SGCEP BIOL 1010K
Introduction to Biology I
Spring 2012 Sections 20585 & 20586

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Human genetics

Naturally the genetics of our own species, Homo sapiens, is of great interest to most all people. This lecture will cover several aspects of human genetics — linkage maps, autosomal and sex-linked genetic disorders, sex determination, and X inactivation.
Remember chromosomes . . .

- Are a discreet package of DNA and its associated proteins (especially histones).
- There's a characteristic number per species. This has nothing to do with complexity.
- Humans have 23 pairs, for 46 total.
- 22 homologous autosome pairs, and . . .
- One pair of sex chromosomes – XX or XY.
- A karyotype is a chromosome spread arranged by size, banding pattern, and centromere position (after staining cells chemically arrested in prophase).
The poison colchicine interferes with microtubule formation and thereby arrests cells at prophase.
Chromosome linkage maps

* By definition linked genes are inherited together; this is because they are carried on the same chromosome.

* And when they are close enough together, then they do not assort independently during meiosis. We’ll see why.

* This was initially discovered in the early 1900’s when pea plant offspring ratios were different from what Mendel’s laws predicted.

* Two types of F2 peas were more abundant than expected.
Standard dihybrid ratios . . .

As we saw last time.

a. *PpLi* self-cross, genes not linked

\[ F_1 \]

\[ F_2 \]

Possible female gametes

\[
\begin{array}{cccc}
PL & PPLL & PPLI & PpLL & PpLI \\
PL & PPLL & PPLI & PpLL & PpLI \\
\end{array}
\]

Possible male gametes

\[
\begin{array}{cccc}
PL & PpLL & PpLI & ppLL & ppLI \\
pl & PpLI & PpLI & ppLL & ppLI \\
\end{array}
\]

9:3:3:1 phenotypic ratio
But if the genes are linked . . .

Then they act like one entity, versus two, and we get the monohybrid 3:1 ratio.
However, sometimes they saw that . . .

- Some offspring had trait combinations not seen in either parent.
- This was due to crossing over – exchange of genetic material between homologous chromosomes during meiosis.
- Recombinant chromosomes – mix of maternal and paternal alleles.
- Parental chromosomes – retain allele combinations from each parent.
But this “homologous recombination” can only occur if the genes are far enough away from one another. If too close, they act as one. How close?
Linkage maps come from this, and . . .

- Are based on the correlation between crossover frequency and the distance between genes. This provides a . . .
- Diagram of gene order and spacing.
- They previously were only based on phenotypes.
- But now genetic markers can associate known, detectable DNA sequences with particular phenotypes (this is known as QTL mapping).
- Plus genome sequencing gives us "physical maps."
The concept is illustrated here.

They act like they're on different chromosomes, i.e. unlinked.

They act like they're stuck together, i.e. linked.

This linkage distance is measured in “centimorgans” after Thomas Hunt Morgan, a famous American geneticist who won the Nobel Prize in 1933 proving that genes lay on chromosomes, using Fruit Flies.
Genome map browsers allow us to ‘see’ chromosome maps.

* [http://genome.ucsc.edu/](http://genome.ucsc.edu/)
* [http://www.ensembl.org/](http://www.ensembl.org/)
* [http://www.dcode.org/](http://www.dcode.org/)

* These four are particularly useful.
Pedigrees help us see this.

- "Mendelian traits" – determined by single genes with alleles that are either dominant or recessive.
- Several thousand human genes are inherited in this pattern. Remember http://omim.org/about.
- Most are on the autosomes.
- Autosomal dominant – one dominant allele results in the condition.
- Autosomal recessive – two recessive alleles are required to inherit the condition.
- A heterozygote is a "carrier" of the recessive allele.
Here’s some examples:

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Genetic Explanation</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Autosomal recessive inheritance</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albinism</td>
<td>Mutant allele of gene on chromosome 11 encodes faulty gene in biochemical pathway required for pigment production</td>
<td>Lack of pigmentation in skin, hair, and eyes</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>Mutant allele of gene on chromosome 7 encodes faulty chloride channel protein</td>
<td>Lung infections and congestion, poor fat digestion, infertility, poor weight gain, salty sweat</td>
</tr>
<tr>
<td>Phenylketonuria</td>
<td>Mutant allele of gene on chromosome 12 causes enzyme deficiency in biochemical pathway that breaks down the enzyme phenylalanine</td>
<td>Buildup of metabolic byproducts causes mental retardation</td>
</tr>
<tr>
<td>Sickle cell disease</td>
<td>Mutant allele of gene on chromosome 11 causes abnormally shaped hemoglobin protein</td>
<td>Joint pain, spleen damage, high risk of infection</td>
</tr>
<tr>
<td>Tay-Sachs disease</td>
<td>Mutant allele of gene on chromosome 15 causes deficiency of lysosome enzyme</td>
<td>Buildup of byproducts causes nervous system degeneration</td>
</tr>
<tr>
<td><strong>Autosomal dominant inheritance</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Achondroplasia</td>
<td>Mutant allele of gene on chromosome 4 causes deficiency of receptor protein for growth factor</td>
<td>Dwarfism with short limbs, normal size head and trunk</td>
</tr>
<tr>
<td>Familial hypercholesterolemia</td>
<td>Mutant allele of gene on chromosome 2 encodes faulty cholesterol-binding protein</td>
<td>High cholesterol, heart disease</td>
</tr>
<tr>
<td>Huntington disease</td>
<td>Mutant allele of gene on chromosome 4 encodes protein with extra amino acids that cause it to misfold and form clumps in brain cells</td>
<td>Progressive uncontrollable movements and personality changes, beginning in middle age</td>
</tr>
<tr>
<td>Marfan syndrome</td>
<td>Mutant allele of gene on chromosome 15 causes connective tissue disorder</td>
<td>Long limbs, sunken chest, lens dislocation, spindly fingers, weakened aorta</td>
</tr>
<tr>
<td>Neurofibromatosis (type 1)</td>
<td>Mutant allele of gene on chromosome 17 encodes faulty cell signaling protein</td>
<td>Brown skin marks (café-au-lait spots), benign tumors beneath skin</td>
</tr>
<tr>
<td>Polydactyly</td>
<td>Multiple genes on multiple chromosomes; unknown mechanism</td>
<td>Extra fingers or toes or both</td>
</tr>
</tbody>
</table>
Polydactyly is seen here:

It's an autosomal dominant so it typically appears in every generation. There's a 50/50 chance that a gamete from the afflicted will have the gene if they are heterozygous. Often these types of traits can't be homozygous since they are often lethal that way.
Albinism is recessive.

So it may appear to disappear for a generation, only to reappear later.
Sex chromosomes

* The human X chromosome has 1606 genes – most have nothing to do with sex determination.
* The human Y chromosome plays the largest role in sex determination, but only has 397 genes.
* All human embryos start with rudimentary female structures.
* The SRY gene encodes a protein that switches on other genes that direct the undeveloped testes to secrete testosterone. This begins a cascade . . . .
* The SRY protein also dismantles the embryonic female structures.
* See http://helixweb.nih.gov/cgi-bin/moldraw?1HRY
This is what the X and Y chromosomes look like.

Obviously not to the same scale.
Of course it’s 50/50 whether an X or a Y will end up in a sperm, but eggs will always get an X.
There are some great Internet resources related to human sex determination.

* I wrote a sample manuscript for a comparative genomics course I taught several years back: http://www.bio.fsu.edu/~stevet/CompGen/SRY.manuscript.pdf.

* The Howard Hughes Medical Institute has a wonderful sight named “Biointeractive” that has a sex determination module: http://www.hhmi.org/biointeractive/gender/index.html.

* The Annenberg Foundation’s “Rediscovering Biology” has a unit on it: http://www.learner.org/courses/biology/units/gender/index.html. We’ll watch their video for the next half hour.

* The premier British science journal Nature has a special focus on the Y chromosome: http://www.nature.com/nature/focus/ychromosome/.
Let’s move on to sex-linked genes.

- The alleles controlling sex-linked genes are either on the X or on the Y (in many, but not all animals).
- For example, in fruit flies eye color is sex-linked.
- Fruit fly eyes are normally red. But sometimes there’ll be white eyed individuals. These...
- White-eyed flies are more often than not males.
- Therefore, the recessive white-eye allele must be on the X chromosome. At least that’s the reasoning. Because...
- The male expresses whatever is on his only X; he is “hemizygous” for that allele, i.e. he’s only got one.
- The female has to inherit two recessive alleles to have white eyes.
Here’s Morgan’s first experiment.

In the first part (P) he crossed white-eyed, hemizygous, recessive ♂’s with red-eyed, homozygous, dominant ♀’s to get all red-eyed F1’s, regardless of sex.

Then in the second part (F2) using the hemizygous dominant F1 ♂’s mated with the heterozygous F1 ♀’s he got different results depending on whether the ♀ contributed her dominant or recessive allele.
In the second experiment...

He did the reverse thing. That is he crossed a red-eyed (P) hemizygous ♂ with white-eyed (P) ♀ to get the two different F1 progeny. Their cross yields all possible F2 combinations.

Had the trait not been sex-linked, the results of both experiments would have been the same!
X-linked recessive disorders

★ Very few Y-linked disorders exist. Two examples include certain forms of hereditary deafness and retinitis pigmentosa.
★ Most X-linked disorders are recessive.
★ Males have only one X chromosome, so they express every allele on it whether it’s dominant or recessive (hemizygous).
★ Females exhibit an X-linked recessive disorder only if they inherit recessive alleles from both parents (homozygous).
Here's some example X-linked traits.

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<td></td>
</tr>
<tr>
<td>Duchenne muscular dystrophy</td>
<td>Mutant allele for gene encoding dystrophin</td>
<td>Rapid muscle degeneration early in life</td>
</tr>
<tr>
<td>Fragile X syndrome</td>
<td>Unstable region of X chromosome has unusually high number of CCG repeats</td>
<td>Most common form of inherited mental retardation</td>
</tr>
<tr>
<td>Hemophilia A</td>
<td>Mutant allele for gene encoding blood clotting protein (factor VIII)</td>
<td>Uncontrolled bleeding, easy bruising</td>
</tr>
<tr>
<td>Red–green color blindness</td>
<td>Mutant alleles for genes encoding receptors for red or green (or both) wavelengths of light</td>
<td>Reduced ability to distinguish between red and green</td>
</tr>
<tr>
<td><strong>X-linked dominant inheritance</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extra hairiness (congenital</td>
<td>Mechanism unknown</td>
<td>Many more hair follicles than normal</td>
</tr>
<tr>
<td>generalized hypertrichosis; some</td>
<td></td>
<td></td>
</tr>
<tr>
<td>forms)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypophosphatemic rickets (some forms)</td>
<td>Mutant allele for gene involved in phosphorus absorption</td>
<td>Low blood phosphorus level causes defective bones</td>
</tr>
<tr>
<td>Retinitis pigmentosa (some forms)</td>
<td>Mutant allele for cell-signaling protein; mechanism unknown</td>
<td>Defects in retina cause partial blindness</td>
</tr>
</tbody>
</table>
Hemophilia A (B too) is...

* One of the more infamous X-linked recessive disorders. It is caused by the...
* Absence or deficiency of protein clotting factor VIII (IX in B) and greatly slows blood clotting.
* Usually only male family members can have hemophilia, ...
* But rare homozygous females can survive.
* Many females are heterozygous “carriers.”
* They have no symptoms because the dominant allele makes enough functional clotting protein.
The most famous case arose in Queen Victoria and spread through European royalty.
X inactivation

- Females have a double dose of every gene on the X chromosome. Males only have a single dose.
- A mechanism has evolved to compensate for this – every cell shuts off all but one X chromosome. This happens very early in embryonic development.
- The inactivated X chromosome can be seen as the Barr body in every cell nucleus in females.
- Which X is inactivated, from the mother or father, is a random event, and since it happens early in development, female’s bodies are actually a mosaic of X-linked genes.
- This can be seen in Calico and Tortoiseshell cats, which are almost always female (a male Calico would be XXY).
- Patches of color are determined by the maternal or paternal X, each of which is one or the other codominant allele.
This is shown here
Next time, the Section III Exam!

- This will cover the most important concepts of the cell cycle, mitosis, why sex evolved, meiosis, and classical and human genetics.
- Only one more sectional exam after this one — try to do better on this one than last time.