History

Thomas Hunt Morgan, who worked at Columbia University in the early 1900s, was the first researcher to use the fruit fly, *Drosophila melanogaster*, in the study of gene inheritance patterns. Fruit flies are tiny insects that feed on a fungus that grows on fruit, and they are an excellent species choice for the study of genetics. Their small size allows thousands of flies to be stored in a small space, and because they reproduce quickly, many generations can be grown and observed in relatively short time frames. Through his work Morgan identified 80 separate mutants and was the first person to demonstrate through experimentation, that one gene can be isolated to one chromosome. Morgan was awarded the Nobel Prize in 1933 for his work on fruit flies.

The nematode *Caenorhabditis elegans* was introduced as a model system in the 1960s by Sydney Brenner at the Medical Research Council Laboratory in Cambridge, England. *C. elegans* has many characteristics that make it an ideal laboratory organism. It is small (10,000 worms can be raised on one Petri dish) and easy to keep (it feeds on bacteria, such as E.coli). *C. elegans* takes about three days to develop from an egg to a reproducing adult. A wild-type *C. elegans* is made up of only about 959 cells. Because it is transparent, each cell that makes up a *C. elegans* has been identified and can easily be traced throughout the life of the worm. Understanding the lineage of every cell allows scientists to ask questions about how genes influence individual cells within a living organism. *C. elegans* was the first multicellular eukaryote to have its genome sequenced.

Functional genetic studies typically rely on mutating a particular gene, then looking for physical or behavioral changes in the organism. Obviously, such experiments cannot be performed in humans, so biologists study physiology, cell biology, and many other biological functions in model organisms. Although *C. elegans* and *D. melanogaster* might seem unlikely models for human biology, much of their cell biology, biochemistry, and development is similar to humans. Thus, they have become key model systems for studying gene function.

Gene > Protein > Trait

A gene is a sequence of DNA that encodes the information to make a protein and to determine how much of that protein will be made. The genetic sequence for a protein is called the genotype; the observed result, or the trait, is called the phenotype. Proteins have three major functions in cells: they provide structure, act as biological catalysts called enzymes and serve as hormones. Proteins in turn, confer human traits, or phenotypes. For example, keratin is the structural protein for hair. The chemical structure of keratin changes the shape of hair. Curly hair has a different chemical structure than straight hair. Melanin is a pigment protein in skin and hair. If skin cells produce an abundance of melanin, the result is dark-toned skin; if skin cells make less melanin the result is light-toned skin. If melanin is not produced, the result is a disorder called albinism (a total lack of melanin or pigment). Differences in traits are caused by changes in the genes that create these proteins. The genetic differences between people are referred to as genetic diversity or variability. A change in the sequence of DNA, which encodes a gene, is called a mutation. Because genes encode the information for the production of proteins, a change in a gene can result in a change in the protein and therefore in the phenotype. A change in DNA results in a chemical re-arrangement of the DNA molecule. These changes occur specifically to the base pairs, re-arranging the nucleotides (adenine, thymine, guanine, and cytosine) or removing whole sequences. For the purpose of instruction it can be useful to compare DNA to a recipe. DNA contains the information for a trait. Thus it is expected that a change in the recipe will result in a change in the trait. However, not all mutations result in changes to traits. There are many mutations that are silent. They have no effect upon the expression of a gene or upon a phenotype.
How do mutations occur?

Spontaneous mutations occur during DNA replication in the process of mitosis (cell division). There are enzymes in the cell that proof-read newly replicated DNA, but if they miss a change, this change gets incorporated into the DNA and will be maintained when the DNA is replicated in the future. There are many silent mutations in DNA that do not have an effect on the health or the activity of the cell.

Mutations can also occur due to exposure to mutagens. Mutagens are substances that interact specifically with the DNA molecule and change the genetic sequence. Some mutagens are commonly known as carcinogens, substances that cause cancer. Ultra-violet radiation and smoking are both excellent examples of mutagens. Both of these interact with the DNA and can make changes to genes. It is known that both ultra-violet radiation and smoking can cause cancer.

Cancer

Cancer is understood to be a genetic disease within the cell. Changes to genes with important replication or developmental functions in a cell have been implicated in the development and progression of cancer. This occurs when the genes that are supposed to control a cell’s division are altered. Cancerous cells are typified by their inability to turn off their cell division stage. Normally a cell that is malfunctioning will destroy itself, but in this case the gene to instruct the cell to die is also mutated. The cell can no longer do the job it was meant for and it cannot destroy itself. It can only make more cells just like itself continuously. Cancer is also understood to be associated with an accumulation of mutations in the cell. That is, the cell requires a certain number of mutations or changes to its genes, before it becomes cancerous. For this reason, exposure to mutagens increases the number of mutations in a cell and thereby increases the likelihood of a cell becoming cancerous. Therefore, exposure to a mutagen is a risk factor for the development of cancer. The older a cell is, the greater the likelihood that it has accumulated mutations. Additionally, greater exposure to mutagens increases the likelihood that a cell will become cancerous. It is for these two reasons that older people have greater chances of developing cancer. However, it is important to note that mere exposure to a mutagen does not guarantee that a cell will become cancerous; rather, exposure increases the chances that enough mutations will be accumulated to result in a cell stuck in the on position. Cancer in humans is an excellent example of the harmful effects of mutagens. However, not all mutations are harmful, as will be discussed further.

Why Study Mutations?

The study of mutations is a tool used to explore the function of a gene. If a mutation in a gene elicits a phenotypic change, the function of the gene can be better understood. This is the case for all organisms, from bacteria to man, and is often an approach researchers use to determine a gene’s function in a cell.

In humans, genetic mutations can often be associated with disease. For example, sickle cell anemia is a disease that results due to a mutation in a protein. Hemoglobin is the structural protein of red blood cells. The hemoglobin in red blood cells binds oxygen and carries it throughout the body. In the hemoglobin gene, there is a mutation that disrupts the shape of the protein and changes the shape of the red blood cell from round to sickle-shaped. These hemoglobin molecules bind oxygen less favorably than normal hemoglobin does. This results in an anemic state. Also, the sickle shape of the red blood cell causes difficulties. Sickles do not move as easily through veins and can accumulate at points inside the affected person. Sickle cell anemia provides an excellent example where a change in the hemoglobin gene results in a phenotypic change in cell shape and function. Understanding the function of healthy (or wild-type) genes can help researchers to understand the mechanism of disease and develop potential treatments. This approach can lead to the use of gene therapy for genetic disease. Gene therapy is the use of healthy genes to treat an individual with a disease caused by mutation.
Mutations and Evolution

With the publication of The Origin of Species in 1859, Charles Darwin introduced his famous theory of Natural Selection. This theory was a result of observations he made on his famous trip on the HMS Beagle. He observed morphological differences between finches that lived on different islands in the Galapagos. Darwin hypothesized that the finches had originated from the same population and had spread out over numerous islands. Some birds developed physical traits, specifically distinct beak shapes, which gave them an advantage in their new habitats and made it easier for them to access food. Darwin suggested that these advantageous traits were passed on to the offspring and over the course of numerous generations the new trait became the predominant trait in the population.

At the time that Darwin suggested his theory, DNA was not understood to be the basis of inheritance. However, it has been elucidated that changes in DNA, which underlie changes in morphology, are the mechanisms of evolution. Natural selection is a spontaneous event. An organism cannot make changes to its own DNA. Rather an existing change, which benefits an organism, will remain in the population and potentially become the predominant trait observed in that population. This process can also be referred to as adaptation not because the animal changes, but because, the animal has a trait that benefits it in the habitat where it lives and this trait may be selected for when it provides the animal with an advantage. The long neck of the giraffe is an excellent example of natural selection. Giraffes with longer necks found it easier to access food. So, long necked giraffes had a higher survival rate and thus more offspring.