If you’re thinking of starting a family or adding to your brood, you may be wondering what your little ones will look like. Will they get your eyes or your dad’s hairline? If you know your family’s medical history, you may also have significant worries about diseases such as cystic fibrosis, Tay-Sachs, or sickle cell anemia. You may worry about your own health, too, as you contemplate news stories dealing with cancer, heart disease, and diabetes, for example. All these concerns revolve around genetics and the inheritance of a predisposition for a particular disease or the inheritance of the disorder itself.

Genetic counselors are specially and rigorously trained to help people learn about the genetic aspects of their family medical histories. This chapter explains the process of genetic counseling, including how counselors generate family trees and estimate probability of inheritance and how genetic testing is done when genetic disorders are anticipated.

Getting to Know Genetic Counselors

Like it or not, you have a family. You have a mother and a father, grandparents, and perhaps children of your own. You may not think of them, but you also have hundreds of ancestors — people you’ve never met — whose genes you carry and may pass down to descendants in the centuries to come.

Genetic counselors help people like you and me examine our families’ genetic histories and uncover inherited conditions. They work with medical personnel like physicians and nurses to interpret medical histories of patients and their families. Although they aren’t trained as geneticists, they usually hold a master’s degree in genetic counseling and have an extensive background in genetics (and can solve genetics problems in a snap; see
Chapters 3 through 5 for some examples) so that they can spot patterns that signal an inherited disorder. (For more on genetic counselors and other career paths in genetics, see Chapter 1.)

Genetics counselors perform a number of functions, including

- Constructing and interpreting family trees, sometimes called pedigrees, to assess the likelihood that various inherited conditions will be (or have been) passed on to a particular generation.
- Counseling families about options for diagnosis and treatment of genetic conditions.

Physicians most commonly refer the following types of people or patients to genetic counselors:

- Couples who are concerned about exposure to substances known to cause birth defects (such as radiation, viruses, drugs, and chemicals)
- Couples who have experienced more than one miscarriage or stillbirth or who have problems with infertility
- Parents of a child who shows symptoms of a genetic disorder
- People with a family history of a particular disorder, such as cystic fibrosis, who are planning a family
- People with a family history of inherited diseases like Parkinson disease or certain cancers such as breast, ovarian, or colon cancer who may be considering genetic testing to determine their risk of getting the disease
- Women over 35 who are pregnant or planning a pregnancy
- Women who have had an abnormal screening test, such as an ultrasound, during a pregnancy

I cover many of the scientific reasons for the inheritance of genetic disorders elsewhere in this book. Mutations within genes are the root cause of many genetic disorders (including cystic fibrosis, Tay-Sachs disease, and sickle cell anemia), and I cover mutation in detail in Chapter 13. I discuss the causes and genetic mechanics of cancer in Chapter 14. I explain chromosomal disorders such as Down syndrome, trisomy 13, and fragile X syndrome in Chapter 15. Finally, I cover gene therapy treatments for inherited disorders in Chapter 16.

**Building and Analyzing a Family Tree**

Often the first step in genetic counseling is drawing a family tree. The tree usually starts with the person for whom the tree is initiated; this person is called the proband. The proband can be a newly diagnosed child, a woman planning a pregnancy, or an otherwise healthy person who’s curious about
risk for inherited disease. Often, the proband is simply the person who meets with the genetic counselor and provides the information used to plot out the family tree. The proband’s position in the family tree is always indicated by an arrow, and he or she may or may not be affected by an inherited disorder.

Genetic counselors use a variety of symbols on family trees to indicate personal traits and characteristics. For instance, certain symbols convey sex, gene carriers, whether the person is deceased, and whether the person’s family history is unknown. The manner in which symbols are connected show relationships among people, such as which offspring belong to which parents, whether someone is adopted, and whether someone is a twin. Check out Figure 12-1 for a detailed key to the symbols typically used in pedigree analysis.

<table>
<thead>
<tr>
<th>Male</th>
<th>Female</th>
<th>Sex unspecified</th>
</tr>
</thead>
<tbody>
<tr>
<td>![Male Symbol]</td>
<td>![Female Symbol]</td>
<td>![Sex unspecified Symbol]</td>
</tr>
</tbody>
</table>

### Adoption:
- Brackets = adopted individuals;
- Dashed line = adoptive parents;
- Solid line = biological parents

### Twins:
- Identical
- Nonidentical

### Example pedigree:
Grandfather of the proband died of a heart attack at age 51. Grandfather is from generation I and referred to as I-1; proband, from generation III, is referred to as III-1.

In a typical pedigree, the age or date of birth of each person is noted on the tree. If deceased, the person’s age at the time of death and the cause of death are listed. Some genetic traits are more common in certain regions of the world, so it’s useful to include all kinds of other details about family history on the pedigree, such as what countries people immigrated from or how they're related. Every member of the family should be listed, along with any medical information known about that person, including the age at which certain medical disorders occurred. In the example in Figure 12-1, the
grandfather of the proband died of a heart attack at age 51. Including this information creates a record of all disorders with the relation to the family tree so that the counselor is more likely to detect every inherited disease present in the family. (Medical information doesn’t appear in Figure 12-1, but it’s normally a part of a tree.)

Medical problems often listed on pedigrees include

- Alcoholism or drug addiction
- Asthma
- Birth defects, miscarriages, or stillbirths
- Cancer
- Heart disease, high blood pressure, or stroke
- Kidney disease
- Mental illness or mental retardation

Human couples have only a few children relative to other creatures, and humans start producing offspring after a rather long childhood. Geneticists rarely see neat offspring ratios (such as four siblings with three affected and one unaffected) in humans that correspond to those observed in animals (take a look at Chapters 3 and 4 for more on common offspring ratios). Therefore, genetic counselors must look for very subtle signs to detect particular patterns of inheritance in humans.

When the genetic counselor knows what kind of disorder or trait is involved, he or she can determine the likelihood a particular person will possess the trait or pass it on to his or her children. (Sometimes, the disorder is unidentified, such as when a person has a family history of “heart trouble” but doesn’t have a precise diagnosis.) Genetic counselors use the following terms to describe the individuals in a pedigree:

- **Affected**: Any person having a given disorder.
- **Heterozygote**: Any person possessing one copy of the mutated gene coding for a disorder (an allele; see Chapter 2 for details). An unaffected heterozygote is called a **carrier**.
- **Homozygote**: Any person possessing two copies of the allele for a disorder. This person can also be described as **homozygous**.

The particular way in which most human genetic disorders are passed down to later generations — the **mode of inheritance** — is well established. After a genetic counselor determines which family members are affected or are likely to be carriers, it’s relatively easy to determine the probability of another person being a carrier or inheriting the disorder.
In the following sections, I explore the modes of inheritance for human genetic disorders, how genetic counselors map these modes, and how you (and your counselor) can figure out the probability of passing these traits on to offspring. For additional background on each of these modes of inheritance and the subject of inheritance in general, see Chapters 3 through 5.

**Autosomal dominant traits**

A *dominant* trait or disorder is one that’s expressed (or manifested) in anyone who inherits the mutation for the trait. *Autosomal dominant* means that the gene is carried on a chromosome other than a sex chromosome (meaning not on an X or a Y; see Chapter 3 for more details). In human pedigrees, autosomal dominant traits have some typical characteristics:

- Affected children are born to an affected parent.
- Both males and females are affected with equal frequency.
- If neither parent is affected, usually no child is affected.
- The trait doesn’t skip generations.

Figure 12-2 shows the pedigree of a family with an autosomal dominant trait. In the figure, affected persons are shaded, and you can clearly see how only affected parents have affected children. The trait can be passed to a child from either the mother or the father. Generally, affected parents have a 50-percent chance of passing an autosomal dominant trait or disorder on to each child.

Some common autosomal dominant disorders are

- Achondroplasia, a form of dwarfism
- Huntington disease, a progressive and fatal disease affecting the brain and nervous system
- Marfan syndrome, a disorder affecting the skeletal system, heart, and eyes
- Polydactyly, or extra fingers and toes

The normal pattern of autosomal dominant inheritance has three exceptions:

- **Reduced penetrance**: *Penetrance* is the percentage of individuals having a particular gene (genotype) that actually display the physical characteristics dictated by the gene (or express the gene as phenotype, scientifically speaking; see Chapter 3 for a full rundown of genetics terms). Many autosomal dominant traits have complete penetrance, meaning that every person inheriting the gene shows the trait. But some traits have *reduced penetrance*, meaning only a certain percentage of individuals inheriting the gene show the phenotype.
When an autosomal dominant disorder shows reduced penetrance, the phenotype skips generations. Check out Chapter 3 for more details on reduced penetrance.

- **New mutations:** In the case of new mutations that are autosomal dominant, the trait appears for the first time in a particular generation and can appear in every generation thereafter. You can flip to Chapter 13 to find out more details about mutations — how they occur and how they’re passed on.

- **Variable expressivity:** Expressivity is the degree to which a trait is expressed. Some conditions may be undiagnosed in earlier generations because the condition is so mild, it goes undetected. Turn to Chapter 4 to find out more about expressivity.

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**Autosomal recessive traits**

Recessive disorders are expressed only when an individual inherits two identically altered (or mutated) copies of the gene that causes the disorder. It’s then said that the individual is homozygous for that gene (see Chapter 3 for more details on inheritance). Like autosomal dominant disorders, autosomal recessive disorders are coded in genes found on chromosomes other than sex chromosomes. In pedigrees, such as the one in Figure 12-3, autosomal recessive disorders typically have the following characteristics:

- Affected children are born to unaffected parents.
- Both males and females are affected equally.
- Children born to parents who share common ancestry (such as ethnic or religious background) are more likely to be affected than those of parents with different backgrounds.
- The disorder or trait skips one or more generations, or is present only in a single generation (siblings).
The probability of inheriting an autosomal recessive disorder varies depending on which alleles parents carry (see Chapter 3 for all the details on how the odds of inheritance are calculated):

✓ **When both parents are carriers**, every child born to the couple has a 25 percent chance of being affected.

✓ **When one parent is a carrier and the other isn’t**, every child has a 50 percent chance of being a carrier. No child will be affected.

✓ **When one parent is a carrier and the other is affected**, each child has a 50 percent chance of being affected. All unaffected children from the union will be carriers.

✓ **When one parent is affected and the other is unaffected (and not a carrier)**, all children born to the couple will be carriers. No children will be affected.

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**Cystic fibrosis (CF)** is an autosomal recessive disorder that causes severe lung and digestive problems in affected persons. As with all autosomal recessive disorders, if both members of a couple are carriers for cystic fibrosis, they have a 25 percent chance of having an affected child with each pregnancy they have. That’s because both the man and the woman are heterozygous for the allele that codes for cystic fibrosis, and each has a 50 percent probability of contributing the CF allele. You calculate the probability of both members of the couple contributing CF alleles in one fertilization event by multiplying the probability of each event happening independently. The probability the father contributes his CF allele is 50 percent, or 0.5; the probability the mother contributes her CF allele is also 50 percent, or 0.5. The probability that both contribute their allele is $0.5 \times 0.5 = 0.25$, or 25 percent. For more details on how to calculate probabilities of inheritance, flip to Chapters 3 and 4.
Some autosomal recessive disorders are more common among people of certain religious or ethnic groups, because people belonging to those groups tend to marry within the group. After many generations, everyone within the group shares common ancestry. When cousins or other close relatives marry, such relationships are referred to as consanguineous (meaning “same blood”). Generally, people who are more distantly related than fourth cousins aren’t considered “related,” but in fact, those persons still share alleles from a common ancestor. When populations are founded by rather small groups of people, those groups often have higher rates of particular genetic disorders than the general population; for more details, take a look at the sidebar “Genetic disorders in small populations.” In these cases, autosomal recessive disorders may no longer skip generations, because so many persons are heterozygous and thus carriers of the disorder.

**X-linked recessive traits**

Males are XY and therefore have only one copy of the X chromosome; they don’t have a second X to offset the expression of a mutant allele on the affected X. Thus, similar to autosomal dominant disorders, X-linked recessive disorders express the trait fully in males, even though they’re not homozygous. Females rarely show X-linked recessive disorders, because being homozygous for the disorder is very rare. In pedigrees, X-linked recessive disorders have the following characteristics:
✓ Affected sons are born to unaffected mothers.
✓ Far more males than females are affected.
✓ The trait is *never* passed from father to son.
✓ The disorder skips one or more generations.

Unaffected parents can have unaffected daughters and one or more affected sons. Women who are carriers frequently have brothers with the disease, but if families are small, a carrier may have no affected immediate family members. Sons of affected fathers are never affected, but daughters of affected fathers are always carriers, because daughters must inherit one of their X chromosomes from their fathers. In this case, that X chromosome will always carry the allele for the disorder. The pedigree in Figure 12-4 is a classic example of a well-researched family possessing many carriers for the X-linked disorder hemophilia, a devastating disorder that prevents normal clotting of the blood. For more on the royal families whose history is pictured in Figure 12-4, see the sidebar “A royal pain in the genes.”

The probability of inheritance of X-linked disorders depends on gender. Female carriers have a 50 percent likelihood of passing the gene on to each child. Males determine the gender of their offspring, making the chance of any particular child being a boy 50 percent. Therefore, the likelihood of a carrier mom having an affected son is 25 percent (chance of having a son = 0.5; chance of a son inheriting the affected X = 0.5; therefore, $0.5 \times 0.5 = 0.25$, or 25 percent).

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**Figure 12-4:** The X-linked recessive disorder hemophilia works its way through the pedigree of the royal families of Europe and Russia.
Part III: Genetics and Your Health

X-linked dominant traits

Like autosomal dominant disorders, X-linked dominant traits don’t skip generations. Every person who inherits the allele expresses the disorder. The family tree in Figure 12-5 shows many of the hallmarks of X-linked dominant disorders:

✓ Affected mothers have both affected sons and daughters.
✓ Both males and females are affected.
✓ All daughters of affected fathers are affected.
✓ The trait doesn’t skip generations.

A royal pain in the genes

You can find one of the most famous examples of an X-linked family pedigree in the royal families of Europe and Russia, which you can see in Figure 12-4. Queen Victoria of England had one son affected with hemophilia. It’s not clear whom Queen Victoria inherited the allele from; she may have been the victim of spontaneous gene mutation. In any event, two of her daughters were carriers, and she had one affected son, Leopold. Queen Victoria’s granddaughter Alexandra was also a carrier. Alexandra married Nicholas Romanov, who became czar of Russia, and together they had five children: four daughters and one son. The son, Alexis, suffered from hemophilia.

The role Alexis’s disease played in his family’s ultimate fate is debatable. Clearly, however, one of the men who influenced the downfall of Russia’s royal family was linked to the family as Alexis’s “doctor.” Gregory Rasputin was a self-proclaimed faith healer; in photographs, he appears wild-eyed and deeply intense. He’s generally perceived to have been a fraud, but at the time, he had a reputation for miraculous healings, including helping little Alexis recover from a bleeding crisis. Despite Rasputin’s talent for healing, Alexis didn’t live to see adulthood. Shortly after the Russian Revolution broke out, the entire Russian royal family was murdered. (Rasputin himself had been murdered some two years earlier.)

In a bizarre final twist to the Romanov tale, a road repair crew discovered the family’s bodies in 1979. Oddly, two of the family members were missing. Eleven people were supposedly killed by firing squad on the night of July 16, 1918: the Russian royal family (Alexandra, Nicholas, and their five children) along with three servants and the family doctor. However, the bodies of Alexis and his little sister, Anastasia, have never been found. Using DNA fingerprinting, researchers confirmed the identities of Alexandra and her children by matching their mitochondrial DNA to that of one of Queen Victoria’s living descendants, Prince Philip of England. (To find out more about the forensic uses of DNA, flip to Chapter 18.)
X-linked dominant traits show up more often in females than males because females can inherit an affected X from either parent. In addition, some disorders are lethal in males who are hemizygous (having only one copy of the chromosome, not two; see Chapter 5). Affected females have a 50 percent chance of having an affected child of either sex. Males never pass their affected X to sons; therefore, sons of affected fathers and unaffected mothers have no chance of being affected, in contrast to daughters, who are always affected. The probability of an affected man having an affected child is 50 percent (that is, equal to the likelihood of having a daughter).

**Y-linked traits**

The Y chromosome is passed strictly from father to son. By definition, Y-chromosome traits are considered hemizygous. Y-chromosome traits are expressed as if they were dominant because there’s only one copy of the allele per male, with no other allele to offset the effect of the gene. Y-linked traits are easy to recognize when seen in a pedigree, such as Figure 12-6, because they have the following characteristics:

- Affected men pass the trait to all their sons.
- No women are ever affected.
- The trait doesn’t skip generations.

Because the Y chromosome is tiny and has relatively few genes, Y-linked traits are very rare. Most of the genes involved control male-only traits such as sperm production and testis formation. If you’re female and your dad has hairy ears, you can relax — hairy ears is also considered a Y-linked trait.
Genetic Testing for Advance Notice

With the advent of many new technologies (some of which grew out of the Human Genome Project, which I explain in Chapter 8), genetic testing is easier and cheaper than ever. Genetic testing and genetic counseling often go hand in hand. The genetic counselor works to identify which disorders occur in the family, and testing then examines the DNA directly to determine whether the disorder-causing gene is present. Your physician may refer you or a family member for genetic testing for a variety of reasons, particularly if you

✔ Are a healthy person concerned about certain heritable disorders in your ethnic background or family such as breast cancer or Huntington disease

✔ Are a healthy person with a family history of a recessive disorder, and you’re thinking about having a child

✔ Are a pregnant woman over 35

✔ Are an affected person and need to confirm a diagnosis

✔ Have an infant who’s at risk (because his or her parents are known or suspected carriers)

General testing

Every person the world over carries one or more alleles that cause genetic disease. Most of us never know which alleles or how many we carry. If you have a family member who’s affected with a rare genetic disorder, particularly an autosomal dominant disorder with incomplete penetrance or delayed onset, you may be vitally concerned about which allele(s) you carry. Persons currently unaffected with certain disorders can seek genetic testing to learn if they’re carriers. Most tests involve a blood sample, but some are done with a simple cheek swab to capture a few skin cells. You can find more about
genetic testing for inherited disorders in Chapter 13 and about testing for inherited forms of cancer in Chapter 14. Genetic testing has many ethical implications, as I cover in Chapter 21.

**Prenatal testing**

Prenatal diagnosis is commonly used for unborn children of women over 35, because such women are much more likely than younger women to have children with chromosomal disorders (see Chapter 15). Prenatal testing is designed to allow time for couples to make decisions about treatments to be administered either during pregnancy or after delivery of an affected infant.

**Chorionic villus sampling and amniocentesis**

For definitive diagnosis of a genetic disorder, testing requires tissue of the affected person. Two common prenatal tests used to obtain fetal tissue for testing are chorionic villus sampling (CVS) and amniocentesis. Both tests require ultrasound to guide the instruments used to obtain the samples (see the following section for more info on ultrasound).

✓ **CVS** is usually done late in the first trimester of pregnancy (weeks 10 to 12). A catheter is inserted vaginally and guided to the outer layer of the placenta, called the chorion. Gentle suction is used to collect a small sample of chorionic tissue. The placental tissue arises from the fetus, not the mother, so the collected cells give an accurate picture of the fetus’s chromosome number and genetic profile. The advantages of CVS are that it can be done earlier than most other prenatal genetic tests; it’s extremely accurate; and because a relatively large sample is obtained, results are rapidly produced. CVS is associated with a slightly higher rate of miscarriage.

✓ **Amniocentesis** is usually done early in the second trimester of pregnancy (weeks 15 and beyond). Amniocentesis is used to obtain a sample of the amniotic fluid that surrounds the growing fetus, because amniotic fluid contains fetal cells (skin cells that have sloughed off) that can be examined for prenatal testing. The fluid is drawn directly from the uterus using a needle inserted through the abdomen. Because fetal cells in the fluid are at a very low concentration, the cells must be grown in a lab to provide enough tissue for testing, making results slow to come (about one to two weeks). But the results are accurate, and complications following the procedure (such as miscarriage) are rare.

**Ultrasound**

Ultrasound technology allows physicians to examine a growing fetus visually, along with its spinal cord, brain, and all its organs. Ultrasound can be done much earlier in a woman’s pregnancy than CVS or amniocentesis.
Ultrasound directs extremely high frequency sound waves through the mother’s abdominal wall. The sound waves bounce off the fetus and return to a receiver that then converts the sound wave “picture” into a visual image. New ultrasound technologies include powerful computers that put together a three-dimensional image, giving amazingly crisp pictures of facial features and body parts. Ultrasound is generally used to screen for genetic disorders associated with physical features or deformities. Ultrasound can be used at any time during pregnancy and is completely non-invasive, with little or no risk to mother or baby.

Newborn screening

Some genetic disorders are highly treatable using dietary restrictions. Therefore, all newborns in the United States are tested for two common, highly treatable genetic disorders: phenylketonuria and galactosemia. Both of these disorders are autosomal recessive.

✓ Phenylketonuria causes mental retardation due to the buildup of phenylalanine (an amino acid that’s part of a normal diet) in the brain of affected persons. A diet low in phenylalanine allows such persons to live symptom-free lives. (This disorder and the potential to control it are the reasons certain diet colas contain warning labels regarding phenylalanine content.) Phenylketonuria occurs once in every 10,000 to 20,000 births.

✓ Galactosemia is a disorder similar to phenylketonuria that results from an inability to break down one of the products of lactose (milk sugar). A lactose-free diet allows affected persons to live symptom-free lives. If untreated, galactosemia results in brain damage, kidney and liver failure, and often death. Galactosemia occurs once in every 45,000 births.

Testing for these two disorders isn’t actually genetic testing: rather, the tests are designed to look for the presence of abnormal amounts of either phenylalanine or galactose — the phenotypes of the disorders. As technologies advance, these tests may be replaced with direct DNA examination by gene chips (which you can read more about in Chapter 23).