Teacher Preparation Notes for Genetics and Genetics Supplement

The Genetics Student Handout begins with sections that help students to understand basic principles of genetics, including (1) how genotype influences phenotype via the effects of genes on protein structure and function and (2) how genes are transmitted from parents to offspring through the processes of meiosis and fertilization. Then, a coin flip activity models the probabilistic nature of inheritance and Punnett square predictions; this helps students understand why the characteristics of children in many real families deviate from Punnett square predictions. Additional concepts covered include polygenic inheritance, incomplete dominance, and how a new mutation can result in a genetic condition that was not inherited.

The Genetics Supplement Student Handout includes (1) an alternative version of the introduction to genetic principles that does not require prior completion of our meiosis and fertilization activity; (2) an analysis of the genetics of sex determination that helps students understand the probabilistic nature of inheritance; and (3) analyses of the molecular basis of sickle cell anemia and sickle cell trait, including the multiple phenotypic effects of a single gene and a pedigree analysis.

Before beginning this activity, your students should have a basic understanding of meiosis and fertilization. For this purpose, we recommend the hands-on activity "Meiosis and Fertilization – Understanding How Genes Are Inherited" (available at http://serendip.brynmawr.edu/sci_edu/waldron/#meiosis).

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Learning Goals
In accord with the Next Generation Science Standards:2
- Students will gain understanding of several Disciplinary Core Ideas:
  - LS1.A: Structure and Function – "All cells contain genetic information in the form of DNA molecules. Genes are regions in the DNA that contain the instructions that code for the formation of proteins."

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1 By Drs. Ingrid Waldron and Jennifer Doherty, Dept Biology, Univ Pennsylvania, 2018. These Teacher Preparation Notes and the related Student Handout and Genetics Supplement are available at http://serendip.brynmawr.edu/sci_edu/waldron/#genetics.

o LS3.A: Inheritance of Traits – "Each chromosome consists of a single very long DNA molecule, and each gene on the chromosome is a particular segment of that DNA. The instructions for forming species' characteristics are carried in DNA."

o LS3.B: Variation of Traits – “In sexual reproduction, meiosis can create new genetic combinations and thus more genetic variation. Although DNA replication is highly regulated and remarkably accurate, errors do occur and result in mutations, which are also a source of genetic variation.”

- Students will engage in several Scientific Practices:
  o Developing and Using Models: “Develop and/or use multiple types of models to provide mechanistic accounts and/or predict phenomena, and move flexibly between model types based on merits and limitations…. Develop and/or use a model… to predict phenomena, analyze systems, and/or solve problems.”
  o Constructing Explanations: “Apply scientific ideas, principles, and/or evidence to provide an explanation of phenomena…, taking into account possible unanticipated effects.”

- This activity provides the opportunity to discuss two Crosscutting Concepts:
  o Systems and System Models: Models can be used “to predict the behavior of a system, [but] these predictions have limited precision and reliability due to the assumptions and approximations inherent in the models”.
  o Cause and Effect: Students “suggest cause and effect relationships to explain and predict behaviors in complex natural and designed systems. They also propose causal relationships by examining what is known about smaller scale mechanisms within the system”.

- This activity helps to prepare students for the Performance Expectations:
  o HS-LS3-1, "Ask questions to clarify relationships about the role of DNA and chromosomes in coding the instructions for characteristic traits passed from parents to offspring."
  o HS-LS3-2, "Make and defend a claim based on evidence that inheritable genetic variations may result from: (1) new genetic combinations through meiosis, (2) viable errors occurring during replication, and/or (3) mutations caused by environmental factors."
  o HS-LS3-3, "Apply concepts of statistics and probability to explain the variation and distribution of expressed traits in a population."

More Specific Learning Goals

**Genes in DNA → Proteins → Characteristics**

- The basic way that genes influence an organism's characteristics is: Genes in DNA provide the information necessary to make proteins, and proteins carry out many biological functions and thus influence our characteristics.

- Different alleles (different versions of the same gene) code for different versions of a protein which can result in differences in phenotype (an organism's appearance or other observable characteristics). Phenotype is also influenced by the environment.

- A person is homozygous for a gene if both alleles for that gene are the same. A person is heterozygous if they have two different alleles for the gene.

- For some pairs of alleles, the phenotype of a heterozygous individual is the same as the phenotype of one of the two types of homozygous individual. The allele that results in the same phenotype for both a heterozygous individual and a homozygous individual is dominant. The other allele is recessive.

- In other cases, neither allele is completely dominant or completely recessive. For example, in incomplete dominance, the phenotype of a heterozygous individual is halfway between the phenotypes of the two homozygous individuals.
Many phenotypic characteristics are influenced by more than one gene. A single gene may influence more than one phenotypic characteristic.

**Meiosis and Fertilization → Inheritance**
- The behavior of chromosomes during meiosis and fertilization provides the basis for understanding the inheritance of genes.
- As a result of meiosis, each egg receives one copy of each gene from the mother and each sperm receives one copy of each gene from the father. When the gametes unite in fertilization, the zygote that develops into the child receives one copy of each gene from the mother and another copy of each gene from the father. Repeated mitosis ensures that each cell in a child’s body has the same genes as the zygote. Because children get their genes from their parents, they tend to resemble their parents and their siblings. (Environmental influences also contribute to the similarity of parents and offspring.)
- However, meiosis results in genetically diverse sperm and eggs which, together with random fertilization, results in genetic diversity of the zygotes/children produced by the same mother and father. This can result in phenotypic diversity.

**Punnett Squares → Probabilistic Predictions of Inheritance**
- The processes of meiosis and fertilization can be summarized in Punnett squares which can be used to predict the genotypes and phenotypes of offspring.
- Quantitative predictions from Punnett squares are accurate for large samples, but random variation in the genetic makeup of the sperm and egg that unite to form each zygote often results in substantial discrepancies between the Punnett square predictions and the outcomes observed in small samples such as individual families.
- Each fertilization event is independent of other fertilization events, so the genetic makeup of each child is independent of the genetic makeup of any siblings.

This activity will help to counteract the following common misconceptions.³
- Each trait is influenced by a single gene, and each gene influences only one trait (not recognizing how common polygenic traits and pleiotropy are).
- A person who doesn’t have a characteristic lacks the gene for this characteristic (not recognizing that the person has other alleles for this gene).
- Genes are the sole determinants of traits (not recognizing environmental influences).
- Dominant traits are the most common traits (which is true for some genes, but not all).
- All genetic conditions are inherited (not recognizing the role of new mutations or mistakes in meiosis in causing some genetic conditions).
- Students often fail to recognize the probabilistic nature of Punnett square predictions and inheritance.

**Supplies** for two sections in Genetics

How does a child inherit genes from his or her mother and father? is designed for use after "Meiosis and Fertilization – Understanding How Genes Are Inherited" (available at http://serendip.brynmawr.edu/sci_edu/waldron/#meiosis). For this section of Genetics, you will need chalk, dry erase marker or tape and the model chromosomes used in the prerequisite activity (specifically the model chromosomes used in the section, “Genes are inherited via meiosis and fertilization.”). If your students have not completed the meiosis and fertilization activity and you do not have the model chromosomes, we recommend that you substitute the first

³ These misconceptions are taken primarily from http://knowgenetics.org/common_misconceptions/ and https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2278104/ (especially tables 5 and 6).
module of the Genetics Supplement which covers the same material and does not require model chromosomes.

For **Coin Flip Genetics** you will need:
- Pennies (or checkers) (1 per student)
- Paper cup (optional, 1 per student; having each student shake a coin in a paper cup may result in more random tossing and less chance of coins on the floor)

**General Instructional Suggestions**
In both Student Handouts, **numbers in bold** indicate questions for the students to answer. In the Genetics Student Handout
- **indicates a step in the modeling or coin-tossing procedures** for the students to do.

If you use the **Word version** of the Student Handout to make changes, please check the PDF version to make sure that all formatting and figures are displayed properly in the Word version on your computer.

To maximize student learning, we recommend that you have your students complete groups of related questions in the Student Handout individually or in pairs and then have a class discussion of these questions. In each discussion, you can probe student thinking and help them to develop a sound understanding of the concepts and information covered before moving on to the next part of the activity.

If you would like to have a **key** with the answers to the questions in the Student Handout, please send a message to iwaldron@upenn.edu. The following paragraphs provide additional background information.

**Instructional Suggestions and Background Biology for the Genetics Student Handout**
We recommend that you begin with a class discussion of the guiding question for this activity and the two sub-questions (all shown on the top of page 1 of the Student Handout). This introductory discussion can focus students’ attention on the guiding question, help them to recall relevant information they have already learned, and inform you about your students’ current knowledge and any misconceptions they may have.

**How do genes influence our characteristics?**
Page 1 of the Student Handout reinforces student understanding that genotype determines which proteins are made which in turn influences phenotype. For the albinism example, the specific protein is **tyrosinase**, a crucial enzyme involved in the synthesis of melanin, the primary pigment in skin and hair. The normal allele codes for functional tyrosinase; the allele for albinism codes for a defective, non-functional version of this enzyme. The allele for albinism is recessive because, even when there is only one copy of the normal allele, the normal allele codes for enough functioning enzyme to produce enough melanin to result in normal skin and hair color⁴. Often, a dominant allele codes for a functional protein and recessive alleles code for non-functional protein.

**Questions 2-5** provide the opportunity to discuss the **Cause and Effect Crosscutting Concept**: Students “suggest cause and effect relationships to explain and predict behaviors in complex

⁴ At the molecular level the two alleles are codominant, but at the readily observable whole organism level the allele for functional enzyme is dominant. The Student Handout focuses on the more usual whole organism phenotype and ignores the codominance at the molecular level.
natural and designed systems. They also propose causal relationships by examining what is known about smaller scale mechanisms within the system”.

For this type of albinism, the lack of the pigment melanin affects not only skin and hair color, but also the appearance and function of the eyes. Certain alleles of other genes can also result in albinism. (For additional information about albinism see http://www.nlm.nih.gov/medlineplus/ency/article/001479.htm and http://omim.org/entry/203100).

Additional examples that you can use to reinforce student understanding that genes provide the instructions for making proteins which influence phenotypic characteristics include the following:

- the protein that regulates bone growth (discussed in the achondroplasia example in the last section of the Genetics Student Handout)
- sickle cell vs. normal hemoglobin (discussed in the last section of the Genetics Supplement on sickle cell anemia and sickle cell trait)
- acetaldehyde dehydrogenase (an enzyme that disposes of harmful molecules produced by alcohol metabolism; discussed in the mitosis activity (http://serendip.brynmawr.edu/sci_edu/waldron/#mitosis))
- lactase and clotting proteins (discussed in our introduction to proteins and DNA (http://serendip.brynmawr.edu/exchange/bioactivities/proteins))
- the enzyme that converts phenylalanine to tyrosine and a membrane protein (see discussion of PKU and cystic fibrosis on page 6 of these Teacher Preparation Notes).

How does a child inherit genes from his or her mother and father?
This section of the Student Handout is designed to reinforce student understanding of how meiosis and fertilization result in inheritance of genes (one copy of each gene from the mother and one copy of each gene from the father). Students are instructed to draw the rectangles from this chart on their lab table with chalk. You may prefer to provide them with tape or dry erase marker instead of chalk.

As students model meiosis and fertilization for two heterozygous parents, they should notice that a heterozygous zygote can arise in two different ways (dominant allele from mother or from father). This observation should help students understand why the heterozygous genotype is twice as likely as either homozygous genotype.

In interpreting Punnett squares, it is important for students to realize that the genotype of a person who develops from a zygote is the same as the genetic makeup of the zygote (as discussed in question 9). The zygote undergoes many rounds of mitosis to produce the cells in the person's body, and mitosis produces daughter cells with the same genetic makeup as the original cell.

Questions 6-12 engage students in analyzing examples that illustrate:

- how meiosis and fertilization can result in an offspring who has a phenotype that is different from the phenotype of either parent
how inheritance via meiosis and fertilization contributes to the tendency of children to resemble their parents.

Questions 11 and 12 will help students to realize that parents who have the phenotype associated with a recessive allele must be homozygous for the recessive allele and therefore won't have a child with the dominant allele (unless there is a new mutation). In contrast, two parents who have the phenotype associated with the dominant allele may both be heterozygous so they could have a child who has inherited two copies of the recessive allele and has the associated phenotype. These insights are crucial for pedigree analysis. Students should recognize that question 12a provides the information they need to answer questions 12b and 12c.

Other conditions that are caused by a recessive allele of a single gene, and inherited in the same manner as albinism, include:

- **cystic fibrosis**, which is caused by a faulty membrane protein which indirectly results in difficulty in breathing and shortened life expectancy;
- **phenylketonuria (PKU)** which is due to defective versions of the enzyme that converts phenylalanine to tyrosine. This is an important step in disposing of excess phenylalanine. Excessive levels of phenylalanine result in mental retardation unless phenylketonuria is detected at birth and treated with a special diet. In an individual who is homozygous for the PKU allele, mental retardation can be prevented by minimizing phenylalanine in the diet by avoiding the artificial sweetener aspartame and high-protein foods (e.g. meat, fish, milk, cheese, eggs, nuts, beans, tofu, and even foods with flour) and substituting special low-phenylalanine foods. Minimizing intake of phenylalanine is especially important for babies and young children when the brain is developing rapidly and for pregnant women (to protect the rapidly developing brain of her fetus). For additional information, see [http://www.genome.gov/25020037](http://www.genome.gov/25020037) and [http://www.mayoclinic.com/health/phenylketonuria/DS00514/DSECTION=treatments-and-drugs](http://www.mayoclinic.com/health/phenylketonuria/DS00514/DSECTION=treatments-and-drugs).

For question 13b, students are instructed to include the word alleles in discussing how genes influence a person’s characteristics. They should write about how different alleles code for different versions of a protein, which can result in different phenotypic characteristics. This will avoid the common misconception that characteristics are due to the presence or absence of a gene.

**Coin Flip Genetics**

This section helps students understand the importance of random variation in inheritance, particularly in small samples. Discussion of random variation will help your students to reconcile their experience of variation in outcomes in real world families with the predictions of Punnett squares in the classroom. This module also introduces students to the independence of each fertilization event, so the genotype of each child is independent of the genotypes of any older siblings.
Students will observe that results for an individual family of 4 coin toss children often deviate substantially from the results predicted by the Punnett square. The table below illustrates the high probability that the genotypes of 4 children born to two heterozygous parents will differ from the predictions of the Punnett square.

<table>
<thead>
<tr>
<th>Observed Outcome for 4 Coin Tosses</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 aa</td>
<td>32%</td>
</tr>
<tr>
<td>1 aa</td>
<td>42%</td>
</tr>
<tr>
<td>2 or more aa</td>
<td>26%</td>
</tr>
<tr>
<td>1 AA + 2 Aa + 1 aa</td>
<td>19%</td>
</tr>
</tbody>
</table>

(Calculated using the multinomial calculator available at http://stattrek.com/Tables/Multinomial.aspx)

When your students carry out the coin tosses to create 4 families of 4 children each, there is a 78% probability that they will get at least one family with no albino (aa) children and a 70% probability that they will get at least one family with 2 or more albino children.

The results for larger samples are generally closer to the predicted distribution and less likely to show extreme deviations. For example, for two heterozygous parents a finding of no albino children is expected in 32% of families of 4 children, but in only 1% of samples of 16 children, and less than one in a million samples of 100 children.

The previous section and question 21 in this section illustrate how the Punnett square model is useful for predicting various features of the inheritance of albinism. The analyses in this section also illustrate two limitations of the Punnett square model of inheritance.

- The Punnett square model does not take account of random variation, which has a strong effect on the genotypes of the children in a real family. Therefore, the Punnett square does not reliably predict the composition of individual families (question 21).
- Since Punnett squares do not include information about the population prevalence of different genotypes among the parents, they do not predict the population prevalence of different genotypes among children in the general population (question 22).

After you discuss question 22, we recommend that you discuss the Systems and System Models Crosscutting Concept: Models can be useful “to predict the behavior of a system, [but] these predictions have limited precision and reliability due to the assumptions and approximations inherent in the models.” Many students tend to think of a model as a physical object and may not understand that a Punnett square is a model of inheritance, so you may want to introduce the idea of a conceptual model. "Conceptual models allow scientists… to better visualize and understand a phenomenon under investigation… Although they do not correspond exactly to the more complicated entity being modeled, they do bring certain features into focus while minimizing or obscuring others. Because all models contain approximations and assumptions that limit the range of validity of their application and the precision of their predictive power, it is important to recognize their limitations." 5 To help students grasp what a conceptual model is, you may want to give examples of conceptual models that students may use in their everyday lives, e.g a map, an outline for a paper the student is writing, a diagram of a football play, and a calendar (as a conceptual model of a year).

After your students have completed the section, you may want to use the first episode in "Soap Opera Genetics" (http://serendip.brynmawr.edu/exchange/bioactivities/SoapOperaGenetics) for

review and assessment. You can enhance student learning and retention of important concepts and vocabulary by having your students complete this episode using active recall (without referring to previous notes or materials), and then providing prompt feedback to clarify any points of confusion and correct any misconceptions (e.g. by having a class discussion of student answers).

The Genetics of Human Skin Color

This table summarizes the key points for answering question 23.

<table>
<thead>
<tr>
<th>Type of Dominance</th>
<th>Phenotype of Heterozygous Individual</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dominant-recessive pair of alleles</td>
<td>Same as phenotype of individual who is homozygous for the dominant allele</td>
</tr>
<tr>
<td>Incomplete dominance⁷</td>
<td>Intermediate between phenotypes of the two types of homozygous individual (typically observed for quantitative traits); phenotype different from either homozygous individual</td>
</tr>
</tbody>
</table>

This section introduces the important concept that individual phenotypic characteristics are often influenced by multiple genes, as well as environmental factors. When a phenotypic characteristic is influenced by multiple genes, this is called polygenic inheritance.

The multiple genes that influence skin color include the gene for tyrosinase, an enzyme required to synthesize melanin (see page 4 of these Teacher Preparation Notes). A second important gene that influences skin color is the MC1R gene which codes for the melanocortin receptor. When alpha melanocyte stimulating hormone binds to normal melanocortin receptor this stimulates melanocytes to produce melanin. More than 80 alleles of the MC1R gene have been identified, resulting in various levels of function of the melanocortin receptor and correspondingly varied skin tones. Heterozygotes for these alleles have intermediate skin color, between the lighter and darker homozygotes (called incomplete dominance). The multiple alleles and the effects of incomplete dominance result in multiple different phenotypes for skin color (and hair color).

(Additional information on this gene is available at https://ghr.nlm.nih.gov/gene/MC1R.)

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⁶ Many questions in this section are similar or identical to some of the questions in the second episode in "Soap Opera Genetics" (http://serendip.brynmawr.edu/exchange/bioactivities/SoapOperaGenetics).

⁷ Incomplete dominance can occur when each allele results in the production of a set dose of protein product and the phenotype is proportionate to the amount of protein. This explains why incomplete dominance is sometimes called a dosage effect. The Student Handout uses a capital letter and lowercase letter to indicate the two alleles for a gene with incomplete dominance; you may prefer to use an alternate notation such as b/b⁺ or B/B‘.

This activity does not discuss the concept of codominance. In codominance, the phenotype of a heterozygous individual shows different observable phenotypic effects of both alleles. The phenotype is different from the phenotype of either type of homozygous individual (as is also true for incomplete dominance). Codominance is introduced in the second episode of "Soap Opera Genetics" (http://serendip.brynmawr.edu/exchange/bioactivities/SoapOperaGenetics).
Melanin is produced in melanosomes inside melanocytes and transported into the epidermal cells in the outer layer of the skin. A good explanation is provided in the short video, “How We Get Our Skin Color”.8

Our introductory genetics teaching frequently focuses on inheritance and phenotypic effects of single genes, as illustrated on page 6 of the Student Handout. However, this is only a beginning for understanding the genetics of most traits. For example, as discussed in question 26, a person with a Bb genotype could have lighter or darker skin, depending on whether he or she:

- has developed a tan as a result of sun exposure or tanning booth use
- has alleles for other genes that contribute to darker skin color.

During your discussion of question 26, we suggest that you revisit the previous page of the Student Handout and explain that the genotype/phenotype table and question 24 provide a very simplified introduction to the genetics of skin color.

You may want to reinforce student understanding that phenotype is determined by the effects of both genes and environment, using these examples:

- the effects of sun exposure or tanning booths on skin color (see page 7 of the Genetics Student Handout)
- the effects of environment and behavior on the symptoms of sickle cell anemia and sickle cell trait (see pages 14-16 of these Teacher Preparation Notes)
- the effects of diet on whether a person who is homozygous for the PKU allele develops mental retardation (see page 6 these Teacher Preparation Notes).

This figure provides a somewhat more accurate representation of the Punnett square for inheritance of skin color. Even this relatively complex Punnett square is a simplified representation of reality, since it assumes a simple additive model with only two alleles for each gene and incomplete dominance for all of the alleles.

Additional information on the complex genetics and molecular biology involved in regulation of skin color is available in:

- The Regulation of Skin Pigmentation, [http://www.jbc.org/content/282/38/27557.full](http://www.jbc.org/content/282/38/27557.full)
- Genes Responsible for Diversity of Human Skin Colors Identified, [https://www.sciencedaily.com/releases/2017/10/171012143324.htm](https://www.sciencedaily.com/releases/2017/10/171012143324.htm)
Some genetic conditions are not inherited.
Most cases of **Down syndrome** are due to trisomy 21 that resulted from meiotic nondisjunction. If an egg with two copies of chromosome 21 is produced by meiotic nondisjunction and then fertilized by a normal sperm, the resulting zygote has three copies of chromosome 21. Trisomy 21 causes abnormal development which can result in a fetal death or a child with Down syndrome. In the latter case, the child has a genetic condition that was not inherited. The risk for meiotic nondisjunction is higher in older women; this is probably related to the fact that meiosis in females begins in the fetus and is suspended until after the egg is fertilized. For additional information, see pages 7-8 of http://serendip.brynmawr.edu/sci_edu/waldron/pdf/MeiosisFertilizationTeachPrep.pdf.

The allele responsible for **achondroplasia** results in a protein that is overactive in inhibiting bone growth. The allele for achondroplasia is considered dominant because an individual who is heterozygous for this allele and the normal allele has the dwarf phenotype. However, there are important differences between a heterozygous individual (~7% risk of infant death) and an individual who is homozygous for the achondroplasia allele (~100% early mortality). A major cause of mortality and morbidity is brainstem compression due to abnormalities at the craniocervical junction. This example illustrate how a single gene can affect multiple phenotypic traits (called pleiotropy).

In 80% or more of cases of achondroplasia, neither parent has the allele for achondroplasia; instead, achondroplasia is due to a new mutation which occurred during production of one of the gametes. A new mutation for achondroplasia is most frequently observed in the sperm of older fathers, due to a greater number of cell divisions before differentiation of sperm stem cells and the greater survival of sperm stem cells that have this mutation (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5007215/).

**Question 30** stimulates students to notice that achondroplasia is an example of a condition caused by an allele that is partially dominant, but rare in the population. 99.99% of the population is homozygous for the normal recessive allele for this gene. Achondroplasia is rare because there is substantial selection against inheritance of the achondroplasia allele and the mutation rate is low.

After discussing **question 30**, you may want to discuss the following points with your students.
- Mistakes in DNA replication (new mutations) and mistakes in meiosis can result in a condition which is genetic, but not inherited.
- Mutations and mistakes in meiosis are relatively rare, so most of a person’s alleles have been inherited from his/her parents. These inherited alleles contribute to both similarities and differences between parents and their offspring.

Additional information about achondroplasia is available at
- https://www.genome.gov/19517823/
- https://rarediseases.info.nih.gov/diseases/8173/achondroplasia
Instructional Suggestions and Background Biology for Genetics Supplement
The Genetics Supplement has three independent modules. You can use one or more of these modules, depending on your teaching goals.

Alternative Introductory Section
The first four pages of the Genetics Supplement provide an alternative version of the introductory sections (pages 1-3) in the Genetics Student Handout. This alternative version is appropriate if you do not want to use model chromosomes and/or your students have not completed "Meiosis and Fertilization – Understanding How Genes Are Inherited" (http://serendip.brynmawr.edu/sci_edu/waldron/#meiosis). The background information and suggestions for discussion on pages 4-6 of these Teacher Preparation Notes are relevant for these alternative introductory sections, although the specific questions and page numbers differ somewhat in the two versions.

On page 1 of the Genetics Supplement Student Handout a gene is defined as a segment of DNA that gives the instructions for making a protein. The definition of a gene has changed as scientific understanding has progressed. Initially, a gene was conceived as a unit of heredity that determines a phenotypic characteristic. A more sophisticated contemporary definition of a gene is a segment of DNA that codes for an RNA molecule, which may be messenger RNA that codes for the sequence of amino acids in one or more proteins, ribosomal RNA, transfer RNA or regulatory RNA. There is no single universally agreed-upon definition of a gene at this time. The changing definition of a gene illustrates the constantly evolving nature of science as scientists develop progressively more sophisticated understanding of concepts such as the gene. For additional information about the challenges and complexities of defining a gene, see http://www.biologyreference.com/Fo-Gr/Gene.html.

In answering question 1, your students should recognize that enzymes are proteins, but they may not know that melanin is not a protein. This figure shows part of the structural formula of the most common type of melanin (eumelanin); the arrow shows where the polymer continues.

Genetics of Sex Determination
This module helps students to understand the probabilistic nature of inheritance and the limitations of Punnett square predictions (similar to the “Coin Flip Genetics” section of the Genetics Student Handout).

The Y chromosome contains the SRY gene, which stands for Sex-determining Region of the Y chromosome. If a zygote has a Y chromosome with the SRY gene, the embryo will develop testes and male anatomy (with rare exceptions such as Androgen Insensitivity Syndrome, which is described below). If a zygote does not have a Y chromosome with the SRY gene, the embryo will develop ovaries and female anatomy (with rare exceptions such as Congenital Adrenal Hyperplasia, which is described below). The SRY gene codes for a protein that binds to regulatory DNA and activates multiple genes that stimulate the gonads to develop into testes instead of ovaries. The testes secrete testosterone and other chemical messengers that stimulate the genitalia to develop into penis, scrotum, vas deferens, etc. In the absence of the SRY gene, the gonads develop into ovaries, and in the absence of testosterone the genitalia develop into

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9 Here, we are ignoring that some enzymes are RNA molecules.
clitoris, labia, uterus, etc.; this happens both in XX females and in rare XY individuals whose Y chromosome lacks the SRY gene.

Additional genes on multiple chromosomes contribute to the normal development of male and female reproductive organs. Defects in these genes can lead to anomalies in the development of male or female reproductive organs, e.g. due to defective hormone receptors or defective enzymes to produce hormones. Examples are:

- Androgen Insensitivity Syndrome results from lack of functional molecular receptors for testosterone and dihydrotestosterone. Due to the lack of these molecular receptors, testosterone and dihydrotestosterone do not affect the cells in the fetal genitalia of an XY fetus with Androgen Insensitivity Syndrome, so female external genitalia develop. These individuals are raised and live as females, but they have testes instead of ovaries. They are infertile. This syndrome is typically detected when a teenage female fails to menstruate.

- Congenital Adrenal Hyperplasia (also called Adrenogenital Syndrome) develops when an enzyme needed to produce cortisol is defective or missing, resulting in abnormal hormonal feedback which leads to excessive production of androgens by the adrenal cortex. The elevated androgen levels in a XX fetus result in varying degrees of masculinization of the external genitalia. As a result, the baby's sex may appear ambiguous or even be mistaken for male.

Other anomalies in sexual development are due to too many or too few copies of the sex chromosomes in each cell, e.g. Kleinfelter and Turner Syndromes (see http://ghr.nlm.nih.gov/condition/turner-syndrome, http://ghr.nlm.nih.gov/condition/klinefelter-syndrome). It should be noted that a zygote must have at least one X chromosome to survive and develop into an embryo.

Questions 5-6 are intended to consolidate student understanding of what Punnett squares can accurately predict and what they cannot. The data in question 6a are the actual percent male for the 33 individuals in the 11 nuclear families in three generations of descendants of a woman who was born in the early twentieth century. These data illustrate that a Punnett square does not predict the outcome for any individual family.

Random variation usually averages out in large samples, so the predictions of the Punnett square model are more accurate for larger samples. This table shows the expected ranges of results for different sample sizes.¹⁰ Even with relatively large samples, rather substantial variation from one sample to the next will be relatively common.

<table>
<thead>
<tr>
<th>Number of Children in the Sample</th>
<th>If data were collected for a large number of samples, 68% of results expected to be in this range:</th>
<th>95% of results expected to be in this range:</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>39%-61% males</td>
<td>28%-72% males</td>
</tr>
<tr>
<td>40</td>
<td>42%-58% males</td>
<td>34%-66% males</td>
</tr>
<tr>
<td>80</td>
<td>44.4%-55.6% males</td>
<td>39%-61% males</td>
</tr>
</tbody>
</table>

¹⁰ Ranges were calculated based on the normal approximation to the binomial distribution. It should be mentioned that the ranges in this table have been calculated based on several simplifications. Specifically, we have not taken into account the fact that slightly more males than females are born. Also, there appears to be some biological tendency for some couples to produce more female or more male offspring, and this would increase expected variation in results.
We cannot extrapolate from Punnett squares to the percent of all babies with specific genotypes unless we know the prevalence of each allele in the reproducing population (as discussed in question 22 for the albinism example). For inheritance of sex chromosomes, we can extrapolate from the Punnett square to the percent of male and female babies, because we know that every mother has two X chromosomes and every father has an X and a Y chromosome. Actual sex ratios at birth deviate slightly from the Punnett square prediction. Slightly more males than females are born (51.2% males in the US in 2000, slightly lower for African-Americans and slightly higher for Asian-Americans). This slight deviation from the Punnett square model may be the result of higher mortality for female fetuses.

These analyses illustrate both:
- the usefulness of the Punnett square model of inheritance (predicting the percent male in large samples of children and the probability that a child will be male) and
- the limitations of the Punnett square model (not accurately predicting the makeup of individual families or the sex of a specific child, both of which vary due to random variation in which sperm fertilizes which egg).

This provides the opportunity to reinforce the Crosscutting Concept that models can be useful “to predict the behavior of the system, [but] these predictions have limited precision and reliability due to the assumptions and approximations inherent in models”.

**Sickle Cell Anemia and Sickle Cell Trait**

This module includes:
- the biology of sickle cell anemia and sickle cell trait
- a pedigree analysis with an analysis of the advantages and disadvantages of Punnett squares and pedigrees as models of inheritance
- a reading on sickle cell trait with questions that illustrate several complexities that are common in genetics:
  - A single gene often has multiple phenotypic effects.
  - Alleles are often neither completely dominant nor recessive.
  - Phenotypic characteristics are often influenced not only by genes, but also by environmental and behavioral factors.

**Sickle cell hemoglobin** is less soluble in the watery cytosol of the red blood cells than normal hemoglobin, particularly when oxygen concentrations are low. Thus, sickle cell hemoglobin tends to clump into long stacks or rods of hemoglobin molecules; this results in the sickled and other abnormal shapes of some of the red blood cells in a person who is homozygous for the sickle cell allele. The abnormally shaped red blood cells tend to clog the capillaries, thus blocking the circulation in various parts of the body. Also, these red blood cells do not survive as long as normal red blood cells, contributing to a tendency to anemia. Together, these effects result in the multiple symptoms of sickle cell anemia, including pain, physical weakness, impaired mental functioning, and damage to organs such as the heart and kidneys. Question 1 provides the opportunity to reinforce the Crosscutting Concept, Cause and Effect: Students “suggest cause and effect relationships to explain and predict behaviors in complex natural and designed systems. They also propose causal relationships by examining what is known about smaller scale mechanisms within the system”.

Even in a person who has severe sickle cell anemia, most red blood cells are not sickled. The degree of clumping of sickle cell hemoglobin, sickling of red blood cells, and consequent symptoms are influenced by multiple factors, including oxygen levels in the blood, dehydration,
and other genes. A sickling crisis with pain and organ damage can be triggered by an infection that induces vomiting and diarrhea, resulting in dehydration; dehydration increases the hemoglobin concentration in red blood cells and thus increases the tendency of sickle cell hemoglobin to clump into long rods and produce sickled red blood cells which block the circulation in the small blood vessels. These observations illustrate how environment and genotype interact to influence phenotype.

The **pedigree** (on page 8 of the Genetics Supplement Student Handout) supports the conclusion that the allele for sickle cell anemia is recessive, since two unaffected parents have an affected offspring. (This could be the result of a new mutation for a dominant allele, but this is an unlikely interpretation of this pedigree since an affected offspring of unaffected parents occurs twice within three generations of this family.) This pedigree also indicates that the allele for sickle cell anemia is autosomal recessive and not X-linked recessive, since the affected son (6) inherited an allele for sickle cell anemia from his father (3), but he did not inherit an X chromosome from his father. It should be noted, that the allele for sickle cell anemia is not entirely recessive, as explained in the third paragraph below.

**Question 4** stimulates students to think about and evaluate Punnett squares and pedigrees as models of inheritance. One advantage of **Punnett squares** as a model of inheritance is that a Punnett square summarizes how the processes of meiosis and fertilization contribute to inheritance of different alleles of a gene. For parents with specified genotypes, Punnett squares can identify what combinations of alleles their offspring can have and the resulting possible phenotypes. Punnett squares can make quantitative predictions concerning the frequency of these genotypes and phenotypes in large samples of the children of this type of couple. Limitations of Punnett squares as models of inheritance include the lack of information about likely variation in small samples such as individual families and the lack of information about population prevalence of parental genotypes (so no predictions can be made about population prevalence of offspring genotypes and phenotypes). Also, the predictions of a Punnett square model may be inaccurate if complexities that are not included in Punnett squares play an important role in the inheritance of a specific trait (e.g. the effects of multiple genes or the possibility of mutation). The failure to take account of all the complexities is, of course, a general limitation of models, which are simplified representations of complex processes.

**Pedigrees** can be useful for figuring out the mode of inheritance for a phenotypic condition observed in multiple members of a family, and pedigrees can provide a useful basis for genetic counseling. Pedigrees can be quite complex to interpret, e.g. if a mutation has occurred, if environment influences the phenotype, and/or if more than one gene influences the phenotype. Also, pedigrees do not directly represent the underlying biological processes of meiosis and fertilization. Discussion of question 4 provides the opportunity to reinforce the Crosscutting Concept, Systems and System Models: Models can be useful “to predict the behavior of a system, [but] these predictions have limited precision and reliability due to the assumptions and approximations inherent in the models”.

The boxed reading, “Sickle Cell Trait” (on page 9 of the Genetics Supplement Student Handout), indicates that the sickle cell allele is **not truly recessive**. In a person who has sickle cell trait (i.e.

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11 For example, two blue-eyed parents generally do not have brown-eyed children because the most common allele responsible for blue eyes is recessive. However, exceptions can occur due to complex interactions between the multiple genes that influence eye color or due to mutation (which can reverse the point mutation generally responsible for blue eyes). For an introductory explanation and video, see [http://genetics.thetech.org/ask/ask29](http://genetics.thetech.org/ask/ask29); for a more complete discussion, see [http://sciencecases.lib.buffalo.edu/cs/collection/detail.asp?case_id=562&id=562](http://sciencecases.lib.buffalo.edu/cs/collection/detail.asp?case_id=562&id=562).
heterozygous for the sickle cell and normal hemoglobin alleles), each red blood cell has both sickle cell and normal hemoglobin. The amount of normal hemoglobin is sufficient to prevent the symptoms of sickle cell anemia in almost all cases. At the same time, there is enough sickle cell hemoglobin in each red blood cell to have some important phenotypic effects.

The sickle cell hemoglobin in each red blood cell decreases the severity of malaria in heterozygous individuals because the malaria parasite doesn't grow as well in red blood cells containing sickle cell hemoglobin. Malaria infections are common in many tropical countries where there are lots of the type of mosquitoes that transmit the malaria parasite. In areas where malaria is widespread, people who are heterozygous for the sickle cell allele are less likely to become seriously ill and die. Because the sickle cell allele contributed to increased survival of heterozygous individuals, this allele became relatively common in regions like West Africa where malaria has been common. Since African-Americans are descended from populations in which the sickle cell allele was relatively common, African-Americans have relatively high rates of the sickle cell allele (approximately 8% are heterozygous for this allele and 0.16% are homozygous). This provides a good opportunity to point out that mutations are sometimes beneficial and therefore may spread through the population by natural selection.12

Question 5 asks students to summarize the molecular mechanisms that result in the phenotypic characteristics of heterozygous individuals. This provides another opportunity to discuss the Crosscutting Concept, Cause and Effect: Students “suggest cause and effect relationships to explain and predict behaviors in complex natural and designed systems. They also propose causal relationships by examining what is known about smaller scale mechanisms within the system”. This also provides a good opportunity to discuss how a single gene has multiple phenotypic effects. Most genes affect multiple characteristics, although we often ignore this in teaching introductory genetics, as illustrated by the omission of the effects the albinism allele has on the eyes. The multiple effects of the allele for achondroplasia are discussed in the last section of the Genetics Student Handout.

The sickle cell hemoglobin in the red blood cells of people with sickle cell trait has other health effects, including an increased risk of sudden death during extremely strenuous exercise, although the number of these deaths is very small. (For example, one study found only five sudden deaths in American football players with sickle cell trait during a five-year period; during the same time period, two football players who did not have sickle cell trait died of heat stroke.) There is controversy about whether the best approach to reducing the risk of sudden death during very strenuous exercise should be required testing for sickle cell trait or greater emphasis on adequate hydration and preventing overheating (which would be beneficial for people with or without the sickle cell trait) (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4478149/; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5049987/). This is another example of how environmental and behavioral factors interact with genetic factors to influence a fingerprint it characteristic.

A useful summary of the medical aspects of sickle cell anemia, including symptoms, diagnosis and treatment is available at http://www.mayoclinic.org/diseases-conditions/sickle-cell-anemia/home/ovc-20303267. A good explanation of sickle cell disease is provided at https://www.nhlbi.nih.gov/health/health-topics/topics/sca#.

12 Lactase persistence alleles are an example of beneficial mutations which spread in populations that began to herd milk-producing animals. See the learning resources available at http://www.hhmi.org/biointeractive/making-fittest-got-lactase-co-evolution-genes-and-culture.
**Source for the Figure** on page 7 of the Genetics Supplement Student Handout:

**An Integrated Sequence of Learning Activities for Teaching Genetics**
This genetics activity is part of an integrated sequence of learning activities which is presented in *Genetics – Major Concepts and Learning Activities* ([http://serendip.brynmawr.edu/exchange/bioactivities/GeneticsConcepts](http://serendip.brynmawr.edu/exchange/bioactivities/GeneticsConcepts)). Part I provides an outline of key concepts in genetics. Part II presents common misconceptions. Part III proposes an integrated sequence of learning activities to develop student understanding of the key concepts and counteract common misconceptions. These learning activities are aligned with the Next Generation Science Standards. Part IV suggests supplementary learning activities.