



Inheritance

CHAPTER

15

Many diseases are genetic in origin and consequently, are passed on in families. Most of the immunodeficiency diseases are inherited in one of two different modes of inheritance: X-linked recessive or autosomal recessive. Laboratory studies and family history can be helpful in establishing the possible role of genes or chromosomes in a particular primary immunodeficiency disease and may help to identify a particular pattern of inheritance.

Inheritance of Primary Immunodeficiency Diseases

Most of our physical and chemical characteristics are passed along from parents to children.

Examples of these include the color of our eyes, our hair color, and the chemicals that determine our blood type. In the same manner, many of the primary immunodeficiency diseases are inherited, or passed on, in families. The chemical structures that are responsible for these characteristics, and the tens of thousands of other characteristics that make an individual unique are called genes. These genes are packaged on long, string-like structures called chromosomes. Every cell in the body contains all the chromosomes and consequently, all of the genes necessary for life.

Each of our cells contains 23 pairs of chromosomes, hence, 23 sets of gene pairs. One of each pair of chromosomes is inherited from our mother while the other is inherited from our father. Since genes are on these chromosomes, we also inherit one gene (or message) for a certain characteristic (such as eye color) from our mother and one gene for the same characteristic from our father.

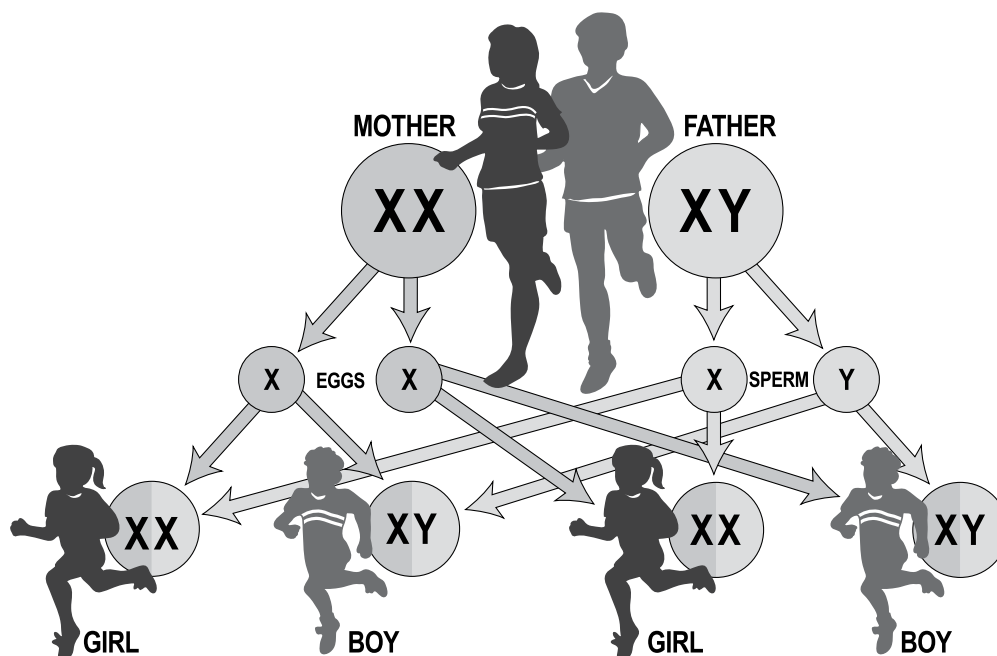
During egg and sperm production, the total number of 46 parental chromosomes (23 pairs) is divided in half. One chromosome of each pair, and only one,

is normally passed on in each egg or sperm. When fertilization of the egg occurs, the 23 chromosomes contained in the egg combine with the 23 chromosomes in the sperm to restore the total number to 46. In this way each parent contributes half of his/her genetic information to each offspring.

All of the chromosomes except the sex chromosomes are called autosomes and are numbered from 1-22 according to size. One additional pair of chromosomes determines the sex of the individual. These are called the sex chromosomes and are of two types, X and Y chromosomes. As shown in *Figure 1*, females have two X chromosomes, and males have an X and a Y chromosome. As a result of having two X chromosomes, females can only produce eggs that have an X chromosome. In contrast, since men have both an X and Y chromosome, half of the sperm produced will contain an X chromosome and half will carry a Y chromosome. The sex of the baby is determined by which type of sperm fertilizes the egg. If the sperm that fertilizes (or combines with) the egg carries an X chromosome, the child that results will be a female. If the sperm carries a Y chromosome, the child that results will be a male.

CHAPTER 15; FIGURE 1

The Sex Chromosomes



Types of Inheritance

Many diseases are genetic in origin and are passed on in families. Most of the primary immunodeficiency diseases are inherited in one of two different modes of inheritance; X-linked recessive or autosomal recessive. Rarely, the inheritance is autosomal dominant. Laboratory studies can be helpful in establishing the possible role of genes or chromosomes in a particular primary immunodeficiency disease. In addition, family history information may help to identify a particular pattern of inheritance, as can comparisons to other families with similar problems.

Consult the appropriate handbook chapter or your physician to learn whether a particular immune deficiency disease is genetic, and if so, what form of inheritance is involved.

X-linked Recessive Inheritance

One type of single gene disorder involves those genes located on the X chromosome. Since women have two X chromosomes, they usually do not have problems when a gene on one X chromosome does not work properly. This is because they have a second X chromosome that usually carries a normal

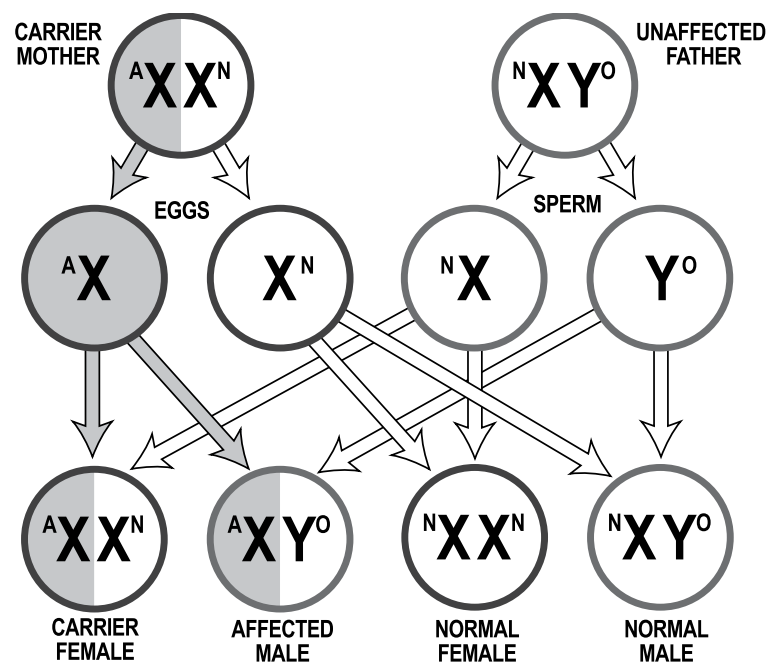
gene and compensates for the abnormal gene on the affected X chromosome. Men have only one X chromosome, which is paired with their male-determining Y chromosome. The Y chromosome does not carry much active genetic information. Therefore, if there is an abnormal gene on the X chromosome, the paired Y chromosome has no normal gene to compensate for the abnormal gene on the affected X chromosome, and the boy (man) has the disorder. This special type of inheritance is called X-linked recessive.

In this form of inheritance, a family history of several affected males may be found. The disease is passed on from females (mothers) to males (sons). While the males are affected with the disease, the carrier females are generally asymptomatic and healthy even though they carry the gene for the disease because they carry a normal gene on the other X chromosome. The diagram in *Figure 2* illustrates how this kind of inheritance operates in the usual situation.

X-linked agammaglobulinemia is used as the specific example. Parents in the situation shown in *Figure 2* can have 4 different types of children with respect to X-linked agammaglobulinemia.

CHAPTER 15; FIGURE 2

X-linked Recessive Inheritance—Carrier Mother



Types of Inheritance continued

The X chromosome is diagrammed as an “X.”
An X chromosome that carries the gene for agammaglobulinemia is represented by an “AX.”
A normal X chromosome is represented by an “XN.”
A “Y” represents a Y chromosome.

The mother, who is a carrier, can produce two kinds of eggs—one containing an X chromosome carrying the agammaglobulinemia gene (AX), and one containing an X chromosome with a normal gene (XN). The father, who is unaffected, can produce two kinds of sperm—one containing a normal X chromosome (XN), and one containing a Y chromosome.

If the egg containing the agammaglobulinemia X chromosome (AX) combines with (or is fertilized by) the sperm containing the normal X chromosome, then a daughter who is a carrier (AX/XN) is produced. The gene for agammaglobulinemia is balanced out by the normal gene on the other X chromosome.

If the egg containing the agammaglobulinemia X chromosome (AX) combines with the sperm containing the Y chromosome (Y), then a male who is affected with agammaglobulinemia (AX/Y) is produced. In this case, there is no gene

Examples of Primary Immunodeficiency Diseases with X-linked Recessive Inheritance:

X-Linked Agammaglobulinemia
Wiskott-Aldrich Syndrome
Severe Combined Immunodeficiency (one form)
Hyper IgM syndrome (two forms)
X-Linked Lymphoproliferative Disease
Chronic Granulomatous Disease (one form)

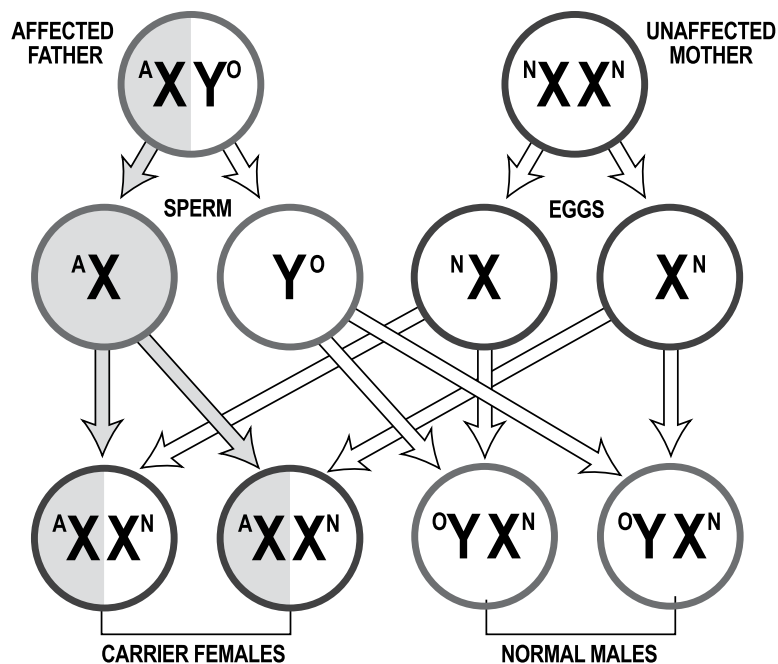
on the Y chromosome that corresponds to the agammaglobulinemia gene, and only the agammaglobulinemia gene is active in the child.

If the egg containing the normal X chromosome (XN) combines with the sperm containing the normal X chromosome (XN) then a normal female (XN/XN) is produced. In this case the child does not carry the agammaglobulinemia gene.

Finally if the egg containing the normal X chromosome (XN) combines with the sperm containing the Y chromosome (Y), then a normal male (XN/Y) results.

CHAPTER 15; FIGURE 3

X-linked Recessive Inheritance—Affected Father



Types of Inheritance continued

The chances for a given egg combining with a given sperm are completely random. According to the laws of probability, the chance for any given pregnancy of a carrier female to result in each of these outcomes is as follows:

Carrier female—1 in 4 chance or 25%

Agammaglobulinemia male—1 in 4 chance or 25%

Normal female—1 in 4 chance or 25%

Normal male—1 in 4 chance or 25%

It should be noted that the outcome of one pregnancy is not influenced by the outcome of a previous pregnancy. Just as in coin flipping, the fact that you get a “heads” on your first toss doesn’t mean you will get a “tails” on the next. Similarly, if you have a son with agammaglobulinemia with your first pregnancy you are not guaranteed to have an unaffected child with your second pregnancy; your chances of having a son with agammaglobulinemia are still 1 in 4 (25%) with each pregnancy.

In most of the X-linked primary immunodeficiency diseases, carrier females can be identified by laboratory tests if the mutation in a given family

has been determined. Consult with your physician or genetic counselor to learn if carrier detection is available in your specific situation.

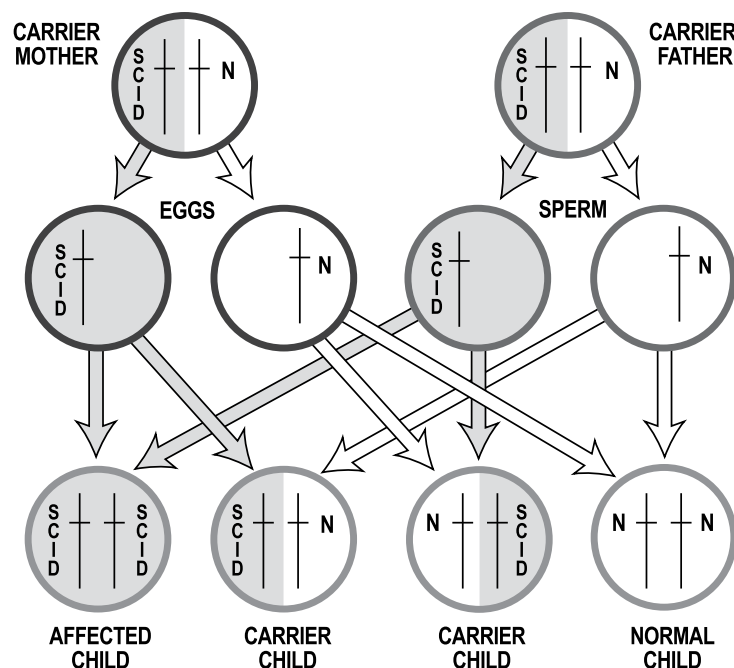
With earlier diagnosis and improved therapy, many young men with X-linked disorders, such as agammaglobulinemia, are reaching adult life and having children of their own. *Figure 3* illustrates the kind of children that a man with X-linked agammaglobulinemia would have if he married a woman who did not carry the gene for agammaglobulinemia. As can be seen in *Figure 3*, all of the daughters of an affected male would be carrier females and none of the sons would be affected.

Autosomal Recessive Inheritance

If a primary immunodeficiency disease can only occur if two abnormal genes (one from each parent) are present in the patient, then the disorder is inherited as an autosomal recessive disorder. If an individual inherits only one gene for the disorder; then he or she carries the gene for the disorder but does not have the disorder itself.

CHAPTER 15; FIGURE 4

Autosomal Recessive Inheritance—SCID Example



Types of Inheritance continued

In this form of inheritance, males and females are affected with equal frequency. Both parents carry the gene for the disease although they themselves are healthy. *Figure 4* illustrates how this kind of inheritance operates in the usual situation. One form of severe combined immunodeficiency disease (SCID) is used as the specific example.

As illustrated in *Figure 4*, these parents, each of whom is a carrier, can have 3 different types of children with respect to SCID. The chromosome carrying the gene for SCID is diagrammed as a vertical line with the initials SCID next to it. The normal chromosome is diagrammed as a vertical line with the initial "N" next to it. The mother can produce two kinds of eggs—one containing the chromosome carrying the SCID gene and one containing a chromosome carrying the normal gene. Similarly, the father can produce two kinds of sperm—one kind containing the chromosome carrying the SCID gene and the other containing the chromosome carrying the normal gene. If an egg containing the SCID chromosome combines with a sperm containing the SCID chromosome, then a child with SCID is produced; in this case the child has two genes for SCID and no normal genes to counteract them. If an egg containing the chromosome carrying the SCID gene combines with a sperm containing a normal chromosome then a carrier child results; in this case the gene for SCID is balanced by a normal gene and the child is well, but still carries the gene for SCID. Similarly, if an egg containing the normal chromosome combines with a sperm containing the chromosome carrying the SCID gene, a carrier child is also produced.

Examples of Autosomal Recessive Inheritance:

Severe Combined Immunodeficiency
(several forms)

Chronic Granulomatous Disease (several forms)

Ataxia Telangiectasia

Finally, if an egg containing the normal chromosome combines with a sperm containing the normal chromosome, a normal child who is neither a carrier nor has the disease is produced.

The chances for a given egg to combine with a given sperm are completely random. According to the laws of probability, the chance for any pregnancy of carrier parents to result in each of the following outcomes is as follows:

Affected child—1 in 4 chance or 25%

Carrier child—2 in 4 chance or 50%

Normal child—1 in 4 chance or 25%

Again, it should be noted that the outcome of one pregnancy is not influenced by the outcome of a previous pregnancy. Just as in coin flipping, the fact that you get a "heads" on your first toss doesn't mean you will get a "tails" on your next. Similarly, if you have a child with SCID with your first pregnancy you are not guaranteed a normal child or a carrier child with your second pregnancy; your chances of having a child with SCID are still 25% or 1 in 4 with each pregnancy.

Carrier Testing

In many primary immunodeficiency disorders, carrier parents can be identified by laboratory tests. Consult with your physician or genetic counselor to learn if carrier detection is available in your specific situation.

Reproductive Options

After the birth of a child with a special problem, many families face complicated decisions about future pregnancies. The risk of recurrence and the burden of the disorder are two important factors in those decisions. For instance, if a problem is unlikely to occur again, the couple may proceed with another pregnancy even if the first child's problem is serious. Or if the risk of recurrence is high, but good treatment is available, the couple may be willing to try again. On the other hand, when both the risk and the burden are high, the circumstances may seem unfavorable to some families. It should be emphasized that these decisions are personal. Although important information can be gained from speaking to a pediatrician, immunologist, obstetrician and/or genetic counselor, ultimately the parents should decide which option to choose.

There is a number of options available regarding family planning for families with family members with genetically determined (inherited) primary immunodeficiency diseases. In some situations, prenatal testing of a fetus in the uterus can determine whether the infant will be affected by the primary immunodeficiency disease. Chorionic villus sampling (CVS) or amniocentesis can be performed to obtain a fetal sample for chromosome, gene or biochemical testing. CVS is usually scheduled at 10-13 weeks of pregnancy and involves the retrieval of a tiny sample of the developing placenta from the womb. Amniocentesis is typically performed at 16-17 weeks of pregnancy and involves the withdrawal of fluid that surrounds the fetus. Both procedures have a small risk of miscarriage that should be balanced against the benefits of the testing.

Chromosome studies can be performed on cells from CVS or amniocentesis. In addition to determining the chromosome number and structure, this study will identify the sex of the fetus. For conditions that are X-linked, identification of the sex will help determine whether the fetus could be affected by the disease (if male) or a possible carrier (if female).

The fetal sample can also be used to provide DNA (deoxyribonucleic acid) for gene testing. There are two main types of DNA studies: direct and indirect. For some of the primary immunodeficiency diseases, specific gene changes, or mutations, can be identified in affected individuals. If the specific change, or mutation, is known in the affected family member who has the disorder, the mutation can then be tested for in the DNA from a fetal sample obtained during a subsequent pregnancy. This direct testing of the DNA for a specific mutation is the most accurate form of DNA testing. If a specific mutation has not been identified, or cannot be identified, a family linkage study may be possible to follow the mutated gene's transmission through the family. Normal DNA variations near the gene in question, called polymorphisms or markers, can be identified in some families. The inheritance of these markers near the gene of concern can be used to determine whether the gene has been passed on to the fetus.

Finally, for some conditions, biochemical measurement of a particular enzyme or protein in the fetal cells may provide an alternative method of testing for the disorder. Absence or severe deficiency of the enzyme produced by the gene mutation would indicate the presence of the disorder.

In certain situations, other prenatal testing techniques may provide information about the risk of an affected fetus. A detailed sonogram at 16-18 weeks of pregnancy can often identify the sex of the fetus. This information can be helpful to families deciding whether to undergo amniocentesis for an X-linked disorder. For some families, testing chorionic villus or amniotic fluid cells will not provide the proper information about the fetus's status, but testing of the fetus's blood will provide the proper information. This procedure can be performed after 18 weeks of pregnancy and involves the insertion of a needle into the fetus's umbilical cord or liver vein to withdraw a small amount of blood for testing.

If an affected fetus is identified through prenatal testing, the couple can then decide whether they wish to continue the pregnancy.

Reproductive Options continued

Some couples at risk for autosomal recessive disorders elect to use donor sperm through a process called artificial insemination. Alternatively, in both autosomal recessive and X-linked recessive disorders, donor eggs can be used. The risk for an affected child is reduced substantially by using a donor, as the donor would be unlikely to be a carrier of the same condition. Finally, for certain conditions, testing of the early embryo may be possible after in vitro fertilization (conception outside the womb). This process, called pre-implantation diagnosis, allows for those embryos unaffected with the genetic condition to be transferred to the woman's uterus. Afterwards the child is carried like any other until birth. Although this type of procedure is not yet readily available for any of the primary immunodeficiency diseases, it may be accessible in the future.

Some couples may choose to adopt a child, if they do not wish to attempt a pregnancy themselves. Although this process can be frustrating and lengthy, many couples are successful in locating a baby or child to join their family. Finally, the option of maintaining the current family size may seem best to some couples. This may be because the possibility of having an affected child is unacceptable or because the demands of the current family are high. Expansion of the family just may not be desired.

Careful consideration of these options is important before decisions can be reached. In addition, periodic consultation with the medical staff can be helpful in keeping current with recent medical advances that could potentially provide more information for your family. Once again, it should be emphasized that these decisions are personal. Although important information can be gained from speaking to your pediatrician, immunologist, obstetrician and/or genetic counselor, ultimately the parents should decide which option they choose.