Autosomal Dominant Inheritance

More than half of all mendelian disorders are inherited as autosomal dominant traits. The incidence of some autosomal dominant disorders is high, at least in specific geographical areas: for example, 1 in 500 for **familial hypercholesterolemia** in populations of European or Japanese descent.

Many autosomal dominant disorders are individually much less common, they are so numerous in the aggregate that their total incidence is appreciable.

When they are transmitted through families, they become problems not only for individuals but also for whole kindreds, often through many generations.

The risk and severity of dominantly inherited disease depend on whether one or both parents are affected and whether the trait is strictly dominant or incompletely dominant. Denoting *D* as the mutant allele and *d* as the normal allele, matings that produce children with an autosomal dominant disease can be between two heterozygotes (*D/d*) for the mutation or, more frequently, between a heterozygote for the mutation (*D/d*) and a homozygote for a normal allele (*d/d*):

Parental Mating	Offspring	Risk to Offspring
Affected by unaffected *D/d* × *d/d*	1/2 *D/d*, 1/2 *d/d*	1/2 affected 1/2 unaffected
Affected by affected *D/d* × *D/d*	1/4 *D/D*, 1/2 *D/d*, 1/4 *d/d*	If strictly dominant: 3/4 affected 1/4 unaffected If incompletely dominant: 1/2 affected similarly to the parents 1/4 affected more severely than the parents 1/4 unaffected

Each child of a *D/d* by *d/d* mating has a 50% chance of receiving the affected parent's abnormal allele *D* and a 50% chance of receiving the normal allele *d.* In the population as a whole, the offspring of *D/d* by *d/d* parents are approximately 50% *D/d* and 50% *d/d*. theoretical expected ratio of 1:1, especially if the sibship is small. Typical autosomal dominant inheritance can be seen in the pedigree of a family with a dominantly inherited form of hereditary deafness

In medical practice, homozygotes for dominant phenotypes are not often seen because mating's that could produce homozygous offspring are rare. Again denoting the mutant allele as *D* and the normal allele as *d,* the mating's that can produce a *D/D* homozygote might theoretically be *D/d* by *D/d, D/D* by *D/d,* or *D/D* by *D/D.*

Practically, only the mating of two heterozygotes need be considered because *D/D* homozygotes are very rare and generally too severely affected to reproduce. In the case of two heterozygotes mating, 3/4 of the offspring of a *D/d* by *D/d* mating will be affected to some extent and 1/4 unaffected. In theory, the 3/4 affected could all have the same condition if it is a pure dominant, or 1/3 of the affected would be homozygotes and much more severely affected than the *D/d* heterozygotes if it is an incompletely dominant condition.

Characteristics of Autosomal Dominant Inheritance

- The phenotype usually appears in every generation, each affected person having an affected parent.
- Any child of an affected parent has a 50% risk of inheriting the trait.
- Phenotypically normal family members do not transmit the phenotype to their children.
- 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.

X-LINKED INHERITANCE

The X and Y chromosomes, which are responsible for sex determination, are distributed unequally to males and females in families. For this reason, phenotypes determined by genes on the X have a characteristic sex distribution and a pattern of inheritance that is usually easy to identify. Approximately 1100 genes are thought to be located on the X chromosome, of which approximately 40% are presently known to be associated with disease phenotypes.

Because males have one X chromosome but females have two, there are only two possible genotypes in males and three in females with respect to a mutant allele at an X-linked locus. A male with a mutant allele at an X-linked locus is **hemizygous** for that allele, whereas females may be homozygous for either the wild-type or mutant allele or may be heterozygous. For example, if XH is the wild-type allele for the gene for coagulation factor VIII and a mutant allele, Xh, causes hemophilia A, the genotypes expected in males and females would be as follows:

	Genotypes	Phenotypes
Males	Hemizygous X_H	Unaffected
	Hemizygous X_h	Affected
Females	Homozygous X_H/X_H	Unaffected
	Heterozygous X_H/X_h	Unaffected (usually)
	Homozygous X_h/X_h	Affected

Recessive and Dominant Inheritance of X-Linked Disorders

X-linked “dominant” and “recessive” patterns of inheritance are distinguished on the basis of the phenotype in heterozygous females. Some X-linked phenotypes are consistently expressed in carriers (dominant), whereas others usually are not (recessive).

The difficulty in classifying an X-linked disorder as dominant or recessive arises because females who are heterozygous for the same mutant allele in the same family may or may not demonstrate the disease, depending on the pattern of random X inactivation and the proportion of the cells in pertinent tissues that have the mutant allele on the active versus inactive chromosome.

X-Linked Recessive Inheritance:

The inheritance of X-linked recessive phenotypes follows a well-defined and easily recognized pattern. An X-linked recessive mutation is typically expressed phenotypically in all males who receive it but only in those females who are homozygous for the mutation. Consequently, X-linked recessive disorders are generally restricted to males and rarely seen among females.

AFFECTED MALE BY NORMAL FEMALE: $X_h/Y \times X_H/X_H$

	X_H	X_H	
X_h	X_H/X_h	X_H/X_h	Daughters: *all* carriers
Y	X_H/Y	X_H/Y	Sons: *all* unaffected

Hemophilia A is a classic X-linked recessive disorder in which the blood fails to clot normally because of a deficiency of factor VIII, a protein in the clotting cascade. The hereditary nature of hemophilia and even its pattern of transmission have been recognized since ancient times, and the condition became known as the “royal hemophilia” because of its occurrence among descendants of Britain’s Queen Victoria, who was a carrier.

As in the earlier discussion, Xh represents the mutant factor VIII allele causing hemophilia A, and XH represents the normal allele. If a hemophiliac mates with a normal female, all the sons receive their father's Y chromosome and a maternal X and are unaffected, but all the daughters receive the paternal X chromosome with its hemophilia allele and are obligate carriers: Now assume that a daughter of the affected male mates with an unaffected male. Four genotypes are possible in the progeny, with equal probabilities:

NORMAL MALE BY CARRIER FEMALE: $X_H/Y \times X_H/X_h$			
	X_H	X_h	
X_H	X_H/X_H	X_H/X_h	Daughters: 1/2 normal, 1/2 carriers
Y	X_H/Y	X_h/Y	Sons: 1/2 normal, 1/2 affected

Mitochondrial Inheritance

The Mitochondrial Genome

- A small and important fraction of proteins is encoded by genes within the mitochondrial genome.
- Mitochondrial genome consists of a circular chromosome, 16.5 kb in size, that is located inside the mitochondrial organelle, not in the nucleus.
- Most cells contain at least 1000 mtDNA molecules, distributed among hundreds of individual mitochondria.

A remarkable exception is the mature oocyte, which has more than 100,000 copies of mtDNA, composing about one third of the total DNA content of these cells.

- Mitochondrial DNA (mtDNA) contains 37 genes. The genes encode 13 polypeptides that are subunits of enzymes of oxidative phosphorylation, two types of ribosomal RNA, and 22 transfer RNAs required for translating the transcripts of the mitochondria-encoded polypeptides. The remaining polypeptides of the oxidative complex are encoded by the nuclear genome.

More than 100 different rearrangements and 100 different point mutations have been identified in mtDNA that can cause human disease, often involving the central nervous and musculoskeletal systems (e.g., myoclonic epilepsy with ragged-red fibers). The diseases that result from these mutations show a distinctive pattern of inheritance because of three unusual features of mitochondria: **replicative segregation, homoplasmy** and **heteroplasmy,** and **maternal inheritance.**

Replicative Segregation

The first unique feature of the mitochondrial chromosome is the absence of the tightly controlled segregation seen during mitosis and meiosis of the 46 nuclear chromosomes. At cell division, the multiple copies of mtDNA in each of the mitochondria in a cell replicate and sort randomly among newly synthesized mitochondria. The mitochondria, in turn, are distributed randomly between the two daughter cells. This process is known as **replicative segregation**.

Homoplasmy and Heteroplasmy

The second unique feature of the genetics of mtDNA arises from the fact that most cells contain many copies of mtDNA molecules. When a mutation arises in the mtDNA, it is at first present in only one of the mtDNA molecules in a mitochondrion. With replicative segregation, however, a mitochondrion containing a mutant mtDNA will acquire multiple copies of the mutant molecule. With cell division, a cell containing a mixture of normal and mutant mtDNAs can distribute very different proportions of mutant and wild-type

Mitochondrial DNA to its daughter cells. One daughter cell may, by chance, receive mitochondria that contain only a pure population of normal mtDNA or a pure population of mutant mtDNA (a situation known as **homoplasmy**). Alternatively, the daughter cell may receive a mixture of mitochondria, some with and some without mutation. Because the phenotypic expression of a mutation in mtDNA depends on the relative proportions of normal and mutant mtDNA in the cells making up different tissues, reduced penetrance, variable expression, and pleiotropy are all typical features of mitochondrial disorders.

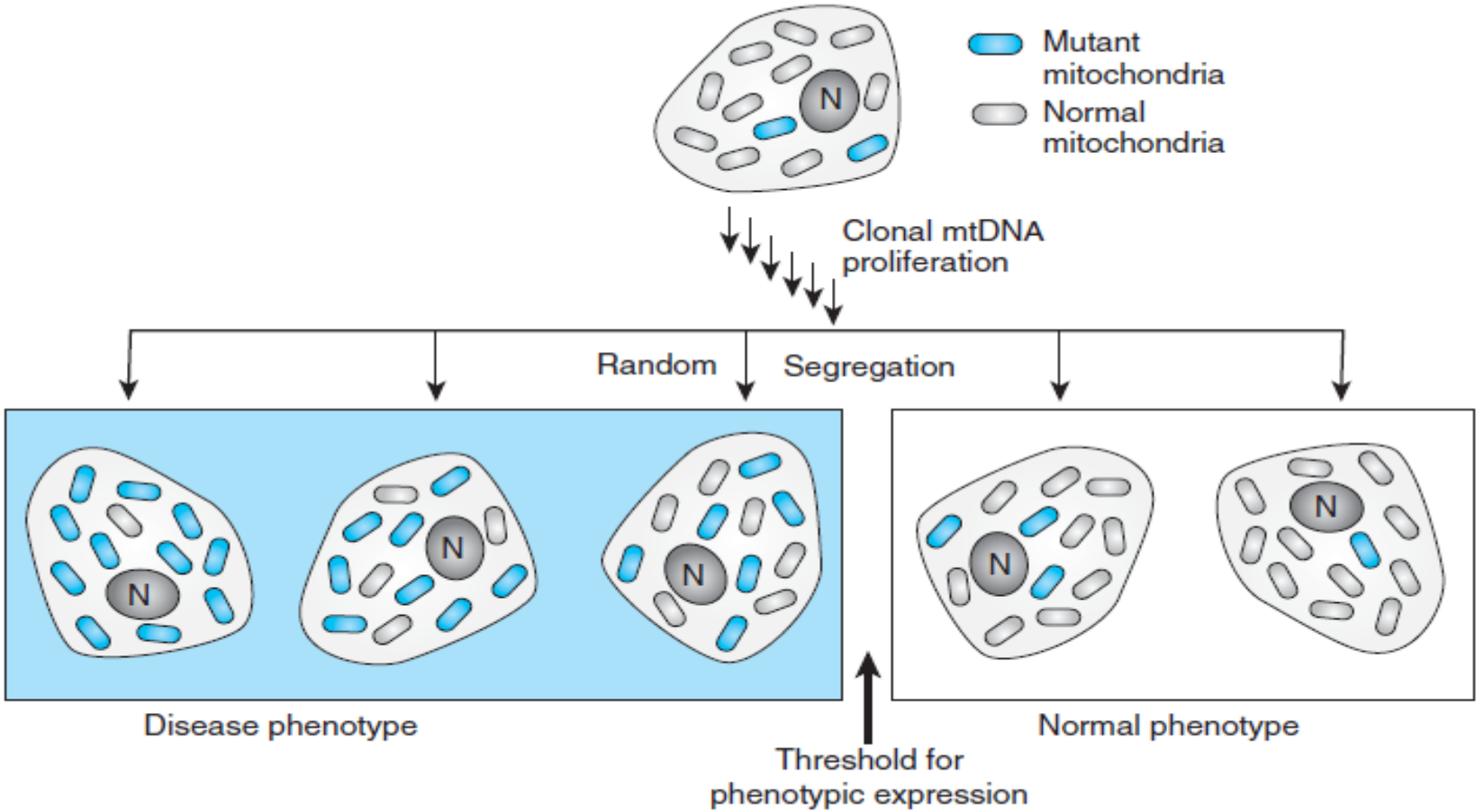

Figure 16. Replicative segregation of a heteroplasmic mitochondrial mutation. Random partitioning of mutant and wild-type mitochondria through multiple rounds of mitosis produces a collection of daughter cells with wide variation in the proportion of mutant and wild-type mitochondria carried by each cell. Cell and tissue dysfunction results when the fraction of mitochondria that are carrying a mutation exceeds a threshold level. N, nucleus.

Maternal Inheritance of mtDNA

The final defining characteristic of the genetics of mtDNA is its **maternal inheritance**. Sperm mitochondria are generally eliminated from the embryo, so that mtDNA is inherited from the mother. Thus, all the children of a *female* who is homoplasmic for a mtDNA mutation will inherit the mutation, whereas none of the offspring of a *male* carrying the same mutation will inherit the defective DNA. The maternal inheritance of a homoplasmic mtDNA mutation causing **Leber hereditary optic neuropathy.**