Basic Genetic Concepts

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Objectives

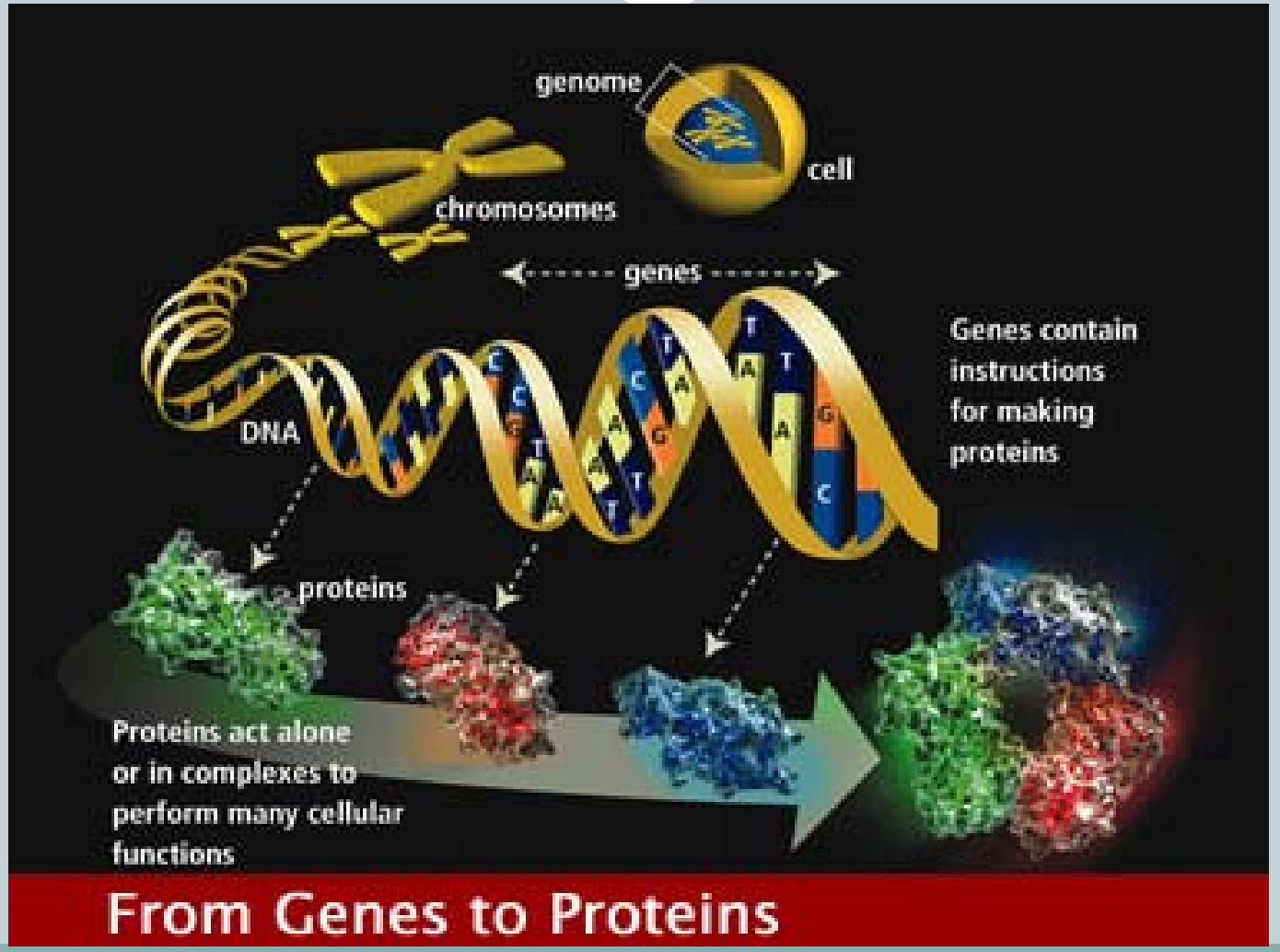
- At the completion of this program, participants will be able to:

1. Become familiar with genetic terminology.
2. Describe basic genetic concepts.
3. Appreciate the interaction of genetic and environmental factors.
4. Understand how dominant and recessive gene expression may result in disability or disease.
5. Envision gene therapy as a treatment modality for health problems.

Why learn about genetics?

- Understanding **patterns of inheritance** and the **linking of specific genes to health issues** has enabled us to understand the pathophysiology of human disease in greater detail.
- Increased understanding of the **biological pathways** that lead to disease is resulting in **new approaches** for prevention and therapy.
- Genetics helps explain why people who have many risk factors for a particular disease live long healthy lives without ever developing the disease. This is due to genetic variations or differences.

Defining Genome: An Organism's Complete Set of DNA



About Genomes

- Genomics is the study of genomes.
- Genomes vary widely in size.
- The smallest know genomes are those of bacteria. They contain about 600,000 DNA base pairs or genetic “building blocks”.
- In contrast, the human genome contains **3 billion** base pairs.
- All human cells, with the exception of mature red blood cells, contain the complete human genome.

DNA: The Basis of Life

- Every living thing on earth, from the smallest bacteria to the largest whale, uses DNA to store genetic information and transmit that information from one generation to another.
- If you were to lay out end to end all the **DNA from just one of your cells, the line would be a little over 6 feet long.**
- The average adult body contains 100 trillion cells.
- Laid out together, the **DNA in your body would stretch to the sun and back nearly 100x.**

More on DNA

- DNA is a **durable** molecule.
- DNA can be recovered from tissue of animals that inhabited planet earth 100,000 years ago.
- Chemically, DNA is simple. It involves 3 components:
  - Molecules of Nitrogen rich substances called **bases- adenine, guanine, cytosine, thymine**
  - **Sugar**
  - **Phosphate**
- These three components come together to form a unit called a nucleotide.
- All 4 bases are flat molecules. They stack up in DNA like a stack of coins enabling DNA to be both very compact and very strong.
- Thousands of nucleotides come together to form one strand of DNA.

The Message in the Helix

- Within the double strand, **matching bases connect** with one another.
- DNA **spirals clockwise** with a full turn, a complete twist, every 10 base pairs.
- The bases are protected on the inside of the spiral.
- They “peep out” just a little when it is time for them to be copied.
- The inside of the helix is dry while the outside is encased in a shell of water.

Another Type of DNA?

- Yes, there is a second type- mitochondrial DNA. (mtDNA)
- Mitochondria, the energy powerhouses of the cell, contain their own DNA which is in a very different form.
- Mitochondrial DNA is inherited only from mother to child.
- Half of a child's nuclear DNA came from mother and half from father, but **all the mitochondrial DNA is passed from mother to child in the cytoplasm of the egg cell.**

The “Construction Crew”

- When it is time for DNA to be copied. The helix unwinds and divides into two half strands called **Template DNA**.
- “Components are assembled: adenine, guanine, cytosine, and thymine, sugar and phosphates, and enzymes.
- Replication by the **enzyme DNA polymerase** proceeds at 2,000 base pairs per minute.
- One in every 100,000 base pairs is incorrectly placed.
- DNA polymerase has the ability to back up and fix errors. In essence, it proofreads, snips the incorrect base out, and replace it with the correct one.
- DNA replication, therefore, is **virtually error free**.
- The error rate is one per 10 million base.

Non-Coding DNA

- Non-coding DNA does not contain messages for building proteins. It is sometimes called junk DNA.
- The end of the strand, the telomere, is junk DNA which gets shorter each time DNA is copied.
- Scientists now believe that the Junk DNA is related to **human aging**. It protects part of the coding DNA from being snipped off during the copying process.
- In fact, this junk DNA is felt by some to be the most important part of the genome.
- **Anti-aging scientists are seeking ways to lengthen telomeres.**

Making Protein

- Our DNA can be compared to the reserve section in a library.
- The message it contains, in this case genetic material, can be read but cannot be taken the nucleus. A copy, however, can be made and transported outside the nucleus.
- **Messenger RNAs** created through **transcription** can carry DNA's message out into the cytoplasm of the cell so that it can be used to construct proteins. An example of an essential protein is **hemoglobin**.

The Transcription Process

- Enzymes identify the right part of the DNA to copy the area needed.
- **The DNA molecule opens up** to allow the code contained in the **order of base pairs** to be read.
- The bases of genes are read in sets of 3 called codons.
- Enzymes build a messenger RNA strand that looks like exactly like the DNA.
- It differs from DNA due to the substitution of uracil for adenine.
- The DNA then releases the messenger RNA strand and snaps shut.
- In this manner, 90,000 different proteins can be made.
- Genes **turn on and off** as needed; they are not producing products all the time.

Copying Errors

- The strand of DNA is read left to right from its beginning to its end in sets of 3 base pairs.
- In rare instances, reading does not start at the beginning.
- When this happens, the message can be garbled (genetic nonsense) or creates a defective product that is non-functional (genetic mis-sense).
- Example: THE FAT CAT

  T HEF ATC AT

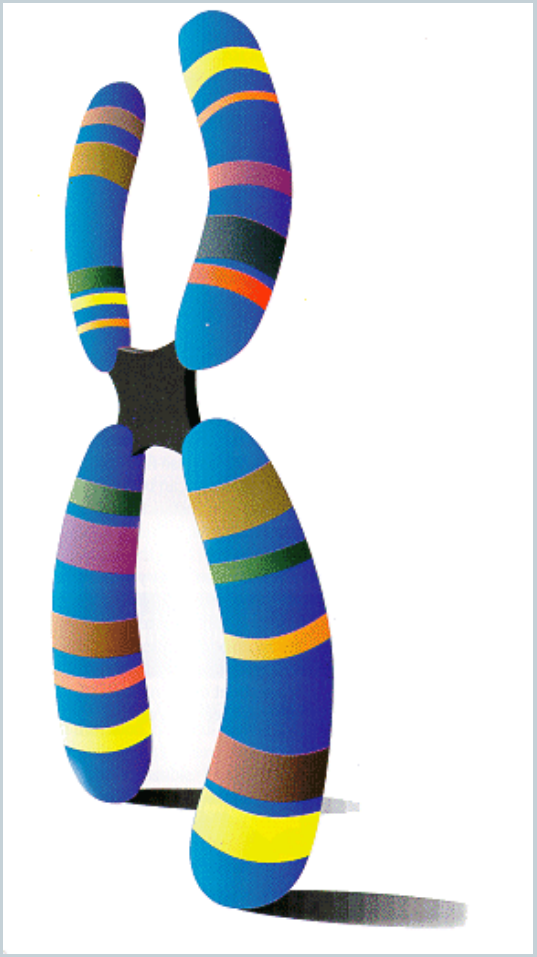
Chromatin to Chromosomes

- Threadlike strands composed of DNA.

Types of Chromosomes

- Humans have **46 total chromosomes** arranged into **23 pairs.**
- The term **ploidy** refers to the number of complete sets of chromosomes in a cell.
- Chromosomes are of two types.
- **Sex chromosomes** that determine gender.
  - Human cells contain two sex chromosomes.
    - If you are female, you have two X chromosomes.
    - If you are male, you have an X and a Y.
    - These "germ" cells are **haploid** (1n).
- **Autosomal chromosomes**
  - These are non-sex chromosomes.
  - There are 22 pairs.
  - They are diploid (**2n**).
  - They are identified by numbers on the basis of length so Chromosome 1 is the longest.

Anatomy of a Chromosome



- **The pinched area is the centromere.**
- **It can be in the middle, closer to the top, or closer to the bottom.**
- **It is the position of the centromere that gives the chromosome its shape.**
- **The various points along the chromosome are called a locus or loci.**
- **The ends of the chromosomes are called the telomeres.**

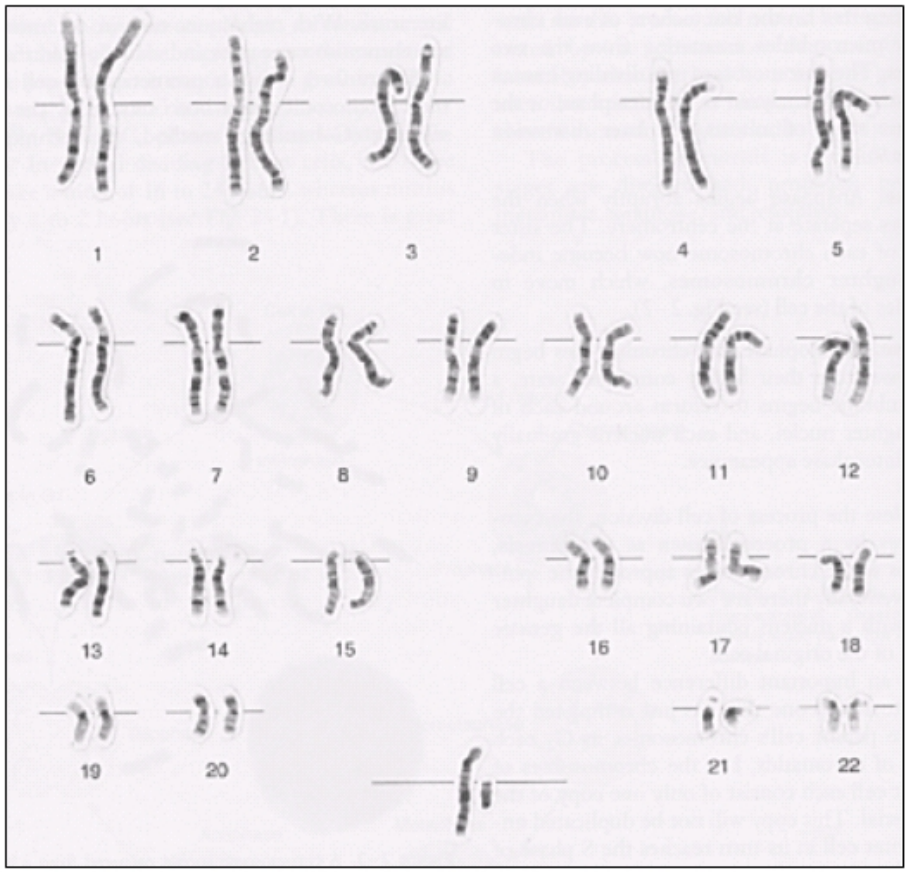
Selected Results from the Human Genome Project

- The human genome contains 3.2 billion base pairs.
- The total number of genes is 22,000, much lower than the estimated 80,000 to 140,000.
- Chromosome 1, the largest, has 3,168 genes; the Y chromosome has the fewest, 344.
- The average gene consists of 3,000 base pairs, but sizes vary greatly. The largest known human gene has 2.4 million base pairs.
- The human genome sequence is almost exactly the same (99.9%) in all people.
- The human genome is still growing.
- At the completion of the project, functions were unknown for more than 50% of the discovered genes.

Aneuploidy

- **Aneuploidy** is a condition in which the chromosomal number in the cell is **not the typical number** for the species.
- This condition gives rise to an chromosomal abnormality in which an extra chromosome is present or one or more chromosomes is lost.
- Down syndrome and Turner syndrome are examples of aneuploidy.
- Diagnosis of genetic conditions begin with karyotyping.

Normal Human Karyotype



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Alleles

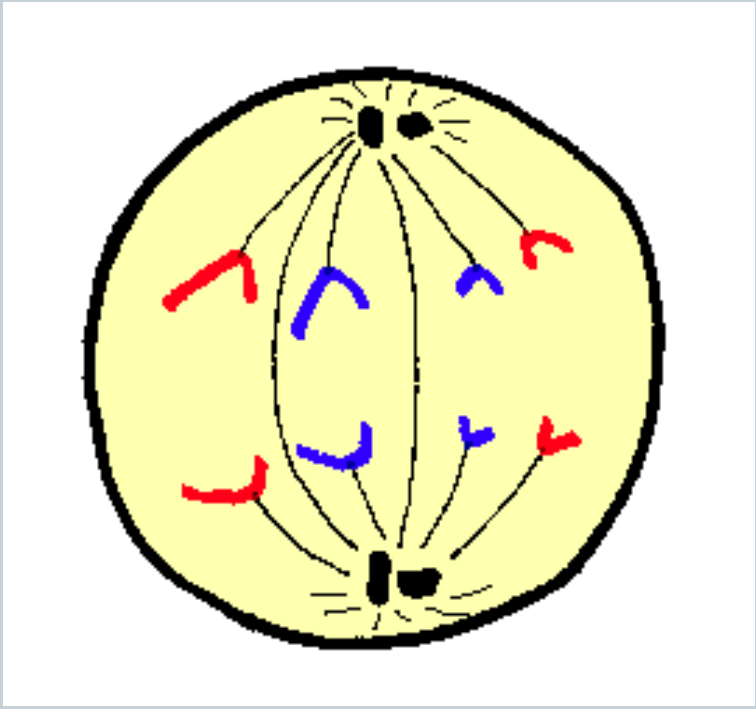
- Alternative versions of genes are called **Alleles.**
- Any gene can have one or more alleles. Alleles code for different **phenotypes**, different physical traits you can see.
- Most phenotypes are caused by multiple genes acting together.
- For example eye color is determined by at least 3 genes that reside on two different chromosomes.
- **Certain alleles are associated with specific diseases including dementias**.

Genotype versus Phenotype

- Your own unique set of alleles (allelic makeup) is called your **genotype**.
- How a trait is expressed in **your** observable appearance (for example hair color and eye color) is called your **phenotype**.
- Health problems such as cardiac septal defects or achondroplasia are manifestations of phenotype.

Cell Replication

- Cells age and need replacing.
- Chromosomes line up at the "equator" of the cell.
- Spindle fibers contract pulling the chromosome pair apart at the centomere.
- Chromosomal pairs are pulled apart.
- Each of the "daughter" cells will have a full set of the original cell's chromosomes.
- The nucleus begins to reform in each of the daughter cells and the cell cleaves in two as telophase comes to an end.
- The result is two cells each of which will contain the entire genome.



What is sex?

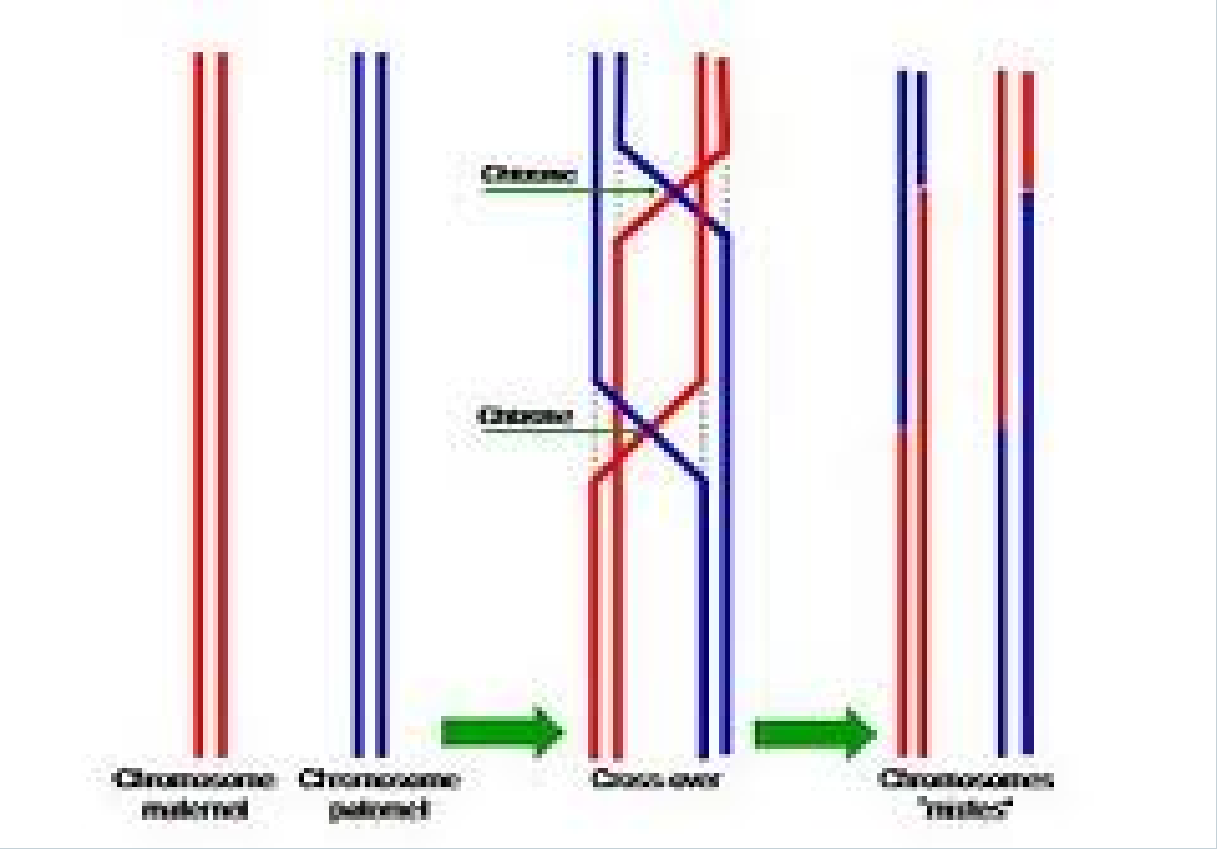
- To geneticists, sex is an inspired strategy or cleverly concocted scheme to **foster the sharing of genetic information** between individuals within species.
- Sexual reproduction guarantees that offspring will be a replicate of neither of the parents. Rather, **offspring are a unique combination of traits inherited from both parents.**

Sexual Reproduction- Meiosis

- **Crossing over-** The male and female chromosomes line up side by side and **exchange parts**. The process of swapping genes is called **crossing over** or **recombination**.
- When fertilization occurs, the offspring gets a **full set of chromosomes**, **half from each parent**.
- The purpose of recombination is to **increase the diversity of the offspring in terms of their traits or characteristics.**

Crossing Over

- Crossing over is also called **recombination**



Chromosomal Abnormalities

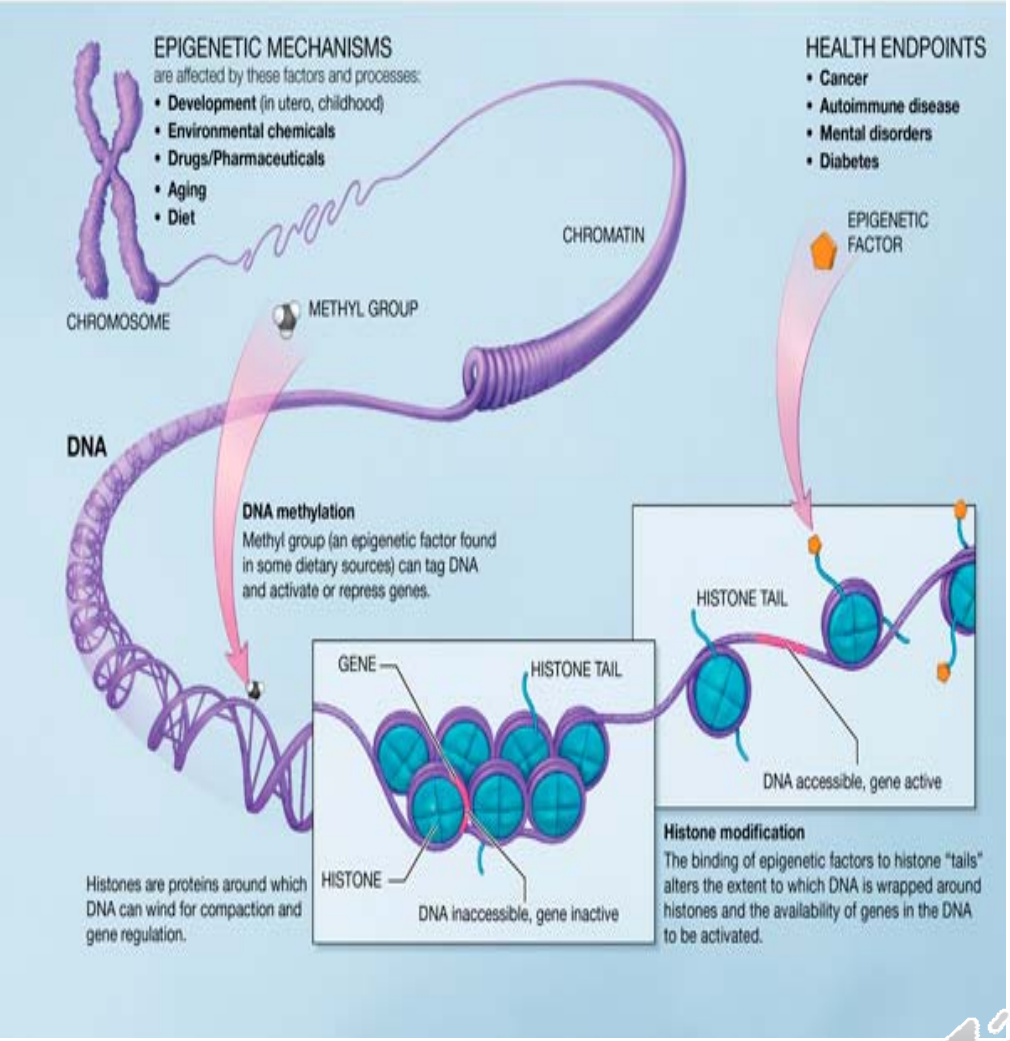
- While cell division and replication almost always occur as expected, abnormalities can occur,
- Abnormalities are organized into two basic groups:
  - **Numerical abnormalities** in which the individual is either **missing a chromosome** from a pair (monosomy) or has **more than two of the same chromosomes** (e.g., a trisomy).
  - **Structural abnormalities** of various types.
  - Errors **typically** occur when chromosomes are being duplicated in preparation for mitosis or meiosis or when they are pulled apart by the spindle fibers.

Types of errors

- **Deletions**: a part of a chromosome is missing. Deletions are associated with serious consequences.
- **Duplication**: a part of a chromosome is duplicated more than once resulting in extra DNA in the cell.
- **Translocation**: a portion of a chromosome has been transferred to another chromosome.
- **Inversions**: a portion of the chromosome has broken off then turned upside down and reattached. As a result the genetic material is inverted.
- **Rings**: a portion of a chromosome has broken off and formed a ring.

Epigenetics

- An emerging frontier of genetics that involves changes in the regulation of gene activity that are **not dependent on gene sequence.**
- It is the study of **a single gene or set of genes.**

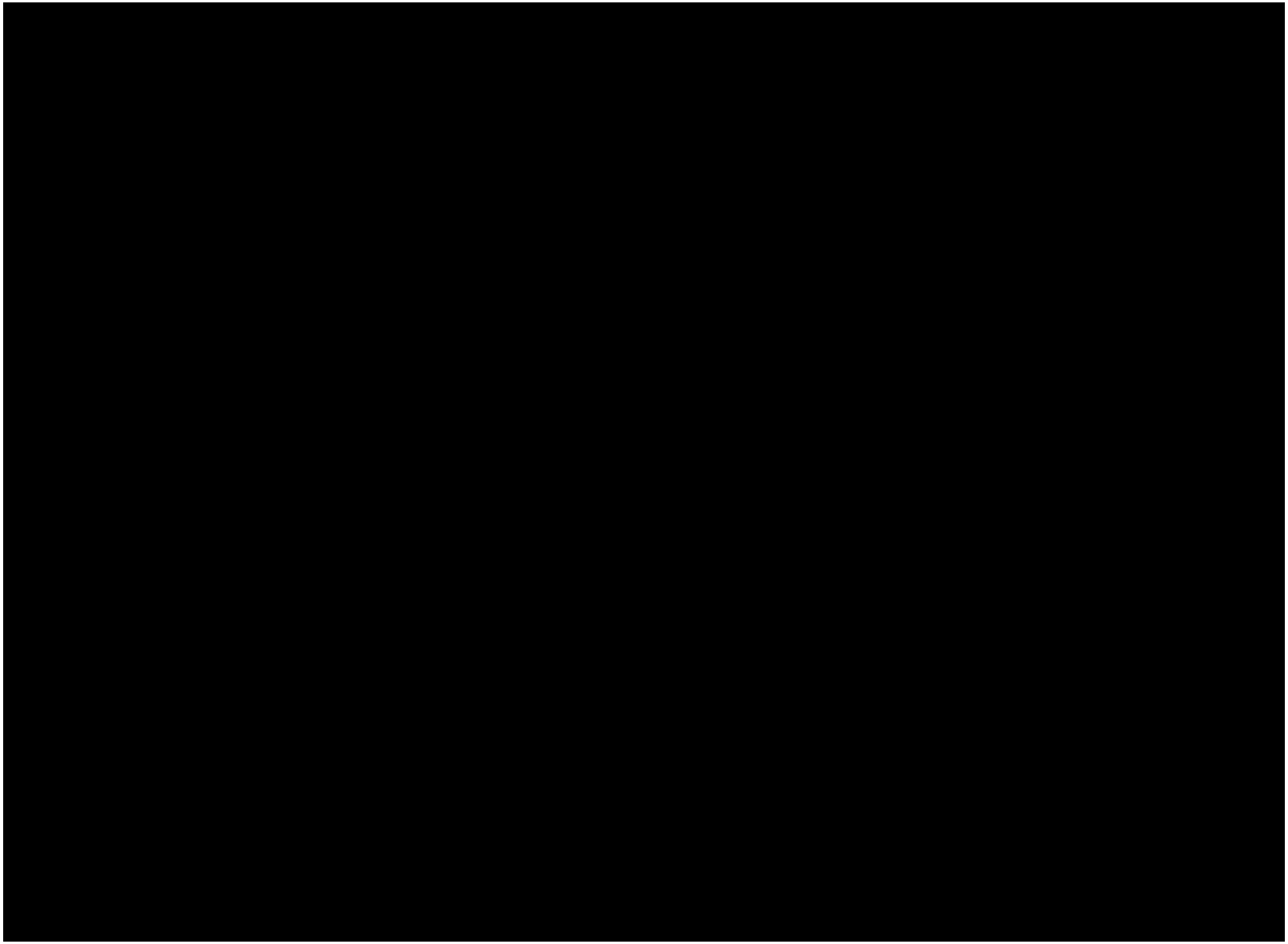


Epigenetic Factors and Processes

- Exposures impacting development in utero
- Environmental chemicals
- Pharmaceuticals
- Aging
- Diet

Epigenetic Switches Starring The Agouti Sisters

Scientists have demonstrated that epigenetic switches and markers can be "dimmed" or turned off or on. In the case of mice carrying the agouti gene, chemical clusters in methyl donors could “turn off” the color (from yellow to brown), hunger and predisposition for certain diseases like diabetes and cancer.

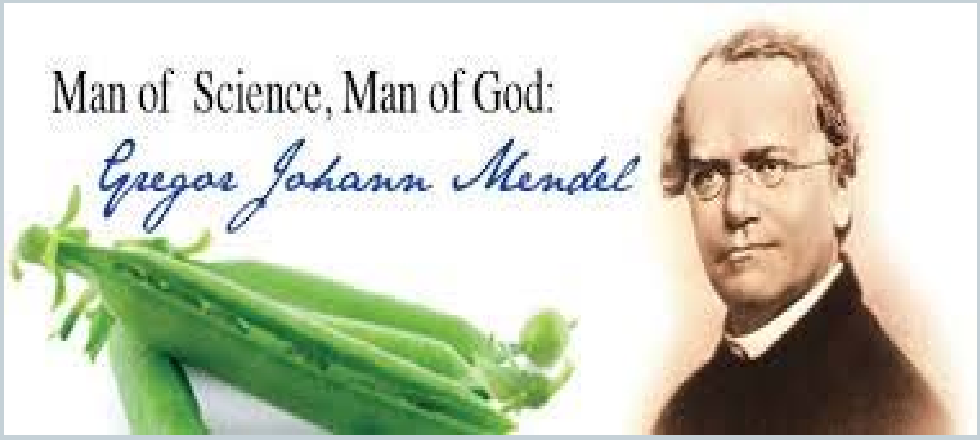


More on the Epigenome

- Methyl groups found in dietary sources and in the environment can tag DNA and activate or repress genes.
- In other words, **methyl groups can turn genes on and off**.
- These marks are not part of DNA itself yet they can be passed on from cell to cell as the cell divides and from one generation to the next.
- Other tags attach to proteins responsible for winding very long molecules of DNA into chromosomes within the nucleus.

Laws of Inheritance

- Laws of inheritance were discovered in the early 1850s by Gregor Mendel, a 19th Century Austrian monk.
- By studying different pea plants, Mendel categorized patterns of genetic inheritance still recognized today.
- This is remarkable since Mendel had no knowledge whatsoever of DNA, genes, or chromosomes.



Building of the Work of Mendel

- Mendel's work was not discovered by scientists for 17 years. His writings were serendipitously found by William Bateson.
- Dr. Bateson introduced Mendel's principles and developed all the key terms we use in genetics today.
- Essentially, we receive half of our genes from our father and half from our mother.
- Genes are classified as **dominant** or **recessive**.
- A dominant gene **always shows itself** it our phenotype.
- A recessive gene does not always show. It only shows if we happen to inherit recessive genes from both parents.

Examples of Simple Inheritence

- Mary and John are expecting a child.
- We know that half of that child's genes will come from each of them.
- For any one of their 22,000 genes, Mary could be dominant or recessive. The same is true for John.
- At the time of conception, the following four reproductive outcomes are feasible.
  - Mary could be homozygous dominant (DD) or heterozygous (Dd).
  - John could be (DD) or Dd).

		maternal A	maternal a
paternal	A	AA	Aa
paternal	a	Aa	aa

Reproductive Outcomes

		maternal	
		A	a
paternal	A	AA	Aa
	a	Aa	aa

- There is a one in 4 chance that their child will be homozygous dominant (AA).
- There is a two out of 4 chance that their child with be heterozygous (Aa).
- There is a 1 in 4 chance that their child will be homozygous recessive.

Health Applications

- Since the conclusion of the Human Genome Project, medical science has been able to categorize human disease which are genetically transmitted.
- They are identified as Autosomal Dominant or Autosomal recessive.
- An autosomal dominant gene will always manifest, show itself in the phenotype.
- A recessive gene will only express when paired with another recessive gene.
- Cystic fibrosis is a good example. In order for offspring to manifest CF, he or she must inherit 2 recessive genes.

Mutations

- Mutations alter gene expression.
- They have variable effects on health depending on when and where they occur and whether they alter the functions of genes.

- Types of mutations are :
  - **Insertion**: Changes the number of DNA base pairs. The resulting protein made may gain or lose function.
  - **Deletion**: Base pairs are removed from DNA. Entire genes may be deleted. The consequences of deletions can have serious effects on health.
  - **Duplication**: A piece of DNA is abnormally copied several times. Gene function is altered.
  - **Repeat expansion**. Here we have a sequence of 3 or 4 base pairs copied 30 to 70 times. Examples are small cell lung cancer, autism, schizophrenia, Fragile X syndrome, and Huntington Disease.
  - Duplications and Repeat Expansions are termed **Copy Number Variants**.