Introduction to Genetics in the Twenty-First Century

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Course Number: 0504321

Medical Genetics

Sundays: 2:30-3:30

Tuesday 3:30-4:30

CHAPTER OUTLINE

- 1.1 DNA & gene: The Human Genome Project
- 1.2 The Relationship Between Genes and Traits
- 1.3 Genetic diversity

A family portrait
with members of four generations

Why do some of the children look like only one of the parents, while some of the other children look more like the great, great grandparents?

What causes the similarities and differences of appearance and the skipping of generations?

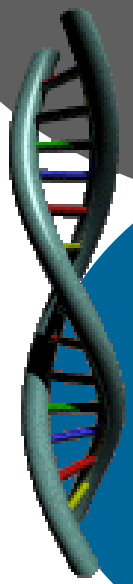
Medical Genetics subgroups

Clinical Genetics- concerned with Clinical manifestation Of genetic diseases

Molecular and biochemical genetics - the study of the structure and function of individual genes.

Cytogenetics - the study of the structure of chromosomes.

Immunogenetics - the study of the genetics of the immune system



Population genetics - the study of genetics of populations.

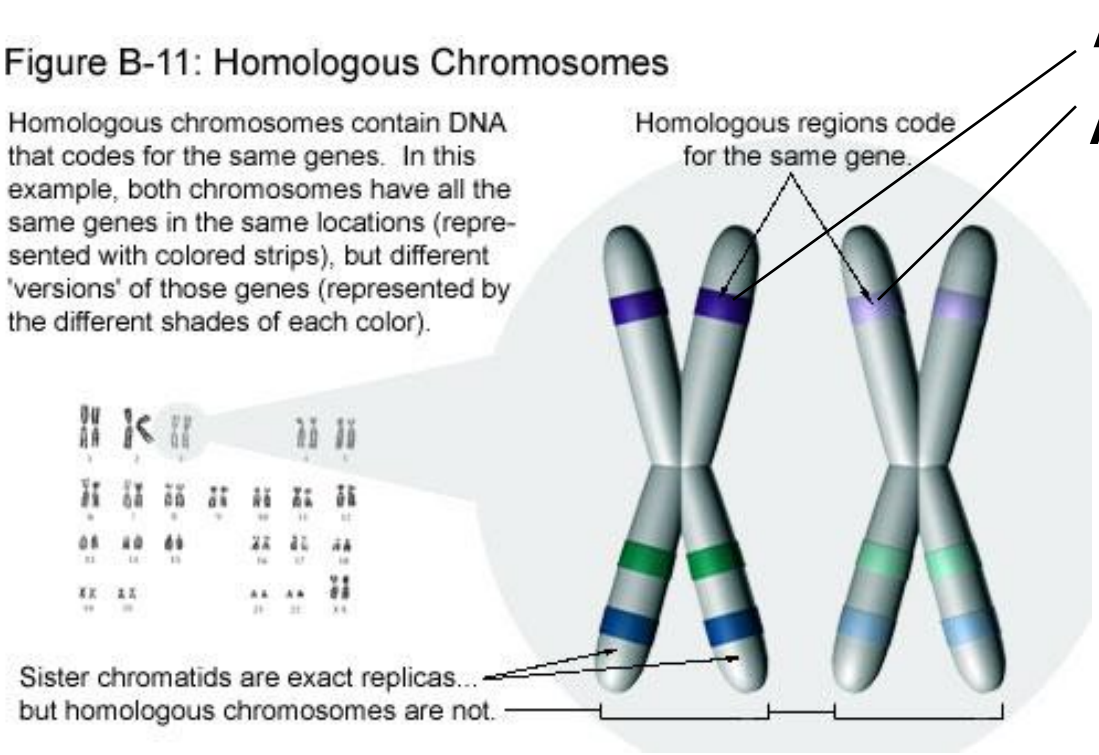
Genetic epidemiology – the study of epidemiology of genetic disease.

Introduction to Genetics

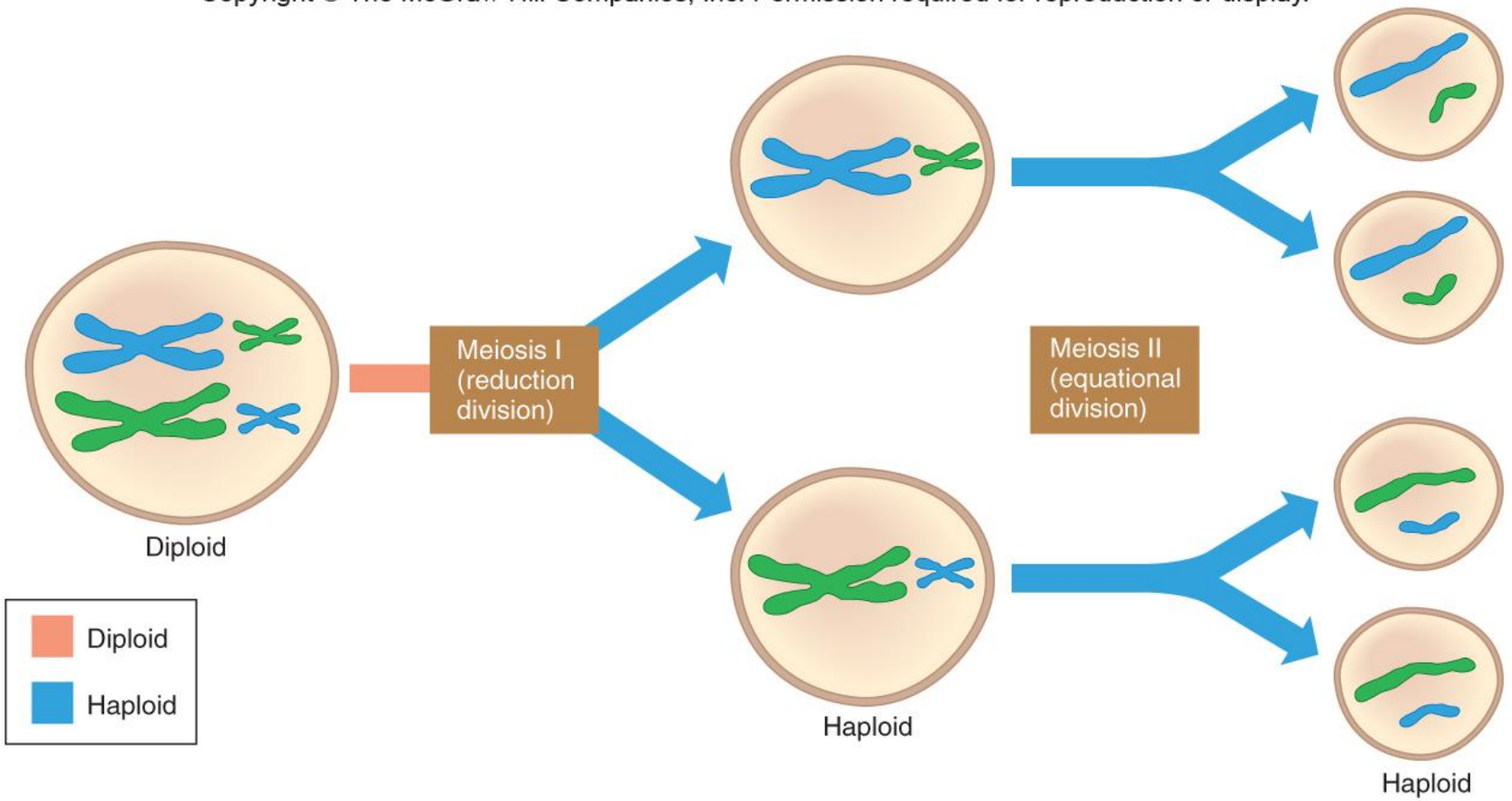
- **GENETICS** – branch of biology that deals with heredity and variation of organisms.

- **Chromosomes** carry the hereditary information (genes)
  - Arrangement of nucleotides in DNA
  - DNA → RNA → Proteins

- Chromosomes (and genes) occur in pairs
  Homologous Chromosomes
- New combinations of genes occur in sexual reproduction
  - Fertilization from two parents



Meiosis

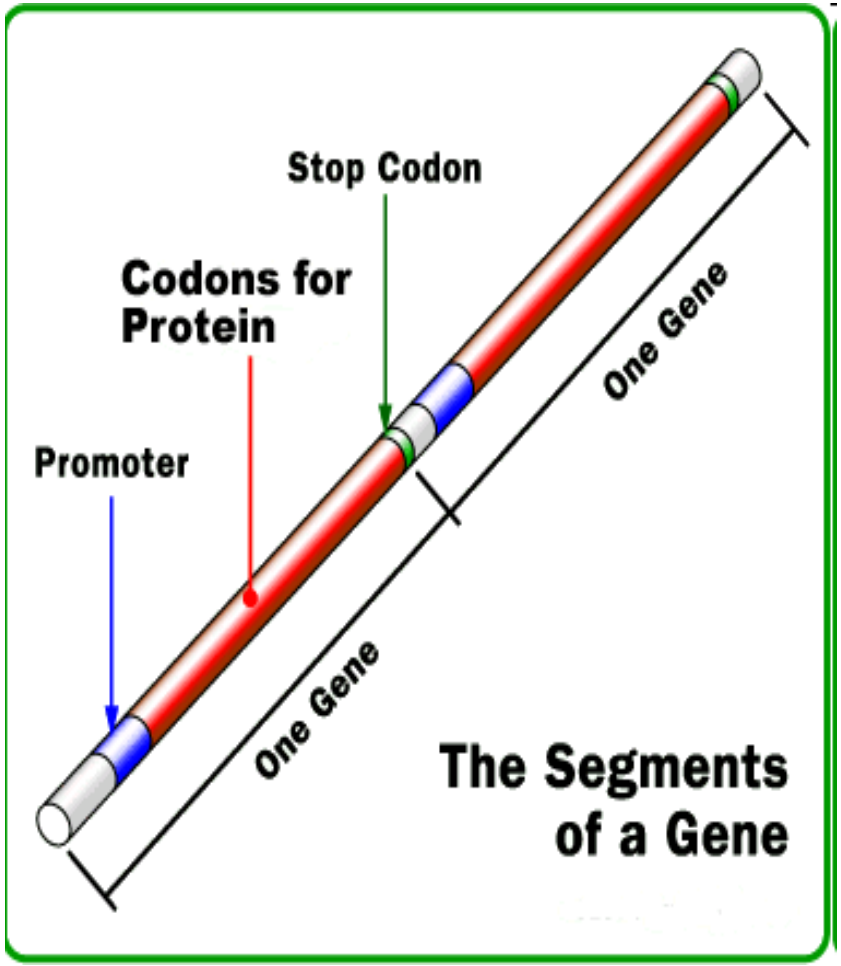


Overview of Genetics

- Genetics – branch of biology that deals with heredity and variation of organisms.
- The complete genetic composition of a cell or organism is called a **genome**.
- The **genome** encodes all of the proteins a cell or organism can make.
- Many key discoveries in genetics are related to the study of **genes** and **genomes**.
- Medical genetics is the science of human biological variation as it relates to health and disease

What is a Gene???

- A **gene**, the basic unit of inheritance; it is a segment within a very long strand of **DNA** with specific instruction for the production of one specific protein.
- **Genes** located on a chromosome on it's place or **locus**.



Mendelian Inheritance

- **Alleles:** are the individual copies of a particular gene.
- **Genotype:** genetic constitution of any individual with respect to a particular trait.
- **Phenotype:** physical manifestation of a trait.
- Trait can be transmitted as **autosomal** or **sex linked** and as **Dominant** or **Recessive** traits.
- **Dominant allele**: allele that mask or hides the expression of its alternative .
- **Recessive allele** : the allele which is masked or hidden.
- **Sex-Linked Genes**: Genes located on a sex chromosome

Three milestones in genetics

- Mendel – basic laws of inheritance – 1865
- Watson and Crick – structure of DNA – 1953
- Human Genome Project and Celera – sequence and annotation of human genome - 2003

Gregor Mendel discovered the basic principles of genetics

- **Mendel** inferred laws of genetics that allowed predictions about which traits would appear, disappear, and then reappear
- **Mendel's** paper "Experiments in plant hybrids" was published in 1866 and became the cornerstone of modern genetics

Gregor Mendel discovered the basic principles of genetics

- **Mendel's law of segregation**: *The two alleles for each trait separate (segregate) during gamete formation, and then unite at random, one from each parent, at fertilization.*
- **Mendel's law of Independent Assortment:** *The alleles of different genes assort independently of each other.*

Genetics explains the mechanisms that determine the inheritance of traits

Genes underlie the formation of every heritable trait,
e.g. *cleft chin, hair loss, color of hair, skin,* and *eyes*

- Some traits are causes by a single change in a single gene, e.g. ***sickle-cell anemia***
- Some traits are caused by complex interactions between many genes, e.g. ***facial features***

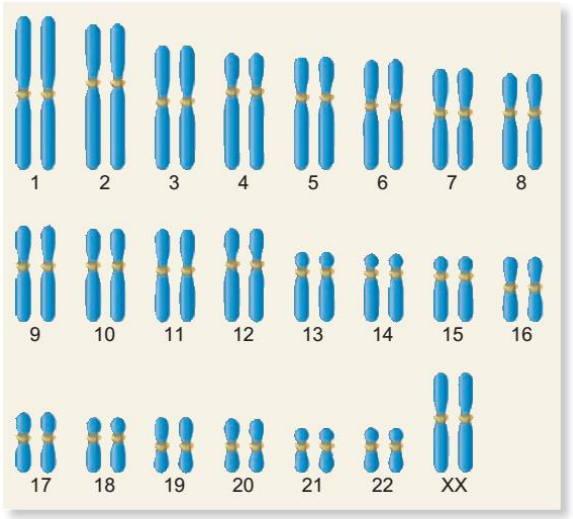
Organization of genetic information in cells

Chromosomes are organelles that package and manage the storage, duplication, and expression of DNA

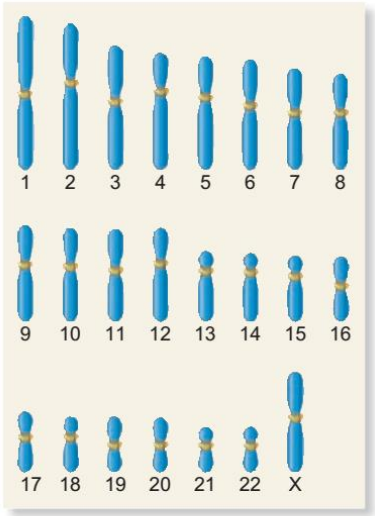
Genomes are the entire collection of chromosomes in each cell of an organism (24 kinds of chromosomes)

- The haploid human genome contains approximately 3 billion base pairs of DNA packaged into 23 chromosomes.
- Of course, most cells in the body (except for female ova and male sperm) are diploid, with 23 pairs of chromosomes. That makes a total of 6 billion base pairs of DNA per cell.

- Encodes 20,000 – 30,000 genes
- Human also have a small amount of DNA in their mitochondria, which has also been sequenced.



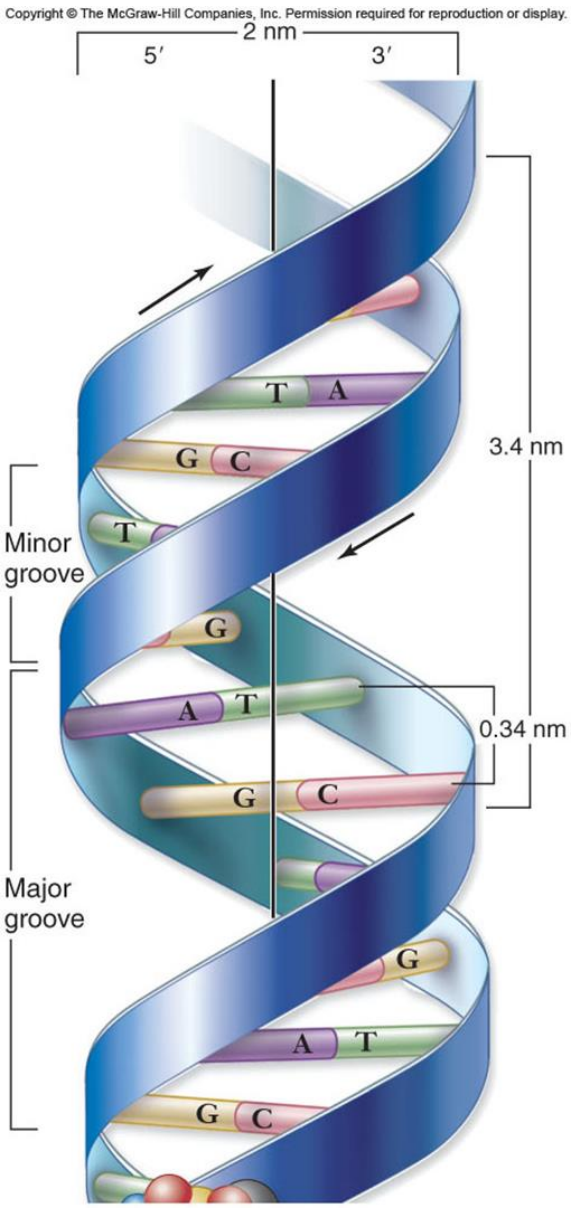
(a) Chromosomal composition found in most female human cells (46 chromosomes)

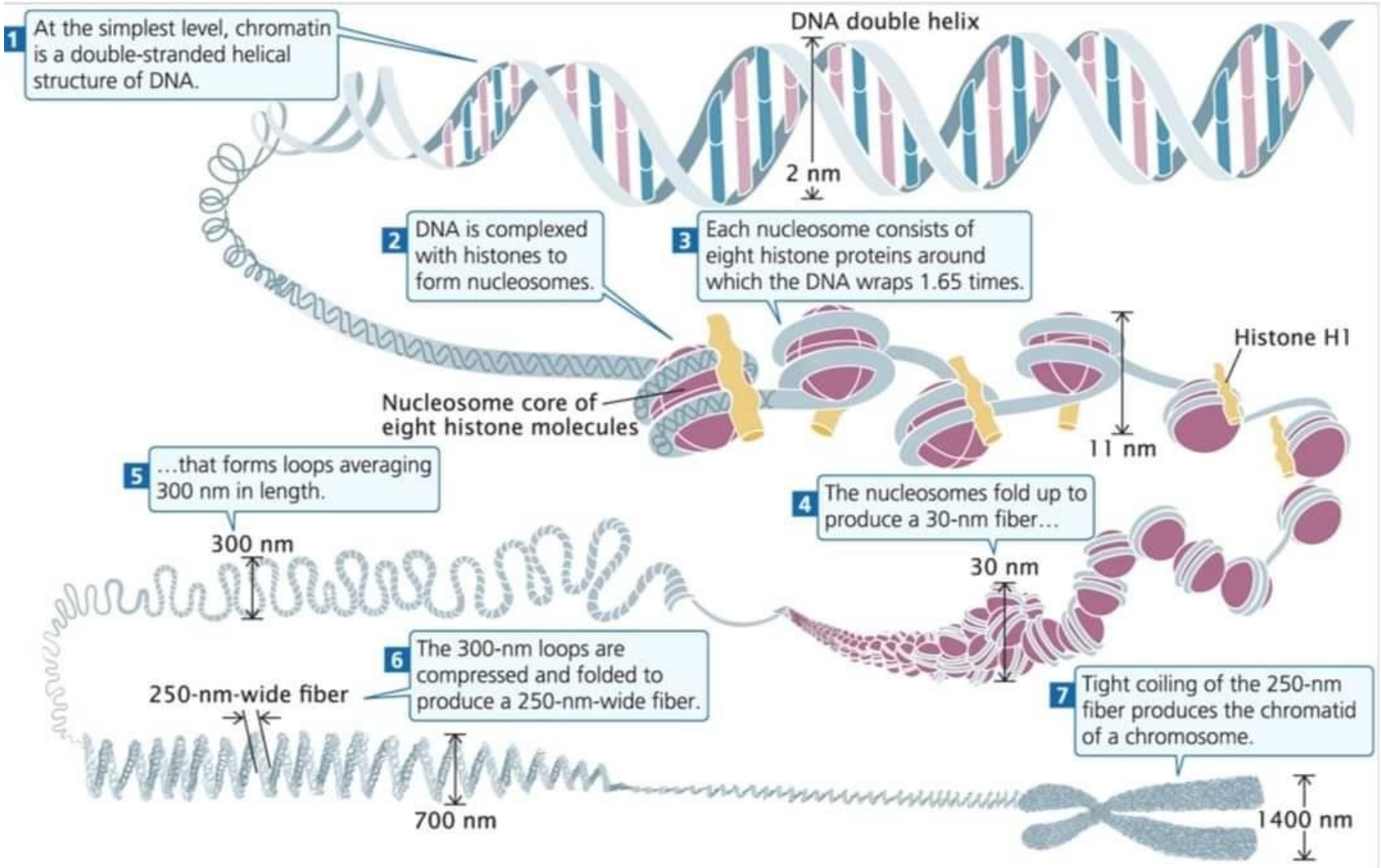


(b) Chromosomal composition found in a human gamete (23 chromosomes)

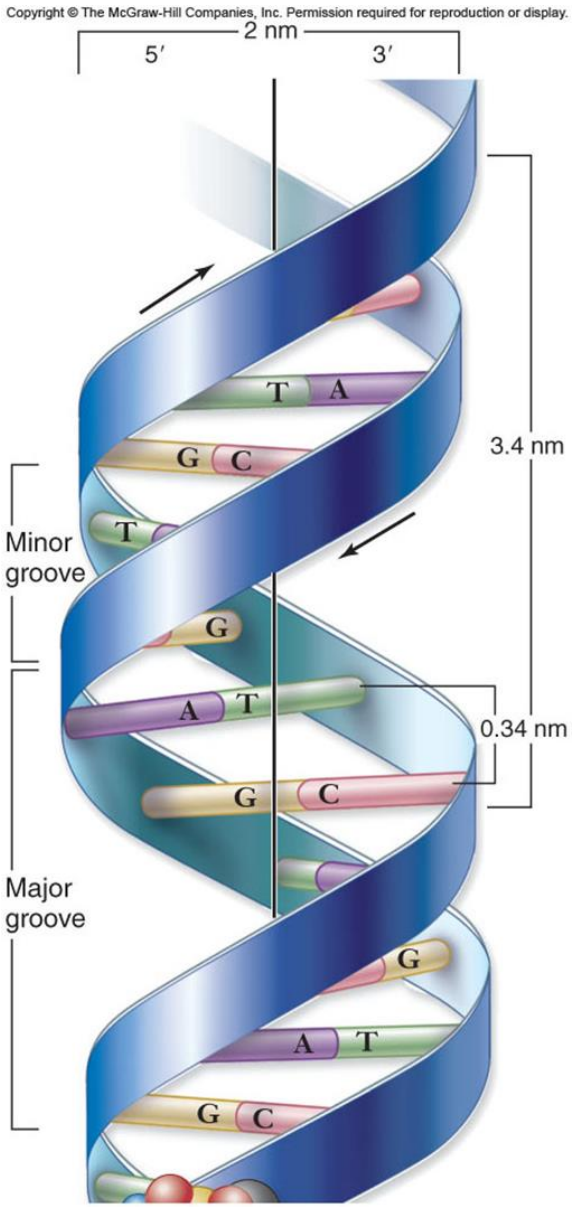
Eukaryotic genome

- Each base pair is ~ 0.34 nanometers long (a nanometer is 1/ 10^9 of a meter)
- Each diploid cell => contains ~ 2 meters of DNA [$(0.34 \times 10^{-9}) \times (6 \times 10^9)$]
- Our body contains about >37 trillion cells, which works out to 100 trillion meters of DNA per human.
- Now, consider the fact that the Sun is 150 billion meters from Earth. We enough DNA to go from here to the Sun and back more than 300 times!
  - It needs to squeeze into 5-10 μm nucleus reducing its length as much as 10,000 fold
- How is this possible?
- This is accomplished by the packing of linear DNA molecules into chromatin (DNA with its associated proteins).




1 At the simplest level, chromatin is a double-stranded helical structure of DNA.
DNA double helix
2 nm
2 DNA is complexed with histones to form nucleosomes.
3 Each nucleosome consists of eight histone proteins around which the DNA wraps 1.65 times.
Histone H1
Nucleosome core of eight histone molecules
11 nm
5 ...that forms loops averaging 300 nm in length.
4 The nucleosomes fold up to produce a 30-nm fiber...
300 nm
30 nm
6 The 300-nm loops are compressed and folded to produce a 250-nm-wide fiber.
250-nm-wide fiber
7 Tight coiling of the 250-nm fiber produces the chromatid of a chromosome.
700 nm
1400 nm

DNA/RNA?



Genes are made of **nucleic acids**

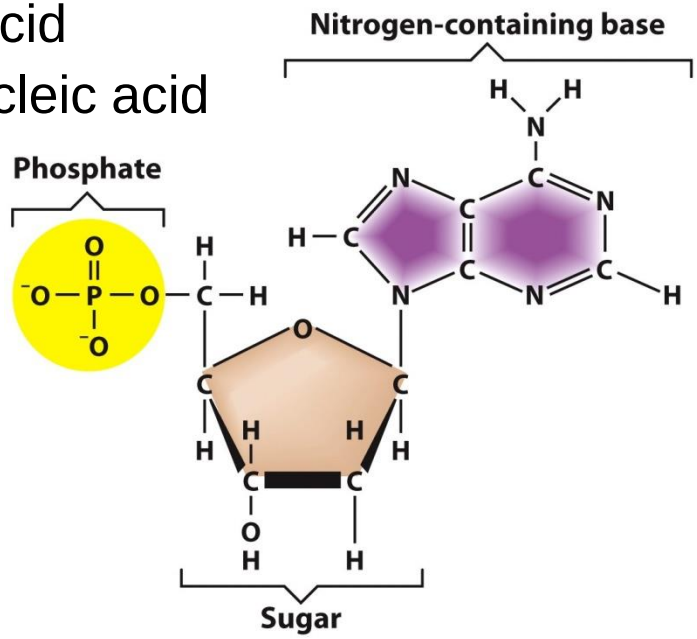
Nucleic acids are made of building blocks called **nucleotides**

Nucleotides have three components

- Sugar molecule (ribose or deoxyribose)
- Phosphate molecule
- Nitrogen-containing molecule (adenine, guanine, cytosine, thymine, uracil)

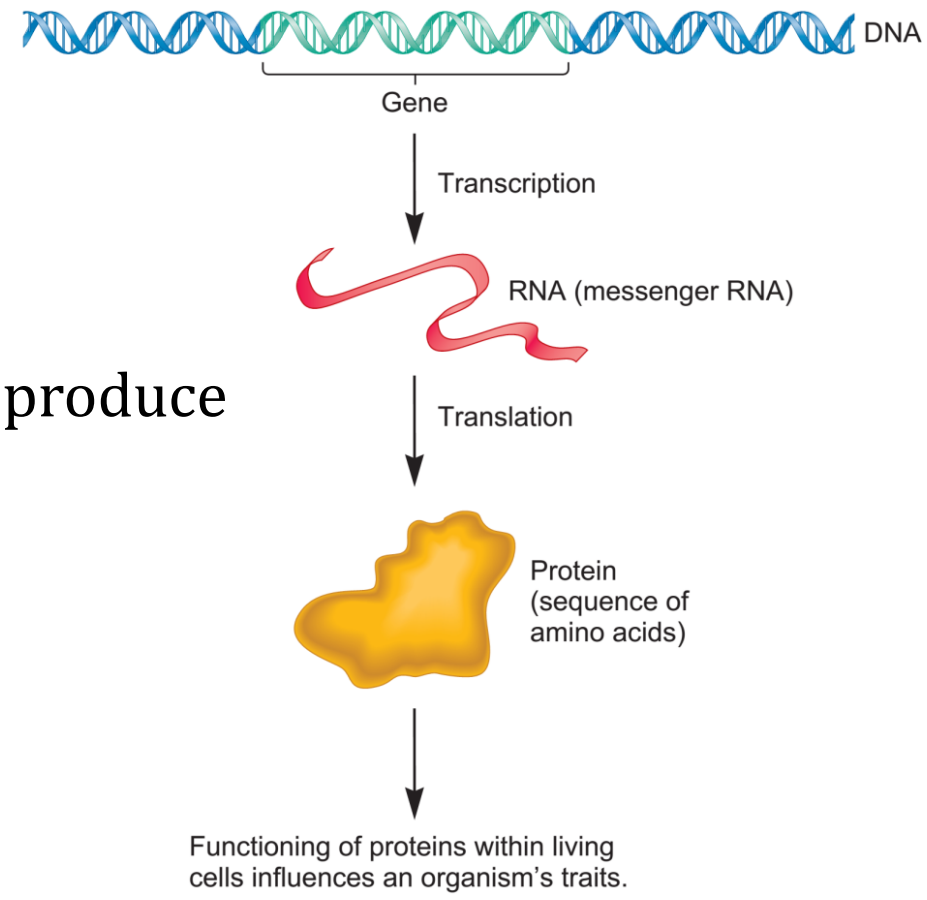
RNA is ribonucleic acid

DNA is deoxyribonucleic acid



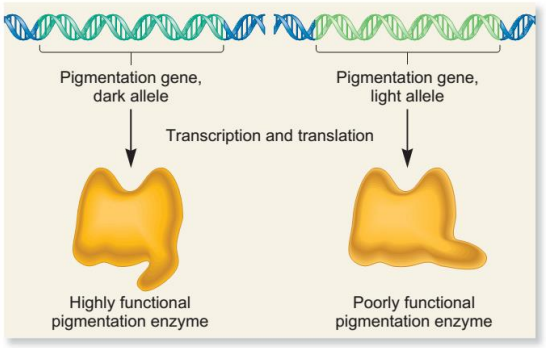
The Relationship Between Genes and Traits

- Most **genes** encode polypeptides that are units within functional proteins.
- **Gene expression** at the molecular level involves ***transcription*** to produce **mRNA** and ***translation*** to produce a **polypeptide**.

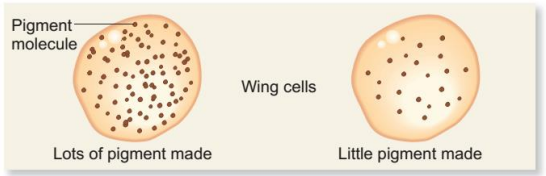


The Relationship Between Genes and Traits

- **Genetics**, which governs an organism's traits, spans the **molecular**, **cellular**, **organism**, and **population** levels.
- **Genetic variation** underlies variation in ***traits***.
- In addition, the **environment** also plays a key role in genetic ***variation***.

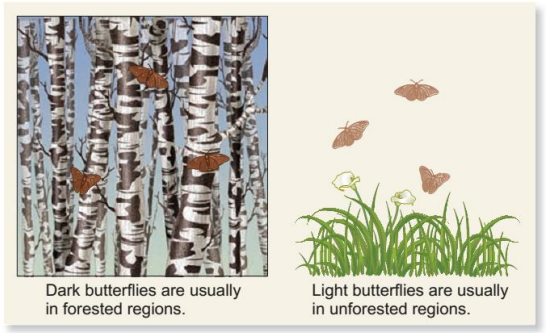


(a) Molecular level



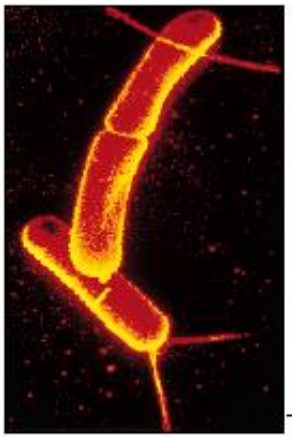
(b) Cellular level

(c) Organism level



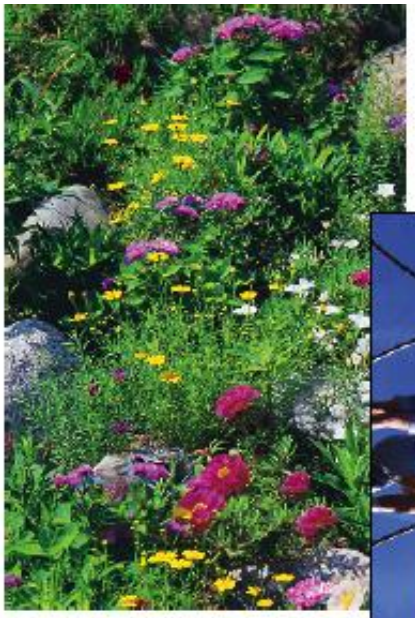
(d) Population level

The biological information in DNA generates an enormous diversity of living organisms



(a) Bacteria

(b) Dolphin



(c) Plants

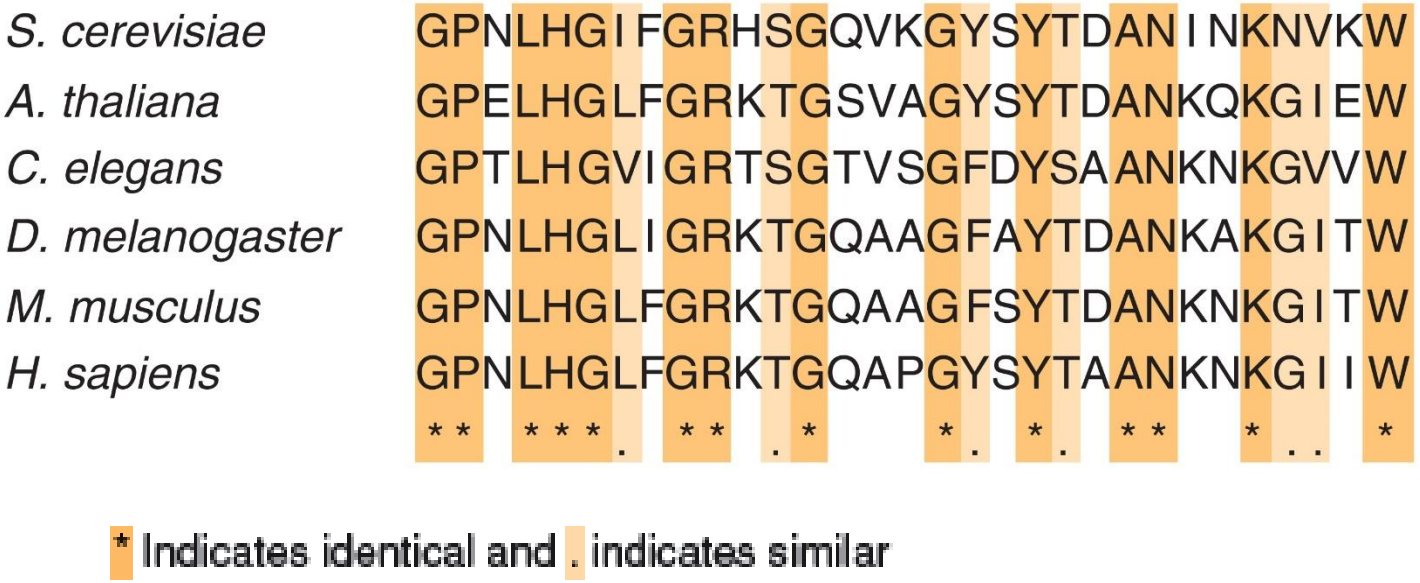
(d) Mouse

(e) Humans

Many genes have similar functions in different organisms

Comparison of gene products in different organisms can reveal **identical** and **similar** amino acid sequences

e.g. ***cytochrome C*** protein from six species



A gene from one organism can functionally replace a gene in another organism

Example: ***Pax6*** gene is required for eye development in insects, mice, and humans

Expression of human *Pax6* gene in *Drosophila* can induce eye development

(a)

(b)

Two critical functions of DNA

1. Replication – necessary to ensure that genome is replicated each cell division and each generation - heredity

2. Code for proteins *(and functional RNAs)*:
   – gene transcription → RNA
   – translation – nucleotide sequence of mRNA specifies amino acid sequence of a polypeptide.
     - *transcription may also generate untranslated RNAs that have functions (eg. rRNA, tRNA, miRNA).*

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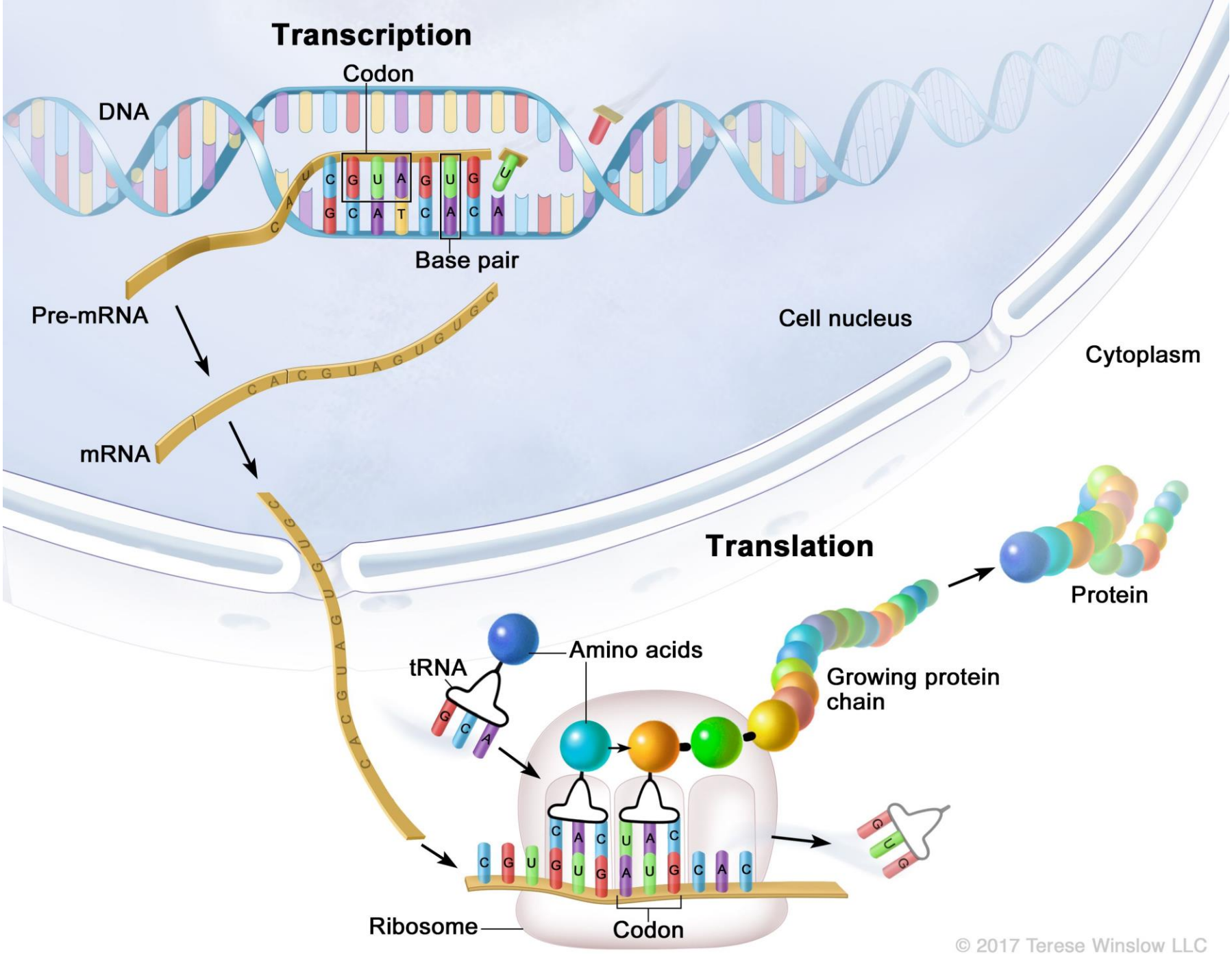


The amino acid sequence determines the three-dimensional shape of the protein

Chemical formulas for two amino acids

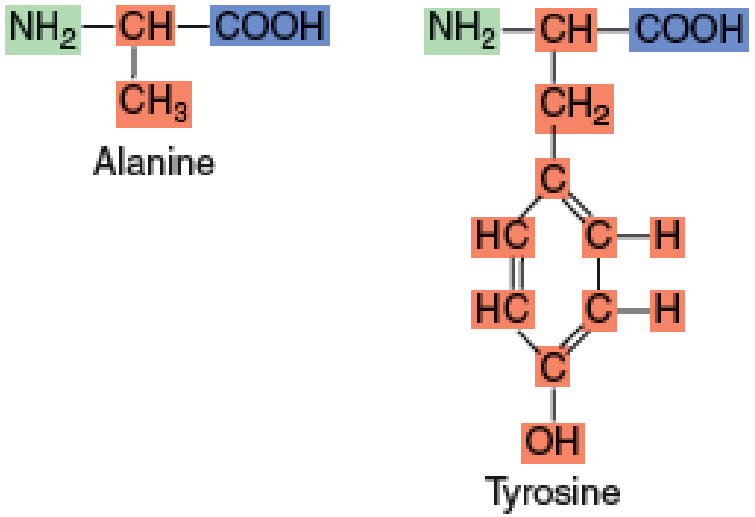


Figure 1.5a

Three-dimensional shapes of two proteins

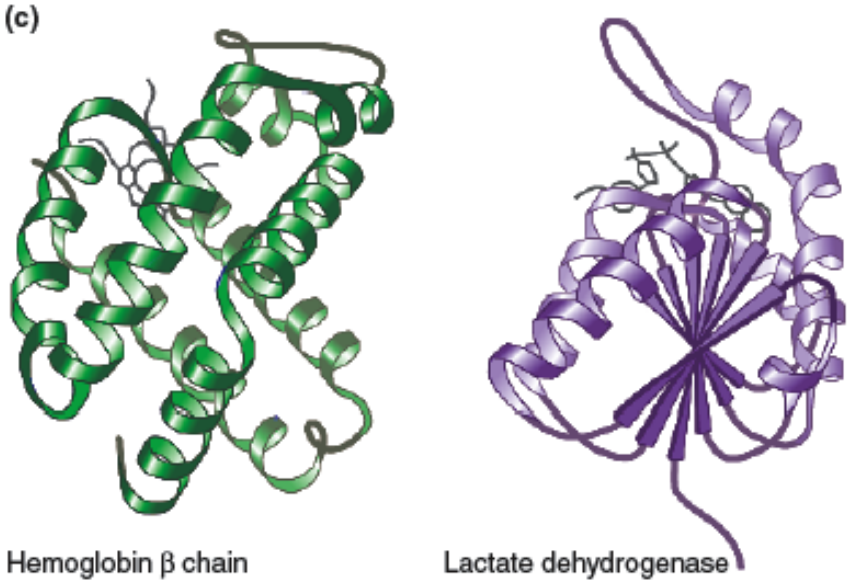


Figure 1.5c

Proteins

- make up most of the mass of a cell
- regulate all cellular processes directly or indirectly
  - enzymes involved in energy utilization, energy storage.
  - enzymes for biosynthesis or breakdown of other macromolecules (including DNA).
  - proteins form scaffolds to hold other proteins and macromolecules in place – to organize the cell.
  - proteins regulate transport into and out of cells and signaling between cells.
  - motor proteins and other proteins regulate intracellular transport.

Molecular Diagnosis

Molecular diagnosis of human disorders is the detection of the various disease-causing variants in DNA and /or RNA samples

Molecular Diagnostics

- Is the use of molecular biology techniques to increase the scientific knowledge of the natural history of a certain diseases, identify individuals who are at risk for developing specific diseases, and make diagnosis of human disorders
- -Advance in the understanding of the structure and chemistry of nucleic acids have facilitated the development of technologies that can be employed effectively in molecular diagnostics

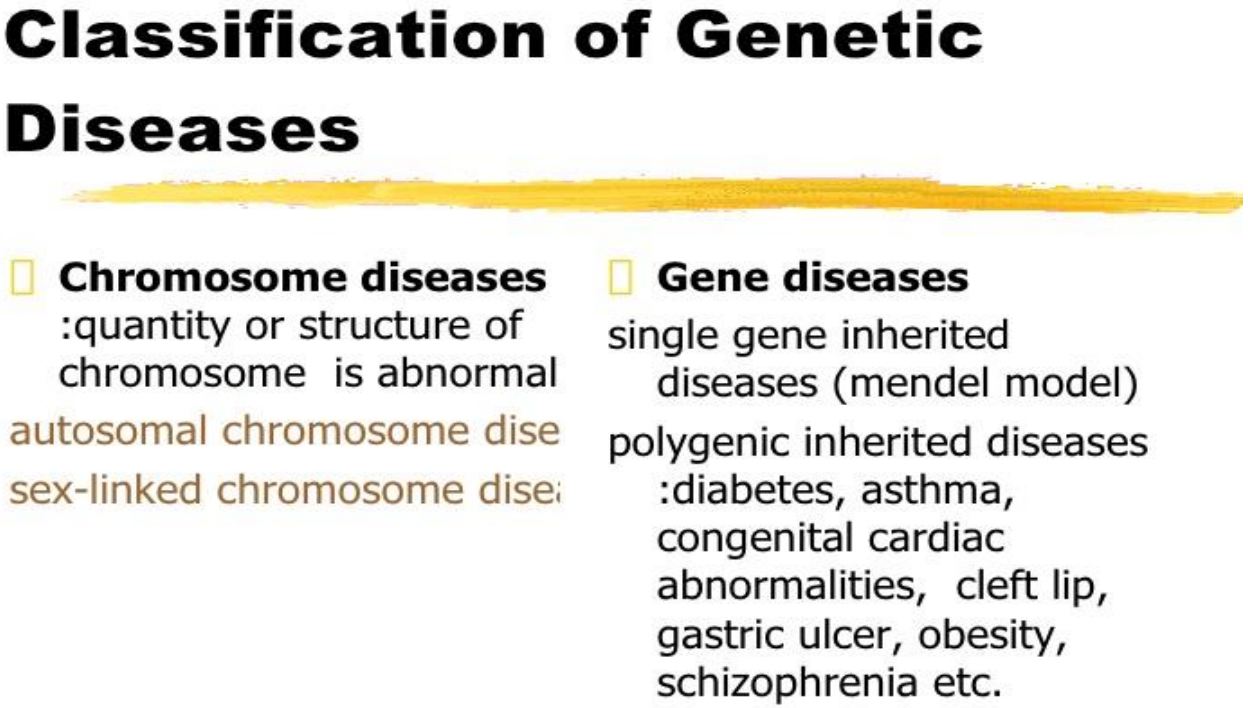
Cytogenetics

- Cytogenetics: is the study of the structure, and function of chromosomes (material of inheritance in the cell nucleus), chromosomal behavior during somatic cell division in growth and development (mitosis) and germ cell division in reproduction (meiosis), chromosomal influence on the phenotype and the factors that cause chromosomal changes (Hare & Singh, 1979)

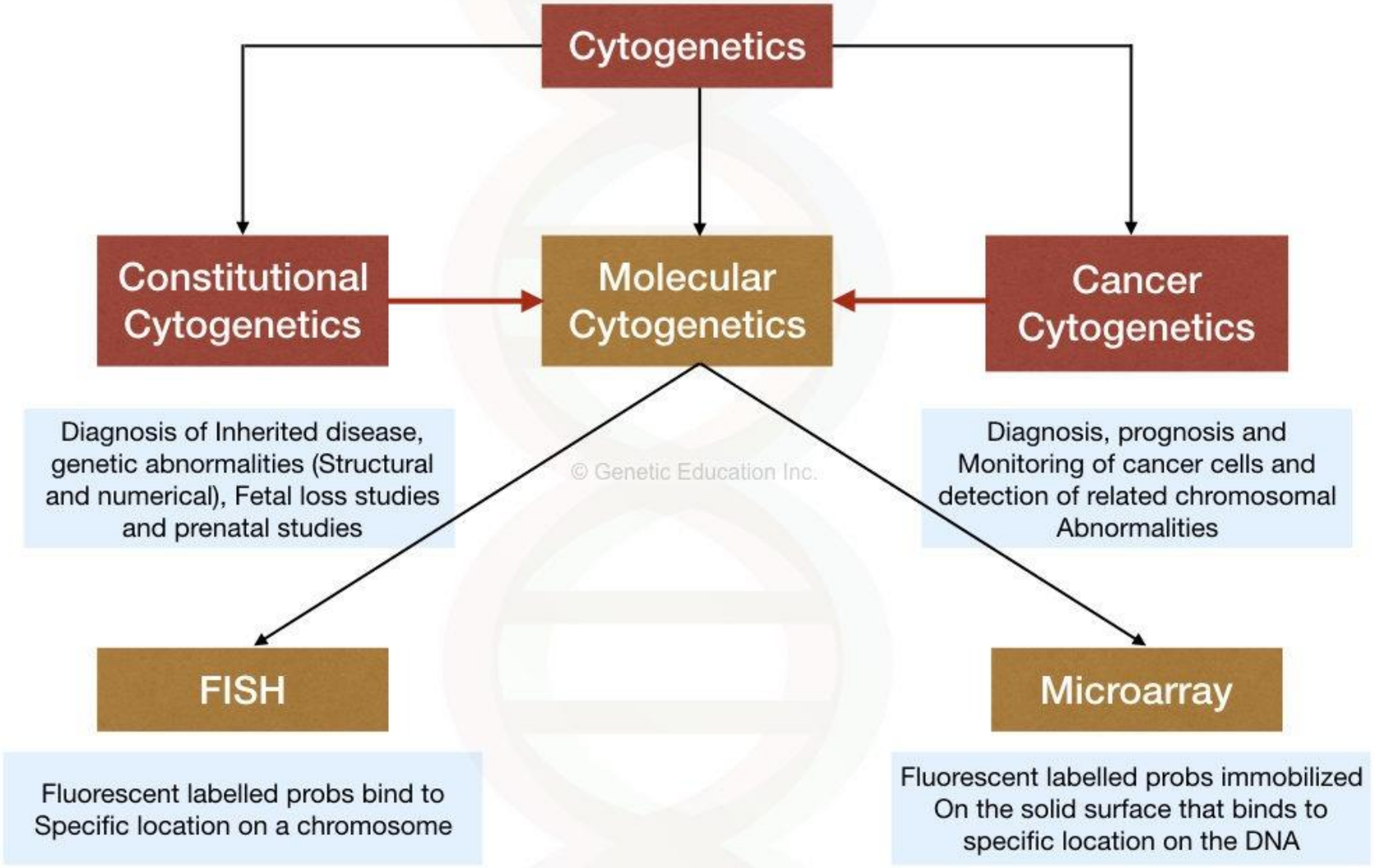
- Human cytogenetics is concerned with how these process may go wrong, because change in number or in structures of certain chromosomes(s) can cause diseases

Problem solving

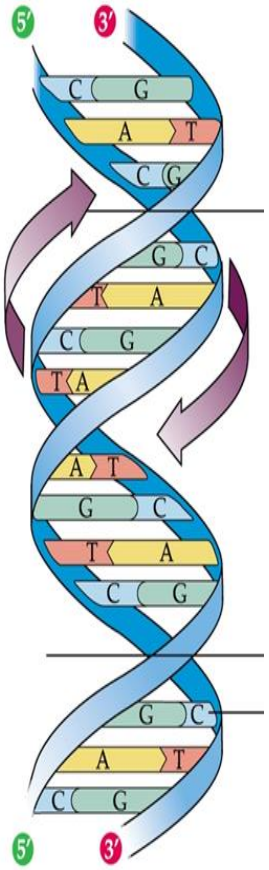
- Genetic diseases



What else?!


Cytogenetics
Constitutional Cytogenetics
Molecular Cytogenetics
Cancer Cytogenetics
Diagnosis of Inherited disease, genetic abnormalities (Structural and numerical), Fetal loss studies and prenatal studies
© Genetic Education Inc.
Diagnosis, prognosis and Monitoring of cancer cells and detection of related chromosomal Abnormalities
FISH
Microarray
Fluorescent labelled probs bind to Specific location on a chromosome
Fluorescent labelled probs immobilized On the solid surface that binds to specific location on the DNA

Genetic variation (at DNA or RNA level) ➔ the clinical phenotype



- There are lots of different mutations/ variations that can occur in our DNA.
- Large-scale mutations/ variations
- Small- scale mutations/ variations

Tentative Topics Table (tentative means subject to change)

Week	Topic
1	Genetic diversity, and laws of segregation and independent assortment
	Karyotyping, Chromosome structure and nomenclature
2	Autosomal chromosomes and numerical chromosomal aberrations
	Sex chromosomes, structural chromosomal aberrations
3	Translocation, aneuploidy, mosaics and chimera
	Live meeting
4	Contrasting Mendelian and non- Mendelian inheritance
	Features of autosomal dominant and autosomal recessive pedigrees & diseases
5	X-inactivation and features sex linked pedigrees and diseases
	Mode of inheritance pedigrees examples
6	Phenotypic expression, imprinting and dynamic variants
	Live meeting
7	Risk assessment I
	Risk assessment II
8	Human genetic variation
9	Clinical variant interpretation
10	Biochemical Genetics
11	Cancer Genetics
12	Pharmacogenomics
13	Lysosomal storage disorders
14	Transport and Metal Disorders
15	mitochondrial disease
16	Gene Therapy

Suggested textbook:

New Clinical Genetics, fourth edition Paperback – December 15, 2020, by Andrew Read (Author), Dian Donnai (Author). ISBN-10 : 1911510703 ISBN-13 : 978-1911510703