Early History

Why do certain characteristics run in families?

Humans have always been curious about inheritance. Until the 1800s, the mechanism of *how* traits were passed from parents to children was debated by philosophers and theologians, but almost no scientific analysis was performed.

Please note: definitions of terms that are in boldface in the text as well as other terms can be found in the Glossary.

In the mid-1800s, there was as yet no knowledge of genes or their molecular basis. However, a central European monk named Gregor Mendel became intensely curious about the mechanism of genetic inheritance. Born in what is now the Czech Republic and educated in a local monastery, Gregor excelled in the natural sciences and remained at the monastery into adulthood. One area of particular interest for him was an understanding of the mechanism by which certain physical traits were passed on from parents to their offspring. In pursuit of this, he began performing experiments with field peas in an attempt to determine how certain traits such as flower colour, plant height, and pea shape were passed from parent plants to offspring plants.

Although he had no knowledge of genes or the DNA of which they are mainly composed, Mendel was able to develop certain principles of inheritance that are now known to apply also to other living creatures, including humans. For these discoveries and others, he has become known as the "Father of Modern Genetics."

Nearly 100 years after Mendel's experiments, Francis Crick and James Watson discovered the structure of **DNA (deoxyribonucleic acid)**. Understanding the molecular composition and function of genes has led to a much better understanding of the relationship between genes and characteristics that they express as well as the interaction between genes, the environment, and human health.

The Composition of a Human Cell

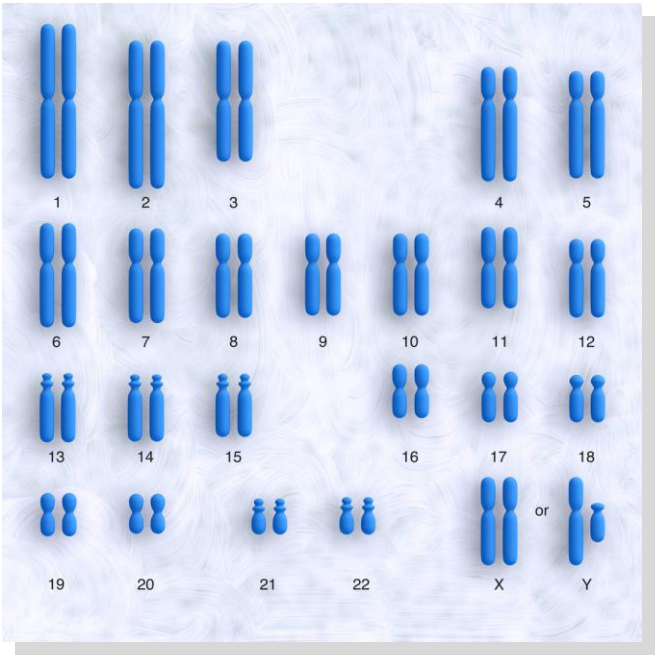
To understand the importance of genetics, one needs to understand some anatomy at the organ and cellular levels.

In the human body, each organ (e.g., the lungs, kidneys, brain, heart, etc.) is made up of tissues. These are types of cells that function differently but work together to keep each organ functioning normally.

Although the cells that make up different parts of the body – skin, bones, brain, heart, lungs, and everything else! – have different structures and compositions, all cells of the

human body share some basic physical and biological attributes.

All cells are composed of a liquid, known as the cytoplasm, within which are located the nucleus and other smaller structures. This cytoplasm is surrounded by a membrane that keeps the cell intact. The **nucleus** acts as a control centre for the cell. Each nucleus contains a full set of **chromosomes**, known collectively as a **genome**. The nucleus of all body cells contains 23 pairs of chromosomes (46 total chromosomes), including a pair that determines the gender of the person. (The exceptions are **germ cells** (sperm and eggs), which have only 23 chromosomes each.)



An illustration of a normal complement of human chromosomes

Each chromosome pair contains genes, the backbone structures of which are DNA. This DNA guides the formation of proteins, which are building blocks for the structure and functioning of each cell. Each gene has two copies or **alleles**, one on each of the paired chromosome. These alleles may be structurally identical or may vary to different degrees. Thus, each allele of each gene has an identical or structurally different "twin" on the other chromosome in that pair. Structural variations of normal alleles of a given gene are called **mutations**. Mutations that cause an allele to differ even slightly from the normal allele may have a profound impact on the expression of that gene.

Although each gene has only two alleles in each cell (except germ cells which have one allele per gene), there may be many different varieties of alleles in a human population. This is the case with traits such as height as well as hair and eye colour and explains the wide variety of these traits in some populations.

The genome of each person is identical in the nucleus of every cell in the body. So your brain cells have exactly the same genes as the cells in your lungs, your inner ear, and the tendons of your big toe. However, your brain appears different, and functions differently, from your big toe because not all of the same genes are at work in your brain cells as are at work in the cells of your toe. That is, during your development as an embryo and fetus, inherited genetic instructions in certain genes turned off the functioning of other genes (called silent genes). Different genes were turned off in different types of cells, allowing the functioning of the different genes in each type of cell. This variation in the genes turned on and turned off in each type of cells led to the diversity of appearance and function necessary for your development as a unique newborn human being.

A Sidebar: DNA Outside of the Nucleus

Besides the nucleus, cells also have small, distinct structures in the cytoplasm called **organelles**, each type of which has its own function. One type, known as the mitochondrion, carries important energy-producing components of the cell. Each mitochondrion contains a very small amount of additional genetic material containing DNA. This genetic material is passed on through the mother's genetic line because the egg from the mother carries nearly all of the cytoplasm that is contained in the **zygote** (that is, the cell produced by the union of a sperm and an egg at conception).

Mutations of this mitochondrial genetic material have been linked to an increasing number of distinct health disorders, although there are also mitochondrial disorders due to DNA in the nucleus. One or more organs may be affected and symptoms vary among disorders. Symptoms that may occur include muscle weakness and lack of coordination, visual or hearing problems, nerve problems, mental disorders, and diabetes. We will not discuss this type of DNA further but for those interested in more information on this interesting new area of mitochondrial gene-related diseases, see: http://www.ncbi.nlm.nih.gov/books/NBK1224/.

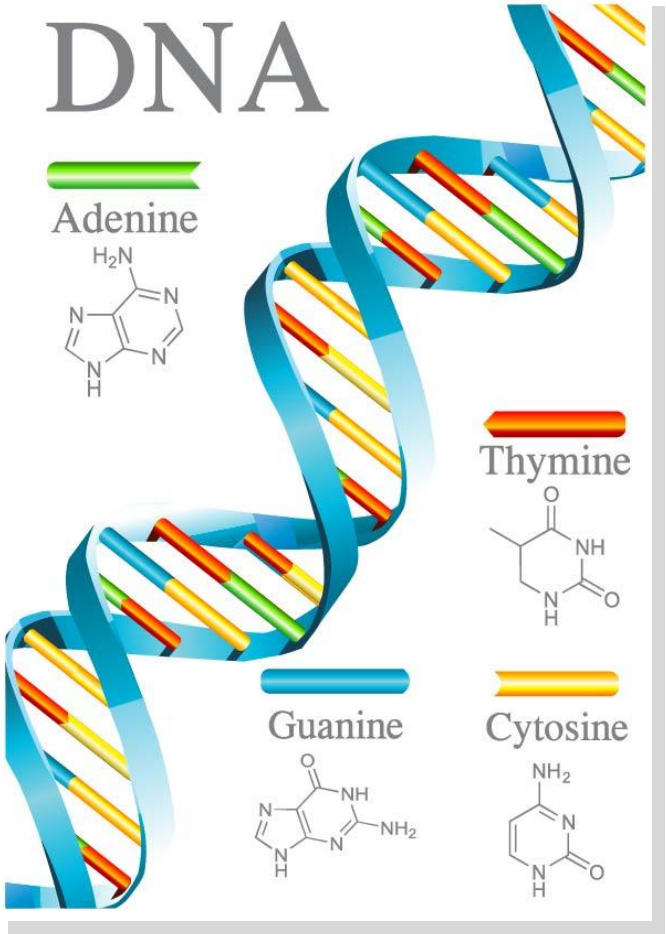
Composition, Characteristics, and Effects of Chromosomes and Their Genes

Chromosomes are composed of **chromatin**, a complex of molecules made up of DNA that is wrapped around special proteins known as **histones**. DNA is the backbone of this complex that contains the information of genetic inheritance. When a cell divides into two cells, each pair of chromosomes can double and separate so that each new (also called daughter) cell has a normal number of the same paired chromosomes that were present in the original (also called parent) cell. While many different kinds of cells are

capable of dividing and replicating in this way during life, sperm and egg cells are unique in that they each have only one of each type of chromosome rather than a pair. When a sperm fertilizes an egg, one set of chromosomes in the sperm (from the biological father) is paired with one set of chromosomes in the egg (from the biological mother). This combination of a sperm and an egg results in a unique set of paired chromosomes in the fertilized egg, now known as a zygote.

How the structure of DNA is translated into proteins that become the molecular basis for functions such as movement, speech, sight, and other workings of our bodies

DNA is a polymer, a type of molecule made up of repeating subunits, like beads on a string. DNA has four subunits: **adenine, guanine, cytosine,** and **thymine** (or A, G, C, and T). These subunits are like codes that determine the production of certain molecules called **amino acids**. These amino acids are like blocks for building proteins. Different combinations of subunits produce different amino acids and different combinations of amino acids determine the formation of different proteins.



The DNA subunits are arranged on the DNA like steps on a ladder. The A and T subunits are always paired to form a ladder rung, as are the G and C subunits. Thus, DNA is like a ladder composed of pairs of subunits that make up the rungs of a spiral ladder. It takes three of these pairs or rungs to make a single amino acid and different sequences of pairs produce different amino acids, which in turn produce different proteins. Multiple layers of combinations can produce a huge number of different proteins that, when combined with other molecules like sugars and fats, constitute the backbone of many bodily functions.

In the cell, the DNA of each gene is translated into specific proteins through the

mechanism just described. These proteins then build vital structures in the cell that serve many essential functions in our bodies. Each gene produces a protein or set of proteins distinct from those of other genes. As mentioned earlier, each gene has two alleles. If each allele is identical, they produce identical proteins. However, if one allele is different (usually due to mutation), the proteins produced by each allele may differ. For example, differences in traits such as eye colour are determined in large part by the structural or functional differences or similarities between the proteins produced by the pair of alleles on a particular gene. In the next section we will explore in more detail the concept of mutations and their important genetic and functional diversity.

Mutations: Alterations in the Order of DNA Subunits and Their Consequences

An alteration in the order of subunits in the DNA of a gene is called a **mutation**. Such mutations can produce an altered subunit of the protein normally produced by that gene, which in turn can sometimes lead to altered structure and function. In a cell, that change or mutation will be inherited by any new cells created when the mutated cell divides. Whether that mutation results in a change in the structure or functioning of these new cells will depend on a number of factors, including the type of gene that was mutated, whether the gene was a functioning or silent gene, what function it had before it was mutated, and so on. Mutations occur all the time. Right now, you are accumulating mutations in your DNA. But fortunately, most mutations are repaired before they can be translated into abnormal proteins. If they are repaired, the mutations have no adverse consequences for the cell, for its progeny that result from cell division, or for the person to whom the cell belongs. This is the case when a mutation occurs in parts of the DNA that don't contain genes or when a structurally altered protein still functions normally.

Sometimes, however, a mutation produces a protein that functions abnormally. For some mutations, these proteins may have no noticeable effect on the person with the mutation. Other mutations may cause the death of the cell itself. Such cell death may have little or no consequence for fully developed persons but could result in the death of a developing embryo or fetus. Still other mutations can cause a change in a desirable or undesirable characteristic such as hair colour or height. Occasionally mutations result in new qualities or functions not typical for that type of person or species.

Spontaneous versus Acquired Mutations

Mutations can occur spontaneously in any cell and at any time. If such a mutation

occurs in a cell other than a sperm or egg cell, that mutation is known as a **somatic mutation** and cannot be transmitted to that person's children. The mutation may have no noticeable effect, may affect only a specific type of tissue or organ, or may noticeably affect the whole person. However, if the mutation occurs in a sperm or egg cell, it is a called **germ-line mutation**. As noted earlier regarding the chromosomes, each egg or sperm has just one allele of each gene rather than the two alleles found in somatic cells. So if a sperm with a mutation of an allele merges with an egg without the mutation on its allele, the gene of the resulting embryo will grow to adulthood having one mutated allele and one normal allele in each cell of its body for the rest of its life.

In a person with a genetically linked disease, the disease may occur through spontaneous mutation of only one allele of a particular gene during embryonic development. In other cases, the disease may occur through the inheritance of an allele that mutated in an earlier ancestor. In still other cases, the disease may occur when a person who inherits a mutation on one allele of a particular gene experiences a spontaneous mutation on the other allele of that gene As we will learn later (in the section, Inherited Disease and Genetic Testing, Predicting Breast Cancer by Genetic Testing) the strength of expression of the mutation for causing the disease will determine whether one or both alleles must carry the mutation for the disease to develop.)

Differences in Genes Can Become Differences in Our Characteristics

Genetic information is passed from parent to offspring mainly by DNA. In cells, this information is translated into proteins that build structures and fulfill important functions for the cell, for the organ or tissues where the cell resides, and for the body as a whole. These structures and functions are evident in characteristics such as eye colour, facial appearance, height, and other features. Because we get our DNA from both of our biological parents at conception, our features and traits often are similar to those of one or both of our parents. A difference (or mutational change) in the molecular structure of a gene is a **genotypic** difference between the original gene and the changed gene. If that genotypic difference results in a difference in the characteristic or function associated with that gene, such as eye colour, that difference is a **phenotypic** difference. In this case, the eye colour would be different between the original gene and the changed or mutated gene.

Epigenetic Changes

Until very recently, geneticists thought that only changes in the DNA of genes (that is, mutations) could lead to changes in phenotypic expression of those changes. They have recently discovered that changes in the non-DNA, or histone portions of the

genome, can alter gene expression. Such changes in histones are known as **epigenetic** changes because they can cause changes in gene (or phenotypic) expression without altering the DNA sequence of the genes

Epigenetic changes can also be brought on by environmental factors. For example, epigenetic changes have been linked to altered stress responses in the brains of individuals who experience childhood abuse. In turn, these changes have been linked to an increased risk of suicide later in life. Very importantly, these changes can sometimes also be inherited by subsequent offspring. Since epigenetic changes can be acquired changes and then transmitted to offspring, this newly understood dimension of genetics has changed fundamentally our concept of genetic change and inheritance.

Along with certain sections of DNA, epigenetic changes appear to be involved in the mechanisms by which different types of cells know which genes to turn on and off as these cells multiply and differentiate into different functions during embryonic and fetal development. Such epigenetic regulation can be involved in the control of normal cell division and tissue growth. However, they can also be involved in disturbances of cell growth in which epigenetic changes can lead to uncontrolled cell growth as cancers.

It is now known that many of the changes of the genome that can lead to uncontrolled growth of a cell and its progeny involve subtle molecular changes of histone proteins associated with DNA. This knowledge is now being exploited to develop new cancer drugs that can alter or negate such epigenetic changes in cancer cells and thus suppress or stop cancer growth. There are already therapies available that target such changes in the genome of cancer cells and more are being developed and approved for use every year.

Different Proteins for Different Functions

Different genetic information in DNA is translated into different proteins. Structural differences in these proteins are associated with different physiological functions. Proteins made in your muscle cells interact with one another to allow your muscles to contract. Proteins in neurons, the main cells that make up the nervous system, produce

the neurotransmitters that allow you to know what to say next. Proteins in the retina of your eye produce molecules that change shape when light hits them, allowing you to see. Fingernails and hair are composed of the protein keratin. Hemoglobin is a protein that transports oxygen from your lungs to the rest of your body. Amylase is a protein made by saliva-secreting cells in your mouth that allows you to digest starch in various foods such as potatoes or crackers.

Practical Implications of Genetic Variation: The Story of Blood Types

Blood can be distinguished into types according to different molecules associated with red blood cells. One system of typing human blood can be instructive in understanding the concept of genetic inheritance. On one of our chromosomes, there is a blood-type gene that contains instructions for producing a protein whose function is to add sugars to the surface of red blood cells. Like other genes, this gene has two alleles, one inherited from the biological mother and the other from the biological father. Each allele can be one of three minor structural variants. The A variant has the recipe for an enzyme that adds A-type sugars to the red blood cells. A mutation that occurred in the far distant past may be the reason for the existence of a second variant, called the B variant, that adds B-type sugars instead of A-type sugars to the surfaces of red blood cells. A third variant (or O variant), possibly also the result of a past mutation, produces a non-functional enzyme that cannot add sugar to the red blood cell surface.

If each allele of your blood type gene has only the A variant (the gene is then designated AA), you and your gene are **homozygous** for Type A blood. If one allele has the A variant and the other the O variant (the gene is designated as AO), you and your gene are **heterozygous** for Type A blood. In both cases, only A-type sugars are present on your red blood cells because variant B is not present and variant O is cannot add sugars. The same pattern follows for the B variant, in which case only B-type sugars are present on the red blood cells and in either homozygous (BB) or heterozygous (BO) situations, the person has Type B blood. If you have neither A-type nor B-type sugars on your red blood cells (or OO), you'll have Type O blood. Finally, if one allele has the A variant and the other the B variant, both sugars will be present and the blood type is AB.

These genetic variants are analogous to different recipes for oatmeal cookies. The allele for blood type A is like a recipe for cookies with raisins (red blood cells with type-A sugar) while the type B blood is analogous to a slight change in the cookie recipe, resulting in cookies with chocolate chips instead of raisins. The O variant is the simplest recipe, with no raisins or chocolate chips included. In the absence of raisins (one A allele) or chocolate chips (one B allele), the resultant oatmeal cookies are just plain (and less flavourful!)

The A and B Variants are Dominant and the O Variant Recessive

Some alleles of particular genes are expressed (that is, result in a characteristic such as eye colour or blood type) more dominantly than other alleles of the same gene. When a gene is heterozygous and one allele is more **dominant** than the other, the dominant allele may be expressed while the other, **recessive** allele is not. A recessive allele can be expressed only when the gene is homozygous for that allele (both alleles have the same recessive mutation), in which case a more dominant allele is not present. In blood typing, the A and B alleles are both dominant and the O allele is recessive.

Summary of the genetics of the ABO blood typing system

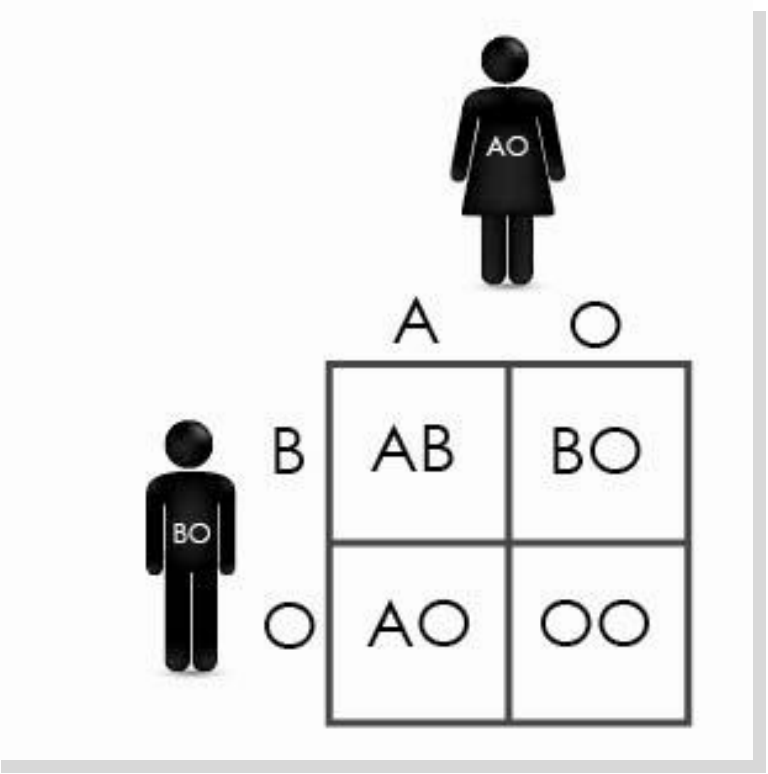
1. In the ABO blood typing system, if you are homozygous or heterozygous for only the A variant (that is, AA or AO), you will express only the A sugar on your red blood cells and will be considered to have Type A blood.

2. If you are homozygous or heterozygous for only the B variant (that is, BB or BO), you will express only that sugar on your red blood cells and will be considered to have Type B blood.

3. In the absence of both A and B alleles (i.e., OO), you have Type O blood. If you have one A allele and one B allele, you have both sugars and thus Type AB blood (or oatmeal cookies with both raisins and chocolate chips)

Predicting the Proportion of Offspring with Traits of a Particular Gene

The Punnett Square is a helpful way to explain the relationship between dominant and recessive genes (see figure). Named after biology professor Reginald Punnett, it is used to predict the genetic contribution of parents to their offspring and the resultant genotypes of those offspring. If two people with the blood types A and B have a child, the results can be predicted using a Punnett Square (see figure). The mother's known alleles (A and O in this case) are placed along the top of the square and the father's known alleles (B and O) are placed along the side of the square. The four squares represent the possible genotypes of their children. Here we see that this couple could have children with any of the four possible blood types and that each time they have a child, there is a 1 in 4 or 25% chance that the child will have blood type AB, O (represented by OO), B (BO) or A (AO).



Similarly, if the parents each have the A and O alleles and therefore each have type A blood (that is, each have AO), the letters can be plugged into the Punnett Square. You will see that there is:

- a 75% chance of their child having blood type A (one out of four squares or 25% has two A alleles while two out of four or 50% have the A and O alleles together) and
- a 25% chance (one square out of four) of having both alleles or blood type O.

This type of inheritance, where one gene controls one measurable characteristic, is called simple Mendelian inheritance, after the monk, Gregor Mendel, who first deduced the mechanism of single-gene inheritance.