



Genetics 101

Genes are the fundamental units of heredity. In everyday terms, we often think of genes as being instructions for a particular trait such as hair or eye color. Genes are made of a chemical called deoxyribonucleic acid, or DNA. Each gene has the chemical instructions for making a specific protein, and each protein has a particular function in the body, such as manufacturing enzymes for biochemical processes.

Individual genes are packaged into structures called chromosomes. Humans have a total of 46 chromosomes, which are located in the center of every cell of the body. We receive half of these chromosomes from our mothers and half from our fathers. Twenty-two pairs of chromosomes are identical in men and women; these are called autosomes. The last pair, the sex chromosomes, differ in men and women. Men have one X and one Y chromosome, and women have two X chromosomes.

Genetic disorders arise when one or both copies of a specific gene have undergone an alteration known as a mutation. When an alteration in just one copy of a gene pair causes a genetic disorder, the disorder is referred to as dominant. When alterations in both copies of a gene are required for the disorder to be present, the disorder is considered recessive.

Autosomal dominant inheritance

Someone who possesses a gene for a dominant disorder usually manifests the disorder and is affected by it. Since each parent passes only one copy of every gene to a child, a child conceived by an affected individual has a 50% chance of inheriting the abnormal copy of the gene (and thus the disorder) and a 50% chance of inheriting the normal copy of the gene. The same risk applies to each conception, regardless of the outcome of previous conceptions.

A dominant disorder sometimes appears in an individual whose parents do not have the disorder. This occurs when a new mutation has arisen in a gene. In such cases the alteration occurred for the first time in the sperm or egg that resulted in the conception of the child, rather than being inherited from one of the parents.

Dominant disorders can occur in multiple generations in a family and do not “skip” a generation. They affect men and women equally. There can be multiple affected family members in one generation. Except when there has been a new mutation, every affected individual has an affected parent.

Autosomal recessive inheritance

In many cases, when a single copy of a gene undergoes a mutation, there is no visible evidence of that alteration. In these instances, the disorder is considered recessive, since the normal copy of the gene appears to compensate for the altered one. When both copies of the gene are

abnormal, however, the disorder becomes apparent. In order for an individual to have two abnormal copies of a gene, an abnormal copy of the gene must be inherited from each parent. Couples who have had a child affected with a recessive disorder, or who are both known to be carriers of a recessive gene by some type of testing, have a 25% chance that any future child will have the disorder, a 25% chance that the child will inherit both normal copies of the gene and a 50% chance that the child will be a carrier, inheriting a normal copy of the gene from one parent and an abnormal copy from the other.

There is typically not a “family history” with autosomal recessive disorders, since these conditions require both parents to be carriers. Carrier parents are expected to be healthy.

X-linked recessive inheritance (Sex-linked inheritance)

Human cells contain 22 pairs of chromosomes, called autosomes, and one pair of sex chromosomes: X and Y for men and X and X for women. A gene that is X-linked is physically located on the X chromosome. For recessive inheritance, a person will be unaffected by a disorder as long as they have one functional copy of a gene present, even if the other copy is not functioning. With X-linked disorders, when there is a mutated gene on the X chromosome, men will be affected because they have only one copy of the X chromosome, or are hemizygous, and have no “backup” copy to make the necessary protein product. Women who have one mutated copy of the gene are generally unaffected because their one functional copy acts as a “backup” to the nonfunctional one, and produces the necessary protein product.

Males receive a Y chromosome from their father and an X chromosome from their mother. Females receive an X chromosome from both parents. Unlike autosomal dominant or autosomal recessive inheritance, very different possibilities can result for affected children, depending upon which parent transmits the defective gene.

If a man is affected with an X-linked recessive disorder, his mutated copy of the gene will be passed to all of his daughters and none of his sons. This is because his daughters receive his X chromosome, which has the mutated gene, and his sons receive his Y chromosome. Therefore all of his daughters will be carriers and none of his sons will be affected. His daughters may have affected sons, but his sons will not have any affected descendants because they do not have a mutated copy to transmit.

If a woman carries a gene for an X-linked recessive disorder (i.e., one of her copies of the gene is mutated and the other copy is normal), she will pass the mutated copy of the gene on to half of her sons and half of her daughters. On average, half of her sons would be affected and half of her daughters would be carriers.

It is possible (but highly unlikely) that a woman would be homozygous recessive for an X-linked disorder and thus be affected by it. In this case, all of her sons would be affected and all of her daughters would be carriers.

Examples of X-linked recessive traits are color-blindness, hemophilia and Glucose-6-phosphate dehydrogenase (G6PD) deficiency .

Manifesting female carriers

Women occasionally are manifesting carriers of an X-linked recessive disorder, which means that although they have only one mutated copy of the gene, they are affected by the disorder. This is also called “skewed Lyonization” or “skewed X-inactivation.”

In order to understand this, it is important to remember that women have two X chromosomes and men have only one. Close to a thousand genes on the X chromosome important to both men and women encode proteins necessary for the body to function. Both men and women normally make the same amount of protein product from these genes. In order for women, who have two X chromosomes, to produce the same amount of protein as men, who only have one X chromosome, a process called X-inactivation occurs in all females during early embryonic development. The process permanently inactivates or blocks gene expression from one of the two X chromosomes in every cell of her body. Which of the two X chromosomes becomes inactivated in each cell is completely random.

For a female carrier of a mutated X chromosome gene, just by random X-inactivation 50 percent of her cells should have a functional copy of that gene on the active X-chromosome and 50 percent should have a mutated copy on the active X chromosome. Thus, due to this randomness, female carriers are usually unaffected by X-linked recessive disorders since on average half their cells are making the necessary protein product, which is usually sufficient to prevent disease symptoms.

Occasionally the inactivation process may be skewed and a woman may have a larger-than-average proportion of her cells with the mutated gene on the active X-chromosome. This may result in signs of the disorder because she would not produce enough of the protein necessary for the body to function normally, and she would be a manifesting female carrier. G6PD deficiency is an example of an x-linked disorder which may affect females in this manner.

What are Jewish genetic diseases?

Jewish genetic diseases are a group of disorders that occur with higher frequency in the Jewish population. The Ashkenazi Jews, those whose ancestors were from Central and Eastern Europe (i.e. Poland, Russia, Germany, Lithuania, etc.) are at higher risk than the general population for several genetic diseases. This is primarily due to the fact that the Jewish communities in Europe were small and isolated, and members tended to marry within those communities. Since it is estimated that all individuals carry a small number of gene changes (called mutations), the ones present in those small groups of European Jews became more prevalent in future generations.

What are the diseases?

Below are the Ashkenazi Jewish genetic diseases for which people are most commonly screened. It is estimated that 1 in 4 Ashkenazi Jews is a carrier of a mutation in at least one of these disease genes:

- Bloom syndrome
- Canavan Disease
- Cystic Fibrosis
- Dihyrolipoamide Dehydrogenase Deficiency (DLD Deficiency)
- Familial Dysautonomia
- Familial Hyperinsulinism
- Fanconi Anemia Type C
- Gaucher Disease
- Glycogen Storage Disease, Type 1a
- Joubert Syndrome
- Maple Syrup Urine Disease
- Mucopolysaccharidosis IV (ML4)
- Nema-line Myopathy
- Niemann-Pick Disease Type A
- Spinal Muscular Atrophy
- Tay-Sachs Disease
- Usher Syndrome Type 1F
- Usher Syndrome Type III
- Walker-Warburg syndrome

How are the Diseases Inherited?

In each of the cells in our bodies, we have tiny structures called chromosomes. There are thousands of genes on each chromosome. Genes are the basic units of heredity that are passed from parent to child. These genes make up who we are and guide the development of the body. For instance, there are genes for eye and hair color. These genes are in pairs; one is inherited from each parent. Sometimes, a change in a gene, called a mutation, causes the gene to malfunction and can lead to disease.

The diseases mentioned here are inherited in an autosomal recessive manner. This means that males and females are equally likely to be carriers and are equally likely to be affected (have a disease). Individuals who are affected with one of these diseases have two mutations, one in each copy of the gene, for that disease. Carriers have one copy of the gene mutation and one normal working copy of the gene. Carriers are healthy individuals with no signs of the disease, and they are not at risk to develop the disease. If both partners are carriers of a mutation in the same disease gene, there is a 25% chance of having an affected child, a 50% chance of the child being a carrier like themselves, and a 25% chance of the child being neither affected nor a carrier.