

Genomic and Precision Medicine

Week 1: Human Genome Structure,
Function, and Variation



Jeanette McCarthy,
MPH, PhD
UCSF Medical Genetics



University of California
San Francisco

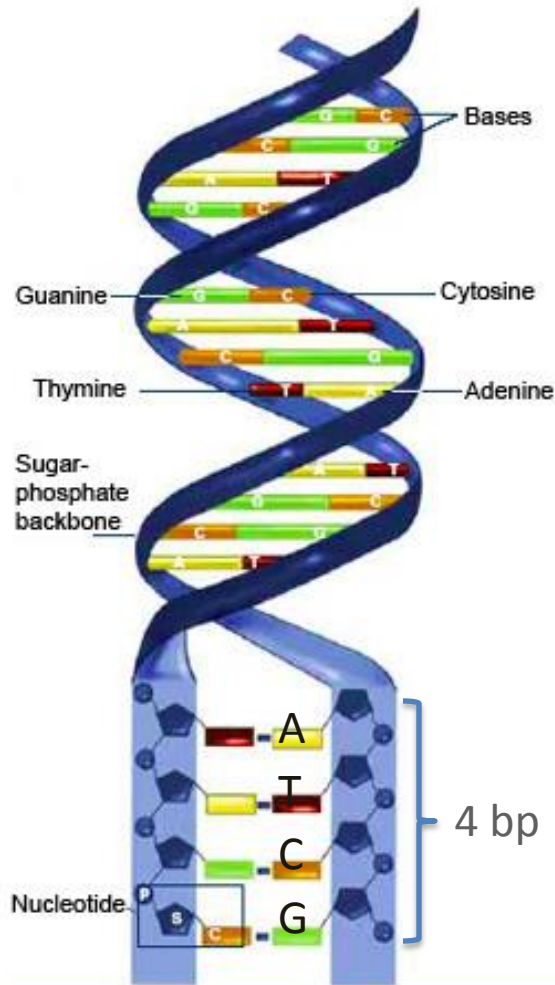
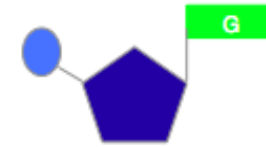
advancing health worldwide™

The Lecture

- **MODULE 1:** The structure of the human genome and how genes work
- **MODULE 2:** Structural variants
- **MODULE 3:** Single nucleotide variants
- **MODULE 4:** Consequences of single nucleotide variants in genes
- **MODULE 5:** Architecture of human genetic variation

MODULE 1: The structure of the human genome and how genes work

DNA is a polymer of nucleotides (sugar, phosphate and one of four nitrogenous bases (A,T,G,C))



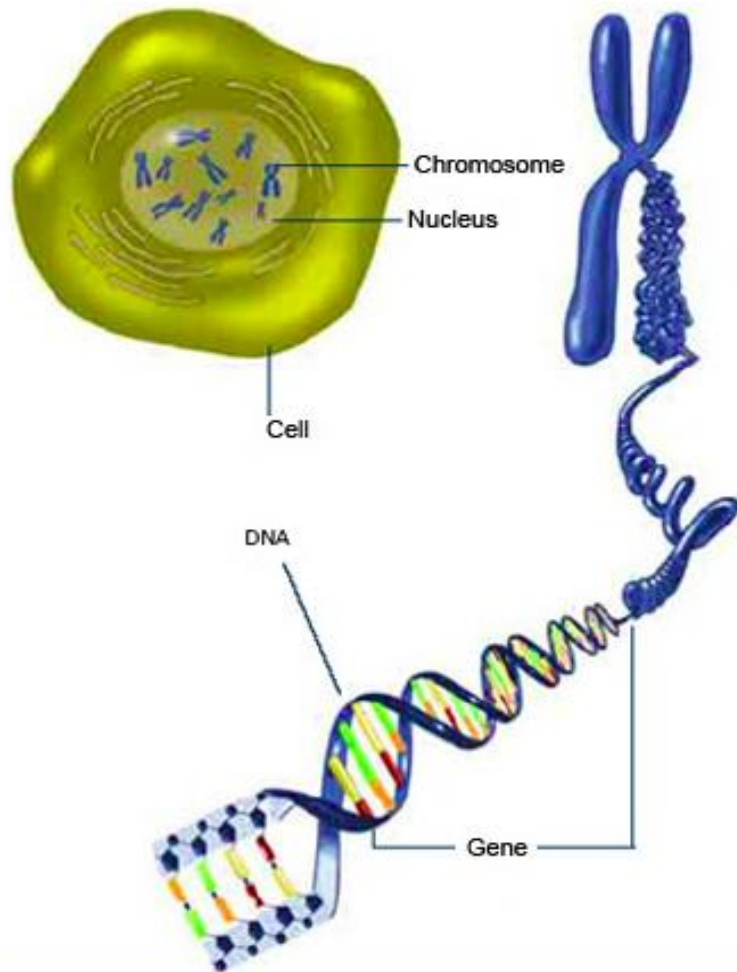
DNA is double stranded, with complementary bases pairing

Size/length unit = **base pairs** (bp), kilobases (Kb), megabases (Mb)

Order of bases along one strand is referred to as the **DNA sequence**

```
ATCGCCGGGCCTGGCGCCGCAGAGCACGAGGGAG
GCCAGGCGCTTCGGGAGGGGCTGCTGTACCTTAGA
```

DNA Structure



- 3.2 billion bp of DNA in the **human genome**
- 2 copies (one from each parent) = 6.4 billion bp
- 23 chromosome pairs
 - XX (female) or XY (male) **sex chromosomes**
 - 22 **autosomes**
- At times DNA is open, other times condensed

The exact function of most of the DNA in the human genome is unknown

Repeats

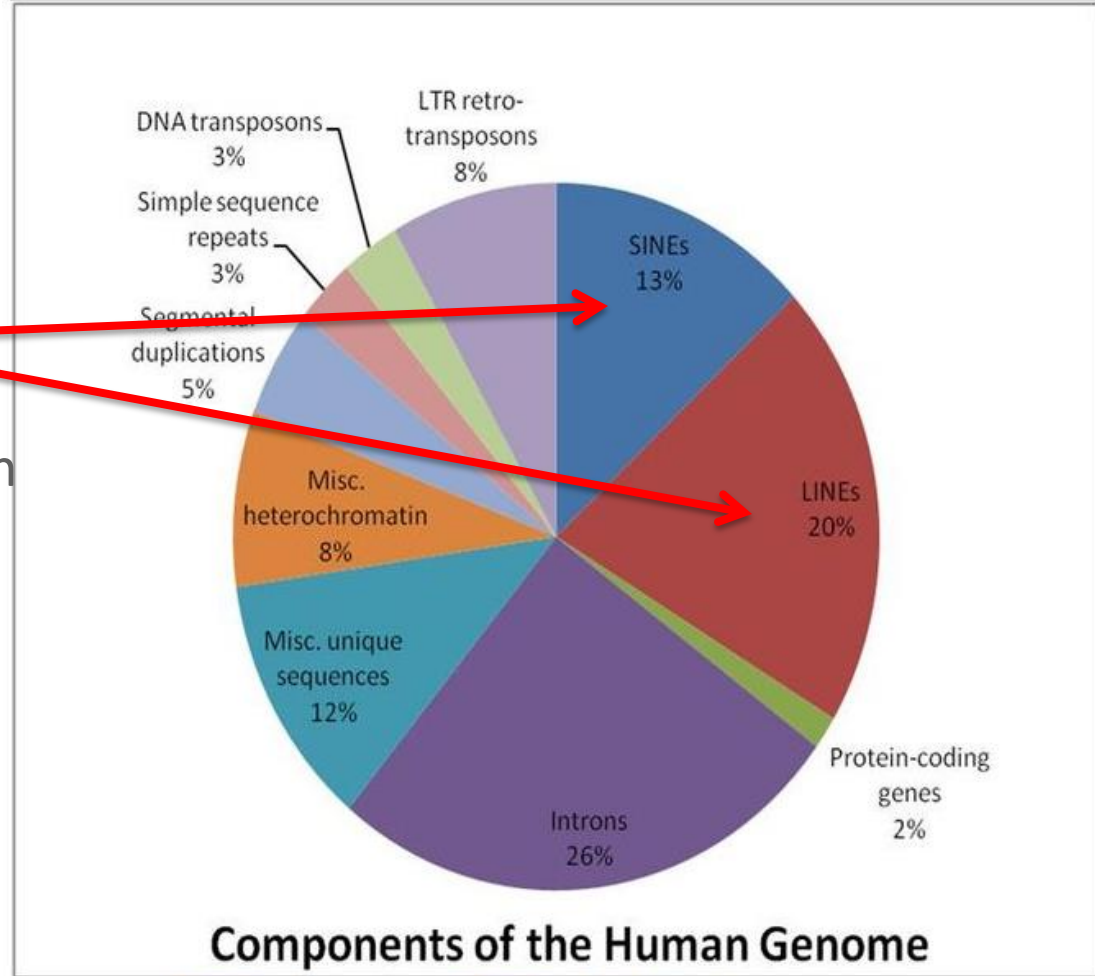
- $\approx 30\%$ - packaging, segregation and replication of chromosomes

Putative functional regions

- $\approx 5\%$ **conserved** across multiple species

Protein-coding genes

- $\approx 1.5\%$



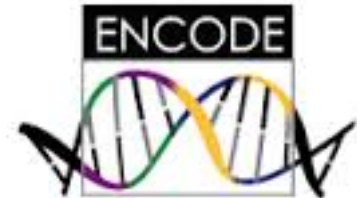
Size of this preview: 666 × 599 pixels. Other resolutions: 267 × 240 pixels | 533 × 480 pixels.

Full resolution (750 × 675 pixels, file size: 40 KB, MIME type: image/jpeg)

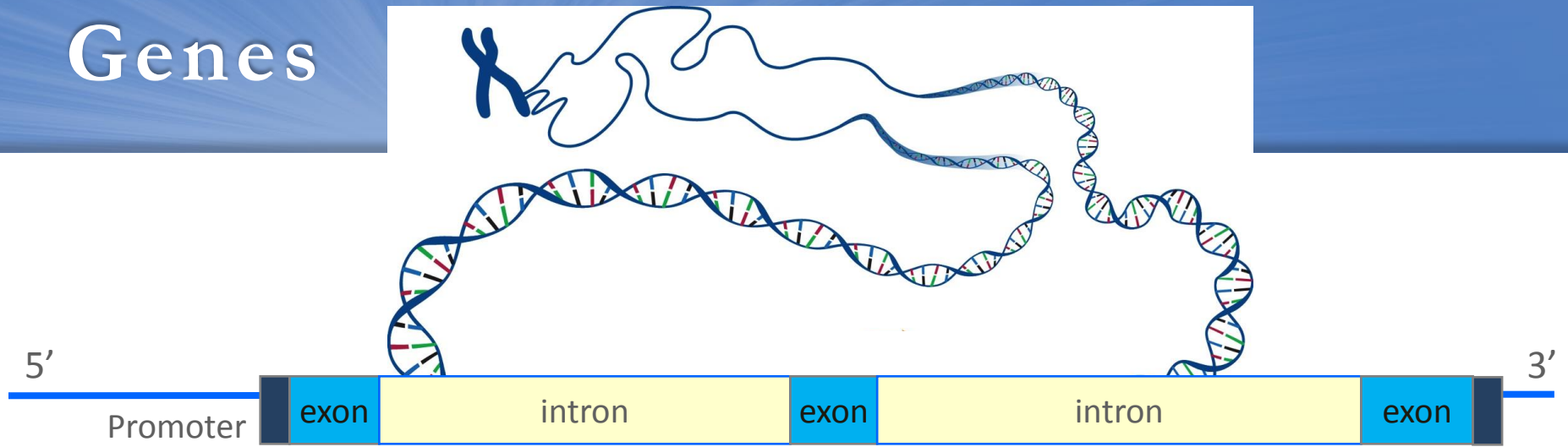
This is a file from the [Wikimedia Commons](#). Information from its

$\sim 80\%$ of genome may be functional

ENCODE project

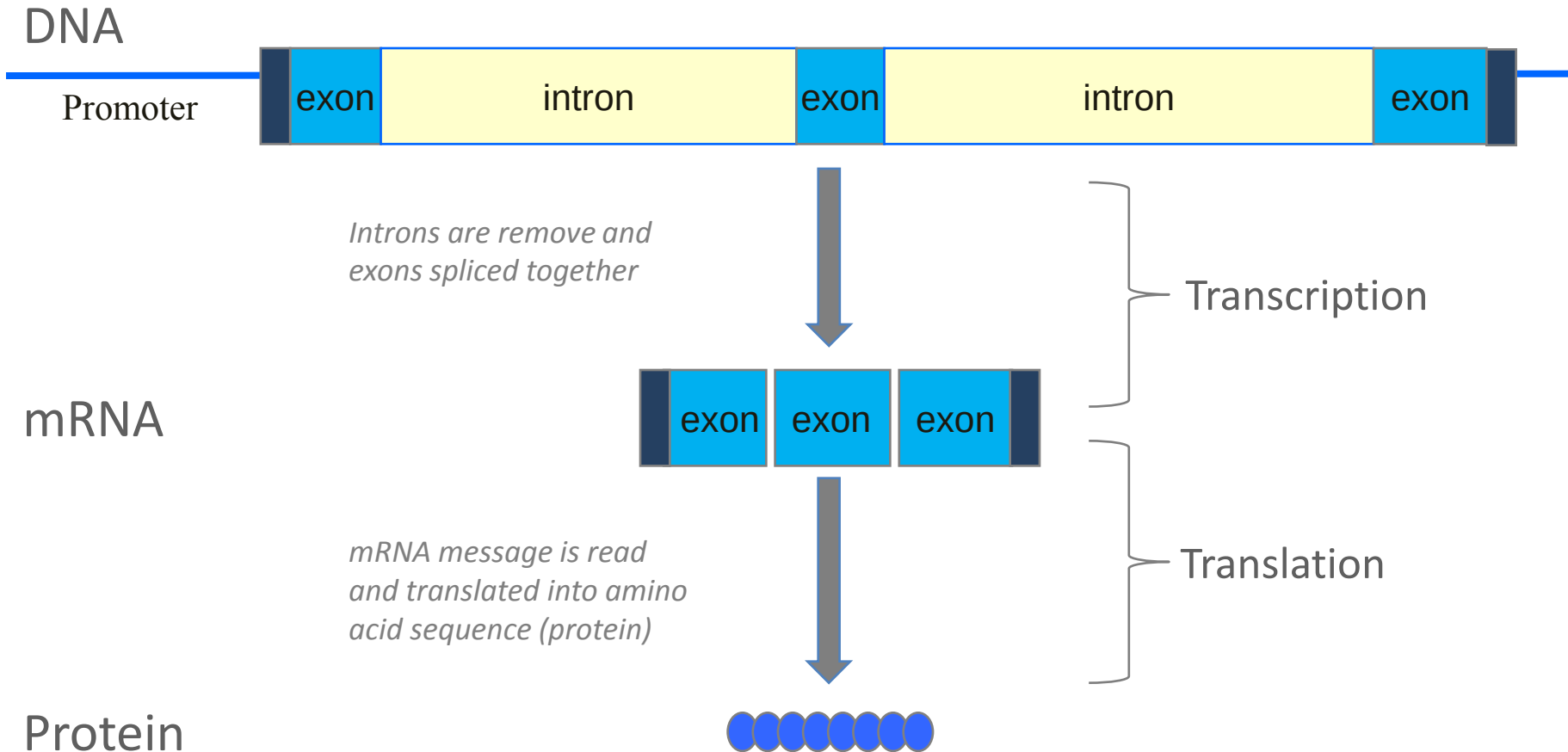


Genes



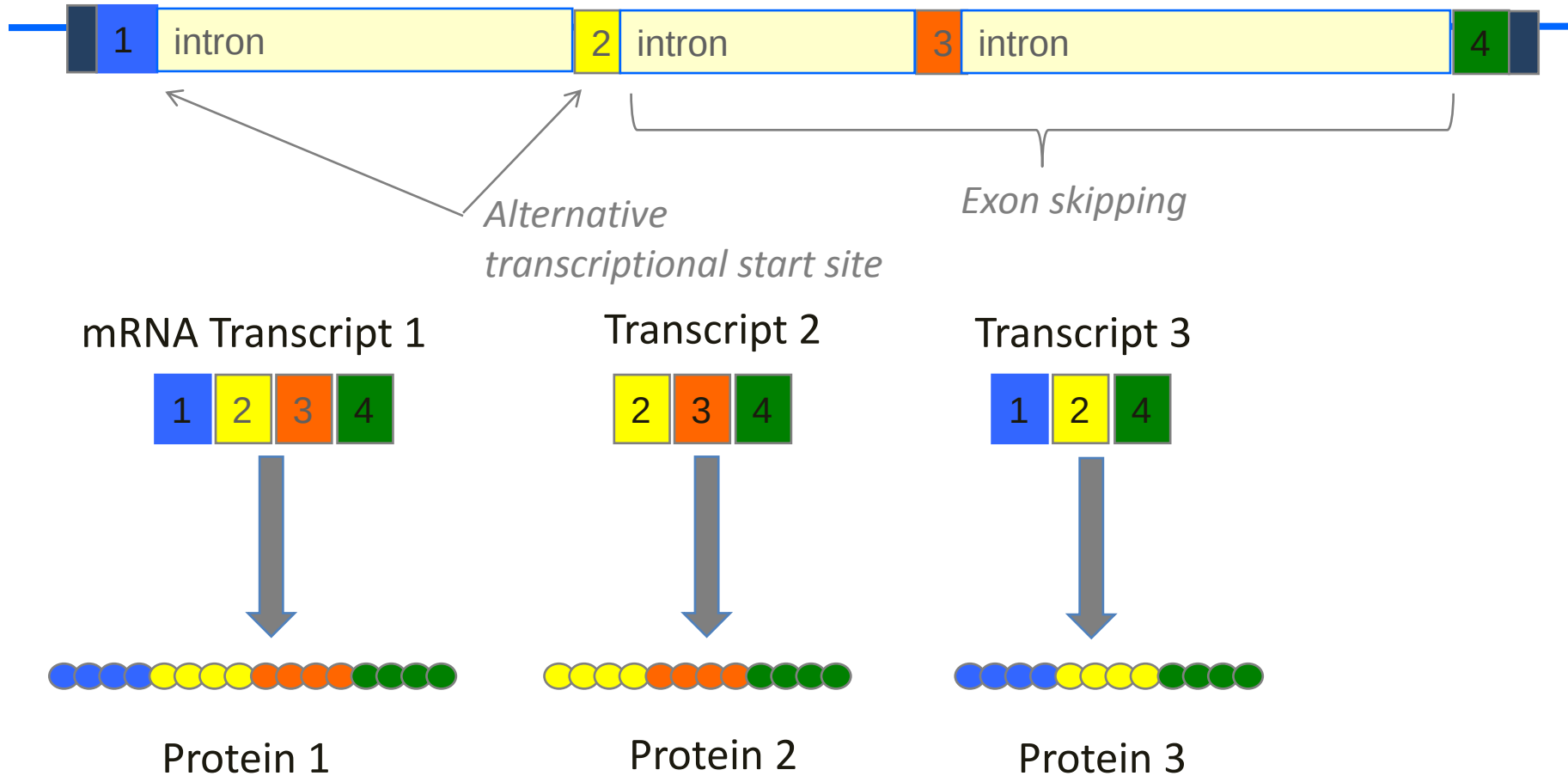
- Blueprint for the production of proteins (enzymes, structural elements, signaling molecules)
- Structure: introns, exons (coding), regulatory regions
- Average size: 20kb, 8 exons, but highly variable
- Estimated 22,000 genes concentrated in random areas along the genome

Protein Synthesis



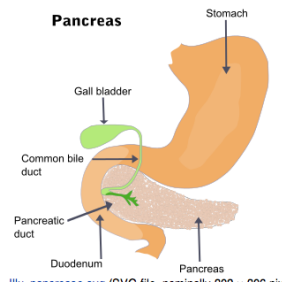
Alternative splicing

Occurs for >90% of genes

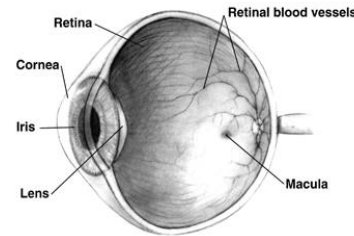


Different cells make different proteins

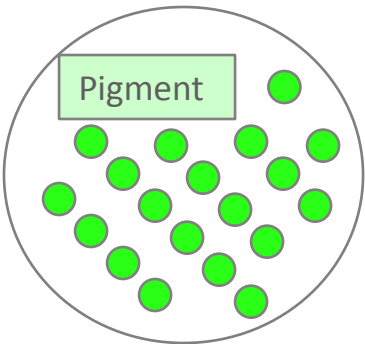
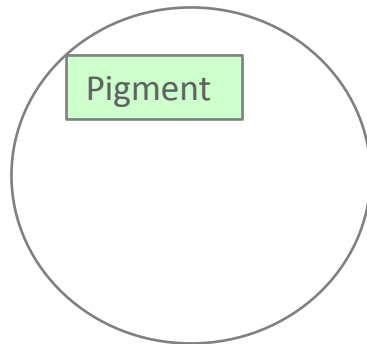
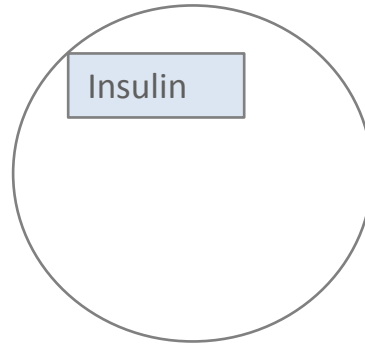
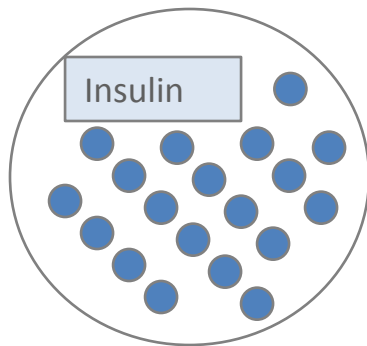
Pancreas



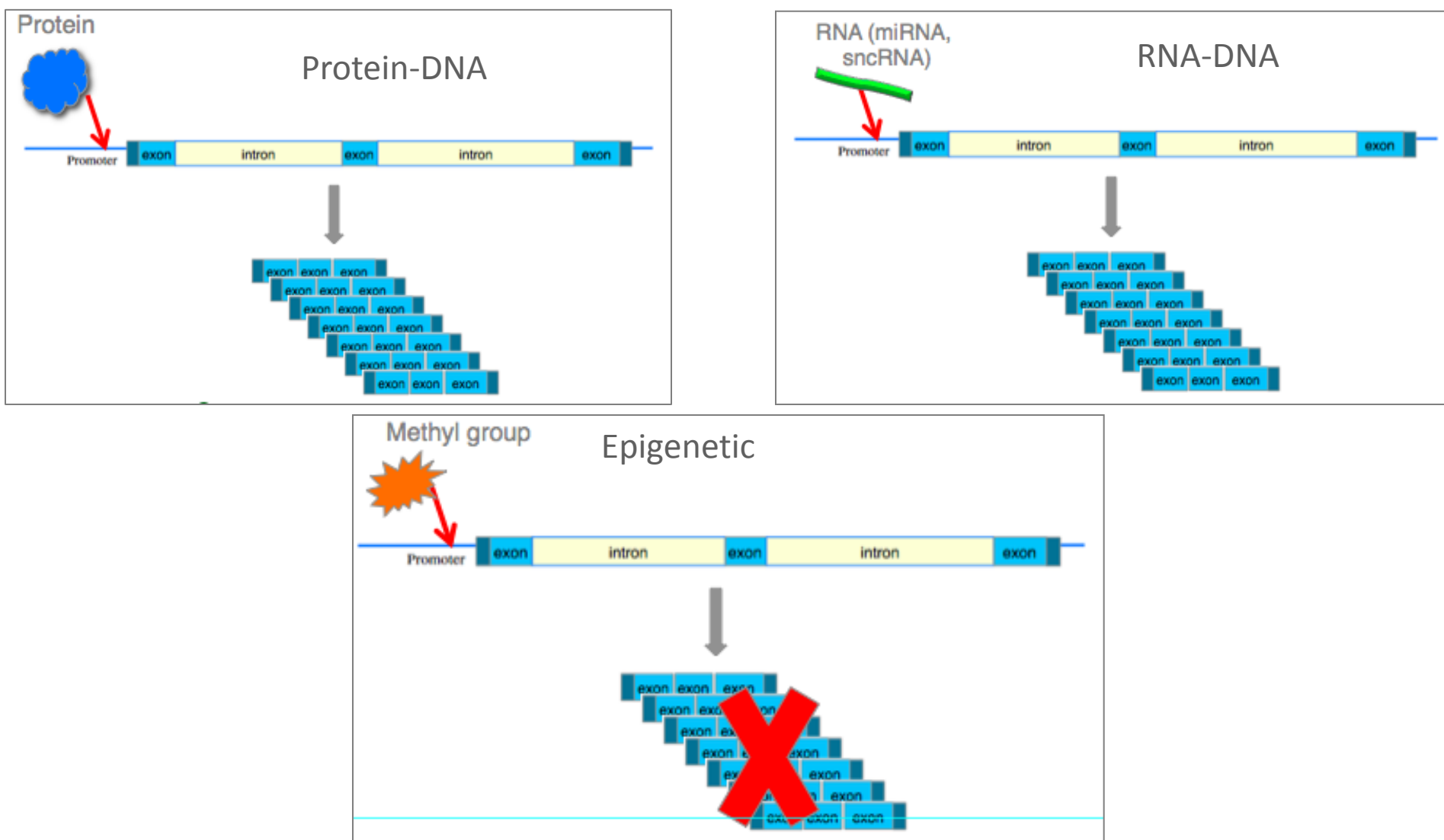
Retina



- Cells with identical DNA can look and behave differently because of differences in gene expression
- Expression of genes in wrong cell at wrong time or in wrong amount can lead to disease



How is gene expression regulated?



Question

What allows for different cell types to express different functional proteins?

- A. Each cell type contains different genes that encode the necessary proteins
- B. Each cell type contains the same genes, but different genes are expressed

Answer

B. Each cell type contains the same genes, but different genes are expressed

For the most part, every cell in your body has the same genes. What differs is the expression of those genes, with some being turned on and others being turned off, different splice forms expressed, etc.