Single-gene disorders

- Single-gene traits caused by mutations in genes in the nuclear genome are often called **mendelian** because, like the characteristics of garden peas studied by Gregor Mendel.
- Mutations in genes result in recessive, dominant, X-linked, and mitochondrial inheritance patterns.

Variation in Genes

- A segment of DNA occupying a particular position or location on a chromosome is a **locus.** If the segment contains a gene, that DNA segment is the locus for that gene. Alternative variants of a gene are called **alleles.**

- For many genes, there is a single prevailing allele, present in the majority of individuals, that geneticists call the **wild-type or common allele.** The other versions of the gene are **variant or mutant alleles** that differ from the wild-type allele because of the presence of a **mutation,** a permanent change in the nucleotide sequence or arrangement of DNA. A given set of alleles at a locus or cluster of loci on a chromosome is referred to as a **haplotype.**

- Variant alleles arose by mutation at some time in the recent or remote past. If there are at least two relatively common alleles at the locus in the population, the locus is said to exhibit **polymorphism.**

- Loci may also have one or more rare, variant alleles. Some of these rare alleles were originally identified because they cause genetic disease; others may increase susceptibility to disease, and yet others are of no known significance to health.
- 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 family, and sometimes merely to indicate a disease-causing mutant allele. Mutation and mutant, however, are never used to refer to the human beings who carry mutant alleles.

Genotype and Phenotype

- 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.
- The **phenotype** is the observable expression of a genotype as a morphological, clinical, cellular, or biochemical trait.
- A single-gene disorder is one that is determined primarily by the alleles at a single locus. When a person has a pair of identical alleles at a locus encoded in nuclear DNA, 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.
- In the special case in which a male has an abnormal allele for a gene located on the X chromosome and there is no other copy of the gene, he is neither homozygous nor heterozygous and is referred to as **hemizygous.**
- The terms homozygous, heterozygous, and hemizygous are not used to describe genotypes at mitochondrial loci.

Autosomal and X-Linked Inheritance

- An abnormal gene is on an autosome or is X linked has a profound effect on the clinical expression of the disease.
- Autosomal disorders, in general, affect males and females equally.
- For X-linked disorders, the situation is quite different. Males have only a single X and are therefore hemizygous with respect to X-linked genes; 46,XY males are never heterozygous for alleles at X-linked loci, whereas females can be heterozygous or homozygous at X-linked loci.

Dominant and Recessive Inheritance

Recessive Inheritance:

- A phenotype expressed only in homozygotes (or, for X-linked traits, male hemizygotes) and not in heterozygotes is recessive.
- Most of the recessive disorders described to date are due to mutations that reduce or eliminate the function of the gene product, so-called **loss-of-function mutations.**

For example, many recessive diseases are caused by mutations that impair or eliminate the function of an enzyme. These are usually inherited as recessive diseases because heterozygotes, with only one of a pair of alleles functioning and the other (abnormal) allele not, can typically make sufficient product (~50% of the amount made by wild-type homozygotes) to carry out the enzymatic reaction required for normal physiological function, thereby preventing disease.

Dominant Inheritance

- A phenotype expressed in both homozygotes and heterozygotes for a mutant allele is inherited as a dominant.
- Dominant disorders occur whether or not there is normal gene product made from the remaining normal allele. In a **pure dominant disease, homozygotes** and heterozygotes for the mutant allele are both affected equally. Pure dominant disorders rarely if ever exist in medical genetics.

- On occasion, phenotypic expression of two different alleles for a locus occurs, in which case the two alleles are termed **codominant.** One well-known example of codominant expression is the ABO blood group system.
- Most commonly, dominant disorders are more severe in homozygotes than in heterozygotes, in which case the disease is called **incompletely dominant (or semidominant).**

- It is the inheritance of a phenotype rather than the allele that is dominant or recessive. However, mutant alleles are often referred to as dominant or recessive on the basis of whether they can cause a change in phenotype in the heterozygous or homozygous state, respectively. Consequently, the terms ***dominant allele or gene and recessive allele or gene are*** widely, albeit loosely, used.

CORRELATING GENOTYPE AND PHENOTYPE

- An important component of medical genetics is identifying and characterizing the genotypes responsible for particular disease phenotypes.
- **Genetic heterogeneity** may be the result of different mutations at the same locus (**allelic heterogeneity),** mutations at different loci (**locus heterogeneity),** or both. Recognition of genetic heterogeneity is an important aspect of clinical diagnosis and genetic counseling.

On the other hand, distinct phenotypes inherited in different families can result from different mutant alleles in the same gene. This phenomenon, known as **clinical or phenotypic heterogeneity,** is well known and must be taken into account in correlating genotype and phenotype.

Allelic Heterogeneity

Allelic heterogeneity is an important cause of clinical variation. Many loci possess more than one mutant allele; in fact, at a given locus, there may be several or many mutations. As one example, nearly 1400 different mutations have been found worldwide in the **cystic fibrosis transmembrane conductance regulator (CFTR)** among patients with cystic fibrosis

Sometimes, these different mutations result in clinically indistinguishable disorders. In other cases, different mutant alleles at the same locus produce a similar phenotype but along a continuum of severity; for example, some CFTR mutations cause patients to have classic cystic fibrosis with pancreatic insufficiency, severe progressive lung disease, and congenital absence of the vas deferens in males, whereas patients carrying other mutant alleles have lung disease but normal pancreatic function, and still others have only the abnormality of the male reproductive tract.

There are, however, some well-recognized exceptions to the observation that compound heterozygotes are more common than true homozygotes. **The first** is when the affected individuals inherited the same mutant allele from consanguineous parents, who both carry the same mutant allele they inherited from a common ancestor. **Second,** one mutant allele may be responsible for a large proportion of the cases of an autosomal recessive condition in a particular ethnic group.

Patients from that group will be homozygous for this allele. The third is when the disorder normally has little if any allelic heterogeneity because the disease phenotype caused by a particular mutation is specific to that mutation.

Locus Heterogeneity

For many phenotypes, pedigree analysis alone has been sufficient to demonstrate locus heterogeneity. For example, **retinitis pigmentosa**, a common cause of visual impairment due to photoreceptor degeneration, has long been known to occur in autosomal dominant, autosomal recessive, and X-linked forms. In recent years, the heterogeneity has been shown to be even more extensive; pedigree analysis combined with gene mapping

has demonstrated that there are at least 43 loci responsible for 5 X-linked forms, 14 autosomal dominant forms, and 24 autosomal recessive forms of retinitis pigmentosa that are not associated with other phenotypic abnormalities. If one includes disorders in which retinitis pigmentosa is found in conjunction with other defects such as mental retardation or deafness, there are nearly 70 different genetic diseases manifesting retinitis pigmentosa.

Phenotypic Heterogeneity

- Different mutations in the same gene can sometimes give rise to strikingly different phenotypes. For example, certain loss-of-function mutations in the *RET gene,* which encodes a receptor tyrosine kinase, can cause dominantly inherited failure of development of colonic ganglia, leading to defective colonic motility and severe chronic constipation (**Hirschsprung disease).**

Other mutations in the same gene result in unregulated hyperfunction of the kinase, leading to dominantly inherited cancer of the thyroid and adrenal glands **(multiple endocrine neoplasia type 2A and 2B**). A third group of mutations in *RET* causes both Hirschsprung disease and multiple endocrine neoplasia in the same individuals.

A comparable situation occurs with the LMNA gene, which encodes lamin A/C, a nuclear membrane protein. Different LMNA mutations have been associated with half a dozen phenotypically distinct disorders, including Emery-Dreifuss muscular dystrophy, one form of hereditary dilated cardiomyopathy, one form of the Charcot-Marie-Tooth peripheral neuropathy, a disorder of normal adipose tissue called lipodystrophy, and the premature aging syndrome known as Hutchinson- Gifford progeria.

Autosomal Recessive Inheritance

Autosomal recessive disease occurs only in homozygotes or compound heterozygotes, individuals with two mutant alleles and no normal allele, because in these diseases, one normal gene copy is able to compensate for the mutant allele and prevent the disease from occurring. Because an individual inherits only one of the two alleles at any locus from one parent, homozygotes must have inherited a mutant allele from each parent (barring uniparental disomy or new mutation, which is rare in autosomal recessive disorders).

Three types of matings can lead to homozygous offspring affected with an autosomal recessive disease. The mutant recessive allele is symbolized as *r* and its normal dominant allele as *R*. Although any mating in which each parent has at least one recessive allele can produce homozygous affected offspring, the most common mating by far is between two unaffected heterozygotes.

Parental Mating	Offspring	Risk of Disease
Carrier by carrier *R/r* × *R/r*	1/4 *R/R*, 1/2 *R/r*, 1/4 *r/r*	3/4 unaffected, 1/4 affected
Carrier by affected *R/r* × *r/r*	1/2 *R/r*, 1/2 *r/r*	1/2 unaffected, 1/2 affected
Affected by affected *r/r* × *r/r*	*r/r* only	All affected

When both parents of an affected person are heterozygotes (**carriers**), their children's risk of receiving a recessive allele is one half from each parent, and so the chance of inheriting two recessive alleles and therefore being affected is 1/2 × 1/2 or 1 in 4. The proband may be the only affected family member, but if any others are affected, they are usually in the same sibship and not elsewhere in the kindred

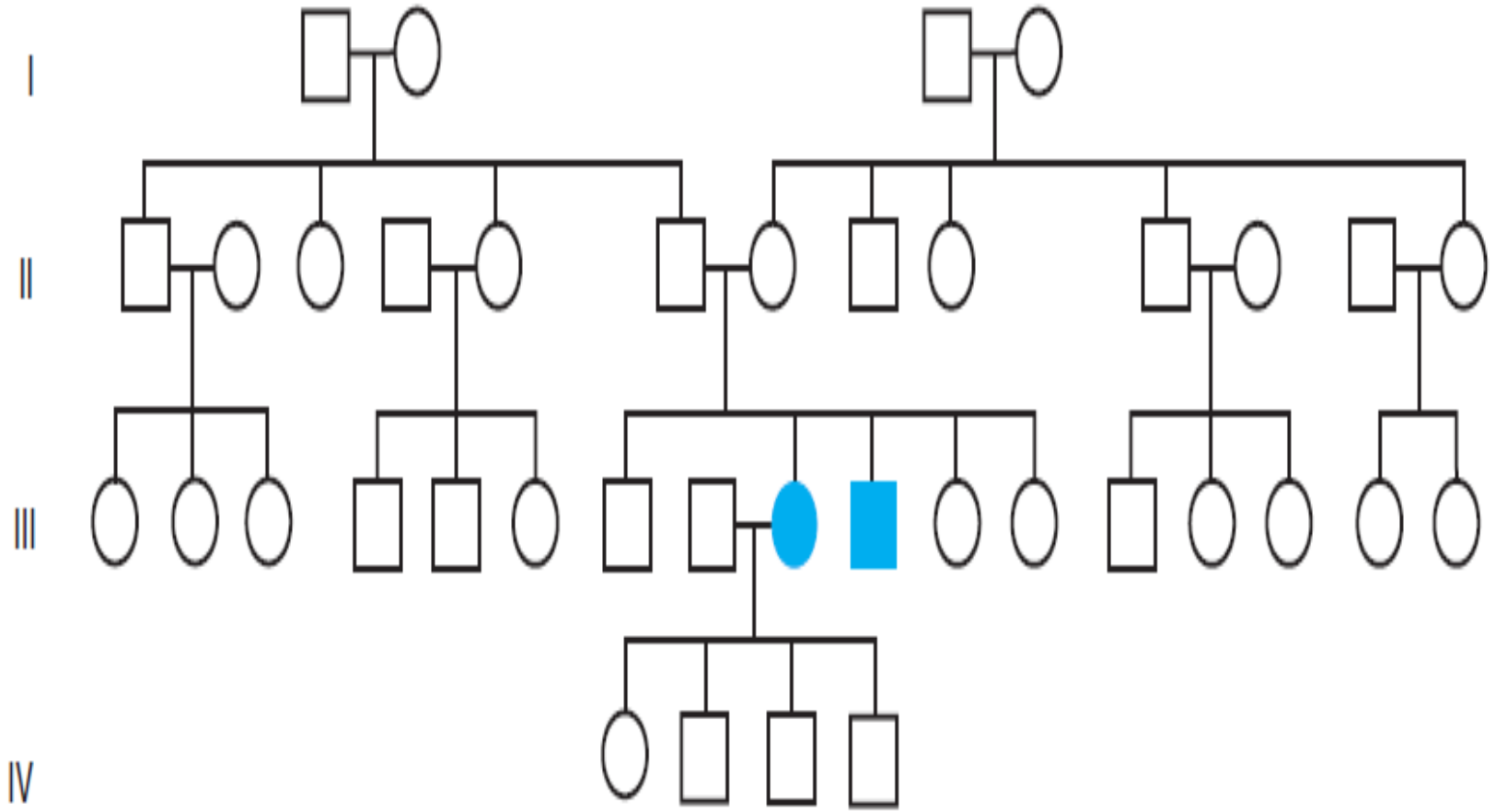

Figure 13. Typical pedigree showing autosomal recessive inheritance.

Sex-Influenced Disorders

- Since males and females both have the same complement of autosomes, autosomal recessive disorders generally show the same frequency and severity in males and females.
- Some autosomal recessive phenotypes are sex-influenced, that is, expressed in both sexes but with different frequencies or severity. Among autosomal disorders, **hemochromatosis** is an example ofa phenotype more common in males.

This autosomal recessive disorder of iron metabolism occurs most commonly in the approximately 0.5% of individuals of northern European extraction that are homozygous for a missense mutation replacing cysteine at position 282 with a tyrosine (Cys282Tyr) in the *HFE* gene. Cys282Tyr homozygotes have enhanced absorption of dietary iron and often demonstrate laboratory abnormalities suggestive of excessive body stores of iron,

although the condition only rarely leads to iron overload and serious damage to the heart, liver, and pancreas. The lower incidence of the clinical disorder in females (one fifth to one tenth that of males) is believed to be related, among other factors, to lower dietary intake of iron, lower alcohol usage, and increased iron loss through menstruation among females.

Gene Frequency and Carrier Frequency

The mutant alleles responsible for a recessive disorder are generally rare, and so most people will not have even one copy of the mutant allele. Among individuals with at least one copy of the mutant allele, however, the frequency of clinically unaffected heterozygotes with one normal allele and one mutant allele is always much greater than the frequency of affected individuals with two rare mutant alleles.

Because an autosomal recessive disorder must be inherited through both parents, the risk that any carrier will have an affected child depends partly on the chance

that his or her mate is also a carrier of a mutant allele or the condition. Thus, knowledge of the carrier frequency of a disease is clinically important for genetic counseling.

The most common autosomal recessive disorder in white children is **cystic fibrosis** (CF), caused by mutations in the *CFTR* gene.

CF is virtually unknown in Asian populations and is relatively rare in African American populations, but in white populations, about 1 child in 2000 has two mutant *CFTR* alleles and has the disease. The frequency of carriers for one of the hundreds of possible mutant *CFTR* alleles can be calculated to be approximately 1/29. In a population of 3247 white individuals, therefore, you can expect 1 CF patient, 112 unaffected carriers of a *CFTR* mutation, and 3134 normal homozygotes.