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# The Embark Protocol: Dog Genomics in Genetics Laboratories 5/5/2020

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THE EMBARK® PROTOCOL: DOG GENOMICS IN GENETICS LABORATORIES

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ABSTRACT
ALEXANDRA L. KISSEL: The Embark® Protocol: Dog Genomics in Genetics Laboratories
(Under the direction of Dr. Sarah J. Liljegren)

In a world of ever-advancing technology, it is imperative that young pre-health professionals are educated according to the most relevant research. One of the most fundamental, foundational concepts of health is genetics. This field is rapidly expanding, and quickly engraining itself into the realm of healthcare. Genetic testing and gene therapies, once subjects of science fiction, have become commonplace. It is more important than ever that health professionals have a concrete knowledge of genetics, and this begins with the proper education of pre-health students.

With this idea in mind, a laboratory protocol was designed for students of the Bisc 336 course at the University of Mississippi to enhance their knowledge of significant genetic concepts. The main focus is understanding genetic diversity and its significance to health. Other key concepts include the distinction between being a carrier and being at risk for a disease, incomplete compared to complete penetrance, and the inheritance of maternal and paternal haplotypes. This protocol was formulated as a worksheet and is structured around having students navigate the online Embark® platform, a collection of canine breed, trait and health information associated with direct-to-consumer DNA genotyping. A pilot study was conducted during the Fall 2019 semester in a Bisc 336 Honors Genetics class to test the efficacy of the worksheet and student question preferences. Assessment of the results was used to revise the worksheet in preparation for

future implementation. Intake and exit surveys were designed to test students' comprehension of the concepts taught and their personal opinions on the protocol.

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# INTRODUCTION

The importance of integrating genomics into health care has been globally recognized, with countries around the world pouring upwards of 4 billion dollars into streamlining this process (Stark et al., 2019). Despite the noticeable rise in the use of genomics in medical practices, there remains an alarming shortage of genetics professionals. Data taken from the US Census and the American College of Medical Genetics shows that there are two genetics professionals per 1 million Americans (Maiese et al., 2019). This trend is true of all science, technology, engineering, and mathematics (STEM) fields. Despite an increased societal demand for more STEM professionals, over half of undergraduate students who begin their academic careers in this track fail to complete their bachelor's degrees (Smith and Wood, 2016). This demonstrates why it is more vital than ever that all pre-health undergraduate students are properly educated in genetics and genomics. One way to accomplish this is to develop laboratory protocols that enhance students' comprehension of important concepts and hold their interest.

Genetics education has undergone massive changes over the last one hundred years (Smith and Wood, 2016). At first, the focus was primarily on Mendelian patterns of inheritance and applying these principles towards the advancement of agriculture. Currently, genetics is treated as a foundational concept for biology (American Association for the Advancement of Science, 2011). Furthermore, its relevance to daily life has increased as a constant stream of news stories describe research advances that impact our health, food, and reproduction (Redfield, 2012). The strategies for teaching

genetics are continuing to evolve. One reason for this is that the sheer amount of content has vastly increased, leading educators to emphasize the importance of conceptual knowledge and understanding how to practice science, rather than simply memorizing facts (Smith and Wood, 2016). Another reason is students' increasingly positive responses to active learning (Freeman et al., 2014). This type of learning often includes peer collaboration on projects requiring analytical thinking. This learning style has been incorporated into a new laboratory protocol I have developed for the Bisc 336 Genetics course at the University of Mississippi.

The idea for my laboratory protocol was inspired by Embark®, a direct-to-consumer genetic testing service for dog owners and breeders. The founders of Embark®, Adam and Ryan Boyko, are two highly accomplished brothers who wanted to establish the equivalent of 23andme for dogs through a partnership with geneticists and scientists at the Cornell University College of Veterinary Medicine (Adams, 2017). The stated mission of Embark® is to "end preventable disease in dogs" through their canine genetic research projects (Fallon and Alexander, 2019).

The Embark® DNA kits for health and breed test over 200,000 genetic markers, as well as 171 mutations, making it the most comprehensive dog DNA kit on the market (Wells, 2019). The company's online platform, embarkvet.com, is designed to be multilayered, so that someone without a scientific background can access information about their dog and easily comprehend it, but further navigation reveals fine details useful for delving deeper into more complex topics (Fallon and Alexander, 2019). An exceptional feature is that links to primary research articles about canine genetics are embedded throughout the descriptions of breed-specific traits and health conditions.

Determining a dog's breed can allow for an owner to be more aware of potential health complications associated with that breed (Grieves, 2020).

As the laboratories in Bisc 336 are currently scheduled, students are exposed to a number of different concepts including meiosis, epistasis, pedigrees, linkage, and mutations, all of which can be modeled by dogs. With these and other fundamental building blocks already in the students' arsenals, they can be introduced to a laboratory protocol designed to improve their grasp of genetic diversity, think about the benefits of heterozygosity, and learn about the concept of haplotyping. The use of dogs as the subjects of active learning-based online research also allows students to connect with a type of animal that is meaningful to many of them as pets.

The relevance of genetic diversity has been recognized for many years in the scientific community (Bihlmeyer et al., 2014). It is a concept that has been correlated with health in numerous ways. One method to define an individual's genetic diversity is by analyzing single nucleotide polymorphisms, or SNPs, which are differences in individual base pairs of DNA (Bihlmeyer et al., 2014). These markers can be used to predict human mortality, such as in a study conducted by Bihlmeyer et al. (2014), which concluded that for every standard deviation above a mean level of genetic variation in a population, an individual is 1.57% less likely to die. Hindorff et al. (2017) has proposed that better understanding of genomic variants among human populations is a necessity for gaining knowledge about how genetics and disease are intertwined and will lead to a higher quality of healthcare. The designed protocol is meant to give the students of Bisc 336 concrete examples of genetic diversity and demonstrate how inherited diseases are linked to different breeds of dogs.

The significance of genetic diversity has led to the rise of precision medicine, which involves designing treatments for individual patients based on their genetic profiles and even searching individual genomes for diagnostic clues (Agusti et al., 2016). While the economic feasibility remains to be resolved, precision medicine offers individualized care while minimizing negative side effects from treatments would be less effective for that individual (Agusti, et al., 2016; Danieli, 2018). These treatments are already changing lives. Eight-year-old Beatrice Rienhoff was fortunate to be born the daughter of a clinical geneticist, who realized that her short stature and poor muscle development did not fit with any known syndrome at the time (Evans, 2015). Her father and a team of scientists were able to find an uncharacterized allele of the Transforming growth factor-beta3 gene that distinguishes Beatrice's disease from Marfan and other related syndromes (Evans, 2015; Rienhoff et al., 2015). The recognition that atypical alleles may be the cause of rare diseases is a practical application of understanding of genetic diversity.

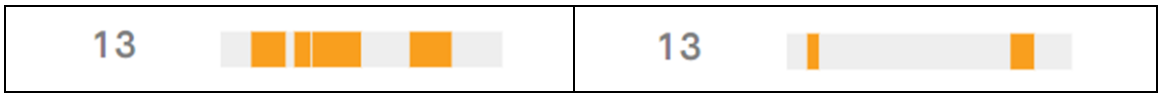
The growing field of pharmacogenetics also uses genetic information to improve the efficacy of and decrease the adverse effects of pharmaceutical drugs (Rahawi et al., 2020). The drug prescribed and even the dosage can be curated specifically for individuals found to have genetic variants that alter drug metabolism. Korei Parker was seven years old when she started bleeding uncontrollably (Maron, 2016). Genetic testing revealed that one of her enzymes worked too well: she was metabolizing a drug that she had been prescribed to stave off infections faster than the average patient. Her doctors immediately switched to a new drug that was metabolized by a different enzyme, and she was able to stay infection free (Maron, 2016). Another individual, Debbie Spaizman,

experienced discomfort and no relief from pain when taking prescription pain medication (Hansen, 2019). When faced with the need to undergo surgery, she was concerned that narcotics would have adverse effects on her body. After her genetic profile was analyzed through a pilot project at Stanford, it was determined that one of her enzymes, CYP2D6, was too slow at metabolizing certain drugs. In her case, she would either need a lower dose of a drug metabolized by this enzyme or a prescription for a different drug (Hansen, 2019). There are many other success stories related to pharmacogenetics that highlight the advantages of understanding genetic diversity at a molecular level.

Heterozygosity is the inheritance of different alleles of a specific gene—one from each parent (Dutra, 2020). Heterozygosity throughout an individual's genome has been associated with multiple health advantages. Xu et al. (2019) found that higher heterozygosity directly corresponds to healthy human aging. Individuals with higher levels of heterozygosity compared to the general population had lower blood pressure and lower levels of LDL cholesterol as they aged (Bihlmeyer et al., 2014). Furthermore, analysis of ten-year survival probability in older men revealed that those with estimates of more than 90% had significantly higher levels of heterozygosity than those with less than 10% (Xu et al. 2019). In contrast, loss of heterozygosity can be hazardous to health. Nichols et al. (2018) found that loss of heterozygosity of specifically selected genes greatly increases an individual's vulnerability to cancer. For instance, in an experiment used to knockout one "resistant" allele of the genes PRIM1 and EXOSC8, the genes were found to be less resistant to destructive, cancerous cells (Nichols et al., 2018). The Embark® laboratory protocol I designed offers the opportunity for students to see what heterozygosity looks like on the chromosomes of the dogs that have been tested. The

chromosomes are color coded to indicate where alleles are the same, and where they diverge.

**Figure 1: Chromosome of a Purebred Dog Compared to a Mixed Breed**




It is necessary for students preparing for health-related professions to understand what heterozygosity means and the advantages associated with it.

The Embark® DNA kit also provides information on canine haplotypes. A haplotype is a set of DNA variations that tend to be inherited together from one parent because they are close together and tend to not recombine (Bailey-Wilson, 2020). The main clinical use of haplotyping is to pinpoint the origin of disease-causing mutations and locate candidate genes on a chromosomal map (Crawford and Nickerson, 2004). Haplotyping is also common practice in transplant procedures, where Human Leukocyte Antigen (HLA) haplotype matching between patient and donor is used to decrease the possibility of rejection (Crawford and Nickerson, 2004). Certain haplotypes can also be used to predict the possibility of diseases such as sickle cell anemia (Crawford and Nickerson, 2004). These practical applications in the health field demonstrate the value for students to fully comprehend the concept of haplotyping.

Dogs can serve as important models for studying human diseases. In the case of transmissible tumors, dogs are one of only two nonlaboratory mammals that share this medical condition with humans (Ostrander et al., 2018). Dogs are also being used in studies of bladder cancers, sarcomas, and squamous cell carcinoma (Ostrander et al., 2018). According to Ostrander et al. (2018) the alignments between canine cancers and

the human equivalents include age of onset, the way the cancers present themselves, responses to treatment, and outcomes. In conducting research about a genetic variant associated with canine brachycephaly (shortened skulls) during a previous semester, I found that dogs are used as models for developing better methods of detection and treatments for Chiari malformations in humans (Whiteman, 2014). These studies are just a few examples demonstrating the usefulness of studying canine health, especially for students planning on entering into health professions.

# MATERIALS AND METHODS

## I. Study Participants and Test Subjects

Nineteen students from Dr. Sarah Liljegren's Fall 2019 Bisc 336 Honors Genetics class at the University of Mississippi participated in the pilot test of this study. Each of the students in this class was a member of the Sally McDonnell Barksdale Honors College.

Embark® is a direct-to-consumer canine genotyping service. Genetic information for four dogs was accessible to students who participated in the pilot study. Presley is a purebred Pug. Harper is a Goldendoodle, a designer breed that is created by mating a purebred Golden Retriever with a purebred Standard Poodle. Sascha is a purebred German Shepherd. Smokey is predicted to be a mix of seven breeds--Rat Terrier, Cocker Spaniel, Dachshund, Chow Chow, Boston Terrier, Siberian Husky and Labrador Retriever.

## II. Embark® Worksheet Design

The main component of the protocol is a worksheet composed of short-answer questions about the information available on the Embark® website (See Appendix A). It is designed to be completed by groups of students and can be graded at the discretion of the professor.

The Embark® website contains four data tabs for Health, Breed, Traits, and Relatives. The worksheet was constructed around these sections, with the central goal of increasing students' understanding of genetic diversity.

For the Health tab, the questions focused on the concept of heterozygosity, what being carrier for a genetic condition means, and the risk of contracting a genetic disease depending on whether the alleles show complete or incomplete penetrance. One dog is a carrier of a SNP associated with a disease and another is at risk for developing a disease, allowing students to learn the difference.

For the Breed and Traits tabs, the questions allow students to visualize the relationship between the level of inbreeding and health and examine the significance of genetic diversity. Students are asked to think about the relationship between the level of inbreeding in purebred dogs compared to dogs composed of a mix of breeds. Students also investigate maternal and paternal haplotypes and use these concepts to construct a family tree. They are guided to construct a graph plotting genetic diversity and the number of conditions for which a dog is either at risk or a carrier.

The Relatives tab gives students the ability to examine shared DNA between the dogs and their DNA relatives in the Embark® database. Segments of shared DNA are color-coded, which allows students to visualize at the chromosomal level what it means to be genetically related.

## III. Protocol Administration

On December 4$^{th}$, 2019, I attended a laboratory session of Bisc 336 Honors to administer the worksheet in person. Nineteen students self-selected to work in three

groups of five students each and one group of four. Each group was informed by Dr. Liljegren that the worksheet would be graded as an in-class work assignment; during the semester this type of laboratory assignment was worth 2.5% of a student's final grade. While the students were completing the worksheet, I was available to answer questions. Completion time ranged from 60 to 90 minutes. Each group was asked to place five stars next to questions that they liked, and five check marks next to questions they did not like.

## IV. Worksheet Assessment and Refinement

The worksheets were reviewed to make note of the students' preferred questions and to assess whether the questions were answered in a satisfactory way. These qualitative data were considered in revising subsequent drafts of the worksheet.

## V. Intake and Exit Surveys

Following the completion of the pilot test, both an intake survey and exit survey were constructed to obtain quantifiable data on the Embark® protocol. The first half of each survey consists of the same set of comprehension questions. By comparing the answers before and after participation in the study, it can be determined which concepts the students had already learned and whether the study was effective in teaching the students concepts that they did not already know.

The second half of the intake survey is composed of opinion-based questions to better understand the way that students feel about biology laboratories. The second half of the exit survey is a set of subjective questions about the worksheet designed to aid in continued improvement of the protocol.

Both surveys are designed to be completed anonymously by individual students; the comprehension questions will not be used in assigning grades. The intake survey also contains a consent statement for the use of data. If a student chooses not to consent, then an alternate activity would be provided.

## VI. IRB Application

The revised study protocol was originally planned for implementation in several Bisc 336 laboratory sections during the Spring 2020 semester. The experimental design included collecting anonymous intake and exit survey data from students who completed the in-class Embark® work assignment compared to data from students who had completed a different assignment. This protocol was submitted for review to the University of Mississippi Institutional Review Board (IRB). Informal feedback was received from IRB staff in February that it would qualify as exempt educational research. Final approval of this status will be requested again prior to the Fall 2020 semester, when an updated version of this study is expected to be introduced by Dr. Liljegren.

The pilot study was conducted as laboratory module for Dr. Liljegren's Fall 2019 Honors Bisc 336 class; this type of educational exercise did not require IRB approval.

# RESULTS

## *Initial Embark® Work*

To familiarize myself with the Embark platform, I carried out a gene function research project during the Spring Semester of 2019. This consisted of deciphering research papers surrounding the function of the *BMP3* gene in determining canine skull shape and putting together a presentation for members of my research laboratory. In my investigation of brachycephaly, or the shortened skull shape that occurs in dog breeds like Pugs, I found that this trait resulted from human-driven breeding (Schoenebeck et al., 2012).

**Figure 2: Side by Side of Regular Dog Skull Shape with Brachycephalic Skull**

Despite the myriad health problems that this trait causes in dogs, from elongated soft palates to collapsed larynxes, this phenotype became aesthetically desirable in breeds like Pugs, English Bulldogs, and Pekinese. The Embark® website contains a link to the Schoenebeck et al. (2012) study, which decisively concluded that differences in skull shape

are caused by one SNP, a homozygotic missense mutation that replaces a phenylalanine with a leucine in the encoded BMP3 protein. This single amino acid change causes an enormous change in the physical appearance of an animal and can have major health consequences such as difficulty breathing (Schoenebeck et al., 2012). Embark® offers students the ability to recognize these mechanisms at work in live organisms, an invaluable resource for understanding the importance of genetic diversity.

*Pilot Study of Embark® Laboratory Module*

On September 4th, 2019, I was invited to the laboratory session of Bisc 336 Honors Genetics to introduce the Embark® platform to students. This was to prepare them to complete their own gene function research projects, akin to the one that I did on *BMP3,* and the Embark® laboratory module I designed later in the semester. I shared a 10 min PowerPoint presentation in the Liljegren lab created to highlight features of the Embark® website and my *BMP3* presentation.

I constructed the main component of my study protocol, the **worksheet** (see Appendix A), around the four-tab data structure of the Embark® website: Health, Breed, Traits, and Relatives. After editing several drafts of the worksheet with Dr. Liljegren, I attended another laboratory session of Bisc 336 Honors Genetics on December 4th, 2019 to administer a revised version as a pilot study. Nineteen students completed the worksheet in four small groups and selected questions they liked or disliked.

*Analysis of Completed Worksheet*

The following observations were made about the answers provided by the students in my pilot study.

*Canine Health: Students Struggle to Connect Breed and Disease*

In the Health section, the main focus of the questions was the heterozygote advantage. I wanted the students to recognize that certain diseases occur more often in certain breeds of dog. Presley is "at risk" for developing degenerative myelopathy, one of three breed-relevant genetic conditions common in pugs. Harper, the Goldendoodle, is a carrier for Ichthyosis, a skin condition that is common in Golden Retrievers. All of the students were able to correctly answer the definition questions and straightforward questions about the dogs' health. However, most groups did not satisfactorily answer two analytical questions (**2f** and **2g**) in this section, as they did not recognize the relationship between dog breed and disease incidence.

| |
|---|
| 2. (f) If any of the dogs are carriers, does this indicate anything to you about a greater incidence of this condition in certain breeds of dog?<br><br>(g) Could there be anything advantageous about being a carrier (think about the dog population as a whole)? |

*Breed: Students Fail to Construct Family Tree Incorporating Haplotypes*

The questions for the Breed tab centered around the concept of haplotypes. I wanted the students to be able to correctly visualize the successive inheritance of paternal haplotype DNA on the Y-chromosome from one paternal great-grandparent to a male

dog, and the inheritance of maternal haplotype DNA on the mitochondrial genome from one maternal great-grandparent to both male and female dogs.

The students were able to identify the haplogroups and haplotypes associated with each dog, as these are easy to locate on the Embark® website. **Figure 3** shows a screenshot of Harper's maternal haplotype.

**Figure 3:** Example of Dog Haplogroup Map


They also successfully recognized the relationship between haplotype and breed, in a pair of questions (**4b** and **4c**) that had them figure out which of Harper's parents was a Golden Retriever and which was a Standard Poodle. Harper's Family Tree prediction confirms her genetic status as a Goldendoodle designer breed, with half of her ancestors being purebred Golden Retrievers and the other half being purebred Standard Poodles, but it does not indicate which side is which. By noting that Harper's maternal haplotype,

A382, occurs most frequently in Labrador Retrievers, Golden Retrievers and Chesapeake Bay Retrievers, they could deduce that Harper's mother should be the Golden Retriever and Harper's father should be the Standard Poodle.

> 4. (b) Discuss the relationship between dog breed and haplotype. Use Harper's haplotype as an example. Where did Harper's ancestors originate?
>
> (c) Can you use this correlation to determine which of Harper's parents is the mother and which is the father?

However, the students struggled to grasp the significance of a male dog's maternal and paternal haplotypes when it came to inheritance (**Question 3f**). Surprisingly, even though Dr. Liljegren had already taught the concepts of pedigree analysis and maternal inheritance of mitochondrial DNA in her lectures, every group failed to draw a family tree that correctly showed the relationships between Presley and the great-grandparents he inherited his maternal and paternal haplotypes from, respectively.

> 3. (f) Construct a family tree for Presley beginning with the great-grandparent generation and using female and male symbols to indicate individuals. Then, trace a line from Presley to his great-grandparents indicating the path of inheritance for his maternal haplotype. How many great-grandparents connect to Presley this way? Repeat the process for his paternal haplotype and clearly label it separately from the first line.

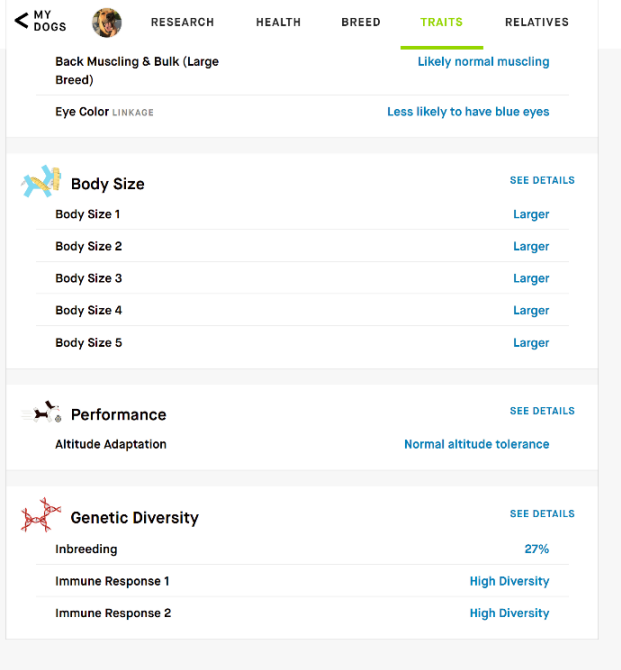
Each group had at least one part of this question completed incorrectly. Additionally, most of the students fell short in simply defining a 'haplotype', and failed to recognize that a haplotype is a set of SNPs on the same chromosome (or mitochondrial genome) inherited together from one parent.

This section also included questions on Breed Mix Matches: dogs identified in the Embark database that share the same breed composition percentages as the dogs in our group (but not the same percentage of shared DNA). The students answered these questions very satisfactorily.

*Traits: Students Struggle with Constructing Scatter Plots of Dog Data*

In the Traits section, I focused on the importance of genetic diversity and its relationship to overall health. Embark® gives an estimated percentage of inbreeding for each dog. For example, Sascha, as a purebred German Shepherd, has an inbreeding estimate of 27% (see **Figure 4)**.

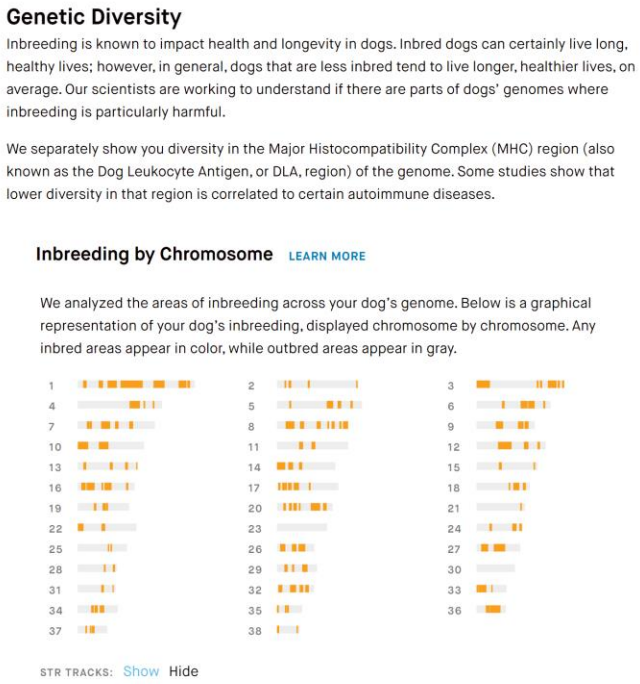
**Figure 4:** Example of Dog Traits




Most of the students were able to properly define inbreeding, and most were able to successfully interpret the graphics (**see Figure 5**) that show the stretches of homozygous

alleles (inbred regions shown in an orange color) on a dog's chromosomes compared to those of heterozygous alleles (outbred regions shown in a gray color).

**Figure 5:** Example of Dog Chromosomes




The most interesting finding in this section is that students struggled with making a scatter plot (**Question 5d**).

> 5. (d) For Sascha, Harper, Smokey, and Presley, do you see a relationship between inbreeding and overall health (number of diseases 'at risk' and carrier)? To answer this question, you can draw a scatter plot with genetic diversity on the y-axis and number of conditions at risk for or carriers on the x-axis for the four dogs.

It was also enlightening to see how the students handled a data set that did not fit their expectations. Since Embark® points out that a negative correlation has been demonstrated scientifically between a dog's level of inbreeding and its health and longevity, the students expected to see that relationship with the data of the four dogs

accessible to them. Instead, because of the small data set, there is not an obvious negative correlation between lower genetic diversity and overall health, and many of the students questioned me about these results.

*Relatives: Students Comprehend Genetic Relationships between Dogs*

The questions about the Relatives tab centered on the dogs' genetic relatedness to other dogs in the Embark® database determined to be their DNA Relatives. Overall, the students were able to recognize the difference between genetic relatedness and familial relatedness, with regard to purebred dogs. For example, Presley shares 47-51% of his DNA with 27 other pugs in the Embark® database, a level of genetic relatedness due to inbreeding that is equivalent to that of full siblings or of a parent/child relationship in humans. This was the section that the students did the best on, but they did struggle with one question (**6e**) that required finding outside sources to answer it.

| |
|---|
| 6. (e) What percentage of DNA do humans typically share with each other? Genetic testing companies focus on SNPs that reveal genetic diversity. What percentage of these SNPs do human parents typically share with one another? |

The main concept of this section is that purebred dogs are much more genetically related than humans are, and all of the students grasped this well.

*Student Question Preferences*

In general, the students preferred straightforward, definition-style questions over those that required analytical thinking and application of the concepts they were learning.

I considered the questions that the students liked and disliked, as well as the ones that needed clarifying, and used this feedback to edit and rework my study protocol.

*Edits to Health Questions*

My **updated worksheet** is shown in Appendix B. The questions relating to the Health tab were well-received by the students overall. The only clarifying question asked by a student pertained to Question 2 (g).

> Could there be anything advantageous about being a carrier (think about the dog population as a whole)?

The student asked if this was about the specific dog (Harper) that was the only carrier in the data set. Since this was not the intentional meaning of the question, I slightly reworded it to include the words "in general" at the end. Most of the questions in this section were fairly straightforward, clear and well ordered, and required no further editing.

*Edits to Breed Questions*

The questions about the Breed tab were reordered to better lead the students into the portions that require higher level thinking. Some questions (**2a** and **2b**) were added to aid in streamlining this section.

> 2. (a) List the breeds of Presley, Sascha, Harper, and Pumpkin.
>
> (b) Now, which dogs are purebreds and which are mixed breeds?

It originally began with questions about haplotypes, but I moved those later in order to

build to this important concept. A question about haplogroups and geographical origins of dog breeds was removed because it did not strongly pertain to the core concept of the importance of haplotype and health. The question that required the students to construct a family tree was reworded and divided into multiple questions for clarity (See **Appendix B**, **Questions 3c – 3f**). This question was one of the more significant analytical questions in the worksheet, so I wanted the students to answer it as fully as possible. The questions pertaining to Harper were reworded to include the idea of a designer breed and give the students more of a foundation to answer subsequent questions (See **Appendix B**, **Questions 4a – 4d**).

*Edits to Traits Questions*

In the editing the Traits section, I replaced the words "genetic diversity" with "inbreeding", since this is the term used by the Embark® website. This section underwent significant editing to improve the flow of the questions. Two questions were added at the beginning of this section to encourage the students to start thinking about genetic diversity and breeding.

| |
|---|
| 5. (a) Based on what you already know about the dogs' breeds, who would you expect to have the highest percentage of inbreeding?<br><br>(b) Who would you expect to have the lowest? |

Since so many of the students experienced challenges with the scatter plot question, I decided to provide a table for the data and axes for the graph (See **Appendix B, Question 5 (g)**). This is another analytical question that I considered vital to my worksheet.

Providing the students with more pieces of the puzzle is expected to facilitate a better response.

*Edits to Relatives Questions*

In the Relatives section, the main goal was to lead the students to closely analyze the chromosomes of the dogs and compare them with genetically related dogs (DNA relatives) in the database. One question required the students to use outside sources to answer it, and many of the groups marked it as a disliked question (See **Appendix A**, **Question 6 (**e)). To alleviate the frustration of not knowing which source to consult for the answer, an appropriate source was suggested in the revised version of this question shown below (**6e**). This question was also simplified so that students were only asked about the overall percentage of DNA that humans typically share with each other (99.9%) instead of also asking about the percentage of SNPs that non-related parents typically share.

| |
|---|
| 6. (e) What percentage of DNA do humans typically share with each other? You can find this information on the Genome News Network. |

The next question (**6 (f)**, shown below) originally referred to the percentage of SNPs that parents of a purebred dog would typically share as compared to non-related human parents.

| |
|---|
| 6. (f) How is this different from the parents of a purebred dog? |

A different question was substituted.

*Addition of Intake and Exit Surveys*

Once the pilot test was complete, I added two components of the protocol – the intake survey and exit survey – in order to have quantifiable data on the students' comprehension of core concepts. This will also allow them a chance to provide more focused feedback. The **intake survey** (see **Appendix C**) consists of multiple-choice comprehension questions about genetic diversity, inheritance patterns, and heterozygosity to gain a baseline of the students' prior knowledge of these topics. The remainder of the questions in this survey are opinion-based, serving to obtain an understanding of how the students feel about their biological laboratories and how much they believe the laboratories help them to comprehend the concepts they learn about in lecture. It also asks the students how they would feel about working with information related to dogs. The survey is designed to be anonymous, and results will be measured by the percentage correct for each of the comprehension questions from the class as a whole. Answers will not count toward the students' grades; they will serve as a reference for improving this teaching module.

The final component of the protocol, the **exit survey** (See **Appendix D**), contains the same multiple-choice comprehension questions that appeared on the intake survey to determine if there is any change in the students' understanding between the start and end of the protocol. This survey will be filled out anonymously and is not part of the students' grades. The results of this will be analyzed question by question, to measure the entire percentage correct for the class as a whole. This survey also contains subjective questions designed to allow for improvement of the worksheet aspect of the protocol. It asks the

students about their overall enjoyment of the protocol and gives them the opportunity to offer constructive criticism.

*Coordination of Expanded Experimental Study of Embark® Protocol*

I received permission from Dr. Linda Mota, who organizes the laboratory schedule for Bisc 336, and Dr. Joshua Bloomekatz, who is teaching the Bisc 336 Spring lectures, to test my revised study protocol in several Bisc 336 sections during the Spring 2020 semester. After consulting with them and further refinement of my protocol, we arranged for my research study to take place on April 6th, 2020. Of the seven laboratory sections for Bisc 336, I planned to administer the protocol to three of these sections, with a total of 64 students, all overseen by the same teaching assistant for consistency. Due to the outbreak of COVID-19, the genetics laboratories were converted to an online format, so my main focus for writing about this project became my pilot study.

# DISCUSSION

The main goal of the Embark® protocol is to challenge students to think about genetic diversity and its relationship to health in a new way. The worksheet encourages the students to investigate different topics related to genetics by using dogs as model organisms. By asking questions related to drawing family trees, constructing scatter plots, and putting together pieces of information to come to conclusions, the students are required to use analytical thinking. This fulfills the purpose of education, to have students think about and engage in understanding complex ideas. With a variety of dogs included in the project, students are able to see that certain breeds are at greater risk for inheriting or being a carrier for a subset of genetic diseases. By considering what genetic diversity looks like in dogs at a chromosomal level, they can apply this knowledge to thinking about precision medicine and human health.

Even though the students, when asked to mark their preferred questions from the worksheet, primarily selected straightforward definition or listing questions, the questions designed to provoke higher thinking were the main focus of my efforts. My assessment is that the strongest area of the worksheet is currently Question 4 (See **Appendix B**), pertaining to the parents of the Goldendoodle, Harper. It holds the distinction of being the only higher-level thinking question that every group answered correctly. The question successfully conveyed that important information can be obtained from knowing an

individual's haplotype. I believe that the lead-in questions were just the right caliber of difficulty and gave the students enough information to properly answer the question.

In other sections, the questions were reworked to reach my overall goal of expressing the importance of genetic diversity. The two areas that underwent the greatest editing in order to improve their accessibility were Question 3f (See **Appendix A**) pertaining to the construction of a family tree based on haplotypes, and Question 5d pertaining to the construction of a scatter plot of the dogs' inbreeding and genetic conditions. I decided that the first of these two questions would be more effective by breaking it into smaller, more manageable questions. The second question was confusing to the students because it utilized a small data set that did not fit their view of how the data should have appeared once graphed. The students expected to see a positive correlation between the dogs' inbreeding percentage and the number of genetic conditions each dog is at risk for or carries. I believe that a stronger relationship would emerge if more dogs are included in the group accessible to the students. This could more clearly demonstrate that inbreeding is associated with a decrease in overall health and fitness, and further emphasize the importance of genetic diversity (Hedrick and Garcia-Dorado, 2016).

I added the intake and exit surveys after the completion of the pilot study because I wanted to gather quantifiable data about students' comprehension of my chosen topics of genetic diversity, haplotypes, and the heterozygote advantage. The originally planned experiment as outlined below would have included data from the intake and exit surveys, as well as a larger sample number of 64 students collaborating in small groups on the worksheet.

My original intention for this thesis project was to administer the revised Embark® protocol to three laboratory sections of Bisc 336 Genetics on April 6, 2020. Dr. Liljegren and I had consulted with Dr. Linda Mota, the instructional professor in charge of coordinating the Bisc 336 laboratories, and Dr. Joshua Bloomekatz, the professor teaching the Bisc 336 lectures for the Spring 2020 semester to carefully coordinate this plan. When the outbreak of COVID-19 led to a transition to online learning and a suspension of all in-person laboratory work at the University of Mississippi after spring break, I decided to focus on writing about my assessment of the pilot study data and the critical revisions I made to my protocol as a result.

This project is meant to be used in the classroom. Dr. Liljegren is expecting to continue testing the Embark® protocol in the Fall 2020 semester of Bisc 336, when she is jointly teaching the lectures with Dr. Ryan Garrick. One exciting possibility is that it could ultimately evolve to allow a few students to volunteer their own pets, adding a personal investment on behalf of the students. Improvements can continue to be made to the protocol based on student feedback, as it comes with its own checks and balances system in the form of the surveys. I believe that there is a great deal of potential in this protocol, as it gives students the ability to visualize genetic diversity and actively investigate its impact on an organism's health.

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# APPENDIX A

Embark® Exploration
The Importance of Genetic Diversity

1. Log on to the Embark® website.

The results are in for four dogs: Presley, Harper, Smokey, and Sascha.

2. Familiarize yourself with the program. Click on Presley. Click on the Health tab.
    a. For what condition is Presley "at risk"? Briefly describe the condition.

    b. Consider the way that alleles are inherited. What does it mean to be "at risk' in the genetic sense? Does this automatically mean that the dog will contract the disease?

    c. Does Presley's condition for which he is at risk display complete or incomplete penetrance? What does this mean?

    d. Are the other three dogs at risk for any diseases?

    e. Are any of the dogs carriers of any diseases? Briefly describe the listed condition(s) and inheritance patterns.

f. If any of the dogs are carriers, does this indicate anything to you about a greater incidence of this condition in certain breeds of dog?

g. Could there be anything advantageous about being a carrier (think about the dog population as a whole)?

3. Now click on the Breed tab. Presley is a purebred Pug. There is a submenu with a tab labeled maternal haplotype.

a. Define the term “haplotype”.

b. Presley and Smokey have a paternal haplotype. Can you explain why they do and why Harper and Sascha do not? From what chromosome does the DNA included in the paternal haplotype get passed from parent to offspring?

c. What are the maternal haplotypes of the four dogs?

d. Do any of them share a maternal haplogroup?

e. What do the maternal haplogroups tell you about where these dogs originated geographically? Compare the four dogs. Do any of them come from the same place? You will need to consult sources outside of Embark® to determine their origins. (A graphic depicting a phylogenetic tree would be useful).

f. Construct a family tree for Presley beginning with the great-grandparent generation and using female and male symbols to indicate individuals. Then, trace a line from Presley to his great-grandparents indicating the path of inheritance for his maternal haplotype. How many great-grandparents connect to Presley this way? Repeat the process for his paternal haplotype and clearly label it separately from the first line.

g. Smokey has an additional tab under the Breed heading denoted “mix matches”. Explain the difference between a mix match and a DNA relative.

h. Can the mix matches be DNA relatives? Why or why not?

i. Do a visual comparison of Smokey’s mix matches and Harper’s mix matches. Which set of dogs share more phenotypic characteristics?

j. Why do you think the mix matches of one of the dogs are so varied in appearance?

4. Click on the tab that says Family Tree under Harper.

a. Can you think of a reason why the genders of Harper’s ancestors are not indicated?

b. Discuss the relationship between dog breed and haplotype. Use Harper’s haplotype as an example. Where did Harper’s ancestors originate?

c. Can you use this correlation to determine which of Harper's parents is the mother and which is the father?

5. Click on the Traits tab. Scroll down to view the Genetic Diversity.

a. Compare all of the dogs' percentages of genetic diversity here.

b. What does it mean to be inbred? What is occurring on some of the dogs' chromosomes that is associated with inbreeding?

c. Compare the chromosomes of the dogs with the highest genetic diversity and the lowest diversity. What differences do you notice?

d. For Sascha, Harper, Smokey, and Presley, do you see a relationship between inbreeding and overall health (number of diseases ‘at risk’ and carrier)? To answer this question, you can draw a scatter plot with genetic diversity on the y-axis and number of conditions at risk for or carriers on the x-axis for the four dogs.

e. Consider the inbreeding graphs for Sascha, Presley, Smokey, and Harper. How do their percentages of inbreeding compare to their breeds as a whole?

f. Does it surprise you that Smokey (a mutt) has a slightly higher inbreeding percentage than Harper (a designer breed)? Can you give an explanation for why this would be the case?

6. Click on the Relatives tab under each dog's profile.

a) For each of the dogs, list their closest relative and the amount of DNA that they share with that relative.

b) How is the shared genetic material represented on the chromosomes?

c) For each of the four dogs, which of their chromosomes contain the longest shared segment of both copies of the chromosome? You can zoom in on the chromosomes to see more detail.

d)Why do you think some of the dogs have closer relatives than others?

e) What percentage of DNA do humans typically share with each other? Genetic testing companies focus on SNPs that reveal genetic diversity. What percentage of these SNPs do human parents typically share with one another?

f) How is this different from the parents of a purebred dog?

g) Does a large amount of shared DNA always mean that dogs are blood relatives?

APPENDIX B

Embark® Exploration

1. Log on to the Embark® website.

The results are in for four dogs: Presley, Harper, Smokey, and Sascha.

2. Familiarize yourself with the program. Click on Presley. Click on the Health tab.
    a) For what condition is Presley "at risk"? Briefly describe the condition.

    b) Consider the way that alleles are inherited. What does it mean to be "at risk' in the genetic sense? Does this automatically mean that the dog will contract the disease?

    c) Does Presley's condition for which he is at risk display complete or incomplete penetrance? What does this mean?

    d) Are the other three dogs at risk for any diseases?

    e) Are any of the dogs carriers of any diseases? Briefly describe the listed condition(s) and inheritance patterns.

f) If any of the dogs are carriers, does this indicate anything to you about a greater incidence of this condition in certain breeds of dog?

g) Could there be anything advantageous about being a carrier in general (think about the dog population as a whole)?

3. Now click on the Breed tab.

a) List the breeds of Presley, Sascha, Harper, and Pumpkin.

b) Now, which dogs are purebreds, and which are mixed breeds?

c) Construct a family tree for Presley beginning with his parents' generation and using female and male symbols to indicate individuals. Work backward until you reach his great-grandparents. Recall that mitochondrial DNA is inherited from an individual's mother, and that mother inherits it from her mother, and so on from there. Using this information, trace a line of inheritance of mitochondrial DNA from Presley to his great-grandparents' generation. This is his maternal haplogroup.

d) How many of Presley's great-grandparents genetically connect to him in this way?

e) Presley is a male dog. Think about from whom Presley inherits his Y chromosome. This would be his paternal haplogroup. Repeat the same process as above, but for paternal haplogroup instead.

f) How many of Presley's great grandparents genetically connect to him in this way?

g) Define the term "haplotype".

h) Presley and Smokey have a paternal haplotype. Can you explain why they do and why Harper and Sascha do not? From what chromosome does the DNA included in the paternal haplotype get passed from parent to offspring?

i) What are the maternal haplotypes of the four dogs?

j) Do any of them share a maternal haplogroup?

k) Smokey has an additional tab under the Breed heading denoted “mix matches”. Explain the difference between a mix match and a DNA relative.

l) Can the mix matches be DNA relatives? Why or why not?

m) Do a visual comparison of Smokey’s mix matches and Harper’s mix matches. Which set of dogs share more phenotypic characteristics?

n) Why do you think the mix matches of one of the dogs are so varied in appearance?

4. Under the Breed section for Harper, click on the tab that says Family Tree.
    a) Harper is a designer breed. This means that she is a breed designed to be an exact 50/50 mix of two dogs. What breeds are her parents expected to be?

    b) Why is this particular mix of dog so desirable? You will have to consult sources outside of Embark® to answer this question.

    c) Discuss the relationship between dog breed and haplotype. Use Harper's haplotype as an example. Where did Harper's ancestors originate?

    d) Can you use this correlation to determine which of Harper's parents is the mother and which is the father?

5. Click on the Traits tab. Scroll down to view the Genetic Diversity.
    a) Based on what you already know about the dogs' breeds, who would you expect to have the highest percentage of inbreeding?

b) Who would you expect to have the lowest?

c) Compare all of the dogs' percentages of inbreeding here.

d) Does it surprise you that Smokey (a mutt) has a slightly higher inbreeding percentage than Harper (a designer breed)? Can you give an explanation for why this would be the case?

e) What is occurring on some of the dogs' chromosomes that is associated with inbreeding?

f) Compare the chromosomes of the dogs with the highest inbreeding and the lowest inbreeding. What differences do you notice?

g) For Sascha, Harper, Smokey, and Presley, do you see a relationship between inbreeding and overall health (number of diseases 'at risk' and carrier)? To answer this question, you can draw a scatter plot with inbreeding percentage on the y-axis and number of conditions at risk for or carriers on the x-axis for the four dogs. Fill in the table to help you.

| Name of Dog | X-Axis<br># of Conditions | Y-Axis<br>Inbreeding Percentage |
|---|---|---|
| | | |
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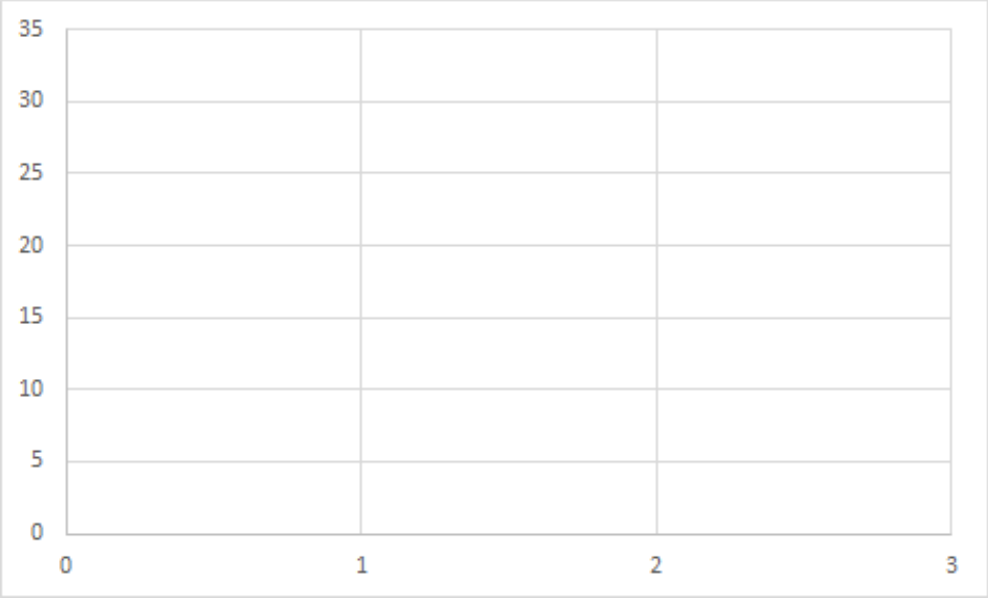


h) Consider the inbreeding graphs for Sascha, Presley, Smokey, and Harper. How do their percentages of inbreeding compare to their breeds as a whole?

6. Click on the Relatives tab under each dog's profile.

a) For each of the dogs, list their closest relative and the amount of DNA that they share with that relative.

b) How is the shared genetic material represented on the chromosomes?

c) For each of the four dogs, which of their chromosomes contain the longest shared segment of both copies of the chromosome? You can zoom in on the chromosomes to see more detail.

d)Why do you think some of the dogs have closer relatives than others?

e) What percentage of DNA do humans typically share with each other? You can find this information on the Genome News Network.

f) How genetically related are different dog breeds to one another?

g) Does a large amount of shared DNA always mean that dogs are blood relatives?

## APPENDIX C

Intake Survey
Please do not write your name so your answers will remain anonymous.
None of the answers on this survey will affect your Genetics grade.
Circle your answers unless otherwise indicated.

Personal Response

1. Are you an adult over the age of 18? Circle your response.

Yes No

2. How many biology-related courses with laboratories have you completed thus far in your academic career?

3. The concepts from the lectures in Bisc 160/162 (Introductory Biology) were clearer to me after completing the corresponding labs.

Strongly Disagree Disagree Neutral Agree Strongly Agree

4. So far this semester in Genetics, I have found that the concepts are clearer to me after completing the corresponding labs.

Strongly Disagree Disagree Neutral Agree Strongly Agree

5. The lab protocol that you are about to complete will include information about dogs. Does the idea of learning about a pet's health and breed appeal to you?

Yes, No Neutral I don't have a pet

Concept Questions
Circle the letter of your answer. This will NOT affect your grade.

1. What is the difference between being a genetic carrier of a disease and being genetically at risk for the disease?

a. A carrier will automatically develop a disorder because they have two defective alleles, while an “at risk” individual will not because they are heterozygous.
b. A carrier will not develop a recessive disorder because they are heterozygous, but an “at risk” individual will because they have two defective alleles.
c. A carrier will not develop a recessive disorder because they are heterozygous, while an “at risk” individual will be more likely to develop the disease.
d. A carrier will automatically develop a disorder because they have two defective alleles, and an “at risk” individual will develop the disorder also.

2. What is incomplete penetrance?

a. Incomplete penetrance is an inheritance pattern in which one allele does not completely mask another (i.e. white and red flowers make pink).
b. Incomplete penetrance is a state in which some individuals with an affected gene exhibit symptoms of a condition while others do not.
c. Incomplete penetrance is a function of how genes interact, in which one gene attempts to displace another gene, but instead fuses with its target.
d. Incomplete penetrance describes the phenomenon that occurs when a virus’s genetic material only partially infects a target’s cells.

3. From which relative do animals inherit their mitochondrial DNA?

a. Paternal grandmother
b. Paternal grandfather
c. Maternal grandfather
d. Maternal grandmother

4. What does it mean to be genetically diverse?

a. Genetic diversity results from sharing large portions of one’s chromosomes with one’s mate.
b. Genetic diversity results in individuals who have lower fitness than the general population.
c. Genetic diversity is the state of having two parents who do not share much genetic similarity, leading to heterozygosity.
d. Genetic diversity happens when two separate species come together to create a hybrid offspring.

APPENDIX D

Exit Survey
Please do not write your name so your answers will remain anonymous.
None of the answers on this survey will affect your Genetics grade.
Circle your answers unless otherwise indicated.

Personal Response

1. Describe one concept that you feel you understand better as a result of this lab.

2. I found this lab protocol to be engaging and helpful.

Strongly Disagree Disagree Neutral Agree Strongly Agree

3. I found the questions in this protocol to be

a. Extremely Difficult b) Difficult c) Neutral d) Easy e) Extremely Easy

4. One thing that I really liked about this laboratory protocol was….

5. One thing that I would change about this protocol is….

Concept Questions
Circle the letter of your answer. This will NOT affect your grade.

1. What is the difference between being a genetic carrier of a disease and being genetically at risk for the disease?
    a. A carrier will automatically develop a disorder because they have two defective alleles, while an "at risk" individual will not because they are heterozygous.
    b. A carrier will not develop a recessive disorder because they are heterozygous, but an "at risk" individual will because they have two defective alleles.
    c. A carrier will not develop a recessive disorder because they are heterozygous, while an "at risk" individual will be more likely to develop the disease.
    d. A carrier will automatically develop a disorder because they have two defective alleles, and an "at risk" individual will develop the disorder also.

2. What is incomplete penetrance?
a. Incomplete penetrance is an inheritance pattern in which one allele does not completely mask another (i.e. white and red flowers make pink).
b. Incomplete penetrance is a state in which some individuals with an affected gene exhibit symptoms of a condition while others do not.
c. Incomplete penetrance is a function of how genes interact, in which one gene attempts to displace another gene, but instead fuses with its target.
d. Incomplete penetrance describes the phenomenon that occurs when a virus's genetic material only partially infects a target's cells.

3. From which relative do animals inherit their mitochondrial DNA?
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4. What does it mean to be genetically diverse?
    a. Genetic diversity results from sharing large portions of one's chromosomes with one's mate.
    b. Genetic diversity results in individuals who have lower fitness than the general population.
    c. Genetic diversity is the state of having two parents who do not share much genetic similarity, leading to heterozygosity.
    d. Genetic diversity happens when two separate species come together to create a hybrid offspring.