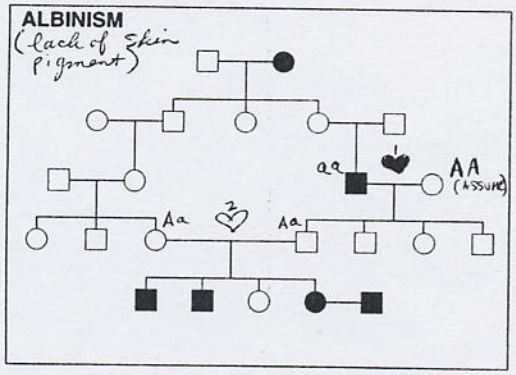
AUTOSOMAL RECESSIVE:

DR NEDWIDEK
SB3P/4G
2/15/2008
2/2009
SL2 5/2009

Ex I

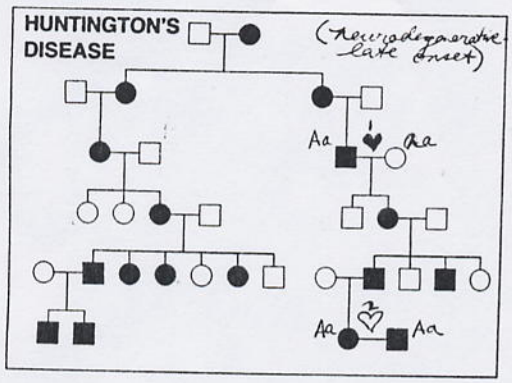


Characteristics of Autosomal Recessive Inheritance

1. An autosomal recessive phenotype, if it appears in more than one member of a kindred, typically is seen only in the sibship of the proband, not in parents, offspring, or other relatives.
2. For most autosomal recessive diseases, males and females are equally likely to be affected.
3. Parents of an affected child are asymptomatic carriers of mutant alleles.
4. The parents of the affected person may in some cases be consanguineous. This is especially likely if the gene responsible for the condition is rare in the population.
5. The recurrence risk for each sib of the proband is 1 in 4.

AUTOSOMAL DOMINANT:

Ex II



Characteristics of Autosomal Dominant Inheritance

1. The phenotype usually appears in every generation, each affected person having an affected parent.

   Exceptions or apparent exceptions to this rule in clinical genetics: (1) cases originating by fresh mutation in a gamete of a phenotypically normal parent; (2) cases in which the disorder is not expressed (nonpenetrant) or is expressed only subtly in a person who has inherited the responsible gene.
2. Any child of an affected parent has a 50 percent risk of inheriting the trait.

   This is true for most families, in which the other parent is phenotypically normal. Because statistically each family member is the result of an "independent event," wide deviation from the expected 1:1 ratio may occur by chance in a single family.
3. Phenotypically normal family members do not transmit the phenotype to their children.

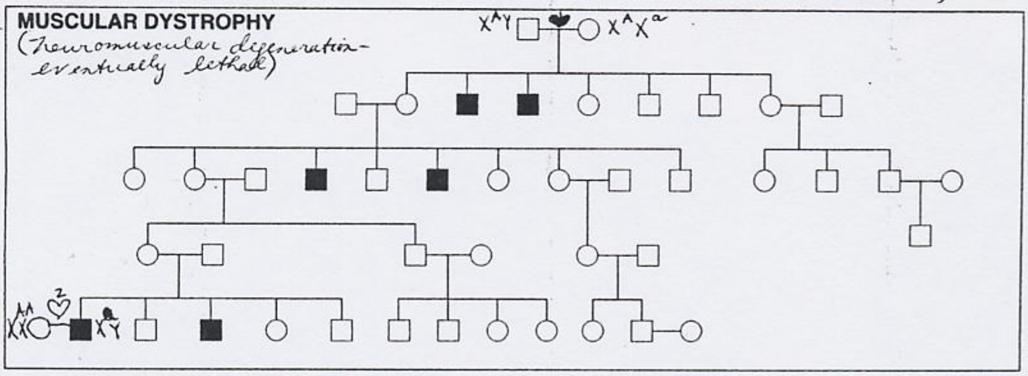
   Failure of penetrance or very subtle expression of a condition may lead to apparent exceptions to this rule.
4. Males and females are equally likely to transmit the phenotype, to children of either sex. In particular, male-to-male transmission can occur, and males can have unaffected daughters.
5. A significant proportion of isolated cases are due to new mutation. The less the fitness is, the greater is the proportion due to new mutation.

EXCERPTS FROM:
THOMPSON & THOMPSON, ELLIOTT

X- LINKED RECESSIVE:

DR. NEDWIDEK
SB3PH4, SL2

Ex

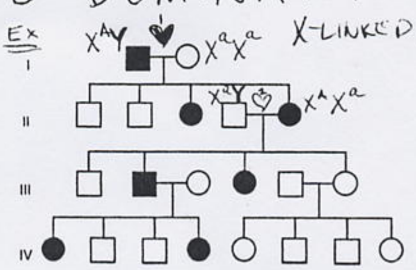


Characteristics of X-Linked Recessive Inheritance

1. The incidence of the trait is much higher in males than in females.
2. Heterozygous females are usually unaffected, but some may express the condition with variable severity as determined by the pattern of X inactivation.
3. The gene responsible for the condition is transmitted from an affected man through all his daughters. Any of his daughters' sons has a 50 percent chance of inheriting it.
4. The gene is ordinarily never transmitted directly from father to son, but it is transmitted by an affected male to all his daughters.
5. The gene may be transmitted through a series of carrier females; if so, the affected males in a kindred are related through females.
6. A significant proportion of isolated cases are due to new mutation.

X- LINKED DOMINANT:

Ex



X-LINKED HYPOPHOSPHATEMIC RICKETS
(Enzyme defect which affects bone growth)

Characteristics of X-Linked Dominant Inheritance

1. Affected males with normal mates have no affected sons and no normal daughters.
2. Both male and female offspring of female carriers have a 50 percent risk of inheriting the phenotype. The pedigree pattern is the same as that seen with autosomal dominant inheritance.
3. For rare phenotypes, affected females are about twice as common as affected males, but affected females typically have milder (though variable) expression of the phenotype.

EXCERPTS FROM:
THOMPSON + THOMPSON,
ALLOTT

FROM THOMPSON + THOMPSON

NEDMDEK

PEDIGREES

5

Patterns of Single-Gene Inheritance

In Chapter 1, the three main categories of genetic disorders—single-gene, chromosomal, and complex—were named and briefly characterized. In the first section of this chapter, the typical patterns of transmission of single-gene disorders are discussed in further detail; the emphasis is on the molecular and genetic mechanisms by which mutations in genes result in recessive, dominant, and X-linked inheritance patterns. In the next section, we describe how gene imprinting and mosaicism can alter or obscure typical single-gene inheritance patterns.

Single-gene traits are often called **mendelian** because, like the characteristics of garden peas studied by Gregor Mendel, they occur on average in fixed proportions among the offspring of specific types of matings. The single-gene phenotypes known so far are listed in Victor A. McKusick's classic reference *Mendelian Inheritance in Man* (12th edition, 1998), which has been indispensable to medical geneticists for decades. The online version of *Mendelian Inheritance in Man* (OMIM) is continually updated and is available through the Internet. As of August 2003, OMIM lists nearly 11,000 genes, 5000 of which are clinically significant diseases inherited in a mendelian pattern. Approximately 1500 genes are known in which mutations have been found to cause over 2000 clinically significant disorders. Thus, of the approximately 30,000 human genes, about 5 percent have already been directly implicated in human genetic disease. The 5 percent figure is likely a great underestimate. The pace of new gene discovery is high, and it appears certain to accelerate because of international efforts dedicated to mapping and sequencing the entire human genome and the genes expressed in differentiated human tissues.

Single-gene disorders are primarily, but by no means exclusively, disorders of the pediatric age range; less than 10 percent manifest after puberty, and only 1 percent occur after the end of the reproductive period. Although individually rare, as a group they are responsible for a significant proportion of childhood diseases and deaths. In a population study of more than 1 million live births, the incidence of serious single-gene disorders was estimated to be 0.36 percent; among hospitalized children, 6 to 8 percent are thought to have single-gene disorders.

TERMINOLOGY

Even though the principles of medical genetics are relatively easy to understand, the unfamiliar terminology may make the subject seem inaccessible at first. To help address the language problem, we review some terms and introduce others that have not been defined previously.

Inherited variation in the genome is the cornerstone of human and medical genetics. As introduced in Chapter 2, alternative variants of genetic information at a particular locus are called **alleles**. For many genes, there is a single prevailing version, present in the majority of individuals, which geneticists call the **wild-type** or normal allele. The other versions of the gene are **mutant** alleles that differ from the wild-type allele by **mutation**, a permanent change in the nucleotide sequence or arrangement of DNA. If there are at least two relatively common alleles at the locus in the population, the locus is said to exhibit **polymorphism** (literally "many forms"), as is discussed in detail in subsequent chapters. In addition to a normal allele or to common polymorphic alleles, loci may also have one or more rare, variant alleles; some of these rare alleles were originally identified because they cause genetic disease, whereas others are of no known significance to health.

The **genotype** of a person is the set of alleles that make up his or her genetic constitution, either collectively at all loci or, more typically, at a single locus. In contrast, the **phenotype** is the observable expression of a genotype as a morphological, clinical, biochemical, or molecular trait. A phenotype may, of course,

be either normal or abnormal in a given individual, but in this book, which emphasizes disorders of medical significance, the focus is on abnormal phenotypes—that is, genetic disorders.

A **single-gene disorder** is one that is determined by the alleles at a single locus. A variant allele, which arose by mutation at some time in the recent or remote past and is usually relatively rare, replaces a wild-type allele on one or both chromosomes. When a person has a pair of identical alleles, he or she is said to be **homozygous** (a **homozygote**); when the alleles are different, he or she is **heterozygous** (a **heterozygote** or carrier). The term **compound heterozygote** is used to describe a genotype in which two different mutant alleles of the same gene are present, rather than one normal and one mutant. These terms (homozygous, heterozygous, and compound heterozygous) can be applied either to a person or to a genotype. The term **mutation** is used in medical genetics in two senses: sometimes to indicate a new genetic change that has not been previously known in a kindred and sometimes merely to indicate a disease-causing allele. Mutation and mutant, however, are not used to refer to the human beings who carry mutant alleles that arose by mutation.

Single-gene disorders are characterized by their patterns of transmission in families. To establish the pattern of transmission, a usual first step is to obtain information about the family history of the patient and to summarize the details in the form of a **pedigree**, a graphical representation of a family tree, using standard symbols (Fig. 5–1). The member through whom a family with a genetic disorder is first brought to attention (ascertained) is the **proband** (synonyms **propositus** or **index case**) if he or she is affected. The person who brings the family to attention by consulting a geneticist is referred to as the **consultand**; the consultand may be an affected individual or an unaffected relative of a proband. A family may have more than one proband, if ascertained through more than one source. Brothers and sisters are called **sibs**, and a family of sibs forms a **sibship**. The entire family is called a **kindred** (Fig. 5–2). Relatives are classified as **first-degree** (parents, sibs, and offspring of the proband); **second-degree** (grandparents and grandchildren, uncles and aunts, nephews and nieces, and half-sibs); **third-degree** (e.g., first cousins), and so forth, depending on the number of steps (in other words, the number of meioses) in the pedigree between the two relatives. The offspring of first cousins are second cousins, and a child is a "first cousin once removed" of his or her parents' first cousins. Couples who have one or more ancestors in common are **consanguineous**. If there is only one affected member in a family, he or she is an **isolated** case or, if the disorder is determined to be due to new mutation in the propositus, a **sporadic** case (see Fig. 5–2).

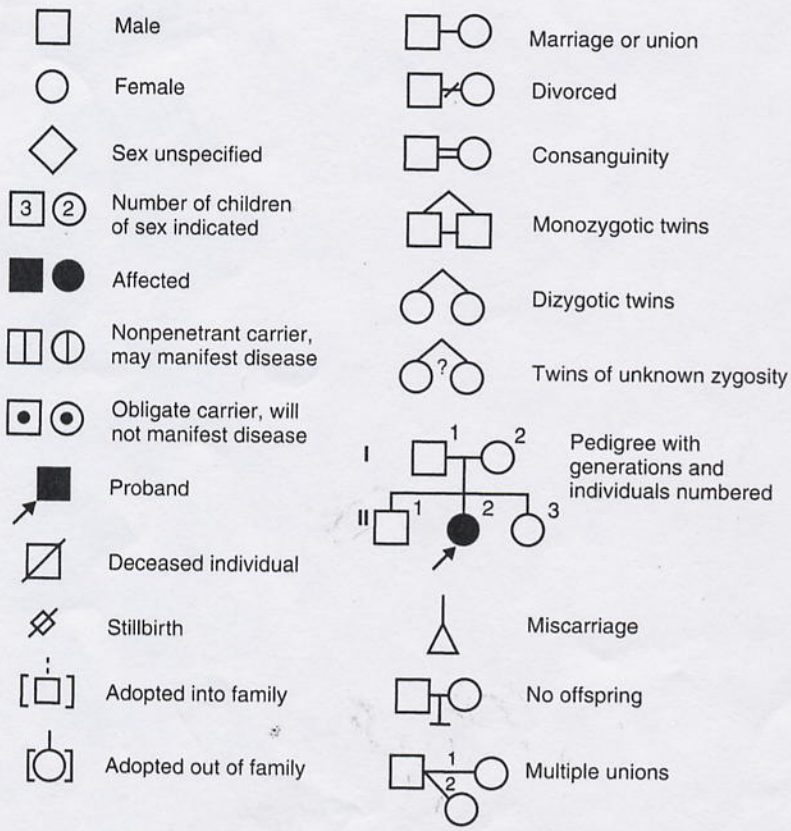


Figure 5–1. Symbols commonly used in pedigree charts. Although there is no uniform system of pedigree notation, the symbols used here are according to recent recommendations made by professionals in the field of genetic counseling. (From Bennett RL, Steinhaus KA, Uhrich SB et al (1995) Recommendations for standardized pedigree nomenclature. J Genet Counsel 4:267–279.)

DR. NEDWIDEK HUMAN GENETICS: PEDIGREES ①

INHERITANCE PATTERN:

PREDICTIONS:

CROSS 1:

			Gametes
Gametes			Offspring

GENOTYPIC RATIO:

CROSS 2:

			Gametes
Gametes			Offspring

GENOTYPIC RATIO: