Coding strand

- has the same sequence as the mRNA that is being transcribed, but is not actually read by the RNA polymerase (5' to 3')

Template Strand

- Is read in the 3' to 5' direction
- RNA polymerase binds onto this and causes it to transcribe
- Is complementary to both coding and mRNA strand

How RNA is produced - transcription

- Step 1 : RNA polymerase binds to promoter
- Step 2: RNA polymerase unwinds the double-stranded DNA and begins assembling RNA nucleotides
- Step 3: Release the RNA transcript

The Genetic Code

- Codons (triplets)
- Unambiguous
- Degenerate
- Initiation and Termination codons
- Nearly Universal

Different initiation points may create overlapping genes.

Identifying ORFS in DNA sequence

- The ribosome establishes the grouping of nucleotides that correspond to codons by the first AUG encountered.
- Read the sequence 5' to 3', looking for stop
- Try each reading frame

Post-translational modification

- Removal or modification of the N-terminus
- Individual amino acids are sometimes modified
- Carbohydrate side chains are added
- Polypeptides chains may be trimmed
- Signal sequences are removed
- Polypeptides complexed with metals
- Addition of poly-a tail
- Addition of 5-guanine gap

Types of Mutations

	Types of Mutations at the DNA level	Results at the molecular level
	No mutation	Codons specify wild-type protein
Point Mutations	Synonymous mutation	Altered codon specifies the same amino acid
	Missense mutation (conservative)	Altered codon specifies a chemically similar amino acid
	Missense mutation (nonconservative)	Altered codon specifies a chemically dissimilar amino acid
	Nonsense mutation	Altered codon codon signals chain termination
Base insertion	Frameshift mutation	Base insertion causes a change in the reading frame
Base deletion	Frameshift mutation	Base deletion causes a change in the reading frame

Structures of DNA

- Genes encode the order of amino acids (primary structure)
- Which sets up amino acid interactions in localized regions (secondary structure)
- Which dictate protein conformation (tertiary structure)
- Changes in the primary structure of proteins can change folding and alter function of a protein

Alleles

- Wild type alleles
  - Usually code for functional proteins
  - Usually dominant
- Mutant alleles
  - Usually code for defective proteins
  - Often recessive

Phenotype

- Physical or observable characteristic
  - Examples include eye color, hair type, ability/inability to digest lactose, synthesis of melanin (pigment)

Loss of function mutations

- Loss of function mutations result in a protein that has little or no enzymatic activity
    - Most mutations associated with a phenotype are Loss of function
        - Many changes that affect the normal tertiary structure would disrupt the active site (even if the mutation affects an amino acid that is far from the active site)
- Most loss of function mutations are recessive
    - Why? Because half the amount of wild type gene product is usually sufficient to give a wild type phenotype.
- General rule for loss of function mutations
    - Half the amount of wildtype gene product is sufficient to give a wild type phenotype.

Example of black cat, tyrosinase.

- Tyrosinase (enzyme) converts tyrosine into melanin
- C gives wild type functioning gene, whereas c gives non-functioning gene
- The presence of C allows for the production of enough tyrosinase to surpass a threshold to show as the black phenotype, thus it is given as a capital letter

Temperature-sensitive proteins

- Proteins unfold upon heating
- Missense mutations can destabilize the secondary and tertiary structures so the protein folds at lower than normal temperatures
    - In the cat example, tyrosinase protein (for melanin) can be encoded by alleles so that it folds properly only in the coolest part of the skin

Mutations in regulatory regions and introns

- If a mutation occurs in the promoter region, it could affect transcription.
- If a mutation occurs in an intron, it could affect splicing.

Nucleotide substitutions

- Transition:Purine to purine or pyrimidine to pyrimidine
- Transversions pyrimidine to purine or vice versa

Rare Exception #1

- **Haploinsufficiency**
    - half the amount of wild type gene product is NOT sufficient to give a wild type phenotype.
        - The product does not exceed threshold levels required to produce the wild-type phenotype

Rare Exception #2

- **No threshold**
    - Snapdragon flower color
    - Heterozygote has intermediate phenotype...incomplete dominance

RareException #3

- **Poisonous subunits**
    - Also called “dominant-negative” mutations
        - Mutation in one of the monomers disrupts the function of the whole complex

GOF: Gain of function mutations

- Result in a functional protein that
    - Is made at the wrong place
    - Is made at the wrong time
        - Example, human lactose tolerance
            - Mutant has gain of function...expect lactose tolerance to be dominant
    - Has a new activity
        - GOF mutations don't need to be beneficial
        - Very few mutations are gain of function mutations
            - Only very specific mutations (e.g., specific amino acid changes) will have this effect

Example of GOF

- Antennapedia in Drosophila
    - Wild type antennapedia gene is only expressed in the thorax; legs are made
        - A mutation cause the antennapedia gene to be expressed in the thorax and also in the head, where legs result instead of antennae

Can GOF mutations be dominant or recessive

- Depends on threshold
- Most gain of function mutations are dominant
    - For example, only a small amount of the altered protein is sufficient to produce this mutant phenotype
- But there could be cases in which the altered protein in combination with the wild type protein gives a wild type phenotype

Roles for genes

- Enzymes (catalyze reactions)
- Signalling (e.g. hormones, messengers)
- Receptors (e.g. adrenergic receptors)
- Constituent (actin,myosin;keratin)

Typical organization of eukaryotic DNA

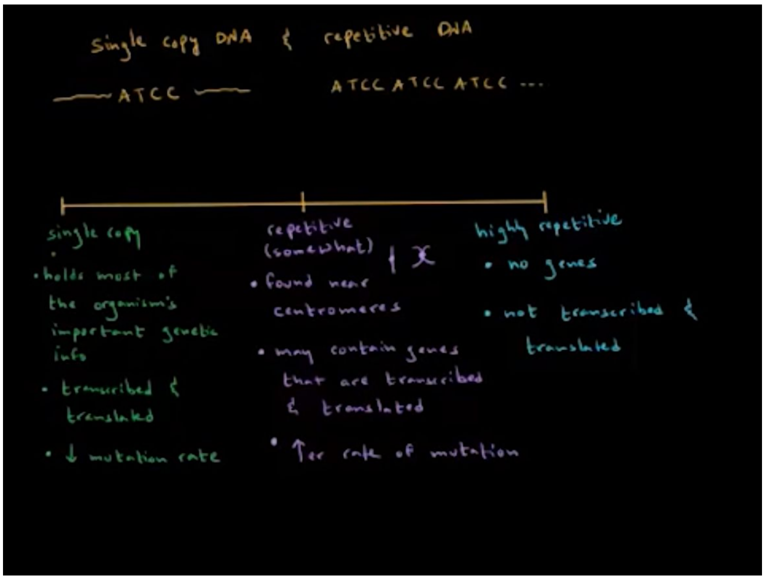
- Naked DNA+octameric histone core>nucleosomes > solenoid > loop domains > chromatid > metaphase chromosome

Euchromatin

- Many expressed genes
- Less chromatin condensation

Heterochromatin
- Condensed chromatin
- Few expressed genes

Repetitive DNA
- Satellite DNA is highly repetitive and consists of short repeated sequences
- Satellite DNA is found in the heterochromatic, centromeric, or telomeric regions of chromosomes
- These repetitive sequences are not found in prokaryotes

Telomeric DNA sequences
- Short tandem repeats
- Protect ends of chromosomes from deterioration
- If there were no telomeres, the chromosome will keep shortening
- Prevent chromosomes from sticking to each other
- 

single copy DNA & repetitive DNA

ATCC

ATCC ATCC ATCC ...

single copy
- holds most of the organism's important genetic info
- transcribed & translated
- ↓ mutation rate

repetitive (somewhat) | X
- found near centromeres
- may contain genes that are transcribed & translated
- ↑er rate of mutation

highly repetitive
- no genes
- not transcribed & translated

Junk DNA
- Important for controlling gene expression
- Since natural selection selects the allele for the phenotype only, the introns have no restrictions

VNTR's (variable number of tandem repeats)
- Clusters 15-100 nucleotides (within & between genes)
- # of repeats at each locus: 2 to 100
- Each length representing 1 allele

Minisatellites
- Clusters of VNTRs

Microsatellites (short tandem repeats, STRs)

STR (short tandem repeats)
- Letters of DNA that repeat over and over.
- 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.
    - Variability between most individuals

Meiosis
- Purpose of meiosis
    - In animals, produces gametes with just half of the parent's genetic material
        - Gametes are haploid
    - Mechanism: only one of each pair of homologous chromosomes gets into each gamete
    - The gametes from the two parents get to fuse, restoring the original number of chromosomes in the fertilized egg(zygote
- Stages of Meiosis
    - Meiosis (in animals) produces 4 haploid cells from 1 diploid cell
    - At the end of the first division (meiosis 1) the 2 cells are already haploid
    - The second division (meiosis 2) splits the 2 sister (identical,replicated DNA) chromatids to 1 chromatid.

The problem
- Ensuring that homologues are partitioned to separate gametes

The solution
- Hold homologous chromosomes together by some means
    - Target homologues to opposite poles
        - Then separate the homologues

Source of genetic variability in meiosis
- Independent assortment
    - Each pair of homologous chromosomes line up at the metaphase 1 plate
    - There is a 50:50 chance that a daughter cell will get one or the other copy of the chromosome
- Crossing over
    - Crossing over can occur anywhere along the autosomes
    - In males, the sex chromosmes (X and Y chromosomes) normally cross over only at their tips
    - The process which produces the recombination of genes by interchanging the corresponding segments between non sister chromatids of homologous chromosomes
- When the two homologous chromosomes line up and form a tetrad, the adjacent non-sister chromatids begin to cross over.
    - A chiasma forms between the non-sister chromatids at the point of crossing over
    - Out of the four chromatids, the two adjacent chromatids are recombinants

- Sex determination
  - In mammals, males have one X and one Y chromosome
  - In male,half the daughter cells formed by Meiosis 1 get an X chromosome and half get a Y chromosome.
  - Following Meiosis 2 and sperm differentiation, half the sperm are X-bearing and Half are Y bearing

SRY (Sex-determining Region of the Y chromosome) Gene

- Early in development, the immature gonads of males and females are indistinguishable
- Males: In the 7th week of development, theSRY gene on the Y chromosome activates a number of genes, and the gonads develop as testes
- Females: With no SRY gene, gonads develop as ovaries by default

Linked

No crossing over

- Meiosis as normal, no swapping of parts, the parental genotypes of a dihybrid will sustain.

Crossing over (but not in between the genes targeted)

- Crossing over occurs, meiosis still results in parental genotypes do to both alleles (linked) on the same chromosome swap at the same time in the same action

Crossing over (in between the two genes)

- When a chiasma occurs between the two genes, it will result in the formation of two recombinant chromosomes, as well as two parental chromosomes.

The chances of linked chromosomes in crossing over increases with the distance between the two genes.

Unlinked

- If the two genes are unlinked, they are going to undergo independent assortment
  - During meiosis when they pair up in the tetrad formation, they can either be on the same side as the other respective paternal/maternal gene, or on the opposite side.
    - There is a 50% chance that they might line up in either form (maternal/maternal,paternal paternal) vs (maternal/paternal, paternal/maternal). The former will result in parental genotypes, the latter in 4 recombinant genotypes for the gamete.

When genes are linked, you expect that most of the gametes will have parental gametes. However, when crossing over occurs between two linked genes, it will result in a new gamete in a dihybrid example. The longer the distance between two unlinked genes, the more likely that crossing over will result in a new genotype for the gamete

- When A and B are unlinked (on different chromosomes), due to independent assortment, you would expect to see 50% parental genotypes of a dihybrid vs 50% chance of a crossing over resulting in new genotypes in the hybrid gamete

Chromosome abnormalities

- Structural aberrations: translocations, inversions, deletions
    - Deletions: chromosomal sequence deleted
    - Duplications: segment of chromosome duplicated
    - Inversion: Flip of a segment, for example “
- Euploidy: addition or loss of complete sets of chromosomes
    - Complete chromosome sets
- Aneuploidy: does not involve whole sets - nondisjunction
    - E.g. monosomy, trisomy
    - Only one kind of monosomy (2n-1) is tolerated in humans
        - Turner syndrome (XO)
    - Most common at birth --trisomy 21 (Down syndrome)
        - 1 in 750 live births
    - Less common
        - Trisomy 18 (Edward syndrome, 1 in 10,000)
        - Trisomy 13 (Patau syndrome, 1 in 20,000)
    - Why is trisomy 21 tolerated better than other trisomies?
        - Small chromosome > fewer genes > less imbalance
    - Aneuploidy hierarchy of tolerance
        - Sex chromosome aneuploidy > autosome aneuploidy
        - Autosomy trisomy > autosome monosome

- Major causes of Aneuploidy
    - Meiosis nondisjunction
        - If disjunction occurs in meiosis 1, all 4 products are defective
        - If disjunction occurs in meiosis 2, 2 are defective, 2 are normal.
    -