1 INTRODUCTION TO GENETICS COMPONENT OF IB 201

1.1 Why Genetics and Evolution?
Genetics and evolutionary biology have been intertwined since the beginning of both disciplines

“Nothing in biology makes sense except in the light of evolution”, quote from geneticist Theodosius Dobzhansky.

Evolution is the unifying principle of biology. Physicists are still looking for their unifying theory, but that for biology was defined in 1859 with the publication of Darwin’s On the Origin of Species by Means of Natural Selection (1973).

Although Darwin did not understand the basic principles of heredity as we do now, heredity (genetics), and evolutionary biology have been inextricably linked from the beginning of both disciplines.

Evolution by natural selection is the logical outcome of four observations proposed and extensively documented by Darwin:

Individuals within species are variable
Some of these variations are passed on to offspring.
In every generation, more offspring are produced than can survive.
The survival and reproduction of individuals are not random. The individuals who survive and reproduce, or who reproduce the most, are those with the most favorable variations. They are naturally selected.

Darwin compiled massive amounts of evidence that all these postulates are true. Using data from wild and domesticated plants and animals, he showed conclusively that individuals within species are variable, and that some of these variations are passed on to the offspring. However, no mechanism to explain how this occurs was known to him, or to any of his contemporaries.

Because the mechanisms of inheritance were not known, two objections were raised against Darwin’s postulates:

Inheritance acts like pigment in paint (“blending inheritance”), so that any new variant would mix with the existing traits and be swamped by them. Thus, even if new variation could be created, it would not persist.
Variation within species is limited. Once the existing variation is exhausted, the process natural selection will grind to a halt.

Ironically, when the Origin was published, an unknown monk was cultivating peas in a monastery garden in what is now the Czech Republic. His work would conclusively demonstrate that objection 1 is invalid. Gregor Mendel would show that inheritance is particulate, not blending. Although he published his work in 1866, no one else understood the implications for another 34 years. It was not until 1900 that three different scientists (Hugo DeVries, Erich Von Tschermak, and Carl Correns), independently published experiments similar to Mendel’s, brought attention to Mendel’s work, and attributed priority of discover to him.

Within a few years of the rediscovery of Mendel’s work, geneticist Thomas Hunt Morgan and his colleagues would show that new hereditary variation (mutation) occurs in every generation, and in every trait of an organism. Therefore, by the beginning of the 20th century, both objections to Darwin’s principles had been conclusively eliminated.
The synthesis of genetics and evolutionary biology

Between 1932 and 1953, a series of landmark books was published that integrated Mendelian genetics and Darwin’s principle of evolution by natural selection. This “Modern Synthesis” showed that Darwin’s four observations could be rephrased as follows.

As a result of mutation creating new alleles, and segregation and independent assortment shuffling alleles into new combinations, individuals within populations are variable for nearly all traits.

Individuals pass their alleles on to their offspring intact (without blending).

In most generations, more offspring are produced than can survive. The individuals that survive to reproduce, or who reproduce the most, are those with the alleles and allelic combinations that best adapt them to their environment.

The outcome of these processes is that alleles associated with higher fitness increase in frequency from one generation to the next.

1.2 Transmission Genetics and Population Genetics

For the next several weeks, we are going to explore the principles of Mendelian genetics, plus extensions and exceptions to Mendelian genetics (together known as: Transmission Genetics). These principles have been demonstrated experimentally, and you will perform similar experiments yourself in the laboratory component of this course. This foundation in transmission genetics will allow you to understand the inheritance of: 1) susceptibility to genetic diseases; 2) economically important traits in domesticated plants and animals; 2) ecologically important traits in wild organisms; and 3) the mechanisms by which evolution has, and continues to, shape the genes and genomes of humans and all other organisms. We will also cover the genetics of traits that are polygenic and influenced by the environment (quantitative traits), and the behavior of genes in populations (population genetics).

1.3 Topics to be covered in this part of the course:

Deviations from Mendelism
   - Epistasis
   - Unusual Modes of Inheritance
   - Pedigree Analysis
Genetic data analysis
   - Probability and Statistics
Chromosomal Inheritance
   - Sex Determination
   - Chromosomal Abnormalities
Genetic Mapping
   - Genetic and Genome Mapping
Traits affected by Genes and Environment (Quantitative Traits)
Genes in Populations
   - Genetic mechanisms of evolution
   - Population genetics of disease and disease resistance
Genomes and Genome Evolution
1.4 Extensions of Mendelian Genetics

In IB 150 you learned about genetics of 2 alleles at a locus, dominant or recessive, that segregate randomly at meiosis, and assort independently of other loci. You also learned about other classes of genes and allelic interactions: incomplete or partial dominance, codominance, multiple alleles, genes that are linked and do not independently assort, and gene interaction (epistasis). Here we will pick up where IB 150 left off, first discussing epistasis in more detail, then discussing other kinds of deviations from strict Mendelian rules of inheritance.

See Review Material for discussion of:
Incomplete dominance
Codominance
ABO blood system
Pleiotropy

1.5 Lethal and Sublethal Alleles:

The Mendelian ratios you have discussed previously strictly apply only to the zygotes produced by different crosses, and implicitly assume that the viability of zygotes of different genotypes are all equal. For example, if homozygous recessives suffer from a disease, their chance of living to adulthood may be less than the chances for other genotypes, so that the 3:1 ratio expected in zygotes is altered if one counts adult offspring. (Sickle cell anemia--expected 1/4 homozygous recessives changes to much less than 25% adult anemics because of the higher mortality for sickle-cell homozygotes (the homozygote is sublethal or lethal).

Another example: genes in some plants can cause lack of chlorophyll--no photosynthesis--> mortality. This is a lethal allele.

True-breeding Manx breeds are not possible because matings between two Manx cats are:

<table>
<thead>
<tr>
<th>P:</th>
<th>Mm</th>
<th>x</th>
<th>Mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>1</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Phenotypic</td>
<td>lethal</td>
<td></td>
<td>normal</td>
</tr>
<tr>
<td>ratio</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Other traits that are caused by an allele with dominant effect in heterozygotes and lethal when homozygous are achondroplasia in humans, Cy (causes curly wings in Drosophila genotype Cy/+), yellow body color in domestic mice.

1.6 Epistasis

When the expression of one gene pair masks or modifies the expression of another. (In the following, assume gene pairs segregate independently.) Epistatic interactions between two loci yield modifications of the 9:3:3:1 dihbrid ratio.
Coat color in domestic mice: recessive genotype at one locus masks the expression of another locus.

Agouti is wild type,

Agouti is dominant to black.

But all color is lost if the mouse is homozygous recessive at a different locus (C locus).

**Epistasis:** recessive allele masks the expression of alleles at a different locus.

<table>
<thead>
<tr>
<th>Locus 1</th>
<th>Locus 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>BB</td>
<td>CC</td>
</tr>
<tr>
<td>Bb</td>
<td>Cc</td>
</tr>
<tr>
<td>bb</td>
<td>cc</td>
</tr>
</tbody>
</table>

**P:** BB CC x bb cc

**F1:** Bb Cc
agouti

**F2:** 9/16 B- C- agouti 3/16 B- cc albino 3/16 bb C- black 1/16 bb cc albino

**Phen. ratio:** 9 agouti: 4 albino; 3 black

*Why is epistasis important? Patterns can be used to infer biochemical interactions:*  

<table>
<thead>
<tr>
<th>Colorless precursor</th>
<th>C enzyme present?</th>
<th>B enzyme present?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes: CC or Cc some melanin produced</td>
<td>Yes: BB or Bb agouti</td>
<td></td>
</tr>
<tr>
<td>No: cc no melanin produced</td>
<td>No: bb black</td>
<td></td>
</tr>
</tbody>
</table>

The cc genotype masks the expression of both alleles at the "B" locus. C gene codes for enzyme tyrosinase, which is involved in the production of melanin. The B gene determines how pigment is distributed along the hair shaft.
Another kind of epistasis: It can also happen that the dominant allele at one locus masks the expression of the alleles at a second locus:

Flower color in sweet peas: At least one dominant allele of each of two gene pairs is necessary for a trait:

<table>
<thead>
<tr>
<th></th>
<th>P:</th>
<th>F1:</th>
<th>F2:</th>
<th>Pheno. ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AA bb white</td>
<td>x</td>
<td>aa BB white</td>
<td>9/16 A- B- purple 3/16 A- bb white 3/16 aa B- white 1/16 aa bb white</td>
</tr>
</tbody>
</table>

Inferred Biochemical Interaction Model:

Colorless precursor---------> Colorless intermed. compound Y-----------> Purple anthocyanins
Gene A
Enzyme
Gene B
Enzyme

Other kinds of epistatic ratios producing different ratios are also possible! When two loci are involved, epistasis will always give a modification of the dihybrid 9:3:3:1 ratio.

1.7 X-Linked Traits in birds and Lepidopterans (butterflies and moths):

X-linked dominant traits have a different pattern of inheritance. Both males and females affected, but the pattern of affected offspring produced by two sexes is not the same.

Example: Feather coloring in Chickens (In birds females are the heterogametic sex)

<table>
<thead>
<tr>
<th>non-barred female</th>
<th>x</th>
<th>barred male</th>
<th>barreled female</th>
<th>x</th>
<th>nonbarred male</th>
</tr>
</thead>
<tbody>
<tr>
<td>( Z^b W )</td>
<td>( z^B z^B )</td>
<td>( Z^B W )</td>
<td>( z^b z^b )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>barreled fem.</td>
<td>( z^B W )</td>
<td>( Z^B )</td>
<td>( z^B )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>barreled males</td>
<td>( z^B )</td>
<td>( Z^B )</td>
<td>( z^b )</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

About half the offspring of affected females should be affected, irrespective of sex.
All female offspring of affected males will be affected, no male offspring will be affected.

How to recognize X-linked inheritance:

Reciprocal crosses result in different phenotypic ratios in the two sexes.
Heterozygous individuals of the homogametic sex transmit each X-linked allele to approximately half their daughters and half their sons.
Hemizygous individuals with an X-linked recessive allele have the recessive phenotype because the Y chromosome does not contain a wildtype counterpart. Affected individuals then transmit the recessive
allele to all the offspring of one sex, and none of the offspring of the other sex. Any individual of the hemizygous sex that is not affected carries the wildtype allele on the X chromosome.

1.8 Y-Linked Traits

Only a few in humans (fewer than 20; either genes that determine maleness (tdf), or genes homologous to genes on X. More common in some other organisms (color patterns in guppies). One putative Y-linked human gene is hairy ear rims. But mode of inheritance difficult to determine b/c it is complicated by variable age at expression (variable expressivity). CHARACTERISTICS: Always passed from father to sons. Never expressed in females.

1.9 Sex-Influenced Inheritance

Premature pattern baldness in humans. Autosomal inheritance, but the expression of the trait is modified by hormonal activity. B is dominant in males, but recessive in females!

<table>
<thead>
<tr>
<th>Genotypes</th>
<th>Phenotypes female</th>
<th>Phenotypes male</th>
</tr>
</thead>
<tbody>
<tr>
<td>bb</td>
<td>Bald</td>
<td>Bald</td>
</tr>
<tr>
<td>bb'</td>
<td>not bald</td>
<td>Bald</td>
</tr>
<tr>
<td>b'b'</td>
<td>not bald</td>
<td>not bald</td>
</tr>
</tbody>
</table>

Phenotypes are not always a direct reflection of genotypes

1.10 Temperature-sensitive mutations.

Some alleles are only expressed in some environments, or have variable expression for other reasons. The effects of these mutations are usually only apparent at high temperatures. Siamese cats have a mutation in the C gene controlling dark pigment formation. The c^h allele of this gene is heat sensitive. The c^h allele can make dark pigment at low but not high temperatures. The permissive temperature for dark-color occurs at the extremities, and a restrictive temperature occurs in the body core.
1.11 **Nutritional effects**
Phenylketonuria is a human nutritional defect that can lead to severe physical and mental disorders in children, but only if they consume phenylalanine. The mutation prevents individuals from metabolizing this amino acid. The disease phenotype can be avoided by eliminating phenylalanine from the diet.

1.12 **Genetic anticipation**
Two dominant genetic disorders, Huntington’s disease, and myotonic muscular dystrophy (MD) show a pattern of earlier age of onset and increase severity of the disorder in successive generations. Individuals with mild MD may develop cataracts as adults, but have no other symptoms. But children that inherit the disorder tend to demonstrate more severe symptoms, and to have an earlier age of onset. In its most extreme form the disease is fatal just after birth. Both the increased severity and the earlier age of onset are associated with the expansion of a 3-bp repeat region of DNA. Normal individuals have 5-35 numbers of repeats, minimally-affected ones have 150 copies, and severely affected individuals have up to 1500 copies of the repeat sequence. The number of repeats tends to increase over generations, thus leading to increased severity and earlier age of onset in each generation.