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Genetic disease

- Caused by inherited change (mutation) in the genetic information
- Passed on from generation to generation

Gene

- Basic unit of inheritance
- Segment of DNA that contains information to make a protein or RNA molecule

Sickle cell disease

- Sickle cell anemia
- Caused by one change in the hemoglobin gene
- Changes the shape of hemoglobin
- Prevents hemoglobin from transporting oxygen to your tissues
- Causes red blood cells to have a sickle shape
- Inheritance pattern is well-established

Hemoglobin

- Protein that carries oxygen
- Consists of four polypeptide chains
- Two alpha and two beta globin chains
- Each chain contains a heme group (Fe)

Red blood cells

- Primary function = oxygen transport
- Don't have a nucleus
- 250 million hemoglobin molecules
- Biconcave disc-shaped

Oxygen transport

- Gases move down a concentration gradient
- External respiration
- After inspiration, the partial pressure of oxygen is greater in the lungs than in the blood

- Oxygen diffuses into the blood and is picked up by hemoglobin to form oxyhemoglobin
- Hb + O2 -> HbO2
- Internal respiration
- At the tissues, the partial pressure of oxygen is less than the partial pressure of oxygen in the blood
- Oxygen diffuses into the tissue in exchange for carbon dioxide

Carbon dioxide transport

- Hemoglobin doesn't bind to carbon dioxide very well
- Carbon dioxide is converted inside of the red blood cell to carbonic acid (H2CO3)
- Carbonic anhydrase converts H2CO3 back into carbon dioxide
- H+ + HCO3- -> H2CO3 -> H2O + CO2

Effects of sickle cell disease on the body

- Circulatory system
- Role
- Deliver oxygen and nutrients to the cells
- Remove cellular waste
- Oxygen transport is inefficient
- Anemia develops
- Sickle-shaped RBCs become sticky and clump together
- Block a capillary
- Prevents blood flow
- Respiratory system
- Role
- Gas exchange
- Sickle-shaped RBCs become sticky and clump together
- Block a capillary near the alveoli
- Prevent gas exchange
- Result = acute chest syndrome
- Acute chest syndrome accelerates anemia
- Results in a sickle crisis
- Entire body
- Blocked capillaries can yield pain anywhere in the body
- Pain most noticeable in the joints
- Spleen becomes enlarged
- Site of red blood cell recycling

- Can cause abdominal pain
- Blocked capillaries in the kidney can prevent blood filtration
- Evidence as blood in the urine
- Reduced blood flow increases susceptibility to infections
- Immune cells use the circulatory system to reach pathogens

Heterozygous advantage

- Homozygous dominant have symptoms
- Heterozygous can be carriers
- Not affected by malaria
- Have an advantage over homozygous recessive

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Storytime

- 1928: Frederick Griffith
- Attempt to create a pneumonia vaccine
- Two strains of pneumonia
- R strain didn't cause sickness
- S strain was virulent and smooth appearance
- The S strain was doing something to the R strain to make it virulent
- Oswald Avery, Colin MacLeod, someone else
- Took heat-inactivated virulent strain, and added protease, RNAse, or DNAse (remove protein, RNA, or DNA)
- Then combined with R strain
- Protease became virulent
- RNAse became virulent
- DNAse did not change
- Hershey and chase
- Used radioisotopes and bacteriophage
- Bacteriophage
- Virus that infects bacteria
- (1) protein and (2) DNA
- Made two batches of bacteriophage
- Radioactively labeled protein (sulfur)
- Radioactively labeled DNA (phosphate)
- Mix radioactively labeled phages with bacteria

- Disconnect phages from bacterial cells
- Centrifuge so that the bacteria form a pellet
- Measure radioactivity in the pellet and the liquid
- The DNA is the material going in

Result: DNA determined to be hereditary material

4 Nucleotides

- Adenine
- Thymine (U instead of T in RNA)
- Cytosine
- Guanine

20 amino acids

3 billion nucleotides in each cell

Adenine binds to thymine

Guanine binds to cytosine

%adenine=%thymine

%guanine=%cytosine

AT the Golf Course

AT GC

Sugar phosphate backbone, and then the bases are on the tips, creating a weak hydrogen bond

Watson and crick stole rosalind franklin’s stuff

DNA is antiparallel

The strands are complementary

Either strand can act as the template

Each strand acts the template for the new strand (when the old strand is broken apart)

So one strand is old and one is new

How does DNA replicate (keep table for exam)

- DNA polymerase: synthesis new daughter strands using the information in the template strand
- Helicase: unwraps the DNA double helix by breaking the hydrogen bonds
- DNA ligase: recombines the strands

1. Helicase: unwinds the DNA double helix and makes some space and aligns it for the next step
2. DNA polymerase: copies the template strand to make the new strand, but only in the 5’ to 3’ direction (on the leading strand)
3. In the other direction on the lagging strand, it makes some fragments and falls off and keeps going in that way (okazaki fragment)
4. DNA ligase helps to fill in the gaps between the fragments

The two identical sets of DNA created are called sister chromatids

The principles of DNA replication ca be mimicked in a lab to make copies

A Bay Area scientist was high in the 1980s and came up with the polymerase chain reaction (PCR)

1. Denaturation (causes the DNA strands to separate
2. Annealing (cool down)
3. A small piece of DNA is added
4. Targets segment of DNA to be copied
5. Heat up a bit
6. DNA polymerase added
7. Comes from a bacteria found in hot springs so it can handle the temp

Purpose of DNA

- Genes encode for proteins

Gene expression

- Not every gene gets converted to a protein in every cell type (all cells have same genetic material, but only some genes expressed)
- Two stages
- Transcription
- Transcribe DNA to RNA in the nucleus
- mRNA goes to the cytoplasm to the ribosome to be converted to a protein
- Start of a gene = promoter

- End of a gene = terminator
- RNA polymerase unwraps DNA
- Uses the template strand to make a complementary strand
- RNA copy
- Instead of thymine, uracil nitrogen-containing base is used
- Translation
- The mRNA is translated into amino acids in the nucleus
- Information read as a series of triplets (codons)
- Key players
- mRNA
- Ribosome
- Reads each codon to understand which amino acid to make
- Looks for the start codon (AUG) methionine
- The tRNA brings in the amino acid
- Builds the protein
- tRNA molecules
- Contains an anticodon complementary to the codon and an amino acid
- Puts the amino acid through the ribosome to bind it

Allele: variation of a gene

- Small changes in the nucleotide sequence within the gene
- Not all changes cause a protein shape change

Chromosome

- DNA is tightly packed
- Consists of DNA and histones
- Nucleosome: DNA wrapped around a histone
- Nucleosomes are compressed together
- 22 autosomes
- 1 sex chromosome (XX - female, XY - male)
- Each gene has a specific location on a chromosome (locus)
- We have 2 copies of each gene
- We have two copies of each chromosome
- Maternal and paternal copy
- The two copies may be two different alleles

Sexual Reproduction

- Gametes contain only one copy of each chromosome (haploid)
- Meiosis
- Reduces the chromosome number from diploid to haploid
- Two rounds of cell division
- Meiosis I
- Prophase I
- Nucleus disintegrates
- Homologous chromosomes pair with each other
- Maternal chromosome next to paternal chromosome
- Form a tetrad
- Allele are shuffled from one homologous chromosome to the other
- Process: crossing over
- Produces a new combination of alles not present in the original chromosomes
- Source of genetic variation
- Metaphase I
- Chromosomes line up in the middle
- independent assortment
- How the chromosomes line up
- They randomly line up in the middle, creates possible variation
- Anaphase I
- Genetic material separates and goes to opposite ends
- Telophase I
- Separates the cell into two parts
- Meiosis II
- Prophase II
-
- Metaphase II
- Anaphase II
- Telophase II
- 4 haploid cells
- Yields 4 haploid cells

Pattern of inheritance

- Gregor mendel
- Austrian monk
- Worked with pea plants
- Curous about patterns of inheritance

- If you crossed a green and yellow, they were all green
- GG / gg = Gg Gg Gg Gg
- Then cross the siblings
- Gg / Gg = GG Gg Gg gg
- Some traits dominate others
- Green is dominant to yellow
- Yellow is recessive to green
- Each individual contains two copies of a trait (gene) but only one copy is passed to the next generation

Law of Segregation

- Each individual has two factors of a trait
- Those factors segregate or separate when gametes form
- Fertilization produces a new individual with two factors

What if two traits were considered at one time (dyhybrid cross)

- Alleles are independent of each other

Table 3.2: Genetic Terms (keep for exam)

Inheritance pattern of sickle-cell anemia (gene)

- Pedigree
- Heterozygous people don’t have symptoms

incomplete dominance

- All of the dominant traits that Mendel looked at completely masked the recessive traits
- Green covered yellow
- Some traits do not completely mask the recessive gene
- Heterozygote expresses a phenotype that is an intermediate between the dominant and recessive phenotypes

Multiple allele inheritance

- 300 different alleles cause cystic fibrosis
- Human ABO blood groups
- Three alleles
- I^A produces the A antigen
- I^B produces the B antigen

- I does not produce any antigens
- This allele is recessive
- Type A blood: IA IA or IA i
- Type B blood: IB IB or IB i
- Type AB blood: IA IB
- Universal acceptors
- Type O blood: ii
- Universal donors

Does environment play a role

- Skin color
- More/less skin darkness: more/less dominant alleles
- More sun = more expression of melanin

Other complications

- Epistatic interaction
- The dominant form of the OCA2 gene yields brown eyes
- A recessive OCA2 gene yield blue eye
- The HERC2 gene can override th dominant OCA2
- The individual can have two copies of the dominant OCA2
- But they have to have two recessive copies of HERC2

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Treatments for sickle cell anemia

- Human genome fully sequenced in 2003
- We now know the location of every gene in the human genome
- Two ways to extract cells from the fetus
- Look at table 4.1
- DNA analysis
- Karyotype
- Images of the chromosomes
- Large deletions and duplications can be observed
- Fluorescently immunohistochemistry in situ hybridization (FISH) can be used to label short pieces of DNA
- DNA sequencing
- Identify the order of nucleotides in the sequence, compare to a healthy version

- Technique uses fluroescent dyes that attach to the four different nucleotides and a laser
- Gene cloning
- Need to copy a genetic sample
- Take small pieces of DNA and use bacteria to copy the gene
- Whats left is recombinant DNA (human gene + bacteria gene)
- Using bacteria as DNA factories
- Genetic markers
- Known sequence of DNA associated with different diseases
- 1. Gene extracted from cell
- 2. restriction enzymes cut DNA in predictable manner
- 3. DNA pieces are observed
- Look at the bands, if they bands look wrong there is something different, may be genetic disease
- DNA microarray
- Use to determine if DNA is being expressed
- 1. Single-stranded genes placed on glass slide
- 2. Fluorescently labelled cDNA from the cell added to glass slide
- 3. Put it onto the glass slide: if it binds it will glow, that wlll tell you that the gene is being transcribed/translated or not
- Bone marrow transplant
- Contain stem cells
- Gene therapy
- Ex vivo
- Delivery of genes outside the body
- In vivo
- Delivery of the gene inside the body
- Gene therapy vectors
- Modified viruses
- Hijacked delivery capability of viruses
- Viruses used are no longer harmful
- All the dangerous components have been removed
- Advantage: can target specific cell types
- Liposomes
- Engineered fat transport vesicles
- Disadvantage: can not be targeted to specific cell types
- Genome editing

- Avoid using delivery vectors
- Gene editing with CRISPR
- Molecular scissors
- Creates a cut in the DNA at a specific location
- First discovered in bacteria as a type of immune system against bacteriophages

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