

Genetics and Genome of Diseases

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Academic Setting

Rio Grande High School is located in the south valley. The school population is about 2000, making it one of the most populated schools in APS. Its student population is mainly minority students as shown in the percent ethnicity comparison chart.

Percent Ethnicity comparison *		
Student	Rio Grande	APS
Ethnicity		
Hispanic	83.9	45.8
Anglo	9.7	42.7
Indian	4.3	4.8
Black	1.6	3.7
Asian	0.1	2.2
Other	0.3	0.7
* 99/00 RDA		

Rio Grande students are of the lowest socio-economic-status within APS. Rio has 44.9% of its students receiving free or reduced lunch compared to 18.5% for APS. As a whole, the biggest problems facing Rio are attendance and dropouts. Rio has an attendance of 87.4% vs. 91.8% for APS, and a dropout rate of 12.5% compared to APS's 9.3%.

Rio Grande has an outstanding Bilingual Education Program with 88% of Rio's students being PHLOTE students. These students are either ESL or Bilingual students. The graduating class of 2001 had 65 out of 350 students receive a bilingual seal on their diploma. Rio Grande is one of few high schools in the nation that offer the bilingual seal. This seal tells future employers that the student has gone through a rigorous program and is fluent in two languages.

This unit is designed for a 9th grade Biology I class. Through various teaching methods, the class will learn the fundamentals of genetics

and the genome; from the history of its study to modern day applications.

Introduction

Genetics

The face of modern genetics was pioneered by an Austrian monk named Gregor Mendel. Genetics is the study of heredity or the passing of traits from parents to offspring. Before the nineteenth century, the common belief about heredity was the Theory of Blending Inheritance. This theory states that the physical characteristics of an organism are a blending of its parents traits. It is easy to see this as a possibility. Can you see something of your parents in you or some of you in your children? But when biologists started looking at the nitty-gritty of genetics, they found discrepancies in this theory.

History

In stepped Gregor Mendel, during the 1850's and 1860's, with his garden pea plants. Mendel worked as a gardener in a monastery in the town of Brno, in what is now the Czech Republic. He also taught in the local high school. Peas are self-pollinating plants, which means that the male part fertilizes the female part of the same flower. Left alone, the offspring plant will continue the pure genetic make up of the parents. Mendel cross-pollinated his pea plants by using the male stamen of one plant and the female pistil from another plant, thereby preventing self-pollination. He then pollinated the pistil with the pollen from the male stamen. This gave Mendel a technique to control the traits that he wanted to study. Mendel studied seven traits: seed shape, seed color, seed coat color, pod shape, pod color, flower position, and plant height.

Genetic Theory

Through his pollination of several generations, Mendel collected data that would be the basis for the theories of modern genetics. There are "merkmal" (German for "characters") that control traits (Miller 184). Today we call them genes. The genes have different forms for each trait, called alleles. These alleles combine with each other to give an organism its traits.

He also came up with what is called the principle of dominance: the alleles for a trait are either dominant or recessive. Dominant alleles are those in which the phenotype shows if combined with a recessive, and a recessive allele will only show if paired with another recessive allele. For example, the allele for a tall pea plant (T) is dominant, while the short allele (t) is recessive. If the gene for height is either

homozygous tall (TT) or heterozygous (Tt), then the phenotype is the dominant tall. The only way to get a recessive short plant is to have a homozygous short (tt) gene.

For clarity:

Dominant allele, tall (T)

Recessive allele, short (t)

Dominant phenotype, tall (either TT or Tt)

Recessive phenotype, short (only tt)

Another deduction is the principle of segregation, where the gamete production randomly chooses the allele to express. For example, green pea pods (G) are dominant over yellow pods (g). If you have a parent that is heterozygous (Gg), in the formation of its gametes it will randomly pick one of the alleles. In other words, each gamete has a 50/50 chance of carrying the dominant or recessive allele.

The conclusion is the principle of independent assortment. In the formation of offspring each trait is independent of any other (i.e. a height gene doesn't affect a color gene).

Genetic Probability

Using Mendel's principles is a tool to predict the possible genotypes and phenotypes of offspring. The genotype of an organism is the combination of their alleles, portrayed as letters such as Gg or Tt. The phenotype is the trait that is shown with the genotype. For example, the genotype of Tt combines a dominant allele (T) for a tall pea plant with a recessive allele (t) for a short plant, giving the phenotype of the dominant allele – a tall pea plant. The principles are used in conjunction with probability to form the tool of a Punnett square. A Punnett square formulates the probabilities of genetic crosses. If you know the parent's genotype, you can find the probable offspring combinations.

I will run through the example of Mendel's tall vs. short pea plants experiment to show the steps for a Punnett square. Mendel started with pure breed plants; plant 1 heterozygous tall (Tt) and plant 2 is heterozygous short (tt). After crossing breeding plants 1 and 2, Mendel found that all of the offspring were tall. What he didn't know was that the first generation of offspring in this situation would be heterozygous (Tt). He then crossed this generation to see what would happen. I will use this crossing as an example for using a Punnett square:

The question is, "What will you get if you cross two heterozygous tall plants?"

Step 1: Write the genotypes of the parents. Picking of the male and female is arbitrary.

Male (Tt)

Female (Tt)

Step 2: Determine the possible gametes that the parents can produce.

Male (Tt)
T or t

Female (Tt)
T or t

Step 3: Enter the possible gametes at the top and side of the Punnett square.

	T	t
T		
t		

Step 4: Complete the Punnett square by cross-multiplying the gametes.

	T	t
T	TT	Tt
t	Tt	tt

Step 5: Determine the possible genotypes of the offspring and their ratios.

Possible Genotypes	Occurrence in square	Ratio of occurrence	% of Occurrence
TT	1	1/4	25%
Tt	2	2/4 or 1/2	50%
Tt	1	1/4	25%
total	4	1	100%

If you cross two heterozygous tall pea plants, you should expect the following genotypes for the offspring: 25% TT, 25% tt, and 50% Tt.

Step 6: Determine the possible phenotypes of the next generation and their ratios. Tall is dominant, so any T in the genotype will produce a tall pea plant.

Possible	Occurrence	Ratio of	% of
Phenotypes	in square	occurrence	Occurrence
TT & Tt - tall	3	3/4	75%
Tt - short	1	1/4	25%
total	4	1	100%

If you cross two heterozygous tall pea plants, you should expect the following phenotypes for the offspring: 25% short, and 75% tall.

Genomics

The genetic story of the day is decoding itself with the mapping of the human genome. The basic definition of genome is all of the genes within an organism. The Human Genome Project has identified all of the genes within the human body. This provides a cornucopia of solutions to problems, and problems to solutions. Some possible uses of this sequencing are personal identification, diagnosis of disease, curing of genetic diseases, retarding aging (fountain of youth syndrome), catching criminals, setting the wrongly accused free, or building a "better soldier" or the "perfect" being. Because of the Human Genome Project ["the ongoing effort to codify and learn the function of the more than 30,000 genes that make up the instruction manual for the human body..." (Lyon 58)], the list above may become reality.

History

With the foundation of the study heredity having been laid by Mendel's work, we can now further our understanding of genetics. Thomas Morgan, working with fruit flies (*Drosophila*), formulated the Theory of Heredity. The Theory of Heredity states that genes arranged on chromosomes carry heredity factors that are expressed in different combinations when coupled with genes of mates (Krock). This is an important theory, but the "how" needed to be answered; in stepped Watson and Crick.

Francis Crick and James Watson used x-rays and molecular models to discover the double helix shape of DNA. They also answered how life is passed on: by DNA replication. DNA, when straightened, looks like

a ladder. When DNA replicates (the reproduction of genetic material) the ladder unzips into two separate half-ladders. The rungs of the ladder are made up of four bases, or nucleotides, called adenine (A), thymine (T), cytosine (C), and guanine (G). The base cytosine (C) is linked to guanine (G), and adenine (A) to thymine (T) as the rungs of the ladder. After the unzipping, each rung needs the corresponding base to be whole. After the half- rungs combine with their corresponding bases, there are two strands of DNA.

Watson and Krick provided the instruction book known, we now need to have the parts list assembled. This is being done with the Human Genome Project. In 2001, the International Human Genome Sequencing Consortium (public) and Celera Genomics (private) announced together that they have a rough draft of the human genome. The project has made some interesting discoveries. The human genome is made up of 34,000 genes, less than the 100,000 expected. Compared to the 19,099 genes of the roundworm or 13,601 in the fruit fly (Begley 62), it makes you wonder how we are as complex as we are. Joseph H. Nadeau of Case Western Reserve University in Cleveland says that the mouse genome is about 85% identical to our own, but what does that mean? If a scientist can do research on mice that he can't do on a human, it will then be easier to develop an understanding of diseases and their cures. The final draft of our genome will be completed by the year 2003. Eric Landers of the Whitehead Institute for Biomedical Research (part of the public consortium) notes that " the text [human genome] is filled with long-sought answers, some amazing surprises, puzzling mysteries, and lots of useful information for medicine."

Genetics and the Genome for a Cure

Almost all researchers are talking about the cures that will come from knowing the makeup of the human genome. I will use two examples to illustrate the possibilities for cures. I will use a simple case of Tay-Sachs and a more complex case of diabetes. I am not saying that Tay-Sachs is a simple disease. I make this distinction because Tay-Sachs is a genetic disorder that has one gene which is responsible for its manifestation. Diabetes has up to eighteen genes responsible (Pennisi 85).

A Simple Case – Tay-Sachs

Tay-Sachs disease (TSD) is a rare, lethal recessive disorder that strikes newborns. It was believed to be a cultural disease among Ashkenazi Jews. Within the Eastern European Jewish population and descendents, 1 in 4100 births are diagnosed with TSD. Doctors are seeing an increase, however small, in other populations. Most

populations have an incidence of 1 in 340,000 births (Kaback).

A newborn with this disease will come home from the hospital appearing normal. The child will exhibit normal benchmarks of development up to six months of age when they start to show decreased motor skills. There is a progressive degeneration leading to blindness, deafness, seizures, lack of motor skills, mental retardation, brain enlargement, and finally premature death by the age of five.

The degradation of cell structure and a build up of a lipid (fatty) membrane in the brain cause the symptoms. The culprit responsible is the enzyme lysosomal hydrolase-13-hexosaminidase A (HEX A). Due to a lack of proper activity by HEX A, the lipid GM[sub-2]-ganglioside is accumulating in the nervous system. (Hechtman). In essence, fat builds up until it squeezes the brain to death.

The Genetics of a Cure

The easiest and earliest "cure" for Tay-Sachs is a pre-conception testing of the parents. If both parents carry the gene, then they are told of the possibility of having children with the disease. The next possible diagnosis is during pregnancy. If both parents are carriers, then a prenatal test is performed. If positive, parents are made aware that their child will have a short life span. They may also be counselled on the possibility of voluntary abortion. The U.S. and Israel have set up Tay-Sachs screening programs which have proven to be successful. In 1980 there were 65% fewer diagnoses than in the decade before (O'Sullivan 97).

Enzyme replacement, gene therapy, and substrate deprivation are possible treatments for this disease. As soon as doctors know the exact sequence for the gene HEX A, they can start gene therapy. The most straightforward gene therapy would be to correct the dysfunctional gene. Creating a new gene to manufacture the correct protein or to correct the present one could do this. The one strategy that doesn't need a genetic blueprint is substrate deprivation. This method is to insert a chemical that will do the work of the nonfunctioning enzyme. In a study done at the University of Oxford, Tay-Sachs mice were given N-butyldeoxynojirimycin (NB-DNJ). The study showed success, the mice that ingested NB-DNJ exhibited a decrease of lipids in the brain (Platt).

A Complex Case – Diabetes

One of the prominent disease candidates for gene therapy and genetic engineering is diabetes. Diabetes is a disease that cuts off the supply

of insulin to the body. Insulin is the protein that regulates the metabolism of sugars. With insulin, the body regulates the breakdown of sugar; without, the sugars create problems. Some of the problems are blindness, heart attacks, strokes, gangrene, the need for amputations, high blood pressure, kidney failure, nerve damage and obesity (Fishman 64). The two types of diabetes are Type one and Type two.

Type One Diabetes

Type one is when pancreas islet cells dies. The islet cells make insulin. Type one diabetes is also called "insulin- dependent" because you have to get insulin from a source outside the body. Out of all of the cases of diabetes, only 5-10 % are Type one which amounts to 1 million Americans (Beaser 18). There are three main factors which contribute to "coming down" with this disease. They are heredity, environment, and auto-immunity.

The heredity of diabetes is simple; the genes that deal with diabetes are passed from parent to child. Diabetes is a recessive trait disease, which means that both parents have to pass the gene on. Diabetics have a prevalence of two genes, called DR3 and DR4. Only 3% of non-diabetics have the DR3/DR4 combination as shown in research. Heredity and genetics is never cut-and-dry. Research shows this in studies of twins. Twins, having the same genes, have only a 50% likelihood of both children developing the disease (Chase p12).

The environmental aspect of this disease deals with a virus, or an allergy (usually food). For whatever the reason, the end result is that the islet cells are targeted as foreign bodies. This means trouble because the immune system will start to kill the cells.

Diabetes is an autoimmune disease. This means that the immune system turns against the body. In many diabetic cases, children have shown evidence of an allergic reaction to their islet cells. The evidence being islet cell antibodies (ICA). When the body detects a foreign object, it then produces antibodies. Antibodies are the warriors of the immune system. ICA and other antibodies show up long before the diagnosis of diabetes. This gives doctors a chance to prevent the disease, if they can see the antibodies before the other symptoms appear.

Type Two Diabetes

Type two diabetics make insulin, but not properly. There are no links (at this time) between Type one and Type two diabetics. This means that the Type one indicators do not apply to Type two. The DR3 and

DR4 genes and the islet cell antibodies (ICA) don't seem to make a difference. Type two is called non-insulin diabetes; it can be regulated with diet and exercise and does not (in most cases) need a regimen of insulin. There are a lot of factors that causes Type two diabetes: insulin resistance, failure for the liver to regulate reduction of sugar, and a dysfunction of the beta cells (produce islet). Obesity is a major cause of Type two which ties into all of the other factors.

Research has shown that a gene which regulates an enzyme called protein tyrosine phosphatase-1B (PTP-1B) is one of the genes responsible (Braunstein 28). Mice that have a defective gene are more likely to be obese and diabetic. This is just a start in our understanding; it is expected that over a hundred genes are important to metabolism, as is PTP-1B.

The Genetics of a Cure

The early gene therapists genetically altered cells by putting genes into them. The purpose was to either induce a beneficial cell process (Type one) or correct a dysfunction of the gene (Type two). (Clark 22).

Type one Diabetes

In theory, the best Type one therapy would be to deliver genes that would prevent the immune system from destroying the islet cells. Research done by C. Garrison Fathman, Professor of Medicine at Stanford University School of Medicine, is targeting genes to the beta cells (of islet cells) in the pancreas. If done at a critical stage, it could help to prevent diabetes. Dr. Fathman is basing his theories on interleukin 4 (IL-4). IL-4 shows an anti-inflammatory response in cells under attack by the immune system. If a gene was inserted which produced IL-4, and targeted at the islet cells causing the islet to produce IL-4, then the islet cells would be protected (Clark p22).

The most promising of developments in research for diabetes is in stem cells. Stem cells are the basis of all cells in the body; all cells start out as stem cells in the fetus. The cells develop into different types of cells based on what the genes tell it to be. Researchers are looking into genetically "turning cells on" to develop specific organs for transplants. It would be possible for diabetics to have a new pancreas, or even to create brain cells for someone with Alzheimer's disease.

Type Two Diabetes

The best way to prevent Type two would be to deliver genes designed to help with the metabolic dysfunction of the disease (Clark 22).

Possible genetic prevention would be to target the genes that regulate the insulin resistant tissue, or the failure of the liver, to properly regulate the glucose production.

Implementation

New Mexico Benchmarks and Standards – Science

Content Standard 2:

Students will use evidence, models, and explanations to explore the physical world.

A: Interpret evidence to understand changes in natural and artificial systems.

1.Trace the history of the idea that nature behaves according to regular, mathematically describable relationships.

Content Standard 3:

Students will use form and function to organize and understand the physical world.

A: Compare and contrast form and function as complementary aspects of units of matter, objects, organisms, and systems. 1.Explain the role of language structures (e.g., DNA in living things) in the functioning of complex natural and man-made systems.

Content Standard 10:

Students will know and understand the characteristics that are the basis for classifying organisms.

A: Apply information about living things to themselves and the world around them including: Cell structure and function; The importance of cell membranes and the process of osmosis; The functions of DNA and RNA in genes and the process of heredity; How almost all human cells contain two copies of 23 chromosomes; How changes in DNA can result in the mutation of an organism; and SBE CHANGE 10-99: Discussion of the evidence that the great diversity of life is the result of more than 3.5 billion years of natural selection and biological evolution, which have filled available niche with life forms. 8.Compare and contrast mitosis and meiosis in their roles in single and multi-celled organisms.

9.Explain the process whereby DNA directs the synthesis of proteins from amino acids.

10.Use manipulatives to model the structure of DNA and the process of replication.

11. Discuss Mendelian and molecular genetics.
12. Explain the uniqueness of human chromosomes.

Content Standard 11:

Students will know and understand the synergy among organisms and the environments of organisms.

A: Explain how the development of specialized cells and structures in multicellular organisms can occur in response to environmental threats to the organism.

1. Use an understanding of normal cell processes to explain how cell malfunctions relate to disease.

3. Describe and explain an example of gene expression.

Include how environmental factors can trigger gene expression within an organism and alter its physiology (e.g., change in coloration of the environment can switch on genes that cause change in coloration in the organism).

C: Predict an organism's behavioral responses to internal changes and to external stimuli as a function of inherited and acquired characteristics.

2. Use Mendelian models for inheritance to predict probabilities of inheritance for some specific traits in several selected organisms.

4. Research the present understanding of how specific organisms may have evolved. Identify the specific mechanisms by which such evolution at a genetic level could have occurred.

Unit Lesson Plans

This is a general unit outline with some possible labs and activities. The possible time frame is very flexible.

History of Mendelian Genetics 6 days

Review Gregor Mendel's pea plant experiments and all of the principles that came from them. This section would include the probability of genetic crosses in the form of Punnett squares. Samples of one-trait crosses and two-trait crosses are included in a mini-worksheet. The lab "Create a Kid" is a good way for students to comprehend the probability of the genetics. The students flip a coin to express the different characteristics for their genetic offspring. An optional project is located at

http://www.accessexcellence.org/AE/AEC/AEF/1995/biggs_tree.html. This project is titled "Developing a Pedigree of a Family Tree." The students create a genetic history of their family.

Chromosomes and DNA 8 days

Information taught in this section would include the scientists involved, genes, DNA, RNA, DNA replication, transcription, translation, and protein synthesis. A good project is for the students to construct models of DNA, RNA, DNA in replication, etc... A good lab to do would be a DNA extraction lab. The students seem to enjoy the "gross" factor. You can get kits from science supply catalogs, many textbooks have them in their lab books, or you can find many on the Internet.

Human Genome Project 6 days

This section is an introduction to the concept of our genome. A 15-minute video documentary and a multimedia CD-ROM on the Human Genome Project are an excellent introduction. You can receive "The Human Genome Project: Exploring our Molecular Selves" educational kit by visiting <http://www.nhgri.nih.gov/educationkit/>. After watching the presentations, the class would have a discussion on the genome and what it means to us. Lead the discussion to medicine. A project to do is a Genetic Disease Presentation, where the students design a pamphlet, Power Point presentation, poster, website, etc... to inform and educate people about an inherited disease. Another possibility would be to show the either the *48 Hours* program titled "Marked for life" or the *Nova* episode called "Cracking the Code of Life". The *48 Hours* program is available from: Ambrose Video Publishing, Inc., 1290 Avenue of the Americas, Suite 2245, New York, NY 10104, 1-800-843-0048. The *Nova* episode is available online at <http://www.pbs.org/wgbh/nova/genome.html> or from a *Nova* catalog.

Testing and assessment 5 days

Quizzes throughout the unit are appropriate to keep the students on task. Rubrics for the projects and lab reports for the labs are good techniques to assess the students.

A fun way to review for the unit test is Genetic Jeopardy™. Let the students make up questions and answers in groups. Then have a competition between the groups. You can then give a the test.

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Other Interent Sources

American Society of Human Genetics

<<http://www.faseb.org/genetics/ashg/ashgmenu.htm>>

Celera Genomics <<http://www.celera.com>>

"Cracking the Code of Life." *Nova* PBS. available online at <http://www.pbs.org/wgbh/nova/genome/> or from a Nova catalog.

"Developing a Pedigree of a Family Tree." Available at http://www.accessexcellence.org/AE/AEC/AEF/1995/biggs_tree.html

Howard Hughes Medical Institute <http://www.hhmi.org>

Human Genome Consortium <http://genome.ucsc.edu>

"Marked for Life." 48 Hours available from: Ambrose Video Publishing, Inc., 1290 Avenue of the Americas, Suite 2245, New York, NY 10104, 1-800-843-0048.

Pharmaceutical Research and Manufacturers of America
<http://genomics.phrma.org>

"The Human Genome Project: Exploring our Molecular Selves" educational kit. Available at <http://www.nhgri.nih.gov/educationkit/>

Genetic crosses for one and two traits mini-worksheet

Crosses involving one trait

Trait	Dominant allele	Recessive allele
Seed coat color	brown (B)	white (b)
Seed coat shape	round (R)	wrinkled (r)
Pod color	green (G)	yellow (g)
Height of plant	tall (T)	short (t)

1. Predict the results of a cross between a heterozygous brown seed plant and a white seed plant.

- a.
- b. genotype ratio
- c. phenotype ratio

2. Predict the results of crossing two heterozygous green plants

- a.
- b. genotype ratio
- c. phenotype ratio

3. Cross a homozygous tall plant with a short plant

- a.
- b. genotype ratio
- c. phenotype ratio

4. Cross a heterozygous round seed shape with a homozygous round

seed shape

- a.
- b. genotype ratio
- c. phenotype ratio

5. Predict the results of a cross between a homozygous brown seed plant and a white seed plant.

- a.
- b. genotype ratio
- c. phenotype ratio

Crosses involving two traits

In mice, the ability to run normal is a dominant trait. Mice with this trait are called running mice (R), The recessive trait causes mice to run in circles only. Mice with this trait are called waltzing mice (r). Hair color is also inherited in mice. Black hair (B) is dominant over brown hair (b).

Cross a heterozygous running, heterozygous black mouse with a homozygous running, homozygous black mouse.

- a.
- b. genotype ratio
- c. phenotype ratio

Cross a homozygous running, homozygous black mouse with a heterozygous running, brown mouse.

- a.
- b. genotype ratio
- c. phenotype ratio

Cross a waltzing, brown mouse with a waltzing, brown mouse.

- a.
- b. genotype ratio
- c. phenotype ratio

Cross a homozygous running, heterozygous black mouse with a waltzing, brown mouse.

- a.
- b. genotype ratio
- c. phenotype ratio

Cross a heterozygous running, brown mouse with a heterozygous running, homozygous black mouse.

- a.
- b. genotype ratio
- c. phenotype ratio_

