

Single-Gene Disorders

✚ Basic Definitions

☺ Chromosomes

There are two types of chromosomes: **autosomes** (1-22) and **sex chromosomes** (X & Y).

Humans are composed of two groups of cells:

- **Gametes.** Ova and sperm cells, which are haploid, have one copy of each type of chromosome (1–22, X or Y).
- **Somatic cells** (cells other than gametes). Nearly all somatic cells are diploid, having two copies of each type of autosome (1–22) and either XX or XY.

☺ Diploid cells

- **Homologous chromosomes.** The two chromosomes in each diploid pair are said to be homologs, or homologous chromosomes. They contain the same genes, but because one is of paternal and one is of maternal origins, they may have different alleles at some loci.
- **X and Y chromosomes,** or the sex chromosomes, have some homologous regions but the majority of genes are different.

☺ Genes

- **Gene.** Physically a gene consists of a sequence of DNA that encodes a specific protein (or a nontranslated RNA; for example: tRNA, rRNA, or snRNA).
- **Locus.** The physical location of a gene on a chromosome is termed a locus.
- **Alleles.** Variation (mutation) in the DNA sequence of a gene produces a new allele at that locus. Many genes have multiple alleles.
- **Polymorphism.** When a specific site on a chromosome has multiple alleles in the population, it is said to be polymorphic (many forms).

☺ Genotype

The specific DNA sequence at a locus is termed a genotype. In diploid somatic cells a genotype may be:

- **Homozygous** if the individual has the same allele on both homologs (homologous chromosomes) at that locus.
- **Heterozygous** if the individual has different alleles on the two homologs (homologous chromosomes) at that locus.
- **Hemizygous** if the individual has one allele on one of the two homologs. And the other allele is missed (as in case of x chromosome alleles in a male)

☺ Phenotype

The phenotype is generally understood as the expression of the genotype in terms of observable characteristics.

☺ Mutations

A mutation is an alteration in DNA sequence (thus, mutations produce new alleles). When mutations occur in cells giving rise to gametes, the mutations can be transmitted to future generations.

Missense mutations result in the substitution of a single amino acid in the polypeptide chain (e.g., sickle cell disease is caused by a missense mutation that produces a substitution of valine for glutamic acid in the β -globin polypeptide).

Nonsense mutations produce a stop codon, resulting in premature termination of translation and a truncated protein.

Nucleotide bases may be inserted or deleted. When the number of inserted or deleted bases is a multiple of three, the mutation is said to be **in-frame**. If not a multiple of three, the mutation is a **frameshift mutation**, which alters all codons downstream of the mutation, typically producing a truncated or severely altered protein product.

Mutations can occur in promoter and other regulatory regions or in genes for transcription factors that bind to these regions. This can decrease or increase the amount of gene product produced in the cell.

Mutations can also be classified according to their phenotypic effects.

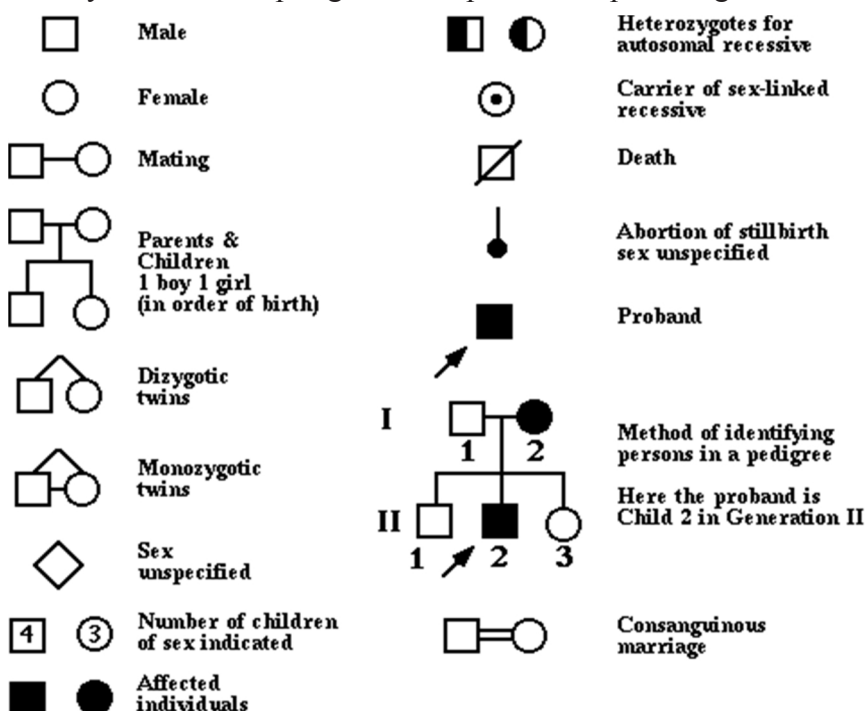
Mutations that cause a missing protein product or cause decreased activity of the protein are termed **loss-of-function**. Those that produce a protein product with a new function or increased activity are termed **gain-of-function**.

☺ Recurrence risk

The recurrence risk is the probability that the offspring of a couple will express a genetic disease.

☺ Pedigrees

A patient's family history is diagrammed in a pedigree (see symbols in the figure). The first affected individual to be identified in the family is termed the **proband**.



✚ Major Modes of Inheritance

✚ Mendelian Inheritance

Mendelian inheritance, described by Mendel in garden peas in 1866, is the transmission of inherited traits or diseases caused by variation in a single gene in a characteristic pattern. These Mendelian traits or disorders are individually rare but collectively numerous and important: over 6000 have been described.

For many disorders, the Mendelian pattern of inheritance is known. If the diagnosis of a condition is uncertain, its pattern of inheritance may be evident on drawing a family tree (pedigree), which is an essential part of genetic evaluation.

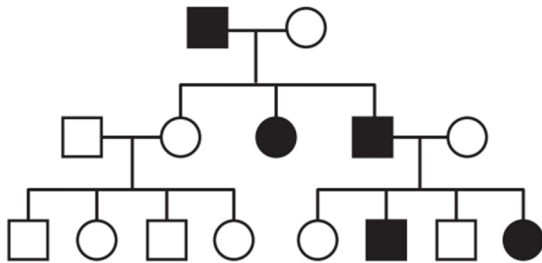
☺ Autosomal Dominant Inheritance

This is the most common mode of Mendelian inheritance.

Autosomal dominant (AD) conditions are caused by alterations in only one copy of a gene pair, i.e. the condition occurs in the heterozygous state despite the presence of an intact copy of the relevant gene. AD genes are located on the autosomes (chromosomes 1–22) so males and females are equally affected.

AD alleles are relatively rare in populations, so the typical mating pattern is a heterozygous affected individual (Aa genotype) mating with a homozygous normal individual (aa genotype), as shown in the figure below.

Note that, by convention, the dominant allele is shown in uppercase (A) and the recessive allele is shown in lowercase (a). The recurrence risk is thus 50%, and half the children, on average, will be affected with the disease. If both parents are heterozygous, the recurrence risk is 75%.



	A	a
a	Aa	aa
a	Aa	aa

A Punnett square: Affected offspring (Aa) are shaded.



Autosomal Dominant Diseases

- Familial hypercholesterolemia (LDL receptor deficiency)
- Huntington disease
- Neurofibromatosis type 1
- Marfan syndrome
- Achondroplasia
- Spherocytosis

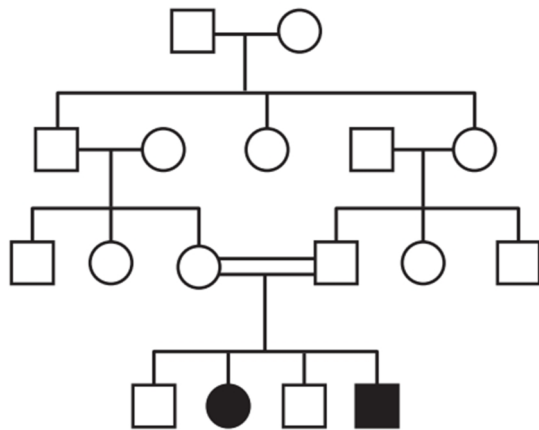
☺ Autosomal Recessive Inheritance

Important features that distinguish autosomal recessive (AR) inheritance:

- Because AR alleles are clinically expressed only in the homozygous state, the offspring must inherit one copy of the disease causing allele from each parent.
- In contrast to AD diseases, AR diseases are typically seen in only one generation of a pedigree (see figure below).
- Because these genes are located on autosomes, males and females are affected in roughly equal frequencies.

Most commonly, a homozygote is produced by the union of two heterozygous (carrier) parents. The recurrence risk for offspring of such matings is 25%.

Consanguinity (the mating of related individuals) is sometimes seen in recessive pedigrees because individuals who share common ancestors are more likely to carry the same recessive disease-causing alleles.



	A	a
A	AA	Aa
a	Aa	aa

The affected genotype (aa) is shaded.

☺ Determining the recurrence risk for an individual whose phenotype is known.

In the above pedigree, Individual IV-1 may wish to know his risk of being a carrier.

Because his phenotype is known, there are only three possible genotypes he can have:

He cannot be homozygous for the recessive allele (aa). Two of the remaining three possibilities are carriers (Aa and aA), and one is homozygous normal (AA).

Thus, his risk of being a carrier is 2/3 or 0.67 (67%).



Autosomal Recessive Diseases:

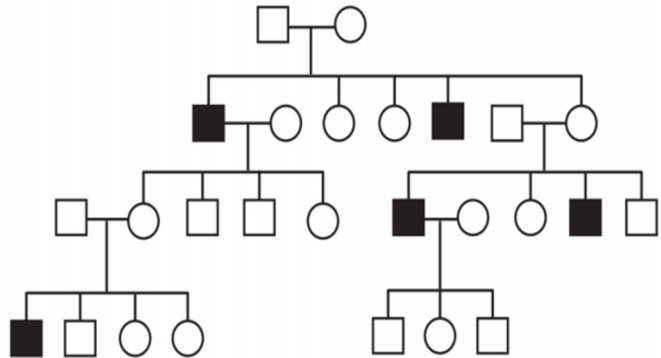
- Sickle cell anemia
- Cystic fibrosis
- Phenylketonuria (PKU)
- Tay-Sachs disease

☺ X-linked Recessive Inheritance

✓ *Properties of X-linked recessive inheritance*

Because males have only one copy of the X chromosome, they are said to be **hemizygous** (*hemi* = “half”) for the X chromosome. If a recessive disease-causing mutation occurs on the X chromosome, a male will be affected with the disease.

- Because males require only one copy of the mutation to express the disease and females require two copies, X-linked recessive diseases are seen much more commonly in males than in females.
- Skipped generations are commonly seen because an affected male can transmit the disease-causing mutation to a heterozygous daughter, who is unaffected but who can transmit the disease-causing allele to her sons.
- Male-to-male transmission is not seen in X-linked inheritance; this helps distinguish it from autosomal inheritance.



✓ **Recurrence Risks.** The figure shows the recurrence risks for X-linked recessive diseases.

- Affected male–homozygous normal female (A): All of the daughters will be heterozygous carriers; all of the sons will be homozygous normal.
- Normal male–carrier female (B): On average, half of the sons will be affected and half of the daughters will be carriers. Note that in this case, the recurrence rate is different depending on the sex of the child. If the fetal sex is known, the recurrence rate for a daughter is 0, and that for a son is 50%. **If the sex of the fetus is not known, then the recurrence rate is multiplied by 1/2, the probability that the fetus is a male versus a female. Therefore if the sex is unknown, the recurrence risk is 25%.**

	x	Y		X	Y
X	Xx	XY	X	XX	XY
X	Xx	XY	x	Xx	xY
A			B		

A. Affected male–homozygous normal female
(X chromosome with mutation is in lower case)

B. Normal male–carrier female



X-Linked Recessive Diseases

- Duchenne muscular dystrophy
- Lesch-Nyhan syndrome
- Glucose-6-phosphate dehydrogenase deficiency
- Hemophilia A and B
- Red-green color blindness)

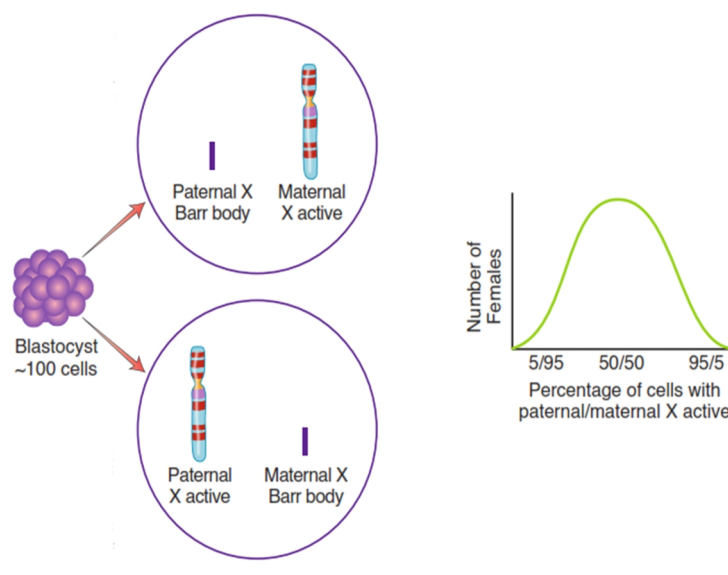
✓ X inactivation (the Lyon hypothesis)

Normal males inherit an X chromosome from their mother and a Y chromosome from their father, whereas normal females inherit an X chromosome from each parent.

Because the Y chromosome carries only about 50 protein-coding genes and the X chromosome carries hundreds of protein-coding genes, a mechanism must exist to equalize the amount of protein encoded by X chromosomes in males and females. This mechanism, termed X inactivation, occurs in the blastocyst (~100 cells) during the development of female embryos (see figure below).

When an X chromosome is inactivated, its DNA is not transcribed into mRNA, and the chromosome is visualized under the microscope as a highly condensed **Barr body** in the nuclei of interphase cells. X inactivation has several important characteristics:

- It is *random*—in some cells of the female embryo, the X chromosome inherited from the father is inactivated, and in others the X chromosome inherited from the mother is inactivated.
- It is *fixed*—once inactivation of an X chromosome occurs in a cell, the same X chromosome is inactivated in all descendants of the cell.
- It is *incomplete*—there are regions throughout the X chromosome, including the tips of both the long and short arms, that are not inactivated.
- All X chromosomes in a cell are inactivated except one. For example, females with three X chromosomes in each cell (XXX females) have two X chromosomes inactivated in each cell (thus, two Barr bodies can be visualized in an interphase cell).



✓ Manifesting (female) heterozygotes

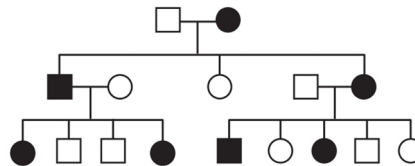
Normal females have two copies of the X chromosome, so they usually require two copies of the mutation to express the disease. However, because X inactivation is a random process, a heterozygous female will occasionally express an X-linked recessive mutation because, by random chance, most of the X chromosomes carrying the normal allele have been inactivated (extreme Lyonisation). Such females are termed manifesting heterozygotes. Because they usually have at least a small population of active X chromosomes carrying the normal allele, their disease expression is typically milder than that of hemizygous males.

☺ X-Linked Dominant Inheritance

There are relatively few diseases whose inheritance is classified as X-linked dominant. Fragile X syndrome is an important example. In this condition, females are differently affected than males, and whereas penetrance in males is 100%, that in females is approximately 60%.

As in X-linked recessive inheritance, male–male transmission of the disease is not seen.

- Heterozygous females are affected. Because females have two X chromosomes (and thus two chances to inherit an X-linked disease-causing mutation) and males have only one, X-linked dominant diseases are seen about twice as often in females as in males.
- As in autosomal dominant inheritance, the disease phenotype is seen in multiple generations of a pedigree; skipped generations are relatively unusual.
- Examine the children of an affected male (II-1 in the figure below). None of his sons will be affected, but all of his daughters have the disease (assuming complete penetrance).



✓ Recurrence Risks

The below figure shows the recurrence risks for X-linked dominant inheritance:

- **Affected male mating homozygous normal female:**

None of the sons are affected; all of the daughters are affected.

Note that in this case, the recurrence rate is different depending on the sex of the child. If the fetal sex is known, the recurrence rate for a

Affected male–homozygous normal female (the mutation-carrying chromosome is upper case)

	X	Y
x	Xx	xY
x	Xx	xY

Normal male–heterozygous affected female

	x	Y
X	Xx	XY
x	xx	xY

daughter is 100%, and that for a son is 0%. **If the sex of the fetus is not known, then the recurrence rate is multiplied by 1/2, the probability that the fetus is a male versus a female. Therefore if the sex is unknown, the recurrence risk is 50%.**

- **Normal male mating heterozygous affected female:**

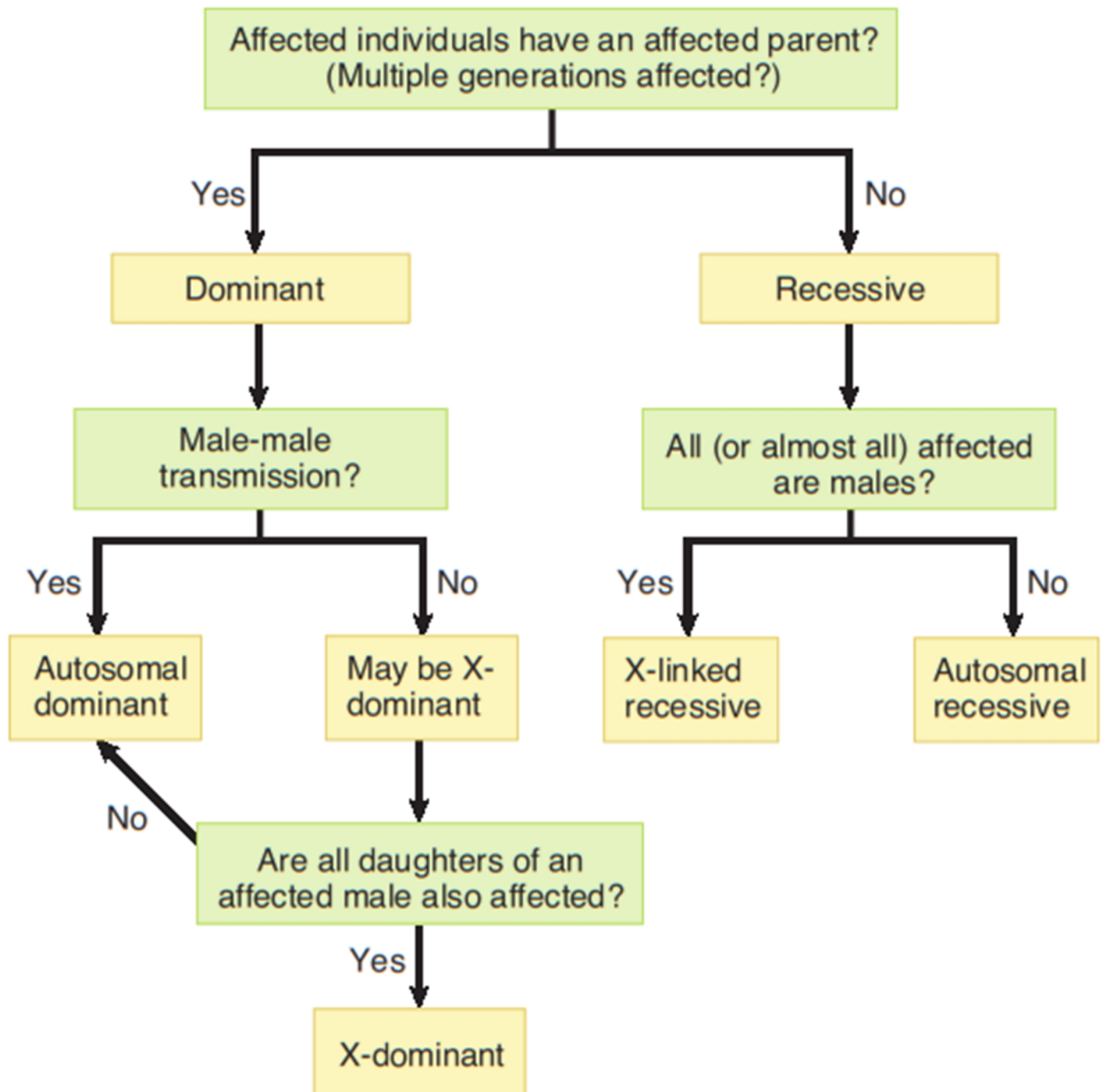
On average, 50% of sons are affected and 50% of daughters are affected.



X-Linked Dominant Diseases

- Hypophosphatemic rickets
- Fragile X syndrome

- ✓ **Summary:** a basic decision tree for determining the mode of inheritance in a pedigree



☺ Mitochondrial Inheritance

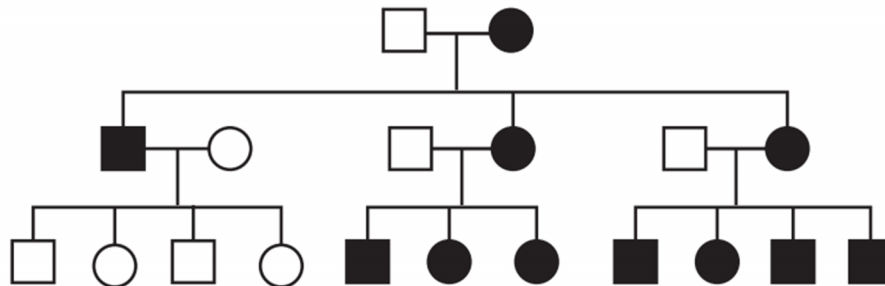
Mitochondria, which are cytoplasmic organelles involved in cellular respiration, have their own chromosomes, each of which contains 16,569 DNA base pairs arranged in a circular molecule. This DNA encodes 13 proteins that are subunits of complexes in the electron transport and oxidative phosphorylation processes. In addition, mitochondrial DNA encodes 22 transfer RNAs and 2 ribosomal RNAs.

Because a sperm cell contributes no mitochondria to the egg cell during fertilization, mitochondrial DNA is inherited exclusively through females.

Pedigrees for mitochondrial diseases thus display a distinct mode of inheritance:

Diseases are transmitted only from affected females to their offspring.

- Both males and females are affected.
- Transmission of the disease is only from a female.
- All offspring of an affected female are affected.
- None of the offspring of an affected male is affected.
- Diseases are typically neuropathies and/or myopathies.



✓ Heteroplasmy

A typical cell contains hundreds of mitochondria in its cytoplasm, and each mitochondrion has its own copy of the mitochondrial genome. When a specific mutation occurs in some of the mitochondria, this mutation can be unevenly distributed into daughter cells during cell division: Some cells may inherit more mitochondria in which the normal DNA sequence predominates, while others inherit mostly mitochondria with the mutated, disease-causing gene. This condition is known as heteroplasmy. Variations in heteroplasmy account for substantial variation in the severity of expression of mitochondrial diseases.



Mitochondrial Diseases

- Leber hereditary optic neuropathy
- MELAS: Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke.
- Myoclonic epilepsy with ragged red muscle fibers

✚ Important principles that can characterize single-gene diseases

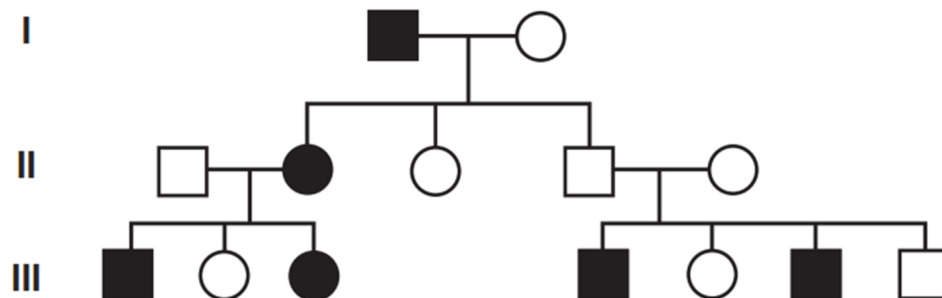
☺ Variable Expression

Most genetic diseases vary in the degree of phenotypic expression: Some individuals may be severely affected, whereas others are more mildly affected. This can be the result of several factors:

1. **Environmental Influences.** The AR disease xeroderma pigmentosum will be expressed more severely in individuals who are exposed more frequently to ultraviolet radiation.
2. **Allelic Heterogeneity.** Different mutations in the disease-causing locus may cause more- or less-severe expression. Most genetic diseases show some degree of allelic heterogeneity. For example, missense mutations in the factor VIII gene tend to produce less severe hemophilia than do nonsense mutations.
3. **Heteroplasmy** in mitochondrial pedigrees.
4. **Modifier Loci.** Disease expression may be affected by the action of other loci, termed modifier loci. Often these may not be identified.

☺ Incomplete Penetrance

A disease-causing mutation is said to have incomplete penetrance when some individuals who have the disease genotype do not display the disease phenotype (see Figure below). Incomplete penetrance is distinguished from variable expression in that the nonpenetrant gene has no phenotypic expression at all. In the pedigree shown in the figure, Individual II-4 must have the disease-causing allele (he passed it from his father to his son) but shows no symptoms. He is an example of nonpenetrance.



The unaffected male in generation II (II-4) has an affected father and two affected sons. He must have the disease-causing mutation, although it shows incomplete penetrance.

☺ **Pleiotropy**

Pleiotropy exists when a single disease-causing mutation affects multiple organ systems. Pleiotropy is a common feature of genetic diseases.

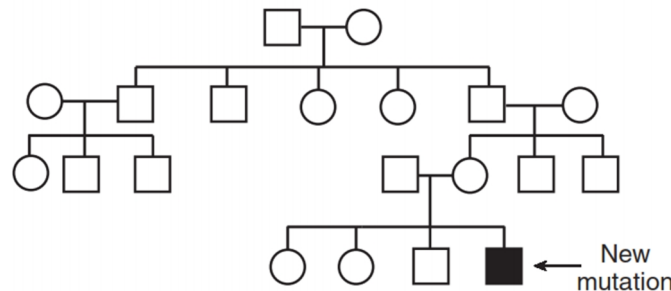
Marfan syndrome provides a good example of the principle of pleiotropy.

☺ **Locus Heterogeneity**

Locus heterogeneity exists when the same disease phenotype can be caused by mutations in different loci. Locus heterogeneity becomes especially important when genetic testing is performed by testing for mutations at specific loci.

☺ **New Mutations**

In many genetic diseases, particularly those in which the mortality rate is high or the fertility rate is low, a large proportion of cases are caused by a new mutation transmitted from an unaffected parent to an affected offspring. There is thus no family history of the disease.



☺ **Delayed Age of Onset**

Many individuals who carry a disease-causing mutation do not manifest the phenotype until later in life. This can complicate the interpretation of a pedigree because it may be difficult to distinguish genetically normal individuals from those who have inherited the mutation but have not yet displayed the phenotype.



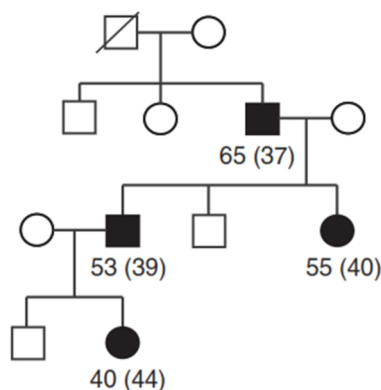
Diseases with delayed age of onset

- Acute intermittent porphyria
- Huntington disease
- Hemochromatosis
- Familial breast cancer

☺ Anticipation

Anticipation refers to a pattern of inheritance in which individuals in the most recent generations of a pedigree develop a disease at an earlier age or with greater severity than do those in earlier generations. For a number of genetic diseases, this phenomenon can be attributed to the gradual expansion of trinucleotide repeat polymorphisms within or near a coding gene.

Huntington disease is a good example of anticipation. The condition results from a gain-of-function mutation on chromosome 4 and is an example of a trinucleotide repeat expansion disorder. Normal *huntingtin* genes have fewer than 27 CAG repeats in the 5' coding region, and the number is stable from generation to generation. In families who eventually present with Huntington disease, premutations of 27–35 repeats are seen, although these individuals do not have Huntington disease. Some of these individuals (generally males) may then transmit an expanded number of repeats to their offspring. Individuals with more than 39 repeats are then seen, and these individuals develop symptoms. Within this group, age of onset is correlated with the number of repeats and ranges from a median age of 66 years old (39 repeats) to less than 20 years old (more than 70 repeats). The Figure below illustrates anticipation in a family with Huntington disease. The ages of onset for the affected individuals are shown along with the number of CAG repeats (in parentheses).



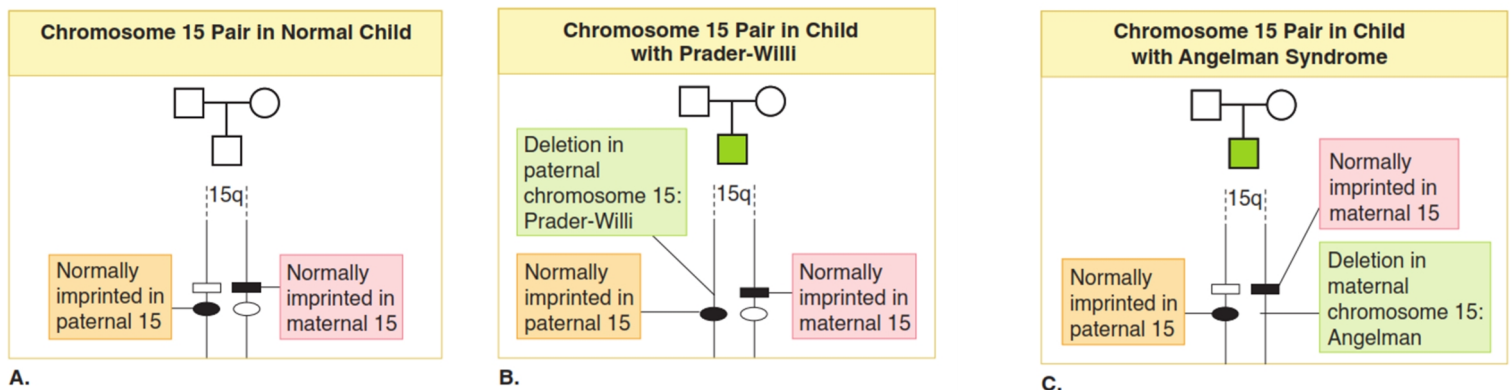
Numbers under pedigree symbols identify age of onset (CAG repeats).

Examples of Diseases Showing Anticipation Associated with Triplet Repeat Expansions	
Disease	Repeat
Huntington disease (autosomal dominant)	CAG
Fragile X syndrome (X dominant)	CCG
Myotonic dystrophy (autosomal dominant)	CTG
Friedreich ataxia (autosomal recessive)	GAA

☺ Imprinting

Imprinting refers to the fact that a small number of genes are transcriptionally active only when transmitted by one of the two sexes. The homologous locus in the other parent is rendered transcriptionally inactive. Thus, for imprinted loci, it is normal to have only the maternal (for some loci) active, or only the paternal (for other loci) active.

Prader-Willi and Angelman Syndromes. On rare occasion, the transcriptionally active gene may be deleted from the chromosome (perhaps by unequal crossover) during gametogenesis. This leaves the offspring with no active gene at that locus. The gene from one parent is inactivated due to normal imprinting, and the gene from the other parent deleted by a mutation. This situation (as shown in Figure below) may result in a genetic disease.



A. Loci normally imprinted on chromosome 15
 B. Deletion causing Prader-Willi syndrome
 C. Deletion causing Angelman syndrome

Prader-Willi syndrome is caused by loss from the paternal chromosome of an imprinted locus mapping to 15q11-13, **Angelman syndrome**, is produced if there is a deletion of 15q11-13 from the maternal chromosome.

☺ Uniparental Disomy

Uniparental disomy is a rare condition in which both copies of a particular chromosome are contributed by one parent.

For example, 25–30% of Prader-Willi cases are caused by maternal uniparental disomy of chromosome 15. A smaller percentage of Angelman syndrome is caused by paternal uniparental disomy of chromosome 15.

