Medical Genetics

Sheet: VII - Patterns of Single Gene Inheritance

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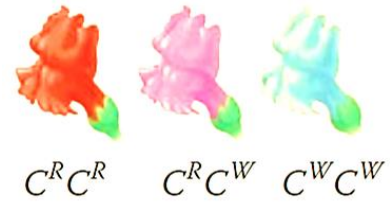
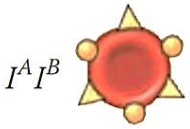
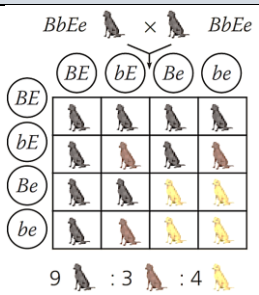
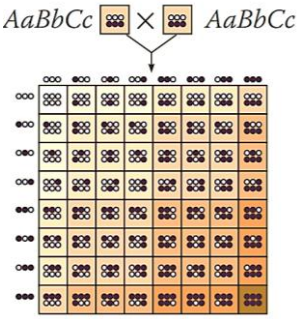
Before digging into the new lecture, let's summarize some -previously discussed- concepts.

RELATIONSHIPS AMONG ALLELES OF A SINGLE GENE	DESCRIPTION	EXAMPLE
Complete dominance of one allele	Heterozygous phenotype same as that of homozygous dominant	
Incomplete dominance of either allele	Heterozygous phenotype intermediate between the two homozygous phenotypes	
Codominance	Both phenotypes expressed in heterozygous	
Multiple alleles	In the population, some genes have more than two alleles	ABO blood group alleles
Pleiotropy	One gene affects multiple phenotypic characters	Sickle-cell disease Cystic fibrosis
RELATIONSHIP AMONG TWO OR MORE GENES	**DESCRIPTION**	**EXAMPLE**
Epistasis	The phenotypic expression of one gene affects the expression of another gene	
Polygenic inheritance	A single phenotypic character is affected by two or more genes	
Multifactorial Characters	An organism's phenotype reflects its overall genotype and unique environmental history.	Cancers Diabetes Cardiovascular disorders Autism Sexual Orientation

Which genetic relationships listed in the first column of the two tables above are demonstrated by the inheritance pattern of the ABO blood group alleles?

Answer: The ABO blood group is an example of **multiple alleles** because this single gene has more than two alleles (I^A, I^B, and i). Two of the alleles, I^A and I^B, exhibit **codominance**, since both carbohydrates (A and B) are present when these two alleles exist together in a genotype. I^A and I^B each exhibit **complete dominance** over the i allele.

Risk genes: These genes *increase* the risk of developing a *multifactorial* disease but are *not* a direct cause of the disease. Researchers have identified several genes that increase the risk of lung cancer. Another example, women with an altered BRCA1 gene have a **50 to 85** percent risk of developing breast cancer by age 70 (i.e. BRCA mutations increase the *risk* of breast cancer). However, this doesn't mean that every woman with BRCA mutations will develop breast cancer.

Concept 14.4: Many Human Traits Follow Mendelian Patterns of Inheritance

Humans are not good subjects for genetic research. The human generation span is long—about 20 years—and human parents produce many fewer offspring than most other species. Even more important, it wouldn't be ethical to ask pairs of humans to breed so that the phenotypes of their offspring could be analyzed! However, basic Mendelian genetics endures as the foundation of human genetics.

Pedigree Analysis

Definition|| A **pedigree** is a family tree that describes the interrelationships of parents and children across generations. Inheritance patterns of particular traits can be traced and described using pedigrees. Pedigrees can also be used to make *predictions* about future offspring. We can use the multiplication and addition rules to predict the probability of specific phenotypes.

A pedigree is a concise summary of the medical family history; it is the symbolic language of clinical genetics and human genetics research. It is an easy, fast, and efficient means of recording a wealth of information about the family.

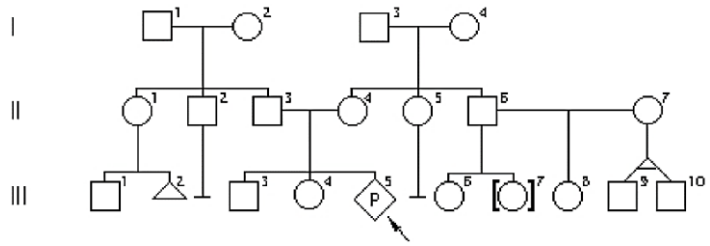
Pedigree Organization || To discuss the applications of pedigree analyses, we need to understand the organization and symbols of a pedigree.

The oldest generation is at the top of the pedigree, and the most recent generation is at the bottom (i.e. vertical lines connect each succeeding generation). Each generation is given a roman numeral designation, and individuals *within* the same generation are numbered from left to right.

Have a look at the examples are described here:

↬ Individuals I-1 and I-2 are the grandparents of III-1, III-2, III-3, III-4, and III-5.

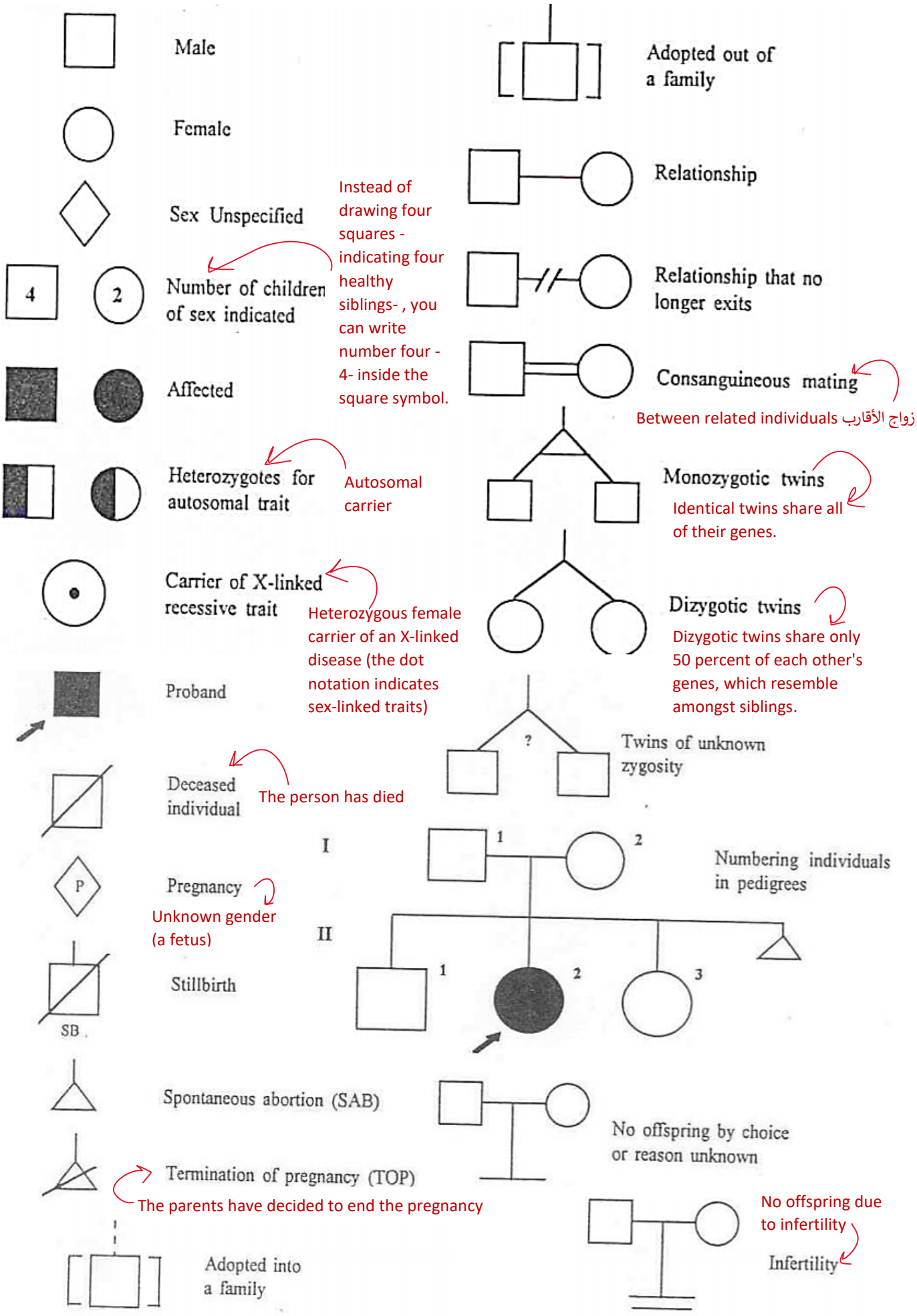
↬Individuals III-3, III-4, and III-5 are brother and sisters.



General Guidelines

- List siblings from oldest to youngest, from left to right.
- Male partner is usually placed to the left of the female partner.
- Record full name, current age and date of birth, or age at death for each individual.
- Record race and ethnic origin of each individual.
- Note health problems and/or cause of death for each individual there are appropriate symbols to use for both adoption and assisted reproductive technologies.

Pedigree Nomenclature ||



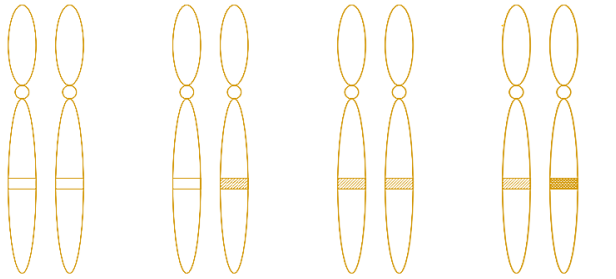
The **proband** is an affected individual coming to medical attention independently of other family members. The proband is designated with an *arrow* in the pedigree, and there may be more than one proband per family. The doctor said that the proband is *the first person in a family to receive genetic counseling and/or testing for suspected hereditary disease.* He added that *the proband may or may not be affected with the disease in question.*

The Gene is the Unit of Inheritance||

The location of a gene on a chromosome is its **locus**. Alternative forms of a gene at a particular locus are referred to as **alleles**.

An individual's **genotype** (genetic composition) at a particular locus is defined by the nature of the alleles at that locus. If both alleles are identical, then the individual is **homozygous** at the locus. Homozygosity may refer to the presence of two *normal* or two *mutant* alleles. If the alleles differ, then the individual is **heterozygous** at the locus.

However, when both alleles of a gene harbor mutations, but the mutations are different (some are nonsense, others are missense…), these mutations are called **compound heterozygous** (e.g. cystic fibrosis).



Just keep in mind that we're discussing monogenic disorders (monogenic traits), which are disorders caused by variation in a *single gene* (e.g. sickle cell anemia, cystic fibrosis, Huntington disease, and Duchenne muscular dystrophy).

Gregor Mendel's Laws of Inheritance

(1) Law of Unit Inheritance - parental characteristics do not blend because there is a **unit of inheritance.** Mendel's "units" are now known as **genes** or **alleles.**
(2) Law of Segregation - the two alleles at a particular locus segregate into different gametes.
(3) Law of Independent Assortment - alleles at different loci are transmitted independently of each other. Linkage is an exception to this rule.

Bear in mind

× For **dominant** traits the capital letter (e.g. A) represents the mutant allele and the small letter (e.g. a) represents the normal allele. For **recessive** traits, the small letter (e.g. a) represents the mutant allele and the capital letter (e.g. A) represents the normal allele.
× Autosomal dominant traits are those traits in which the phenotype of the heterozygote and the homozygote for the dominant allele are the same, i.e., Aa and AA have the same phenotype where A=dominant allele. These traits are expressed when only one copy of the dominant allele is present. In practice, if the heterozygote expresses the trait, then the trait is classified as dominant, even if the phenotype of the homozygote (AA) and heterozygote (Aa) are different.
× Autosomal recessive traits are those traits in which the phenotype is expressed only if homozygous for the recessive allele, i.e., aa where a=recessive allele. Two copies of the recessive allele are necessary for expression.
× X-linked dominant traits are those expressed when either males or females have one copy of the dominant allele, i.e., XAY or XAXa where A=dominant allele.

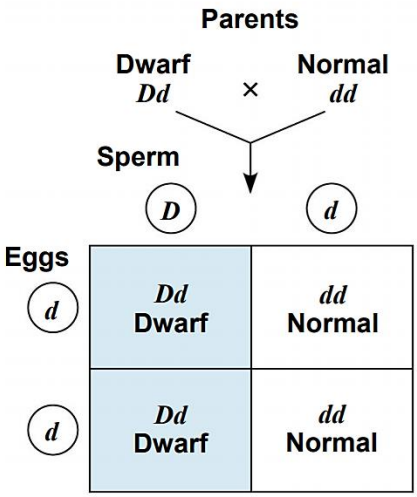
- × X-linked recessive traits are those expressed in males who carry one copy of the recessive allele (i.e., are hemizygous, XaY where a=recessive allele). Two copies of the recessive allele are generally required for females to express the trait, i.e., XaXa.
- × The genotype[1] at a particular locus and the environment [2] in which it is expressed determines the **phenotype** or observed characteristics (traits) of an individual.
- × Traits that are determined by loci on one of the 22 autosomes are autosomal. Traits determined by loci on the X chromosome are **X-linked**, and those determined by loci on the Y chromosome are **Y-linked**.

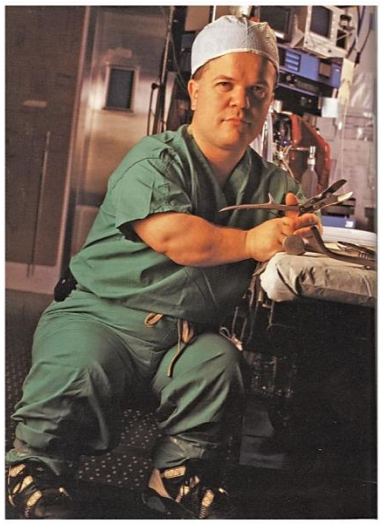
Dominantly Inherited Disorders||

Although dominant alleles *rarely* cause lethal diseases. A number of human disorders are due to dominant alleles. Examples include, (1) familial hypercholesterolemia, (2) Huntington disease, (3) neurofibromatosis type I (NF1), (3) myotonic dystrophy, (4) Marfan syndrome, and (5) **achondroplasia**.

Achondroplasia is the most common form of **dwarfism**. The appearance is of short stature with disproportionately short arms and legs. Although this condition *can be* inherited in an autosomal dominant manner, 80% of cases are due to new, sporadic (acquired; spontaneous; not inherited; de novo) mutations that take place in the developing fetus, or in the parental germ cells. As important, the mutation rate increases with paternal age.

These paternal effects reflect the fact that the older a man is, the more rounds of replication have occurred in his germ line and, with that, the higher the frequency of mutations in sperm cells.





Punnett square tells us clearly that offspring of an affected parent have a 50% chance of being affected.

Another example, a degenerative disease of the nervous system, called **Huntington's disease.** It is caused by a *lethal* dominant allele that has no obvious phenotypic effect until the individual is about 30 to 40 years old (late age of onset). It is caused by gradual degeneration of parts of the *basal ganglia* (responsible for *motor* control).

Myotonic dystrophy is a type of muscular dystrophy, a genetic disorder that impairs muscle function. Symptoms include gradually worsening muscle loss and weakness. Other symptoms may include cataracts, intellectual disability and heart conduction problems. Age at onset varies largely between individuals (**variable onset**). Also, Huntington's disease varies in the degree to which the genotype is phenotypically expressed in individuals (i.e. severity). For instance, one patient may have more severe symptoms than another patient who carries *the same mutated allele.* This phenomenon is described as **variable expressivity.**

Neurofibromatosis (NF type I) is a disease caused by mutations that can cause the Schwann cells in an affected individual's nervous system to grow into tumors (PNS tumors) called *neurofibromas*, which appear as *café-au-lait* colored spots or bumps under the skin. What is interesting is that, not all people who have the mutated gene are **equally** affected by this condition (i.e. the disease displays **variable expressivity**) .

I saw a research saying that family members who carry the same mutated gene can exhibit a range of symptoms, although they all carry the same allele!

Familial hypercholesterolemia (FH) is a genetic disorder characterized by high cholesterol levels. People who have one abnormal copy (are heterozygous) of the gene may develop increased LDL and coronary heart disease at the middle age. Having two abnormal copies (being homozygous) may cause severe coronary heart disease in childhood. Heterozygous FH is more common, and, of course, is inherited in an autosomal dominant pattern.

Marfan syndrome is an inherited disorder that affects connective tissue. People with Marfan syndrome are usually tall and thin with disproportionately long arms, legs, fingers and toes. Faulty connective tissue can weaken the aorta, and the high pressure of blood leaving the heart can cause the wall of the aorta to bulge out forming an *aortic aneurysm,* which is life-threatening. Also, most people with Marfan syndrome suffer from *myopia*. This happens since the connective tissue defect can affect the cornea, lens, and growth of the eye, and cause **lens subluxation** (dislocation).

It's clear that, in Marfan syndrome, a mutation in one gene affects many aspects of growth and development, including height, vision, and heart function. This is an example of **pleiotropy**, or one gene affecting multiple characteristics. Additionally, Marfan syndrome displays variable age of onset between individuals (**onset variability**).

DISEASE	CLINICAL FEATURES Note: Key aspects of phenotypic expression or inheritance features are bolded
Autosomal Dominant	
HUNTINGTON DISEASE	Progressive loss of brain neurons, dementia, loss of motor control Affects 1/20,000 persons of European descent **Late onset, typically between 30–40 years, but may be earlier** (See lecture on unstable trinucleotide repeats.)
MYOTONIC DYSTROPHY	Facial weakness Cataracts Progressive muscular weakness **Variable onset** **Variable expressivity**
NEUROFIBROMATOSIS TYPE I (NFI)	Cafe-au-lait spots (hyperpigmented skin) Lisch nodules (benign growths on the iris) Peripheral nerve tumors **Variable expressivity** High mutation rate
FAMILIAL HYPERCHOLESTEROLEMIA,	Arteriosclerosis, xanthomas **Heterozygotes: Increased LDL coronary heart disease in middle age** **Homozygotes: childhood coronary heart disease**
MARFAN SYNDROME (Connective tissue disorder)	Tall stature with long limbs Narrow facies with high, narrow palate Dislocated lenses & myopia Cardiac manifestations, i.e., aortic aneurysm **Variable expressivity** **Pleiotropy**
ACHONDROPLASIA	Short-limbed dwarfism Megalocephaly Lordosis & Kyphosis **80% new mutations** Increased mutations with increasing paternal age

≡ Features of autosomal dominant inheritance are as follows:

(1) **Vertical transmission** – direct transmission from grandparent to parent to child *without skipping* generations.

(2) Both sexes affected in **1:1 ratio** (it's an *autosomal* pattern of inheritance).

(3) Both sexes may **transmit the trait** (stated differently, an affected father may have an affected daughter and/or an affected son, and an affected mom may have an affected daughter and/or an affected son).

(4) **Heterozygotes** *much* more **common** than homozygotes.

Rule of thumb 👍

When you deal with an individual with an autosomal dominant disorder, suppose that this individual is **heterozygous** unless otherwise indicated.

(5) May see variable expressivity and variable age of onset.

(6) Homozygotes usually more seriously affected than heterozygotes.

(7) May be due to new mutation (spontaneous).

(8) Gene product is usually a *structural* (non-enzymatic) protein.

≡ Transmission probabilities and the use of the Punnett square

If one parent has the disorder (assumed to be Aa) and the other does not (aa) then there is a 50% chance that the child will inherit the disorder and a 50% chance that they will not.

2. If both parents have the disorder (assumed to be Aa x Aa) then there is a 75% chance that their children will inherit the disorder, and a 25% chance that they will not.

Recessively Inherited Disorders ||

Thousands of genetic disorders are known to be inherited as simple **recessive** traits. These disorders range in severity from relatively mild, such as **albinism** (lack of pigmentation, which results in susceptibility to skin cancers and vision problems), to life-threatening, such as **cystic fibrosis.**

In the case of **recessive disorders**, heterozygotes (Aa) typically have the normal phenotype because one copy of the normal allele (A) produces a sufficient amount of the specific protein. Thus, a recessively inherited disorder shows up only in the homozygous individuals (aa) who inherit a recessive allele from each parent. Although phenotypically normal with regard to the disorder, heterozygotes may transmit the recessive allele to their offspring and thus are called **carriers**; most individuals with recessive disorders are born to carrier parents.

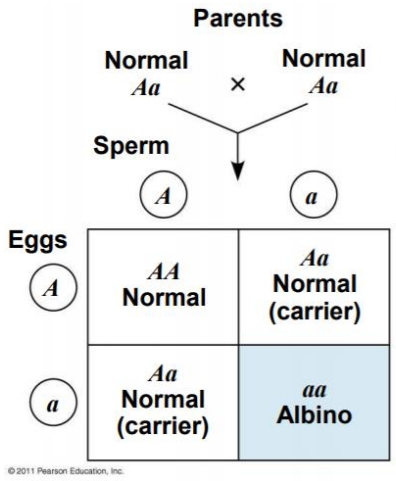
When a disease-causing recessive allele is rare, it is relatively unlikely that two carriers of the same harmful *rare* allele will meet and mate. The probability of passing on recessive traits increases greatly, however, if the man and woman are close relatives (for example, siblings or first cousins). Therefore, **consanguineous matings** (i.e., matings between close relatives) increase the chance of mating between two carriers of the same *rare* allele. Most societies and cultures have laws or taboos against marriages between close relatives.

In general, genetic disorders are not evenly distributed among all groups of people. Stated differently, the prevalence of a disease varies among different ethnic populations. For example, thalassemia is much more common in people from Mediterranean countries. Also, the incidence of Tay-Sachs disease is high among ***Ashkenazic Jews, and French Canadian*** *populations. While sickle cell anemia is high among those of* ***African*** *descent. Cystic fibrosis has higher frequency in* ***European Caucasians.***

Examples of recessive disorders include:

1. Cystic fibrosis
2. Sickle cell anemia
3. Tay-Sachs disease
4. Phenylketonuria
5. most inborn errors of metabolism

Albinism is characterized by the complete or partial absence of pigment in the skin, hair and eyes. It is associated with a number of vision defects, such as *photophobia*. Lack of skin pigmentation increases susceptibility to sunburn and skin *cancers*.



Cystic fibrosis is the most common *lethal* genetic disease in the United States, striking one out of every 2,500 people of European descent.

The cystic fibrosis allele results in defective or absent *chloride transport channels* in plasma membranes leading to a buildup of chloride ions outside the cell. Symptoms include mucus buildup in some internal organs and abnormal absorption of nutrients in the small intestine.

Sickle-cell disease, a genetic disorder with evolutionary implications, affects one out of 400 African-Americans. The disease is caused by the substitution of a single amino acid in the hemoglobin protein in red blood cells.

- In homozygous individuals, all hemoglobin is abnormal (sickle-cell). Symptoms include physical weakness, pain, organ damage, and even paralysis.
- Heterozygotes (said to have **sickle-cell trait**) are usually healthy but may suffer some symptoms. About one out of ten African Americans has sickle cell trait, an unusually high frequency of an allele with detrimental effects in homozygotes.
  Heterozygotes are less susceptible to the *malaria parasite,* so there is an advantage to being heterozygous.

Phenylketonuria (PKU) is an important disease of amino acid metabolism because it is relatively common and responds to dietary treatment. Normally, *Tyrosine* is formed from *phenylalanine* by hepatic *phenylalanine hydroxylase*. A deficiency in *phenylalanine hydroxylase* results in the disease phenylketonuria (PKU). It is characterized by accumulation of **phenylalanine** in tissues, plasma, and urine. **Phenyllactate, phenylacetate,** and **phenylpyruvate**, which are not normally produced in significant amounts in the presence of functional PAH, are also elevated in PKU. These metabolites give urine a characteristic musty ("mousey") odor. Severe intellectual disability, developmental delay, microcephaly, and seizures are characteristic findings in untreated PKU, due to reduced production of catecholamines. Patients may also show a deficiency of pigmentation (hypopigmentation; fair hair, light skin color, and blue eyes). The first step in the formation of the pigment melanin (tyrosine hydroxylation) is inhibited in PKU. No complete loss of pigment because we can obtain tyrosine from diet.

Autosomal Recessive	
CYSTIC FIBROSIS	Chronic, progressive pulmonary disease Pancreatic endocrine insufficiency Elevated sweat chloride **Higher frequency in European Caucasians**
TAY-SACHS DISEASE	Progressive neurological abnormalities Retinal cherry-red spot **Higher frequency in the Ashkenazi Jewish and French Canadian populations** Reduced serum hexosaminidase A Usually fatal in early childhood
SICKLE CELL ANEMIA	Failure to thrive Chronic anemia Vasoocclusive crisis (pain) Increased risk for infection **Higher frequency in those of African descent** Heterozygote advantage

Good luck