Inquiry & Investigation

Epistasis Storyboarded

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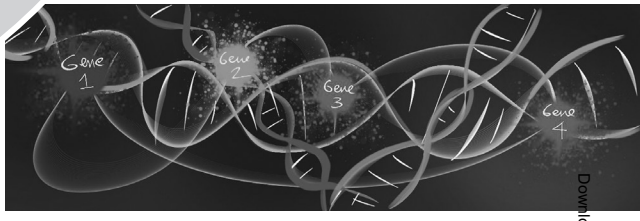

Abstract

Through the artistic planning tool known to comic book artists and animators as storyboarding, students will embark on comic book–style adventures to plan, describe, and visualize the complex life of genes through the non-Mendelian concept of epistasis. Using storyboard templates, conceptual layouts, sketch booking, and cut-out genetic elements, students will construct their interpretation of the gene-gene interactions of epistasis. The incomplete story of the epistasis of human eye color will serve as the theme for this storyboard, which will also become its own assessment tool, inviting educators into a realm of a true STEAM experience.

Key Words *eye color; evolution; storyboard; epistasis; gene interaction; phenotype.*

○ Introduction

It is difficult to find two people with the exact same eye color and pattern since nutrition, environment, age, and expression of genes are variable. This suggests an "eco-evo-devo" element at work for generating novel phenotypes and diversity through the interaction of genes at the developmental level and through environmental cues in a lifespan (Gilbert, 2015). Human interest in eye color is universal, with the eyes being described as the "windows of the soul." A simple inquiry such as "why are there so many different variations in the human iris" is a likely question proffered by students. It is also a question that is not easily answered.

To keep an introduction to genetics simple, for years biology teachers and textbooks have described traits like eye color as brown, blue, dominant, and recessive. However, like most traits, variation is the key and complexity is a given in the progression of genotypes into phenotypes. Mastering the idea of dominant and recessive is challenging enough for students though. Connecting concepts of DNA to genes is abstract, and even the designation of a location on a chromosome of a gene can present a conceptual problem for students. At times, important structural elements like the chromosome are not in the shape of a chromosome, such as in interphase, begging the question, "where is the gene now?" The dominant-recessive Mendelian paradigm implies that a dosage of a protein product is produced: one dose comes from the mother, the other from the father, and the greater dosage is dominant to the lesser dosage, affecting the outcome of the protein, which is connected to the phenotype.

In genetics, eye color is categorized as a non-Mendelian trait because of the presence of Epistasis. Around 1905, William Batson embarked on a variation of the Mendelian dominant-recessive paradigm. He performed a Punnett square experiment that revealed genetic interactions by looking at the trait of chicken combs. He crossed a rose chicken comb with a pea chicken comb, and instead of obtaining the expected ratio of dominant-recessive traits, a new variation of the comb emerged in the progeny: the walnut comb. From this he established the concept that genes in a cell or individuals do not operate in isolation but rather interact with each other, functioning as a complex system within the cell. Epistasis came to be known as any relationship of nonadditive interactions between two or more genes in their combined effects on a phenotype (Phillips, 2008). The term ***epistasis*** takes on different meanings depending upon the context of its use and is often associated with variance.

The complex topic of epistasis is always conveyed through the traditional Punnett square, and some textbooks rely on dog coat color and occasionally eye color to teach this concept. While these teaching models are very helpful in observing inheritance patterns in phenotypes, they also imply a certain neatness and simplicity to a complex, dynamic network of genes and their products. Punnett squares give a one-dimensional feeling to genetics. How could biology teachers broach genetically complex traits with a complementary lesson plan? How can we apply a more three-dimensional, interactive framework to the genotype-phenotype question?

The human palette of eye color is as varied as skin tone and hair color. It utilizes the same protein, melanin, and produces variations of that protein. The dynamics of how this happens, the actual gene interactions, are often missing from textbooks and curriculum because these dynamics are difficult to visualize. This challenge, however, can be facilitated through the arts and with a relatively simple tool: the storyboard. Mendelian inheritance is often presented with its three laws: alleles are dominant and recessive (law of dominance); alleles for one gene act independently of another gene (law of independent assortment); and when gametes form, alleles

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are separated so that each gamete will carry one allele from one gene (law of segregation). Variations of Mendel's themes when reinterpreted through a visualized storyboard can serve as a comparative scaffold to build into complex concepts of epistasis.

In this paper we would like students to recognize that genetic traits are variable, evolving, and interactive. Variation is the key in inheritance and in evolution, and the range in variation of any trait produces an evolutionary pattern. For this lesson plan, the technique of storyboarding may assist in crystallizing genetic complexity into a pattern that makes sense to students and connects to the larger evolutionary perspective. Importantly, epistasis is a source of phenotypic variation, so we may want a student to think in two ways. One is systematic and methodical (to establish the characters) for planning the storyboard. The other is a divergent way (to appreciate the complexity) and express their own ideas. We start with students observing the wide diversity of eye color in humans and pondering that variation. From these observations we aim to show the standard Punnett square of brown and blue eyes, and then we ask students what might be missing. We also incorporate a third perspective of epistasis as a source of variation in a larger evolutionary stage bridging genetics and evolution together. We can ask: Why is nature so diverse, and why is variation important? Is variation an adaptive strategy? Is it related to evolutionary fitness? Evolution relies on Mendel's work and variations (themes) of it to complete the story of natural selection.

○ Transforming Textbook Epistasis

Textbooks describe epistasis as one of the classic variations on Mendel's theme presenting genetic complexity beyond dominant and recessive. Epistasis causes a departure from Mendel's standard segregation ratios (Cordell, 2002). Epistasis is often defined as a gene-gene interaction where one gene masks or modifies the effect of another gene. Epistasis can also be considered from a broader view of expected probabilities of survival for particular traits. That is, epistasis is connected to individual fitness with evolution working at the cellular and molecular level (Wolf, 2000). In this way the storyboard will help students appreciate the context of gene expression and activity. Storyboard backgrounds, which are physical backgrounds on paper, assist in creating mental contexts and help frame dynamics. The problem of dynamics can be worked out on paper through sketching. Students can conceptualize epistatic interactions as a type of cooperative effort within the genome. For example, a gene can mask a phenotypic effect of another gene; it may enhance, inhibit, or override the expression of another gene on another chromosome. In this case, the first gene is "epistatic" to the second gene (Templeton, 2000). Within Mendel's variations, our own definitions of ***epistasis*** vary because epistasis can take a variety of forms and be viewed from multiple perspectives. To complicate this further, the eye colors we observe have an evolutionary history, which means their present phenotype has been shaped by natural selection and the unpredictability of mutational events in time.

○ Visualizing the Manifold Fuzziness of Epistasis

Students often struggle with the large amount of genetics terms and molecular biology that has ushered in an era of abstract and conceptual visualizing that students may not be fully equipped for. This has resulted in greater difficulty with biological information and perhaps a greater indifference to the subject in general. "These different problems are not isolated and may exacerbate each other: students face problems in representing genetics texts into schemes and symbols, and vice versa in reading schemes and symbols" (Kippels, 2005). Given the nonlinear conduit by which phenotypes emerge, a theoretical and intangible biology arises where students and even teachers have great difficulty envisioning the process presented. Teachers may define epistasis, but translating the flattened Punnett square into a human-scale phenotype is an entirely different story. Eye color contains ideas about variation in melanin and variation in genes beyond dominant and recessive traits, with lots of "fuzziness" in between. Untangling some of the fuzziness and visualizing the manifestation of a phenotype in a storyboard can help generate an appreciation of, and a new way of thinking about, the malleability of the genome and its genes.

A storyboard has three important phases: we define our characters and location as individuals, making them more personal and accessible; we sketch out forms and imagine interactions (dynamics) based on the data or observations; and we look for connections that draw entities and concepts together in a temporary big picture. The storyboard remains impermanent like the complex model system it is visualizing. Students during the phases of this process instill into their storyboard their perspective and personal touches. In a critique of the storyboard, we see variations of our own thought processes and interpretations of the same biological concept. For this reason, we present the artistic concept of the storyboard to devise a "network" of genetic and evolutionary outcomes giving students an opportunity to work through the layers of complexity in a creative, fun, and personal way.

For the epistasis storyboard experience, we can simply view epistasis as a communication of genetic elements that produce a final trait that has been selected for over time. In this lab activity we want to enhance the concept of gene-gene interactions and accentuate observational and noticing skills, as well as getting students accustomed to reasoning and visualizing biological dynamics. In the storyboard, students will dissect the current background of the epistasis of human eye color using a storyboard template provided or that they create on their own guiding visual framework.

○ Background on Eye Color Epistasis

To observe the gradated patterns and colors of the human eye, teachers may want to discuss the general structure of the eye and the anatomical location of eye color pigment, the iris. Students may want to explore the range of eye colors right in the classroom with their peers. The iris consists of connective tissue, smooth muscle, and the stroma where melanin pigments are deposited (Sturm & Larsson, 2009). The amount of melanin pigment is genetically determined, providing raw materials that are present in the cell. There are also two types of melanin: pheomelanin and eumelanin. The type and amount deposited partially determines the eye color; also, very light blue eyes have little melanin, and dark brown eyes have much more.

Epistasis is the prelude to melanin synthesis, as genes provide the recipe for the proteins involved in the biochemistry and the cellular physiology. This is a good opportunity for teachers to revisit protein synthesis or to initiate the discussion of protein synthesis through epistatic storyboarding. Gene interactions are dynamic events and are influenced by the environment and

the conditions regardless of their genetic instructions, which will allow teachers to also weave evolution into the storyboard narrative by talking about variation in eye color and what, if any, selective advantage eye colors might have. There are many points in storyboarding where evolution and selection can be introduced. It's also a good time to discuss how new eye colors might arise and if they might continue in certain populations over time. Teachers can also segue into a discussion of chromosomes or genes by describing genes being regulated by the cell in varying amounts or nuances of "on" and "off," similar to that of a light dimmer. The proteins made by the genes in the cell can then also determine the activity of the gene through negative feedback (Carthew, 2006). If teachers extend the eye color storyboard from their genetics unit to the evolution unit, they can do so by talking about primate relatives. This is another good place to ask general questions like, "Do chimps have different colored eyes?" "Do all monkeys have variation in eye color?" Students can research these questions and bring the evolutionary aspect into a continued storyboard. You may also want to show a primate phylogenetic tree with humans on it. "Only two other primate species demonstrate variation in iris color, the Macaques expressing a range from brown to blue" (Zhang & Watanabe, 2007). Lemurs also have either blue or brown eyes (Bradley et al., 2009), and this information casts another perspective on human eye color. We can ask what changes occurred in time and in what structure(s) produced variations. This helps students think about the complexity of a trait through time. This discussion can loop back to a lesson plan on DNA, unifying three topics through the storyboard: genetics, evolution, and DNA.

Human eye color is currently considered an epistatic trait. It is also a polygenic trait (Sturm & Larsson, 2009). In the broadest sense, however, it is also a dominant and recessive trait, where pigmentation is dominant to no pigmentation, and this overarching theme dictates the hierarchy in human eye color: brown is dominant to green, which is dominant to blue. The current story of the epistasis of eye color relates to three eye colors—brown, blue, and green—but we all know that tremendous variation exists beyond these three.

○ Three Eye Colors, Three Genes & Two Chromosomes

For this exercise we will limit ourselves to three genes and two chromosomes. We want students to visualize and internalize the idea of variation through communication between chromosomes. That is, genes and chromosomes are complex interactive genomic systems, and eye color models are theoretical, not absolute. Gene associations have myriad subtle and nuanced activities, similar to lights flickering like constellations inside a cell, within tissues, and within organs, producing variable physiologies and unique phenotypes.

Epistasis is about the performance of genes at multiple locations (loci) and is in a sense a measure of genomic behavior. Alleles, mutations, variants, and single-nucleotide polymorphisms all contribute to the strength of those interactions and confer degrees of variation and novelty. Two variants might have negative effects on their own but have beneficial effects when working together. To introduce our story, students should understand that chromosomes, which contain genes, are part of an entire cellular system. The so-called control center, or nucleus, operates as a component of an entire

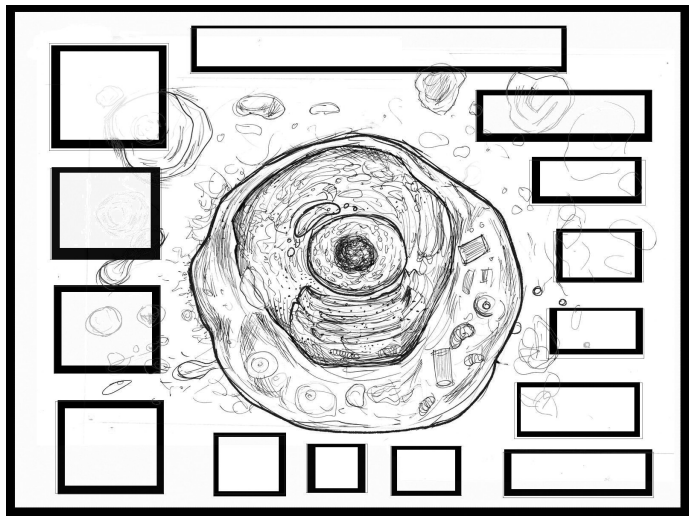

Figure 1. A storyboard background to help students try their hand at the idea of storyboarding before they draw their own. The cell provides the backdrop for the eye color gene interaction. The boxes suggest where images might be placed.

cell, which is influenced by its local environment. Cells live in communities and have ecologies. They communicate with each other, and populations of cells can evolve and adapt. While DNA may hold the code, that code only functions within a contextual cellular environment. So, the cell influences the behavior of a chromosome and of a gene. This cellular regime orchestrates with the genetic code and enacts it (Vermunt et al., 2019). The broader perspective of the cell and its environment is sometimes neglected in classroom discussions because it is just assumed that students carry over the idea of the cell from previous lessons, though they may carry over the rigidity of thinking that the cell is a bunch of "parts" that do certain things. We want to migrate away from this kind of thinking to a more interactive and coherent view of the cell. For students to gain a wider lens of the story, the genetic elements should be framed within the cellular landscape (see Figure 1). In this way, the cell is the vehicle through which the change and events occur over cellular and evolutionary times. Chromosomes are not seen as abstract figures but as actors on the cellular stage; they are both fixed and flexible in those time frames. Their activities are performed within the confines of the cellular entity and yet are broadly impacted over longer time spans.

For our storyboard, we will consider chromosomes as lead actor, and genes a cast of characters with variable potential abilities that make the metabolic theater of eye color happen. The model of eye color is far from resolved but there are two major genes that appear to play the lead roles in the eye color story: HERC2 and OCA2. Both genes are located on chromosome 15, and OCA2 codes for a major transmembrane protein in the melanosome maturation process: P protein (White et al., 2011). "The promoter region for OCA2 is located within the HERC2 gene. The OCA2 gene might be a master gene for eye color, as it is estimated that one genomic region of OCA2 on chromosome 15 could account for 74% of human eye color" (Sturm et al., 2008). Many genes and chromosomes play both pivotal and minor roles in the story, and that list of genes and chromosomes may continue to grow and change.

There are seven types of OCA (ocular associated albinism) (OCA1–7), which is a group of inherited disorders of vision. OCA can describe a condition (ocular albinism) and a gene (OCA2), and it is easy to confuse them. Several genetic variants in the OCA2 gene decrease P protein release, which also may result in lighter eyes (Grønskov, 2007). At least one polymorphism in HERC2 inhibits OCA2 expression and function, lowering P protein production and creating a variation (Eiberg et al., 2008). This mutation in intron 86 occurred most likely from the founder effect, which arose some 6000–10,000 years ago around the Black Sea, and there is a relatively high frequency of this mutation in Europeans (Eiberg et al., 2008).

It is also good to include a brief melanin discussion as this is the protein of interest in eye color. There are two known forms of melanin, pheomelanin (yellow-red) and eumelanin (brown-black). The concentration and amount of these melanin forms may account for the variations of color and the depositions of them. Many factors including diet, environment, and age can alter eye color. This further enhances the understanding of epistatic gene networks for students. In the eye color story, OCA produces the P protein, a melanin sequestering protein, which concentrates melanin in the stroma of the iris as a general function. The HERC protein binds to the promotor region of the OCA gene and activates this process and therefore can affect the output of the OCA gene (Duffy et al., 2017). The GEY gene (chromosome 19) is involved in the green-related pigment of green eyes and, if present, can override the blue condition, therefore establishing a hierarchy of brown over green over blue (Duffy et al., 2017). In one model, if the GEY gene is absent or inactive, then blue eyes result.

○ Predicting Eye Colors & Patterns

Epistasis is important to evolution because epistasis can be measured in terms of the fitness it confers. Does a variant or mutation increase fitness? What is the selection pressure for eye color? Co-expression of genes may yield different results in different tissues, and so context changes everything, which is something worth articulating to students as they work on their storyboard backgrounds. The network of gene elements can be a benefit in one place and a detriment in another. The evolutionary question is how do these epistatic relationships affect the total fitness landscape? Does this combination of genes enhance overall fitness? We can certainly speculate about this with students regarding human eye color. The evolution of eye color genes reveals an interesting history and also offers an opportunity to show the possible relationships and variations of traits over time in populations. Eye color, skin color, and hair color are linked by the melanin synthesis pathways through evolutionary time.

Most people of the world have brown eyes, but Europeans, particularly Northern Europeans, show a greater percentage of blue eyes. This is due to a common polymorphism in the HERC2 gene. With two copies of the allele with this SNP, a person will most likely end up with blue eyes (Sulem et al., 2007). Another expansion of the idea of genes interacting that might interest students is that genes expressed in the iris are also linked to brain development and potentially contribute to brain development networks (Sturm & Larsson, 2009). What evolutionary story is hidden here? Can teachers broaden the lesson plan to physiology, geography, and human migrations? Can the storyboard of eye color be the beginning of a biology unit that binds the cell, genetics, and evolution together? Students references to ecology, niche, and environment can segue into an evolutionary discussion through their storyboard.

○ Preparing Your Script or Storyboard

Once teachers and students feel confident with the current process, terminology, and elements of epistasis in human eye color genes, they can begin considering how they will convey these concepts through the storyboard. Three activities can enhance this experience: designing a variety of storyboard templates; sketching chromosomes and cells; and, in connection with previous two, writing fictional short stories. To make things more fun and interesting, ask students to develop a short story concept that precedes the epistasis story. The fictional or real introduction to the storyboard provides a point of entry for the scene or the launching of our main story on epistasis.

A simple paragraph might be like this: "In the dark of the night, the masked avenger caught the reflection of his arch villain, the sorcerer, in a mirror. All he could remember now were those piercing light blue eyes and he wondered, how did this villain get such pale blue eye color? They were hypnotic and controlling. Where did the color come from?" Then there might be another burst or balloon of information: "During the night, an Avenger, during the day, a mild-mannered librarian, who would now investigate the Epistasis of Human Eye Color to uncover the power behind the sorcerer." This simple two-balloon lead-in allows students to craft an original idea and to inaugurate epistasis with a literary scaffold of their own making.

Once teachers have read and evaluated the background on epistasis of eye color, they can provide students with a "script" similar to the script afforded to actors or written for dialogues in graphic novels and comics. The script is a basic, bulleted outline of the story. Once students have become familiar with the human eye color story, they should try sketching the characters. The characters in this case would be the cell, human eyes, eye color structures, chromosomes, genes, and proteins. We strongly suggest teachers model this activity and demonstrate the sketching process.

○ Storyboarding Procedure

The general idea behind a storyboard is structure and planning with a large degree of freedom. A storyboard can be many things and is often not a final product but rather open to revision, inviting inventiveness and different perspectives, allowing flexibility and idea development. Students should be encouraged to take the data (or current theory) and develop it into a narrative of their own, without scripted directions. Sketching, making several storyboards, revising storyboards, and rethinking the action, characters, and scenes can happen according to the student's time frame. Allowing students to pursue this at their own pace over two weeks would encourage innovation and incubation of ideas. Just like making a movie, plans, action, and sequences can change, the dynamics and how they are portrayed can vary. Figure 2 is a simple example of a quick visual storyboard of epistasis with dialogue balloons. See Figure 3 for a sample "spec sheet" (specifications sketch) of visualized components of the epistasis story. If students want to try to draw

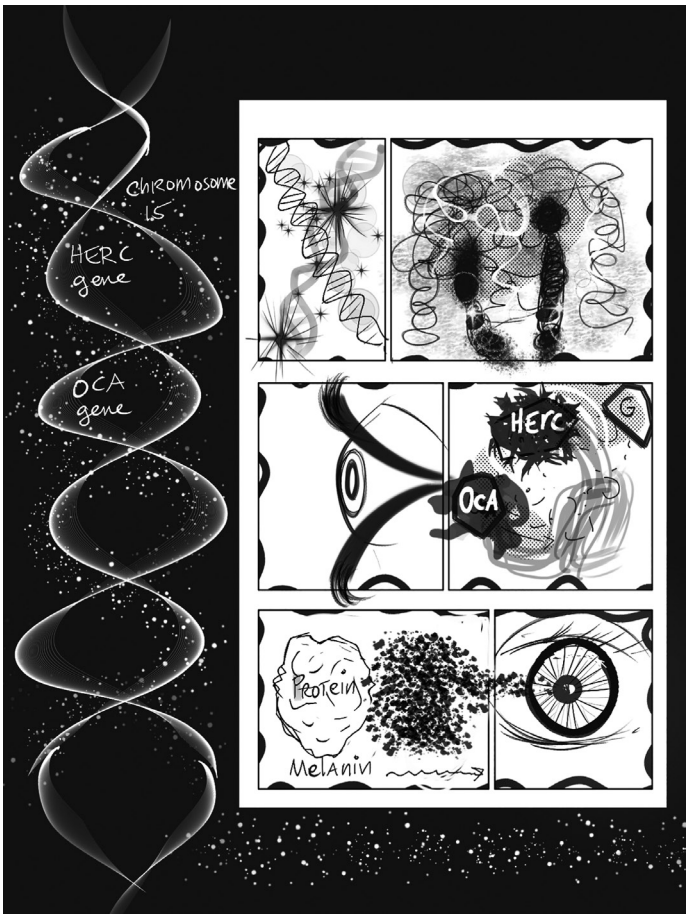

Figure 2. An example of a simple storyboard of epistasis. This style is purely visual, with little text. Text can be added, providing an opportunity for students to work in pairs where one student can illustrate the story and the other can write it.

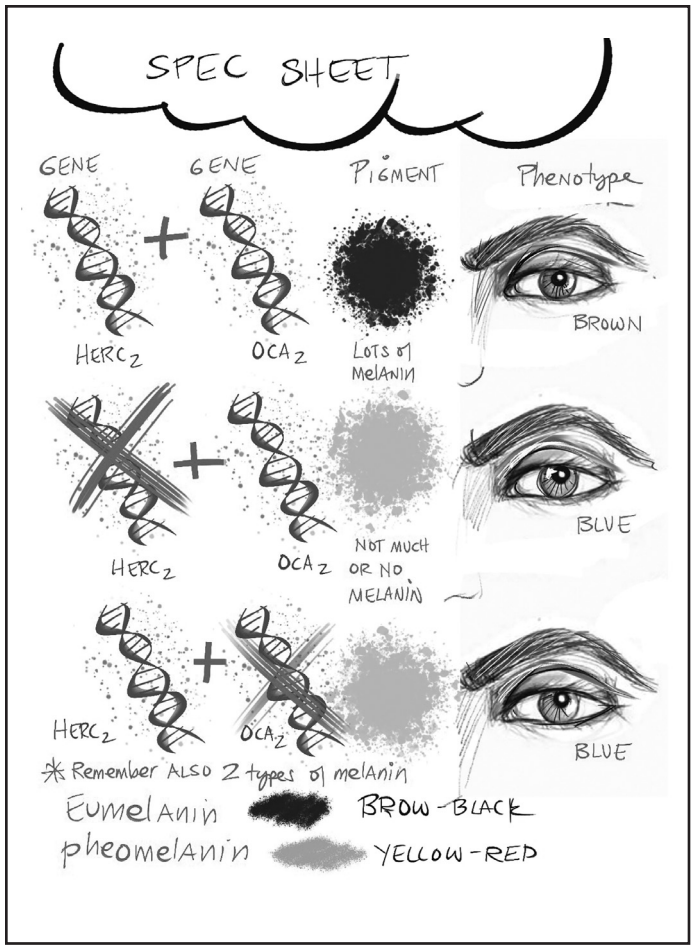

Figure 3. A simple spec sheet, which students or teachers can copy to show how the OCA2 gene and the HERC2 gene work or don't work to create the basic brown-eye and blue-eye phenotype. This simplifies epistasis before starting a storyboard. A spec sheet is used in animations to lay out and define characters and their traits, positioning, and action. Teachers can explore research papers and develop their own spec sheet before they proceed.

their own versions of the genetic/cellular characters, they can get a general idea from these images. The storyboard characters provided can be cut out and pasted into place (chromosomes, genes, proteins), and students can fill in details around them. In animation, spec sheets capture the specific characters or traits of an animated character and help the illustrator define those features. This helps create a consistent character with coherent movements. We have also provided a more biologically related template storyboard of a cell where students can paste the genetic elements or sketch their own in the boxes (see Figure 1) and a very simple storyboard template (figure 4) for multiple tries. If teachers decide to embark on completely original storyboards, we suggest using construction paper or card stock paper for the basic shapes of the storyboard. We strongly suggest students practice sketching, revise sketches, and challenge themselves to come up with at least two variations of their story. This helps students revisit and familiarize themselves with the terminology, the form, and visualization of biological entities such as chromosomes and genes. Once students have chosen a storyboard template, have them check over the list of genetic/cellular elements or characters that are needed (genes, chromosomes, proteins); if they have all the elements let students play with various arrangements and representations of what epistasis might look like in a cell.

○ What to Sketch

What does a gene look like? What does genes interacting with each other look like? Ask students to find images of genes, their products, and their interactions and to find as many illustrated variations as possible. See if students can locate actual images of chromosomes as well and compare the illustrations to the image. This helps students differentiate between what is visible and what is imagined. Ask students if they think there are actually real images of gene interactions or if most of what they are finding is an artist's interpretation.

○ Critiques & Informal Assessments

When art students finish a project, their artwork is typically displayed in a room for everyone to explore. A bowl of fruit interpreted and rendered by twenty students reveals the great diversity of human visualization and perceptual differences. The critique gives students a chance to explain their efforts and for other students to glean

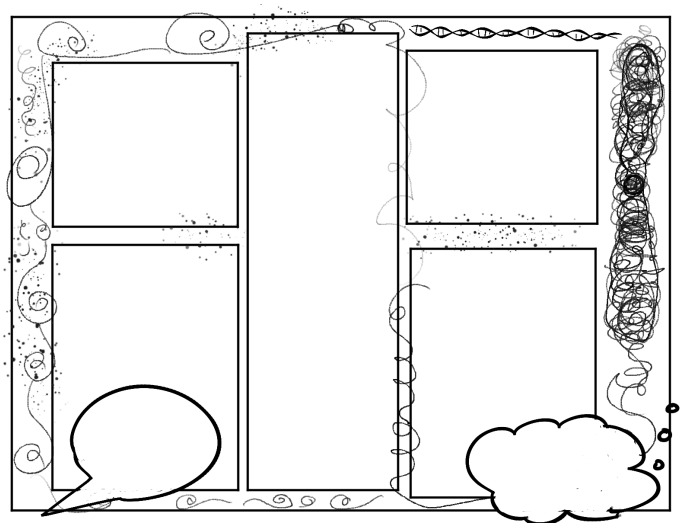

Figure 4. Use this simple storyboard template for multiple versions or to sketch out ideas. The little chromosome on the right side is just a small reminder to integrate visual metaphors into the design. Enlarge and print or make your own.

something from other points of view. This kind of informal assessment can be applied to the storyboarded biology and epistasis story. Have students explain why they made the choices they did for their composition. If all students have participated in the project, they will all have a similar familiarity with the topic and can gain knowledge by observing how the same genetic terms were interpreted differently. Teachers can also consider the critique as an informal assessment. Teachers may ask themselves: Did students really grasp what a gene is? Did they raise valid questions about what we *don't know* about genes? Can they recognize the variable effects of genes? Were they able to convey gene-gene interactions, and were they satisfied with their results? Teachers can also ask students to sum up the difference between Mendelian genetics and non-Mendelian genetics. They can then broaden the critique to include questions about adaption, how blue eyes arose in time, the biogeographical location of certain genes, and much more.

○ Outline for Epistasis of Eye Color (theoretical model)

- The cell and nucleus
- A model of the cell and a video of cells and chromosomes
- Chromosome 15 and 19 cut-outs (Figure 5)
- Chromosome 15 genes: OCA2, HERC2 (cut-outs) (Figure 5)
- OCA2 effects on melanosome maturation and pigment concentration
- Expression increases or decreased (incomplete dominance)
- Melanogenesis involvement of two types of melanin: pheomelanin (yellow) or eumelanin (black), dependent on environment, raw materials, and nutrition
- OCA2 gene mutation not working and resulting in blue eye color
- HERC gene binding to promotor region of OCA gene and regulating OCA gene expression

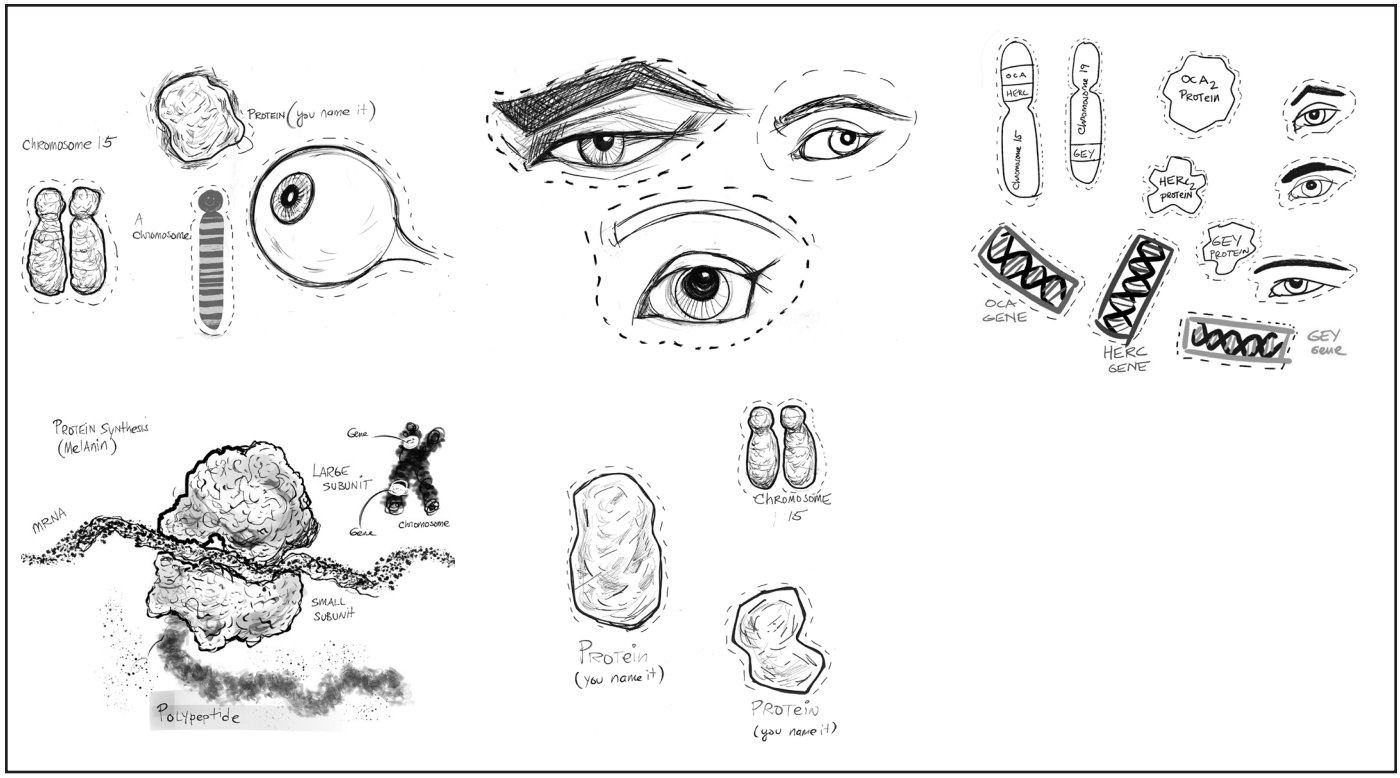

Figure 5. We have provided cut-outs of various characters in the epistasis story to place on the storyboard templates. Students can photocopy, enlarge/reduce these images and label them, and add their own drawings. The cut-outs include chromosomes, unnamed proteins, an eyeball, a protein synthesis representation, and different cartoon eye shapes.

- C-T base pair / glutamine = brown / arginine = blue
- Chromosome 19 gene: GEY, a.k.a. EYCL1 eye color 1 (green/blue)
- GEY genes depositing another type of melanin, possibly a weaker protein, in the stroma of the iris, which may not be resolved yet
- MC1R increasing the probability of green eyes. This is the gene associated with red hair, which explains why some redheads have green eyes; it produces a receptor, which plays a role in pigmentation.
- Genotypes for brown eyes: BB, Bb
- Genotypes for green eyes: bbGg, bbGG
- Genotypes for blue eyes: bbgg

○ Conclusion

The great thing about the storyboard is that teachers and students can create a variety of templates or reuse the same one until they achieve a narrative flow of the story that seems satisfactory. Exploring the genetics of complex traits through epistasis, as well as the evolutionary patterns these gene-gene interactions produce, creates a level of complexity that might benefit from storyboarding layouts and sketches. Through actively creating original storyboards on the process of epistasis, students are encouraged to explore the complex topic of gene-gene interactions, and the variations on Mendel's theme will take on new meaning for students and teachers. Using the artist's planning tool of the storyboard and the technique of sketching, student's monitor their own interpretations of data from current models on the epistasis of eye color. In this way, the storyboard serves as a dynamic space of a genetic landscape functioning within an evolutionary framework and can assist students in mastering complex molecular and genetic concepts. The storyboard can become an appreciation of the synthesis of complex phenotypes through epistatic gene networks and predictive models of gene-gene interactions. Questions can arise regarding the relationships and natural selection of other polygenic traits, such as skin color and hair color. A storyboard can reveal the underlying nature of human diversity around the world and at the same time introduce genomic terms and networked thinking. It also has the potential to serve as a model for other, if not all, complex biological phenomena.

○ Acknowledgments

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