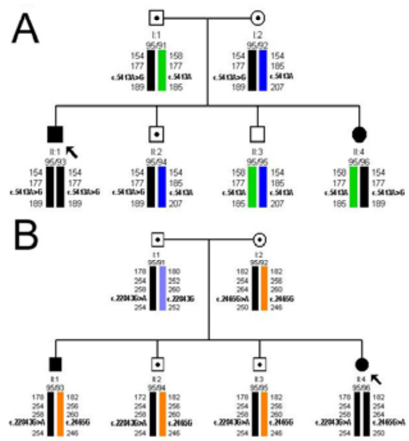
The Scene

Chromosomes, genes, genomes; gene expression (transcription and translation); gene interactions and complementation; mutations; meiosis (segregation, assortment, and gene linkage)



Classical Genetics & Molecular Genetics

Genetic investigations; model organisms; genetic markers; laws of probability; inheritance; family histories; non-Mendelian inheritance; gene linkage and genome mapping; recombinant DNA technology; gene targeting technologies; bioinformatics and genomics; epigenetics; forensics; genetic engineering



Working Knowledge

1) to use the concepts to analyze and interpret biological data and relate them to information from different sources to arrive at a defensible conclusion, and

2) to apply the concepts to formulate hypotheses and predictions and design experimental approaches to test them.

How to study in this course

Review the concepts in such a way to be able:

1) to scrutinize information to form a mental representation of the concepts,

2) to summarize the assumptions underlying biological theories and hypotheses that have led to the concepts.

LEARNING OBJECTIVES

1. **Describe the molecular anatomy of genes and genomes:**

- Discuss the hallmark features and organization of chromosomes.
- Describe the hallmark features and organization of genes and explain the role of each of these features.
- Describe the hallmark organization of genomes.
- Describe the cytological anatomy of chromosomes.
- Discuss different types of DNA sequence organization.
- Define key terms and solve problems.....

Genetics as an investigative tool.

- November 21, 1983, tragic sudden death of 15 yr old girl
- Location – "Black Pad" – lonely footpath dividing cemetery from the local psychiatric hospital in village of Narborough, UK.
- Death – by asphyxia (by strangulation); evidence of sexual assault.

- August 1, 1986, body of another 15 yr old girl found.
- Location – "Ten Pound Lane" in village of Enderby, fairly close to where 1st murder occurred.
- Death – by strangulation; evidence of sexual assault

- Semen found at both murder scenes analyzed – serological protein
- Perpetrator ("contributor") semen found at both murders – had phosphoglucomutase (PGM+1) secretor A status
    - ~ 10% of male population of Britain

Genetics as an investigative tool.

The case of these murders made legal history - why?

- Alec Jeffreys had developed a procedure called 'DNA fingerprinting'
- Used 1st time in this case to compare sample from prime suspect to evidence found at the crime site.
    - Exonerated the suspect as innocent
    - Linked both murders through identical genetic sequence

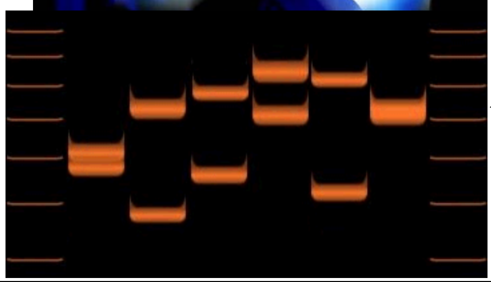
- 1987 – extensive investigation
- Compared > 4 000 serological & genetic profiles of potential male inhabitants in area → ended up matching 1 person
    - Colin Pitchfork arrested;
    - 1988 found guilty; 1st person convicted for murder based on genetic fingerprinting

Genetics as an investigative tool.

What is DNA fingerprinting?

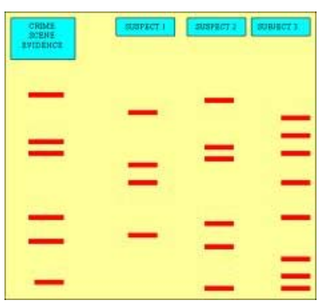
http://users.wmin.ac.uk/~redwayk/lectures/probes.htm

Not DNA fingerprinting



DNA fingerprinting

PCR: http://highered.mcgraw-hill.com/olcweb/cgi/pluginpop.cgi?it=swf::535::535::/sites/dl/free/0072437316/120078/micro15.swf::Polymerase%20Chain%20Reaction



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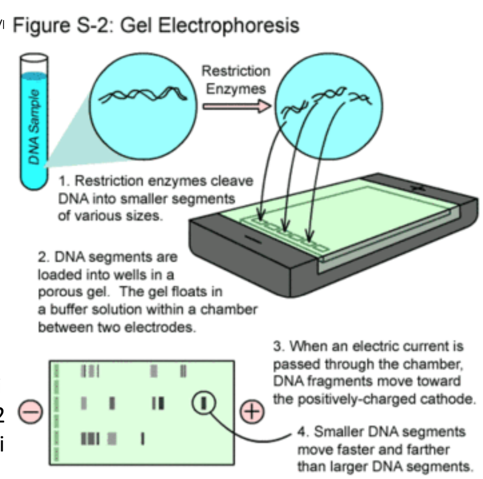
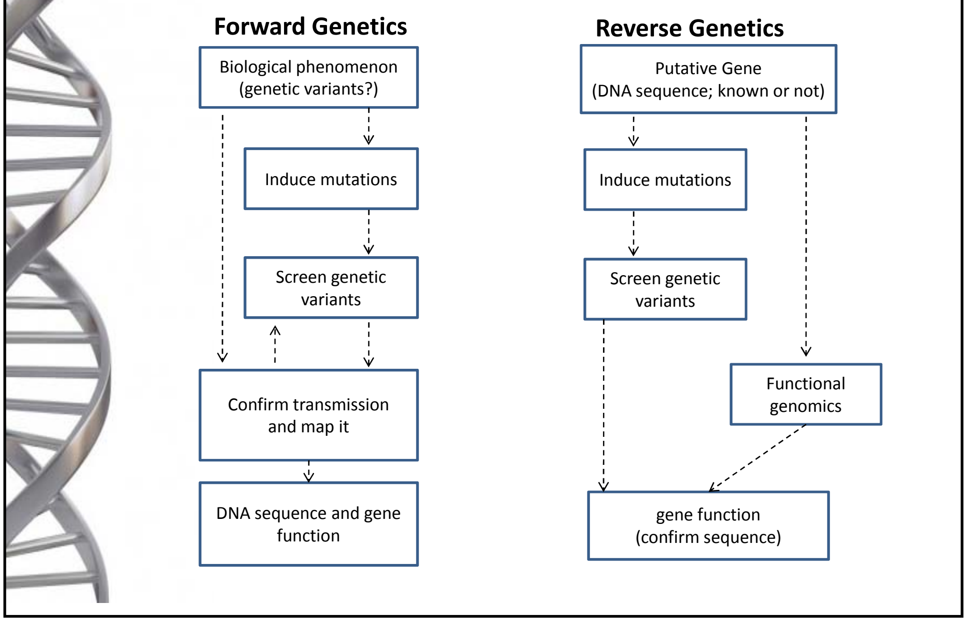


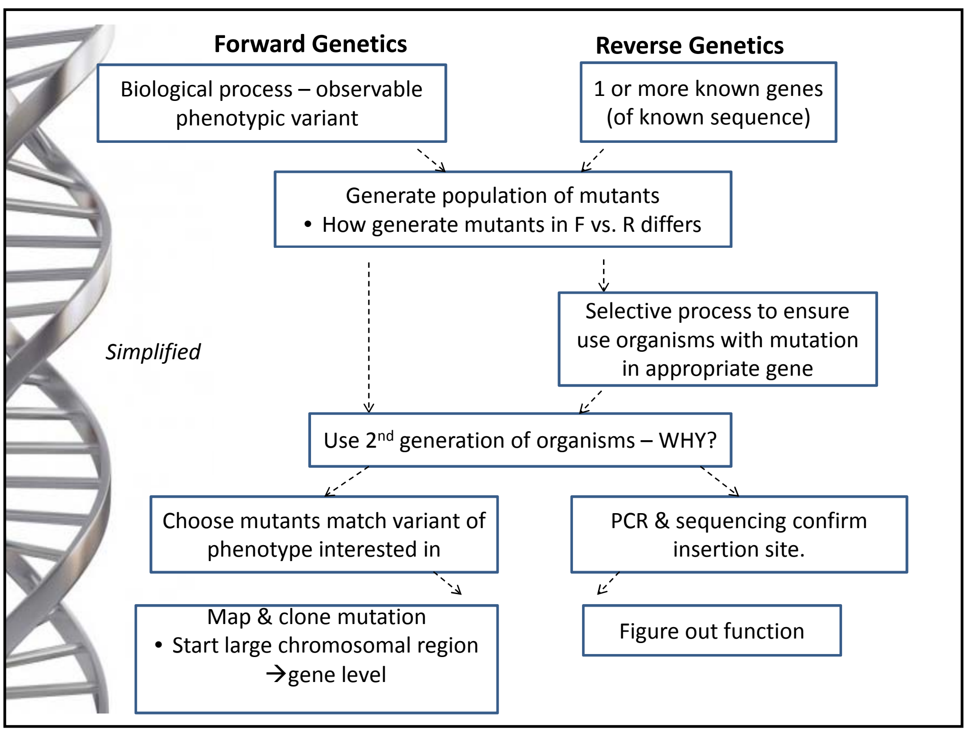
Restriction Enzymes

http://highered.mcgraw-hill.com/olcweb/cgi/pluginpop.cgi?it=swf::535::535::/sites/dl/free/0072437316/120078/bio37.swf::Restriction%20Endonucleases

http://yhs-raines.wikispaces.com/Genetics

Genetic investigation.



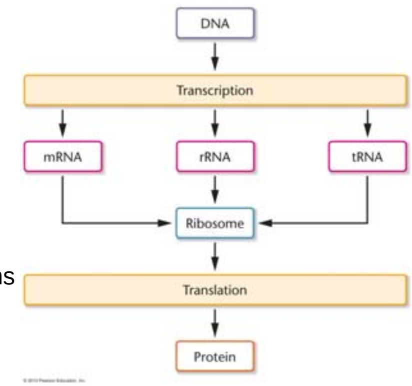


GENETICS AS AN INVESTIGATIVE TOOL

How can we differentiate between individuals – genetically speaking?

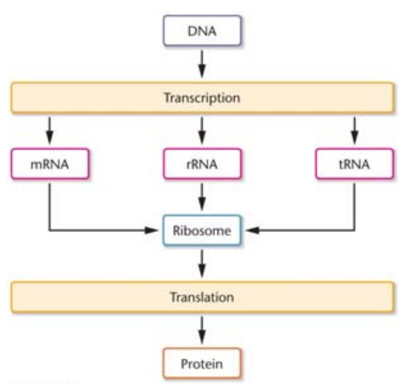
How can investigators estimate the probability of matches?

What concepts and experimental approaches allow us to draw conclusions about inheritance of genetic traits? (predicting outcomes; determining genotypes; genome manipulations;

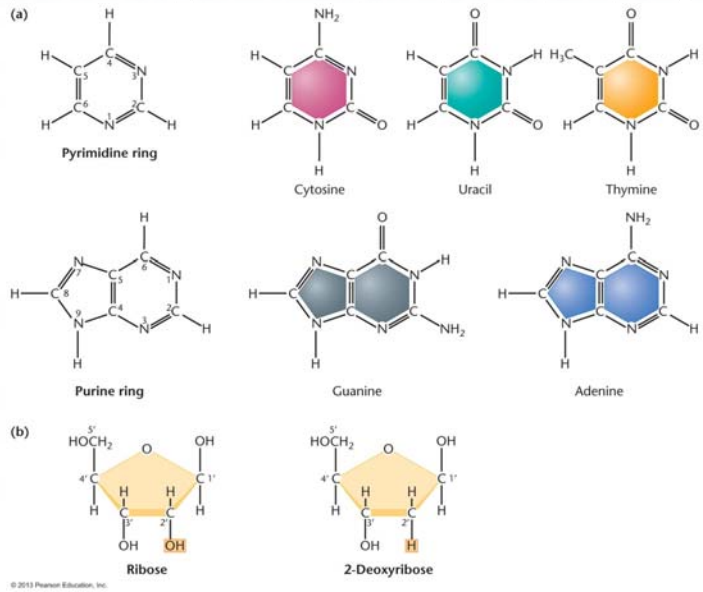


CHARACTERISTICS OF GENETIC MATERIAL

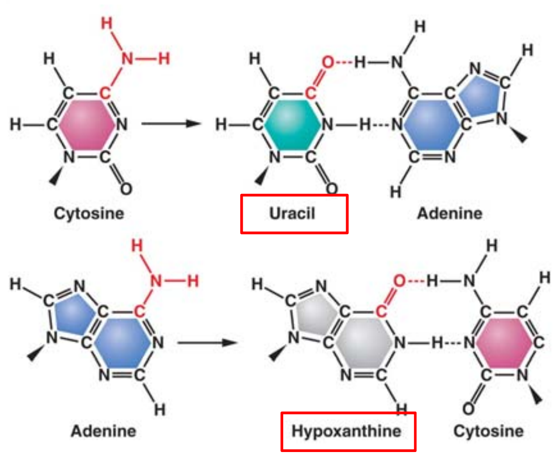
- **Storage of information**
- **Replication**
- **Expression of information**
- **Variation by mutation**



NUCLEOTIDES : BUILDING BLOCKS OF NUCLEIC ACIDS



OTHER TYPES OF BASES



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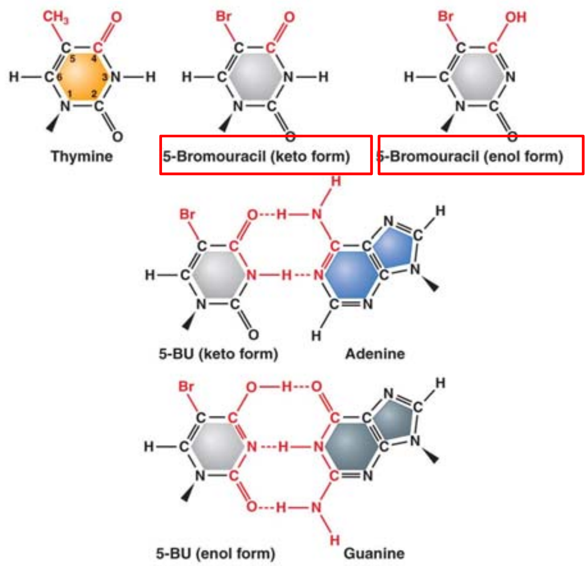

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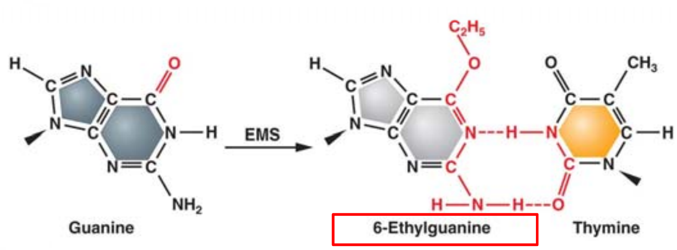
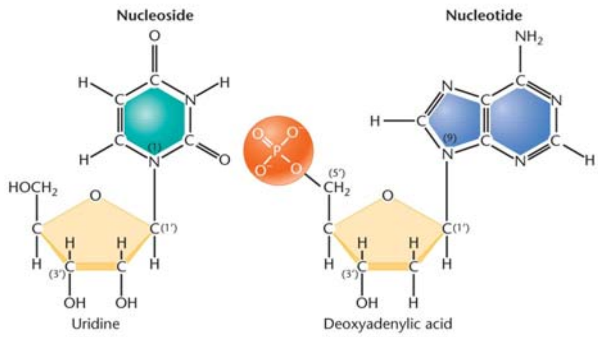
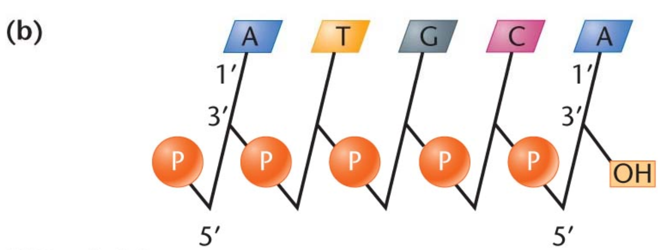


NUCLEOSIDES VS. NUCLEOTIDES



Ribonucleosides	Ribonucleotides
Adenosine Cytidine Guanosine Uridine	Adenylic acid Cytidylic acid Guanylic acid Uridylic acid
Deoxyribonucleosides	**Deoxyribonucleotides**
Deoxyadenosine Deoxycytidine Deoxyguanosine Deoxythymidine	Deoxyadenylic acid Deoxycytidylic acid Deoxyguanylic acid Deoxythymidylic acid

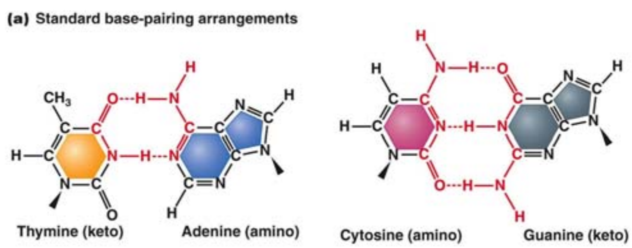
POLYNUCLEOTIDES



Storage of information: Extraordinary <u>variation</u> is possible!

For example, a 1000 polynucleotide chain can be arranged 4^{1000} different ways, each one different from all other possible sequences!

Base pairing

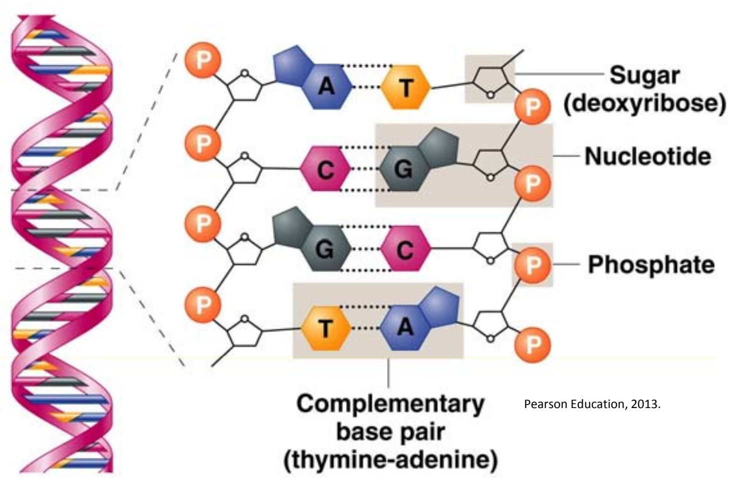


Pearson Education, 2013.

Purine pairs with pyrimidine

DNA Structure

Double helix – complementary base pairing



Pearson Education, 2013.

1 molecule DNA

- Strands anti-parallel
- Phosphates on outside

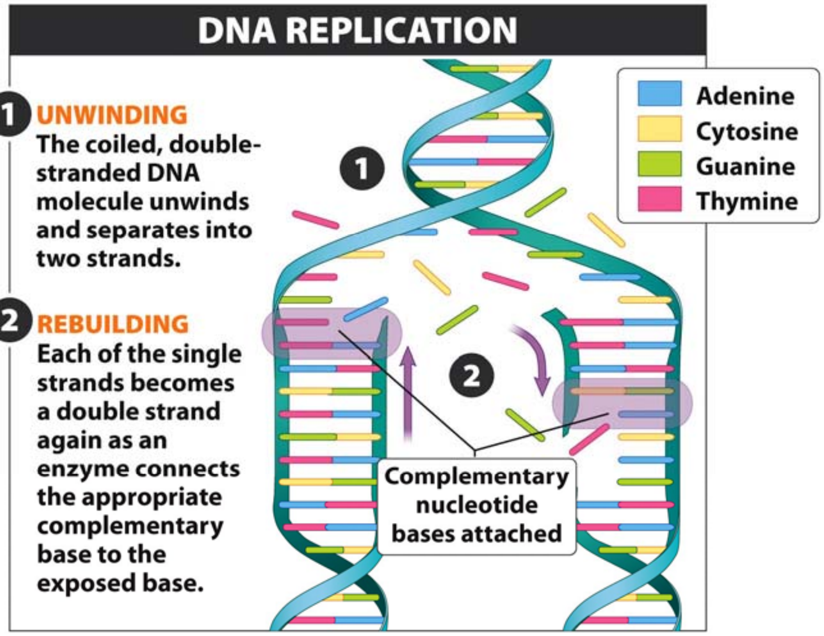
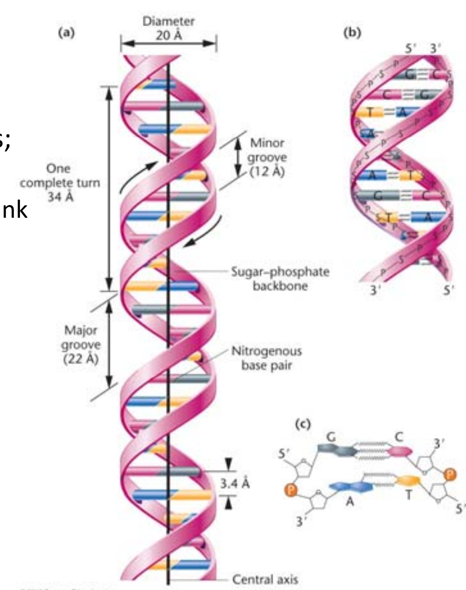


Figure 6-6
What Is Life? A Guide To Biology

Anti-parallel strands within DNA molecule

- Strands anti-parallel
- Bases perpendicular to axis;
- Phosphates on outside (thank you Rosalind Franklin!)



Polymerase Chain Reaction

What do you need to make copies (amplify) of DNA?

PCR – the old way

PCR – the newer way

DNA template + primers + polymerase + dNTPs + chemical stuff (buffer, divalent cations, monovalent cations)

Polymerase Chain Reaction

What do you need to make copies (amplify) of DNA?

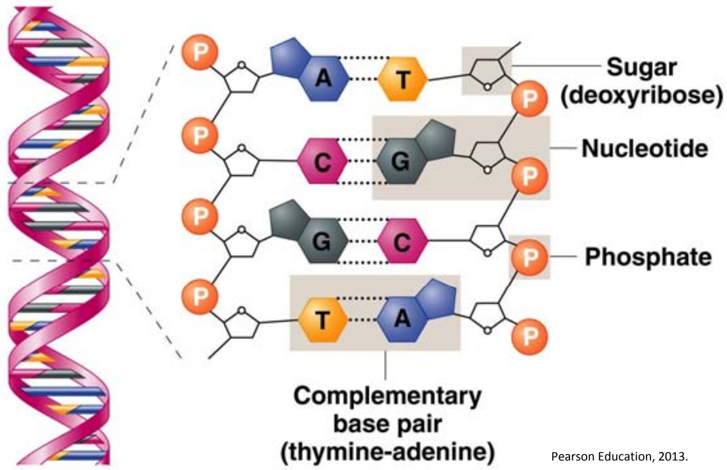
PCR – the old way

PCR – the newer way

Premise still the same: need to denature, anneal, elongate

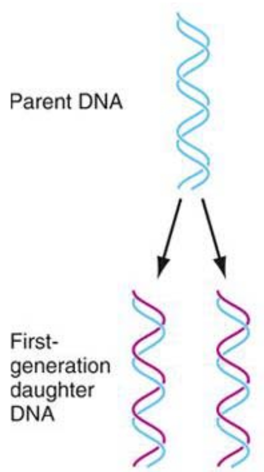
DNA Structure

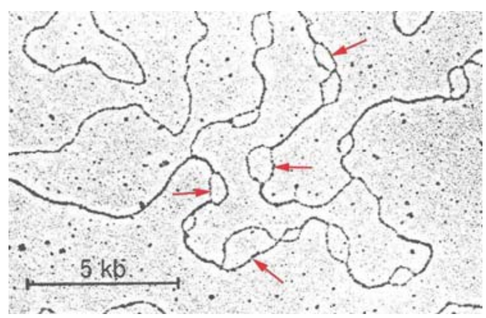
Double helix – complementary base pairing



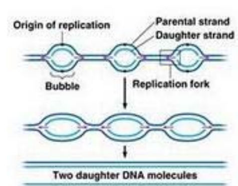
Pearson Education, 2013.

DNA structure facilitates replication





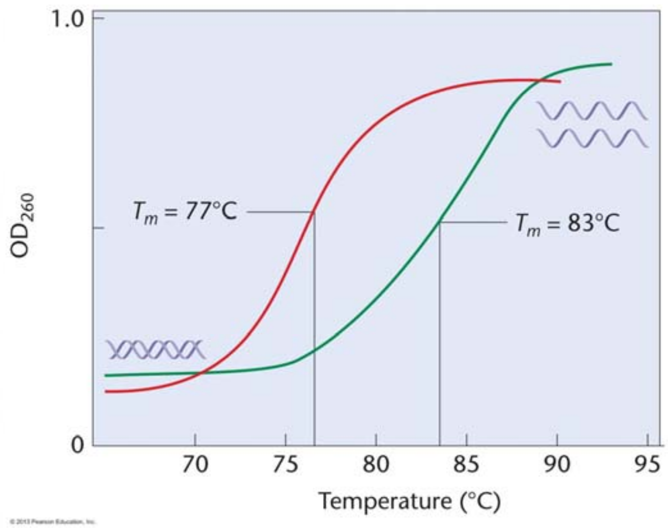
Various origins of replication.
Why?



Semi-conservative replication

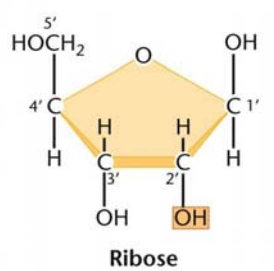
Hartwell et al. 2009 (McGraw-Hill, 2009)

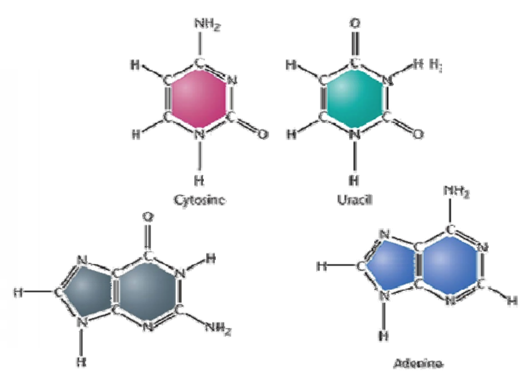
DENATURATION AND RENATURATION OF NUCLEIC ACIDS



RNA – chemically similar to DNA, but different…

1. What are two differences between RNA and DNA?
2. Which is more stable? Why?

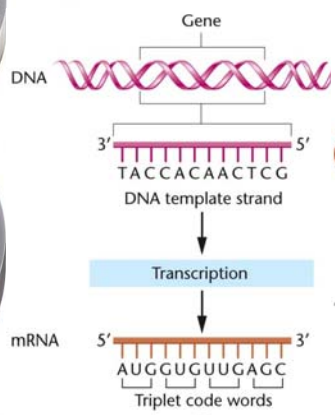




Pearson Education, 2013.

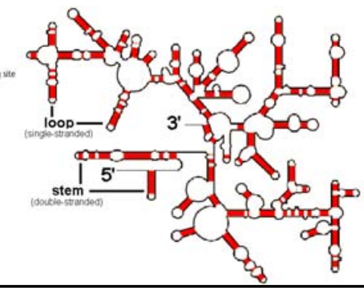
RNA – chemically similar to DNA, but different…

- RNA molecules all originate as complementary copies of one of the two strands of DNA segments during transcription.



tRNA

rRNA

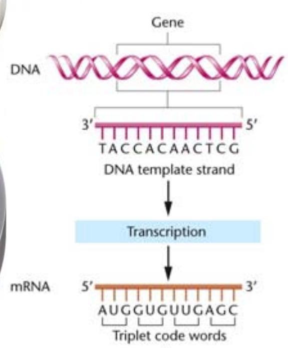


Pearson Education, 2013.

RNA – more than the usual suspects

- RNA molecules all originate as complementary copies of one of the two strands of DNA segments during transcription.

Informational



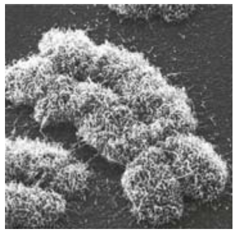
Functional

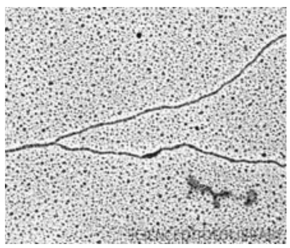
tRNA – transfer RNAs
rRNA – ribosomal RNAs
snRNA – small nuclear RNAs
miRNA – micro RNAs
siRNA – small interfering RNAs
lncRNA –long noncoding RNAs

Pearson Education, 2013.

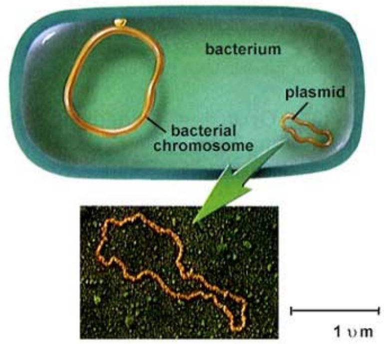
Variations in organization of DNA

Eukaryotic DNA





Bacterial DNA



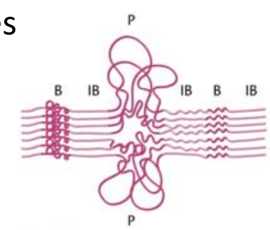
Pearson Education, 2013.

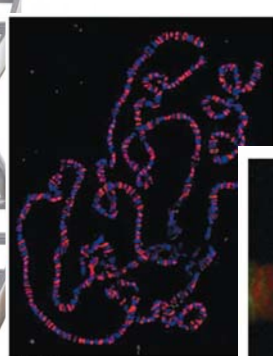
WH Freeman, 2012.

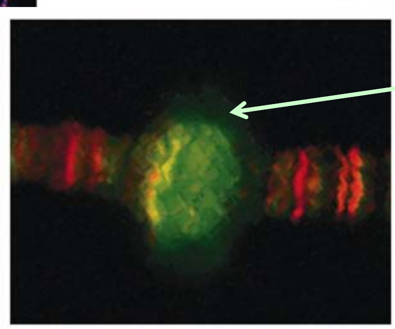
Variations in organization of DNA

Some chromosomes have a structure makes them useful for genetic studies

e.g., polytene chromosome



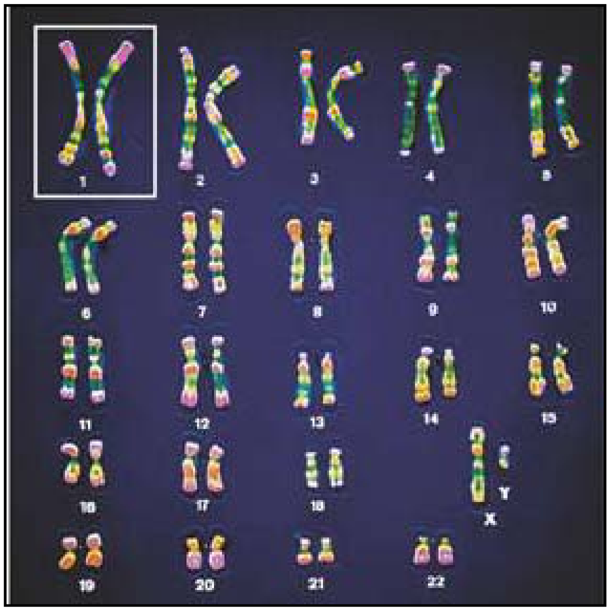




Chromosome puff

Pearson Education, 2013

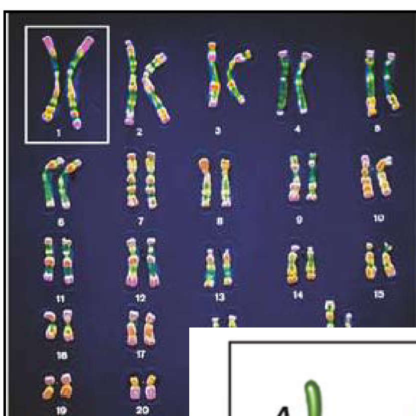
Different chromosomes carry different genes



McGraw-Hill, 2009

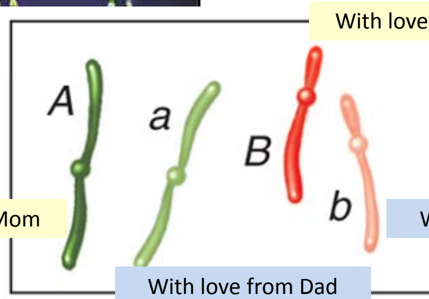
Differences in staining patterns b/w different pairs (*e.g.,* Chr 3 & Chr 17) indicate differences in DNA sequence.

Different chromosomes carry different genes



McGraw-Hill, 2009.

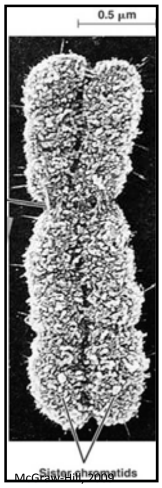
Homologous chromosomes carry the same genes, but may have different alleles.

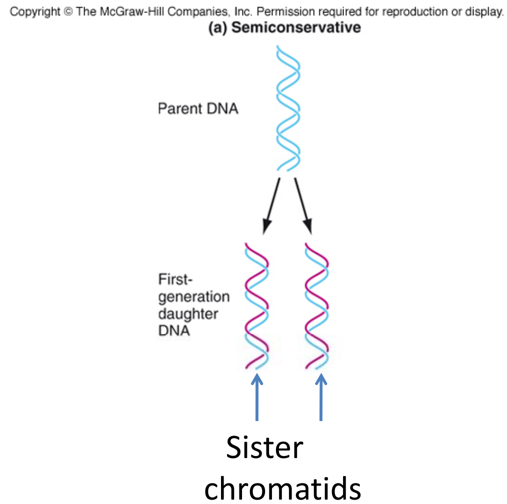


McGraw-Hill, 2009.

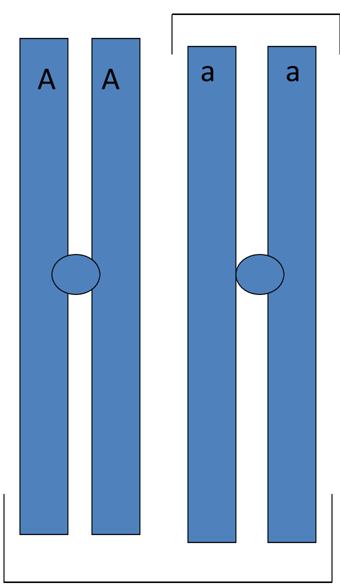
DNA replication precedes cell division

- Sister chromatids



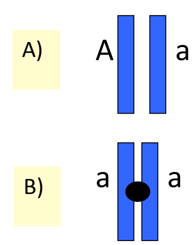


Chromosome Nomenclature



Homologous pair after DNA replication

What does a homologous pair look like before DNA replication?



Ploidy & number of *different* chromosomes

- You should be able to:
  - Define ploidy
  - Identify the number of unique or different chromosomes given a karyotype of ploidy

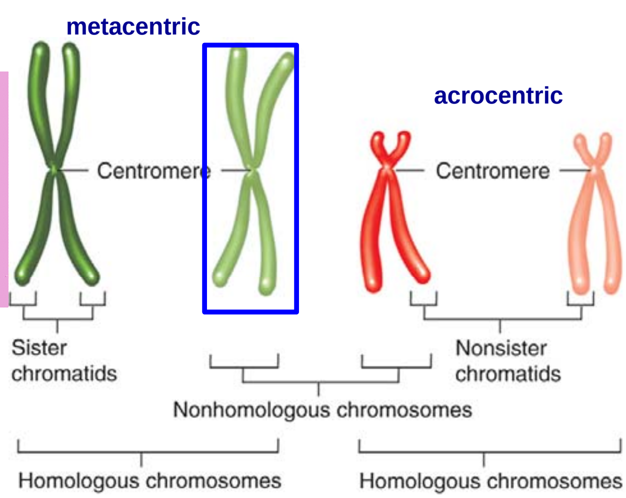
e.g.,

Dogs	2n = 72
Fruit fly	2n = 4
Chimpanzee	2n = 48
Human	2n = 46

Names to identify chromosomes…

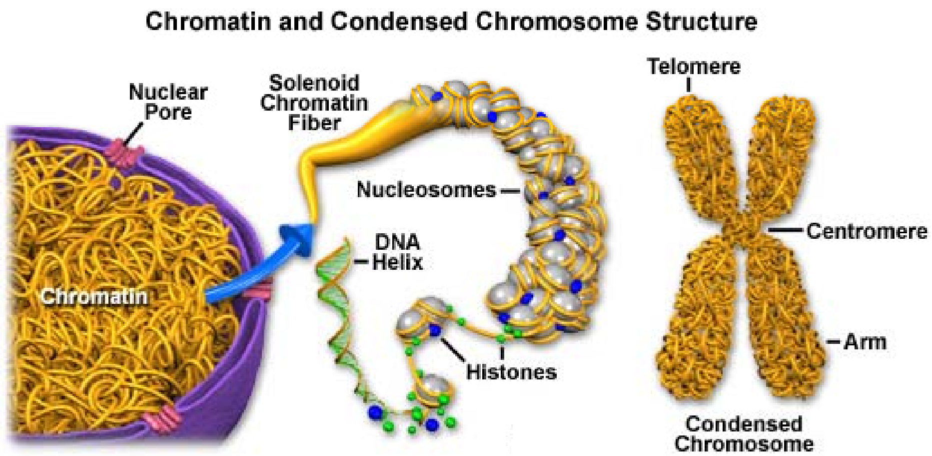
The light green chromosome is a homologue (often spelled homolog) & is one-half of a homologous pair (the 'pair' part indicates two). The other homologue is the dark green chromosome.

Are these drawings of chromosomes before or after replication?
Are the 2 joined sister chromatids 1 chromosome or 2?



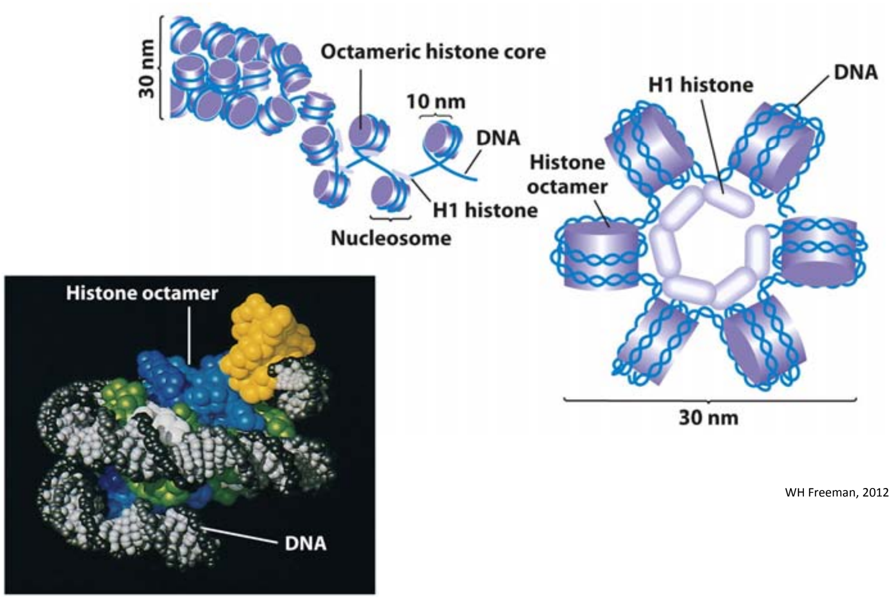
McGraw-Hill, 2009

Typical organization of eukaryote DNA



McGraw-Hill, 2009

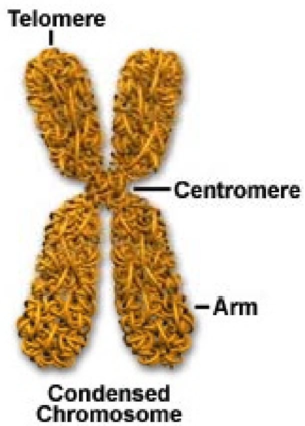
Nucleosomes & DNA compaction

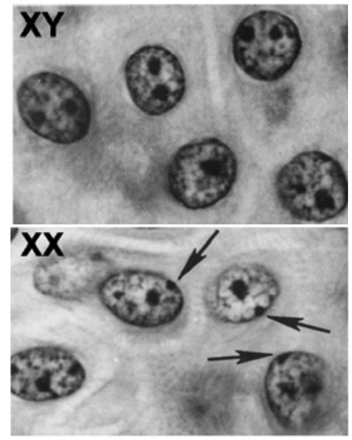


WH Freeman, 2012

Variations in organization of DNA

Euchromatin versus Heterochromatin

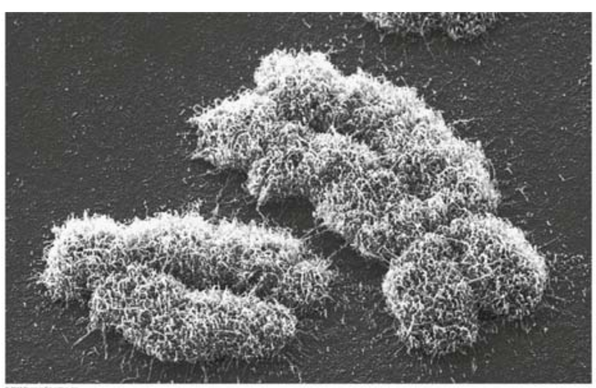


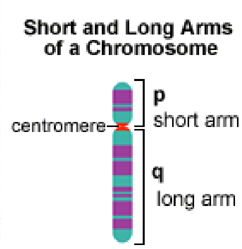


McGraw-Hill, 2009

Chromosome Anatomy

- How do these two chromosomes differ from each other?

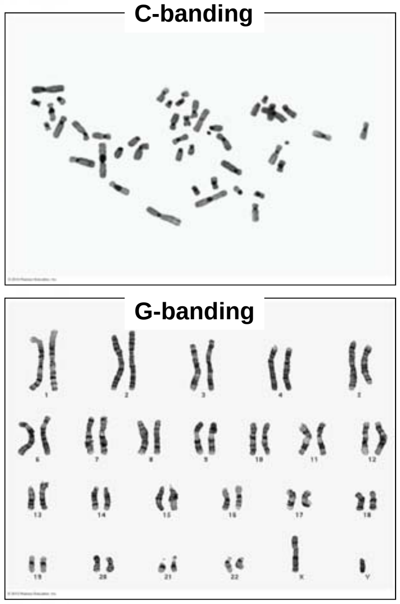




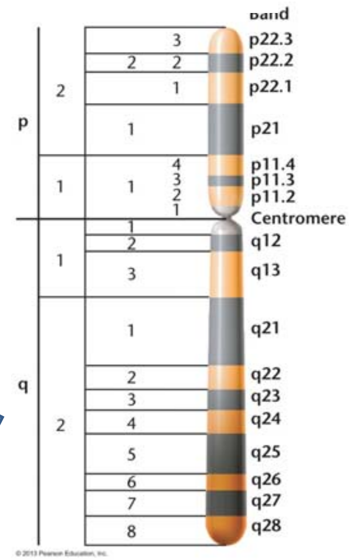
Molecular anatomy of chromosomes

C-banding

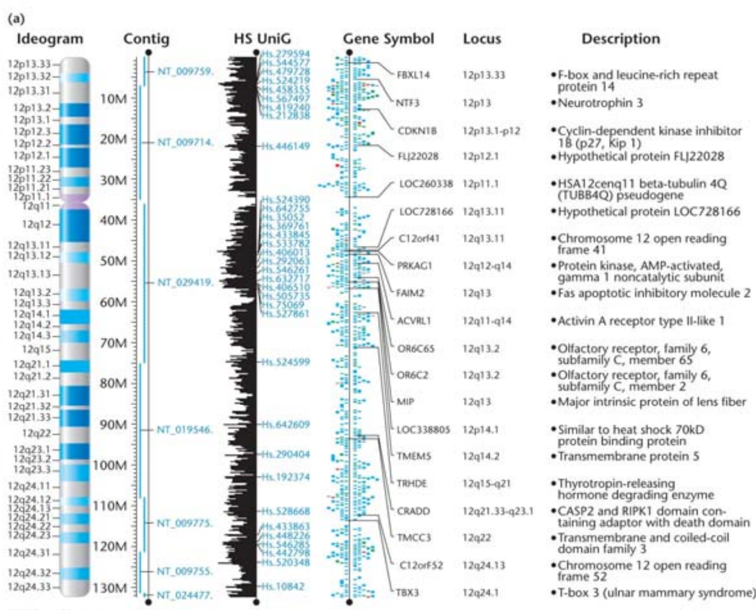
G-banding



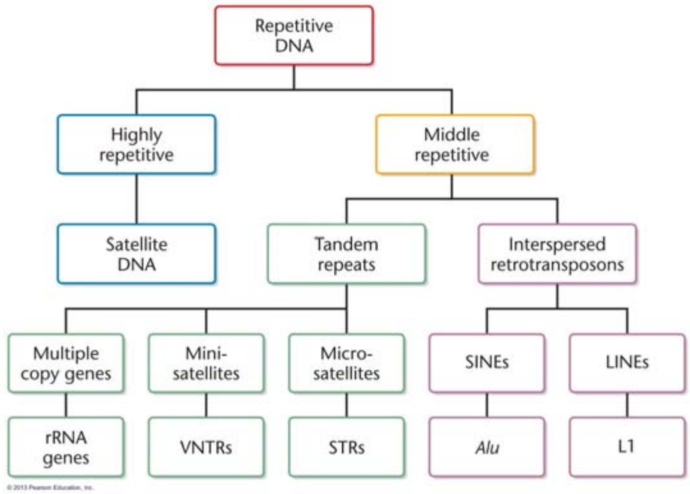
X chromosome



Molecular anatomy of chromosomes

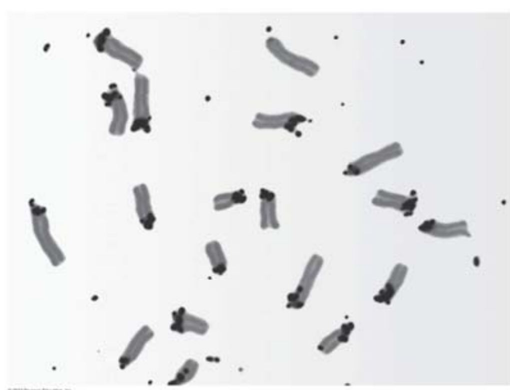


Organization of DNA sequences: repetitive DNA



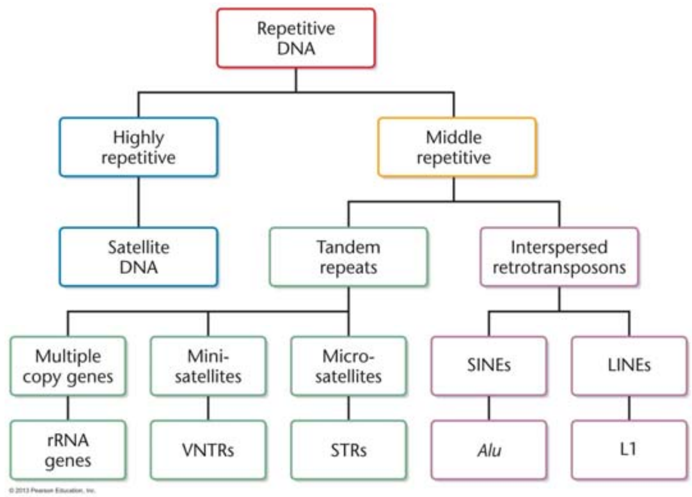
Organization of DNA sequences: repetitive DNA

Highly repetitive : *(Tandem repeat)* Satellite DNA



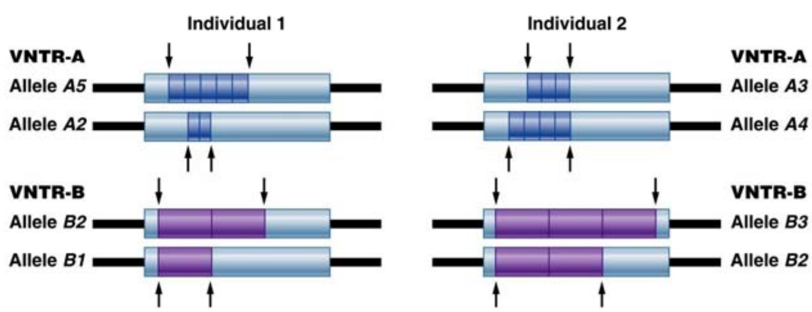
Localized to the heterochromatic centromeric regions of chromosomes

Organization of DNA sequences: repetitive DNA



Organization of DNA sequences: repetitive DNA

Middle repetitive : (*Tandem repeats*) Minisatellites



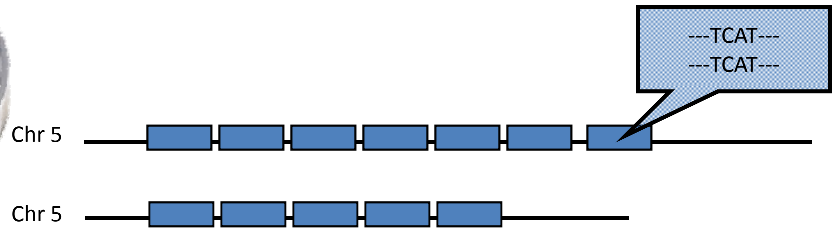
VNTRs (variable numbers of tandem repeats)

- Clusters 15-100 nucleotides (within & between genes)
- # of repeats at each locus: 2 → 100
- Each length representing 1 allele

Why can the number of repeats vary?

Organization of DNA sequences: repetitive DNA

Middle repetitive : Tandem repeats, Microsatellites



STR (Short tandem repeats)

- 2 – 16 nucleotides repeated; repeated sequences directly adjacent to each other
  - Di-,tri-, tetra-, or pentanucleotides
  - STR loci differ in # of repeats between individuals
  - Dispersed throughout the genome

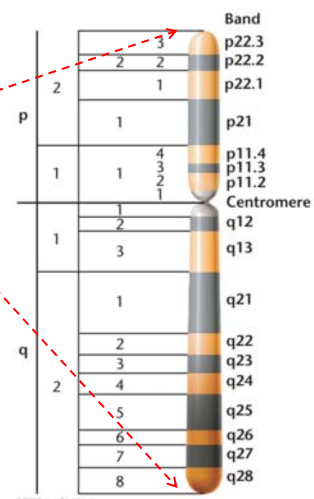
Organization of DNA sequences: repetitive DNA

Other examples of repetitive DNA

Telomeric DNA sequences:

- Short tandem repeats

5’ – TTGGGG – 3’

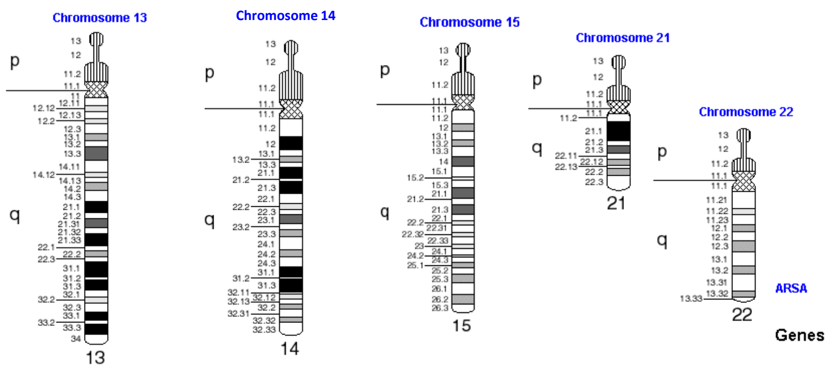


Organization of DNA sequences: repetitive DNA

Other examples of repetitive DNA

Middle Repetitive, Multiple-Copy Genes:

- Functional genes repeated in tandem
- Example: genes for ribosomal RNA (5.8S, 18S, 28S rRNA)

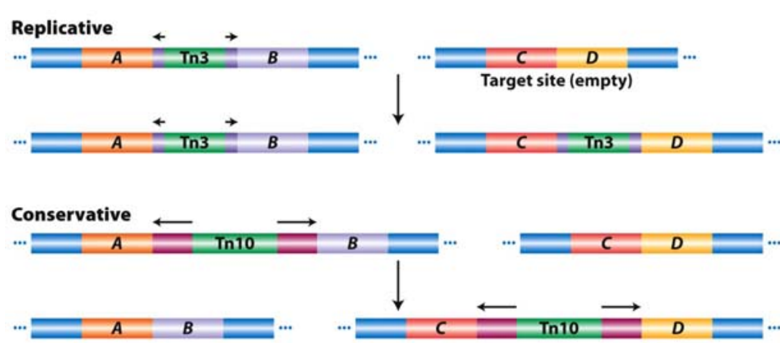


Organization of DNA sequences: repetitive DNA

Other examples of repetitive DNA

Transposable Elements (TEs)

2 modes of transposition



↑ # TE copies

Ø # TE copies

Figure 15-8
Introduction to Genetic Analysis, Tenth Edition

ORGANIZATION OF DNA SEQUENCES

Other examples of repetitive DNA

Repetitive Transposed Sequences:
- SINEs and LINEs

- **SINEs** – Short interspersed elements (~500 bp; ~ 13% of genome)
  - Maybe present 500,000 times in the human genome
  - *Alu* family

- **LINEs** – Long interspersed elements (~6 Kb; ~21% of genome)
  - Present 800,000 times in the human genome
  - retrotransposons
  - L1 family

Chromosomal landscapes

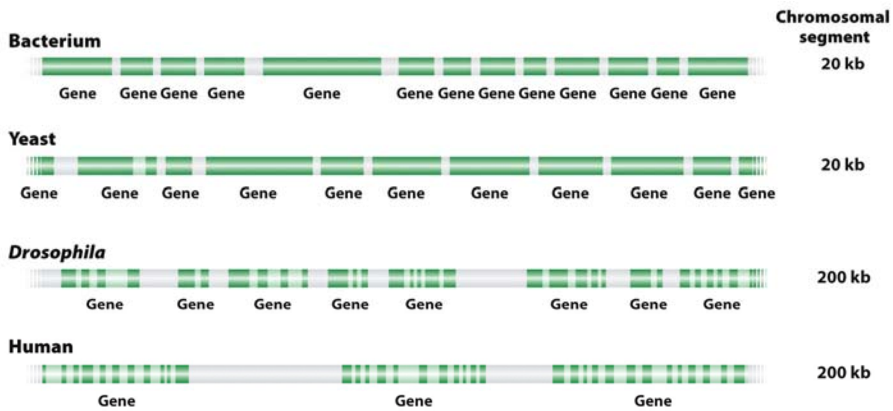
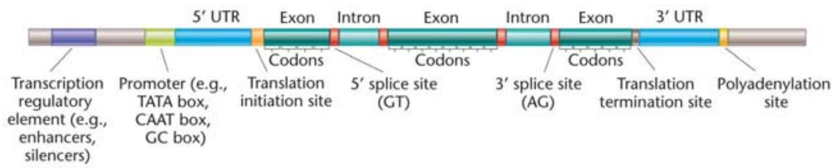
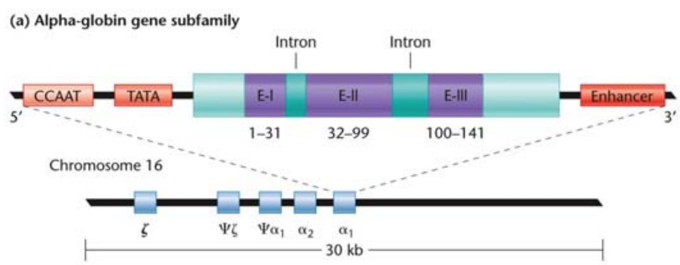


Figure 1-7
Introduction to Genetic Analysis, Tenth Edition

Organization of gene sequences

Eukaryote





ORGANIZATION OF GENE SEQUENCES

```
AAAAGAAGAGCAAGCCGCACGGACAACGCCGACGAGAGAGAGAGACGACCCCCTCACCCA
CCAACCCAGCAGGACCACCACAGTCGTTGCCTCTCTTCGCTCGCACGCTCTGAGGATGAT
                                                       M  M
GAGCTGCTTCGTCGGAGCGCGGGGCTCCGCGCGCGTGTGGCTCTGCGCGCTCGCCCTGTG
  S  C  F  V  G  A  R  G  S  A  R  V  W  L  C  A  L  A  L  C
CCTGCTGGCGAGCGCGTGCGCACGTGGCGCGGCCGCCTTCCCCAACAAGCCCGACAGCCC
  L  L  A  S  A  C  A  R  G  A  A  A  F  P  N  K  P  D  S  P
CGGCGAGGACGCCCCCGCGGAGGAATTGGCCCGGTACCTGTCCGCCGTGCGCCACTACAT
  G  E  D  A  P* A* E  E  L  A  R  Y  L  S  A  V  R  H  Y  I
CAACCTCATCACCCGGCAACGGTATGGAAAGAGGGCGCTTACCGAGCCCTACGTCCCAGA
  N  L  I  T  R  Q  R  Y  G  K  R  A  L  T  E  P  Y  V  P  E
GTTTATATTTCAAGAAAATGGTGGTGACAGGAGCAGCAACCCGAGATTTGACAGCGTGAC
  F  I  F  Q  E  N  G  G  D  R  S  S  N  P  R  F  D  S  V  T
CATGTGGTGATTCGGTTAAAATTGAAGATGCCCGTCAACTCTTCATCCACCTCCCCTCTC
  M  W  *
ATCAACCATCGACCCCCCCCCCAATGGATAAGTCAGAAGTTCCACCACGCTCTGCCAATT
TGACAACAACCATCGGGCCTGCCTCGTTCAGGCGATATAAAATAAAAACACCCTTCCGT
TGAAATGCATGAACCTGTCCCGTATGTCGTGCTGCCCTGGAGTGGTTATACGACTGAAAA
AAAAAAAAAAAAAAA
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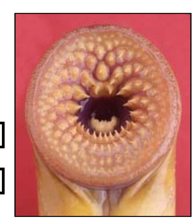

Lamprey Neuropeptide Y gene

Structural organizations of NPY family peptides
(deduced amino acid sequences)