Concept 14.4: Many human traits follow Mendelian patterns of inheritance

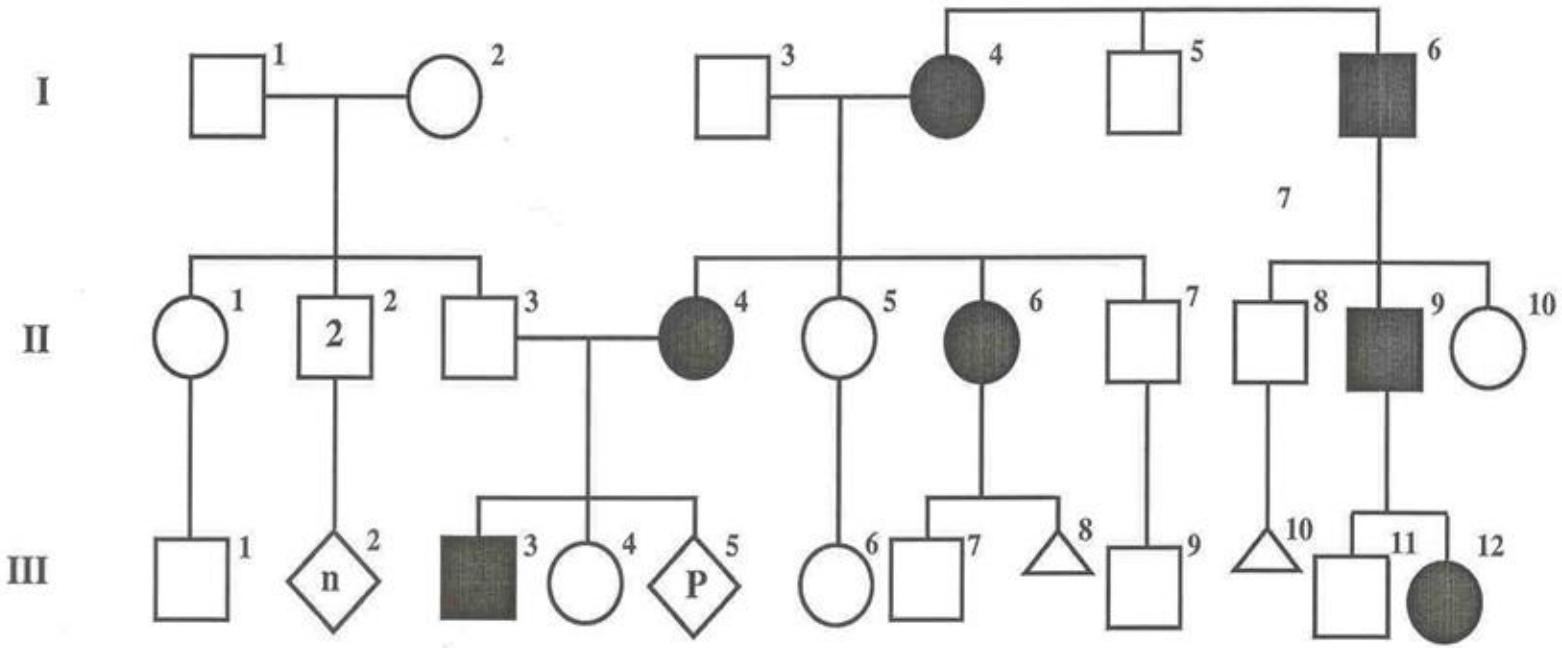
- Humans are not good subjects for genetic research
  - Generation time is too long
  - Parents produce relatively few offspring
  - Breeding experiments are unacceptable
- However, basic Mendelian genetics endures as the foundation of human genetics

Pedigree Analysis

- 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

Sample Pedigree



IMPORTANT TERMS

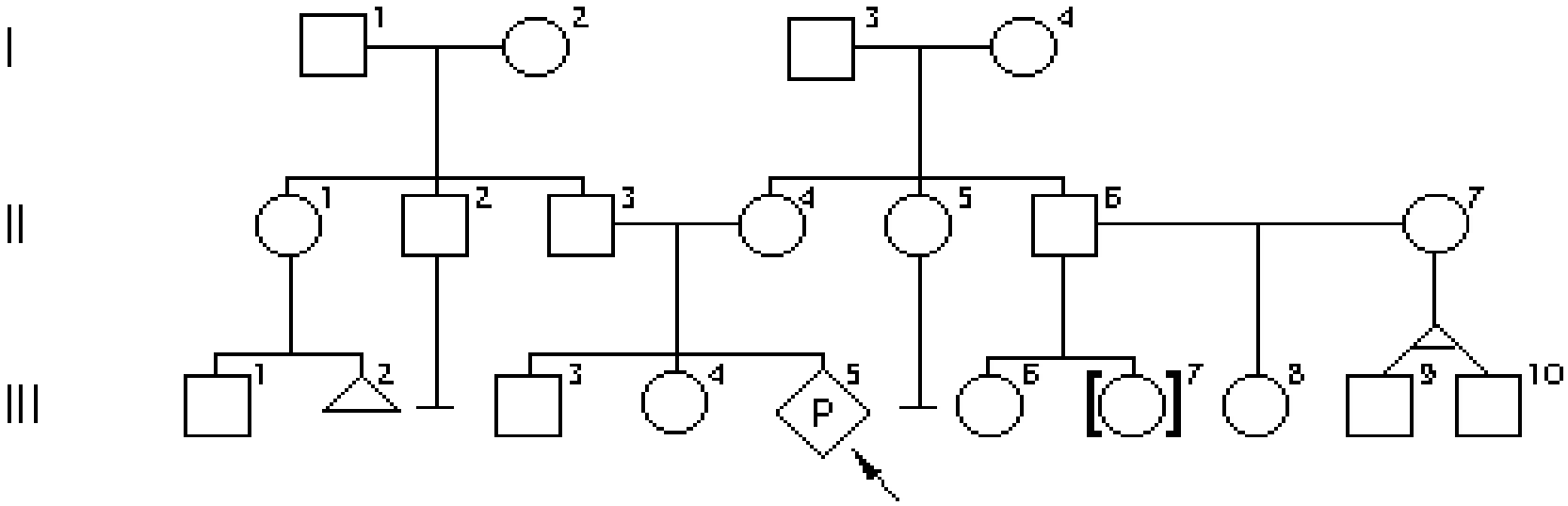
locus	codominant	compound heterozygote
allele	dominant	carrier (obligate heterozygote)
genotype	recessive	genetic heterogeneity
phenotype	homozygous	pleiotropy
autosomal	heterozygous	age of onset
X-linked	hemizygous	sex-limited
penetrance	expressivity	sex-influenced
pedigree	proband	imprinting
trinucleotide repeat		

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.

- Standardization of symbols is essential to facilitate communication - See Robin Bennett's article referenced in resources at the end of the syllabus for more details if interested.

- Nomenclature is an evolving process.
- Several ethical and legal dilemmas - Potential for discrimination, issues of privacy raised, and need for guidelines.



- In pedigrees, each horizontal line represents a generation.
- ✓ Older generations are placed at the top, while younger generations are placed at the bottom.

- Generations are labeled using Roman numerals.
- ✓ Within each generation, individuals are numbered using Arabic numerals.

- Siblings are arranged from left to right according to age, from oldest to youngest.

- The name and age of each individual may be written under the symbol, and race or ethnicity may also be documented.

- The symbol P indicates the **proband**.

Designation of generations and individuals

1. Each horizontal line is a generation
2. Place the oldest generation at the top
3. Use Roman numerals to identify generations
4. Use Arabic numbers to identify individuals within a generation
5. List siblings from oldest to youngest, from left to right
6. **Male partner is usually placed to the left of the female partner**
7. Record full name, current age and date of birth, or age at death for each individual
8. Record race and ethnic origin of each individual
9. **Note health problems and/or cause of death for each individual**
10. **There are appropriate symbols to use for both adoption and assisted-reproductive technologies**

- 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.

Medical status and results of genetic evaluation/testing of family members

1. Shading or fill (hatches, dots, etc.) is used to denote medical status or symptoms of individuals. A key/legend is used to define meaning
2. Results of an evaluation (E) are recorded below the symbol and a key/legend

   defines the notations. Currently this is the least standardized pedigree

   nomenclature

PEDIGREE NOMENCLATURE

Adapted from Bennett RL et al. (1995) AJHG 56:745-752.

Male

Female

Sex Unspecified

Number of children of sex indicated

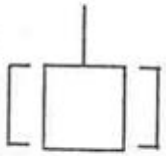
Affected

If it's not filled, it's an unaffected individual

Heterozygotes for autosomal trait

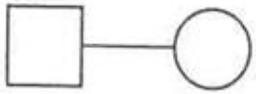
Carrier of X-linked recessive trait

Carrier female

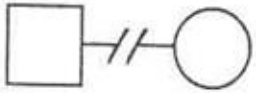


Adopted out of a family

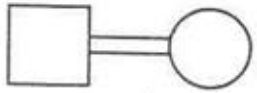
The individual is adopted out of the biological family.
Genetically, the individual belongs to the biological family. However, environmentally, the individual was not raised within that family environment.



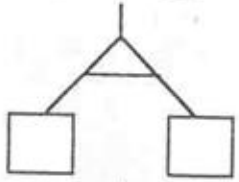
Relationship



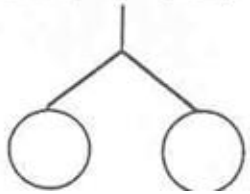
Relationship that no longer exits



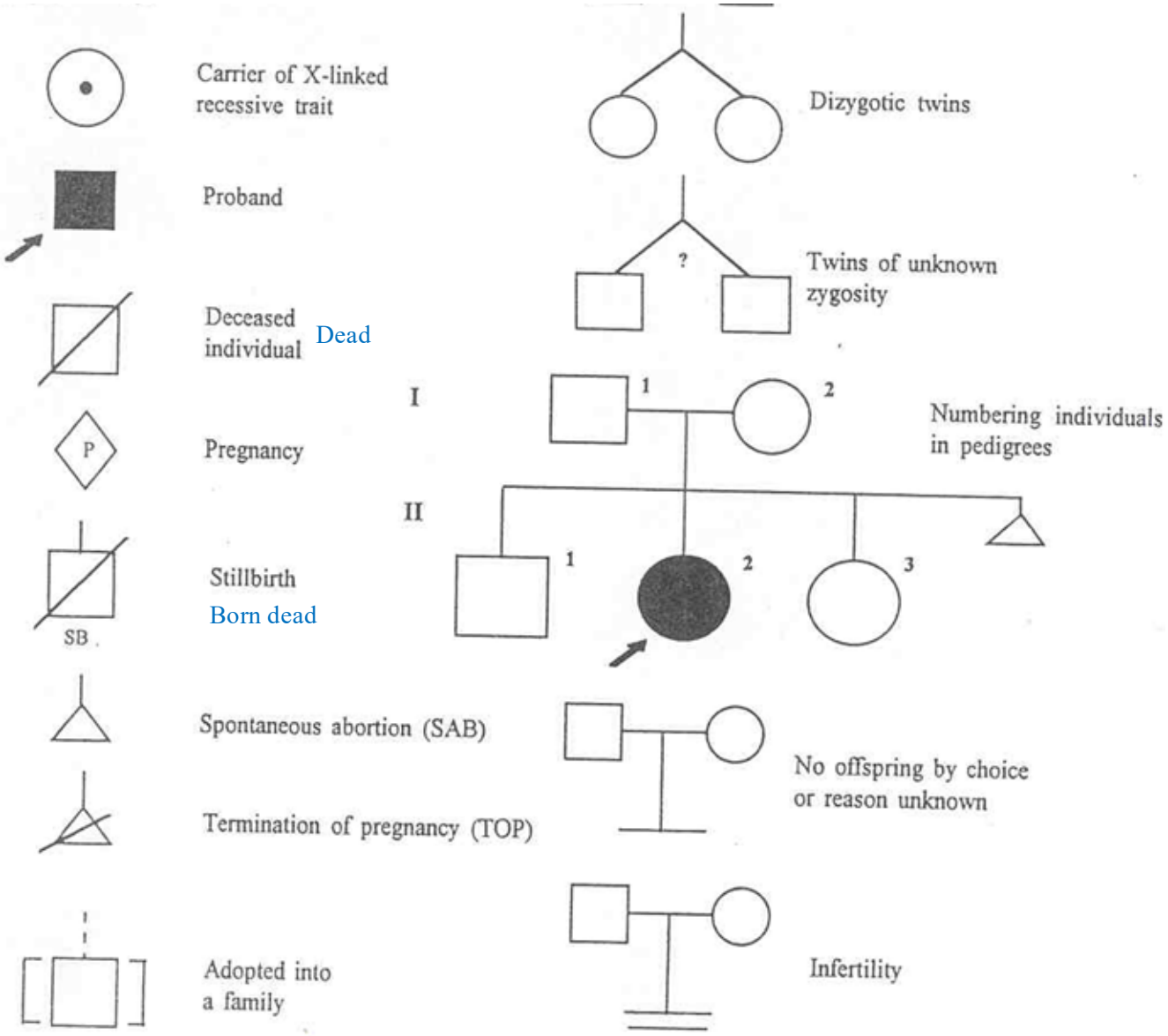
Consanguineous mating



Monozygotic twins



Dizygotic twins



The individual is adopted into the family and is not biologically related to that family.

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.

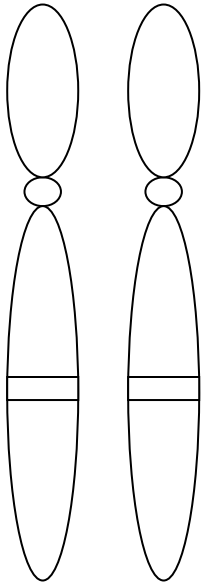
If the alleles differ, then the individual is **heterozygous** at the locus. If two different mutant alleles are present, then the individual is a **compound heterozygote**.

- An allele is a version of a gene.
- ✓ A normal allele means that the gene has a normal DNA sequence.
- ✓ A mutated allele means that the gene carries a mutation.

- Different types of mutations may occur **in the same gene**, such as: amino acid substitution at a specific position, splice-site mutation, deletion, insertion…

- Therefore, multiple alleles can exist for the same gene.

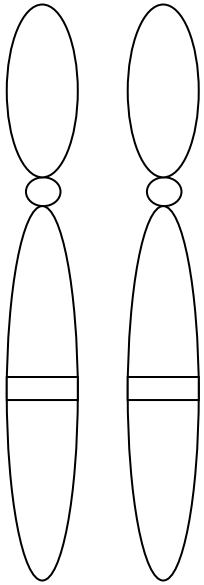
- Each individual has two alleles for each gene, one inherited from each parent, *except for genes located on the sex chromosomes in males.*



A A

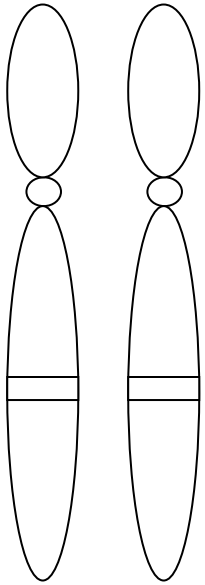
homozygote

A allele



A a

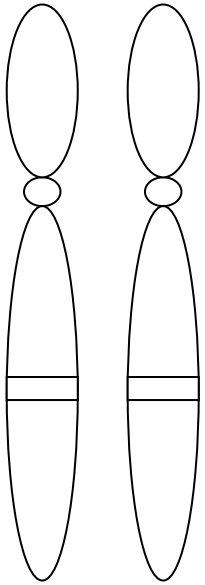
heterozygote



a a

homozygote

a allele



a1 a2

compound

heterozygote

- In a recessive disease, the **normal allele is dominant** over the mutant allele.

  - If an individual is homozygous for the normal allele (AA), both alleles are normal.
  - If the individual is heterozygous (Aa), one allele is normal (A) and the other allele is a mutant disease-causing allele (a).
  - If the individual is homozygous mutant (aa), both alleles carry the mutation.
  - Compound heterozygous means the individual has two mutant alleles in the same gene, but each allele carries a different mutation.

- The genotype at a particular locus and the environment in which it is expressed determines the phenotype or observed characteristics 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**.

Gregor Mendel's Laws of Inheritance

- 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.

- Law of Segregation - the two alleles at a particular locus segregate into different gametes.

- Law of Independent Assortment - alleles at different loci are transmitted independently of each other. Linkage is an exception to this rule.

➢ Mendel's First Law — Law of Segregation:

- On the **gene level**, the law of segregation states that during meiosis, during gamete formation (eggs or sperms), the two alleles of each gene separate into different daughter cells, meaning each gamete receives only one allele.

- On the **chromosomal level**, each chromosome exists as two homologous chromosomes, one inherited from each parent. During anaphase I of meiosis, homologous chromosomes migrate to opposite poles of the cell, and each daughter cell receives one homolog.

- Since each homologous chromosome carries one allele of the same gene, segregation of homologous chromosomes results in segregation of alleles.

➢ Mendel's Second Law — Law of Independent Assortment:

- On the **chromosomal level**, different chromosome pairs segregate independently during meiosis. Chromosome 1 and chromosome 2 assort independently regardless of parental origin.

✓ Thus, chromosome 1 paternal may segregate with chromosome 2 maternal, chromosome 1 paternal with chromosome 2 paternal, chromosome 1 maternal with chromosome 2 paternal, or chromosome 1 maternal with chromosome 2 maternal.

- On the **gene level**, if gene A is located on chromosome 1 and gene B on chromosome 2, and both genes are heterozygous, the alleles assort independently into gametes.

✓ Therefore, gametes may contain:

❑ mutant allele of gene A with mutant allele of gene B
❑ mutant allele of gene A with normal allele of gene B
❑ normal allele of gene A with mutant allele of gene B
❑ normal allele of gene A with normal allele of gene B

Dominant and Recessive Inheritance

- Nomenclature: 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.**

Dominant and Recessive Inheritance

- If the heterozygote (AB) has a different phenotype than either of the homozygotes (AA or BB), then the alleles are said to be **codominant**.

- **X-linked dominant traits** are those expressed when either males or females have one copy of the dominant allele, i.e., X^AY or X^AX^a where A=dominant allele. **(One mutant allele is enough to cause the disease)**

  - Male has only one X chromosome; therefore, he has only one allele for genes located on the X chromosome that are absent on the Y chromosome. In contrast, a female has two X chromosomes and therefore possesses two alleles for the same X-linked gene.

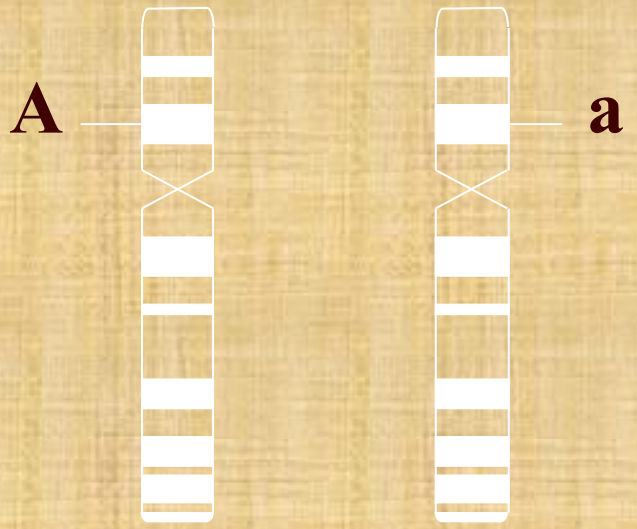
  ✓ Thus, the female can be **heterozygous or homozygous**, whereas the male, having only one allele, is described as **hemizygous**, not homozygous or heterozygous.

- **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) "He has one mutant allele which is enough to manifest the disease ". Two copies of the recessive allele are generally required for females to express the trait, i.e., XaXa. "If she is heterozygous for the mutant allele, she would be a carrier, but typically not affected"

Types of Genetic Disease

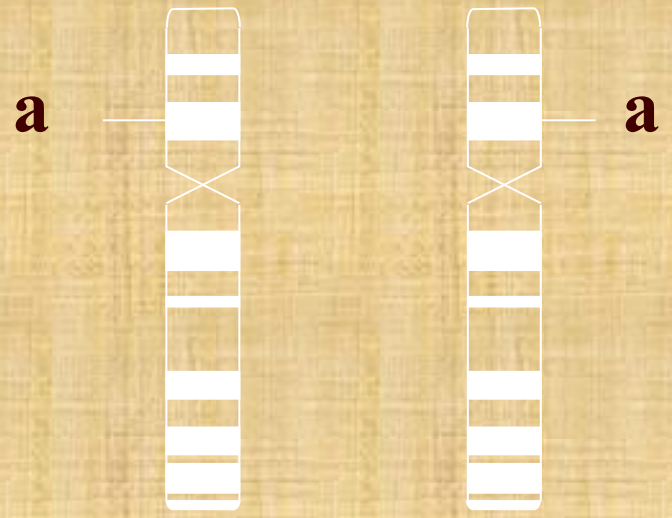
- Chromosomal
- Single gene (Mendelian)
- Multifactorial
- Teratogenic

Examples and Features of Autosomal Dominant Inheritance



Affected individual

A=mutant allele
a=normal allele



Unaffected individual

Examples

- familial hypercholesterolemia
- Huntington disease
- neurofibromatosis type I (NF1)
- myotonic dystrophy
- Marfan syndrome
- achondroplasia

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

See the next slides

➢ **Huntington disease:**

- A neurodegenerative disorder, meaning it shows **progressive deterioration** over time.
- It is characterized by progressive loss of brain neurons, leading to **dementia, memory loss, and loss of motor contr**ol.
- It affects approximately 120,000 individuals of European descent.
- Huntington disease is an example of an autosomal dominant disorder with **late age of onset,** where clinical manifestations typically appear in the late 30s or early 40s, although onset may occur earlier.

➢ **Myotonic dystrophy:**

- A disorder characterized by **progressive muscle weakness**, including **weakness of the facial muscles**, and the presence of **cataracts**.
- This disease demonstrates:

✓ Variable onset → the ***age*** at which symptoms begin differs among affected individuals.

✓ Variable expressivity → disease ***severity*** varies between individuals carrying the same mutation.

➢ **Neurofibromatosis type 1 (NF1):**

- It is characterized by:

❑ **Peripheral** nerve tumors

❑ Benign iris lesions known as **Lisch nodules**

❑ **Hyperpigmented** café-au-lait spots

- NF1 shows **variable expressivity**, meaning affected individuals exhibit different degrees of disease severity.

➢ **Familial hypercholesterolemia:**

- An inherited disorder caused by mutation of the **LDL receptor gene**.
- ✓ ***Heterozygous individuals*** develop elevated LDL cholesterol and coronary heart disease typically in **middle** age.
- ✓ ***Homozygous individuals*** are much more severely affected, developing coronary disease during **childhood**.
- ❖ In autosomal dominant disorders, *homozygous mutants are usually more severely affected than heterozygous individuals.*

➢ **Marfan syndrome:**

- A **connective tissue** disorder.
- Typical clinical features include:
- ❑ **Tall** stature with long limbs
- ❑ **Narrow face** and high-arched palate
- ❑ Lens dislocation, causing **myopia**
- ❑ Serious cardiovascular manifestations, especially risk of **cardiac aneurysm and aortic rupture** due to weakened connective tissue
- Marfan syndrome demonstrates:
- ✓ Variable severity
- ✓ Pleiotropy → one gene mutation producing manifestations in multiple organ systems (skeletal, ocular, and cardiovascular).

➢ **Achondroplasia:**

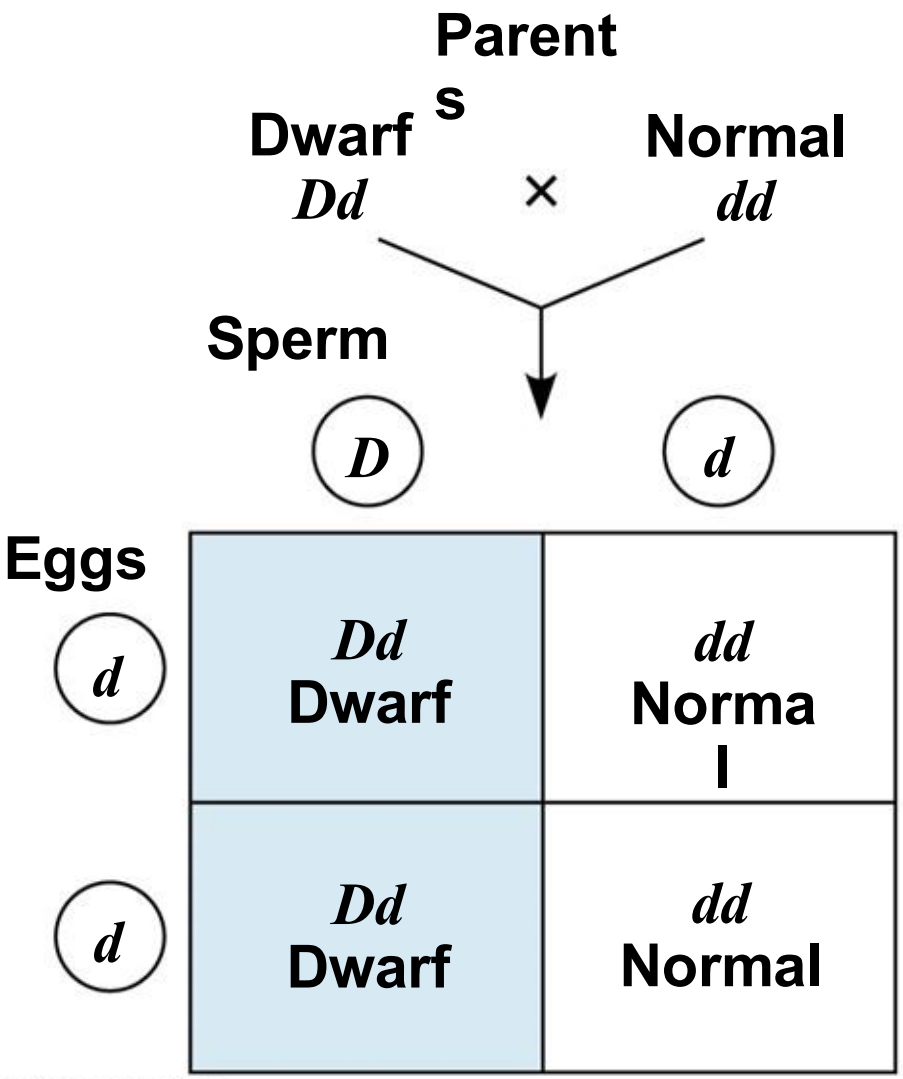
- The most common form of **dwarfism**.
- It is an autosomal dominant disorder characterized by **short limbs** with relatively normal trunk length and **megalocephaly**.
- Approximately 80% of achondroplasia cases result from new mutations occurring during gametogenesis, **rather than inheritance from affected parents.**

✓ ***Autosomal dominant diseases may arise from de novo (spontaneous) mutations.***

Dominantly Inherited Disorders

- Some human disorders are caused by dominant alleles
- Dominant alleles that cause a lethal disease are rare and arise by mutation
- *Achondroplasia* is a form of dwarfism caused by a rare dominant allele

Figure 14.17

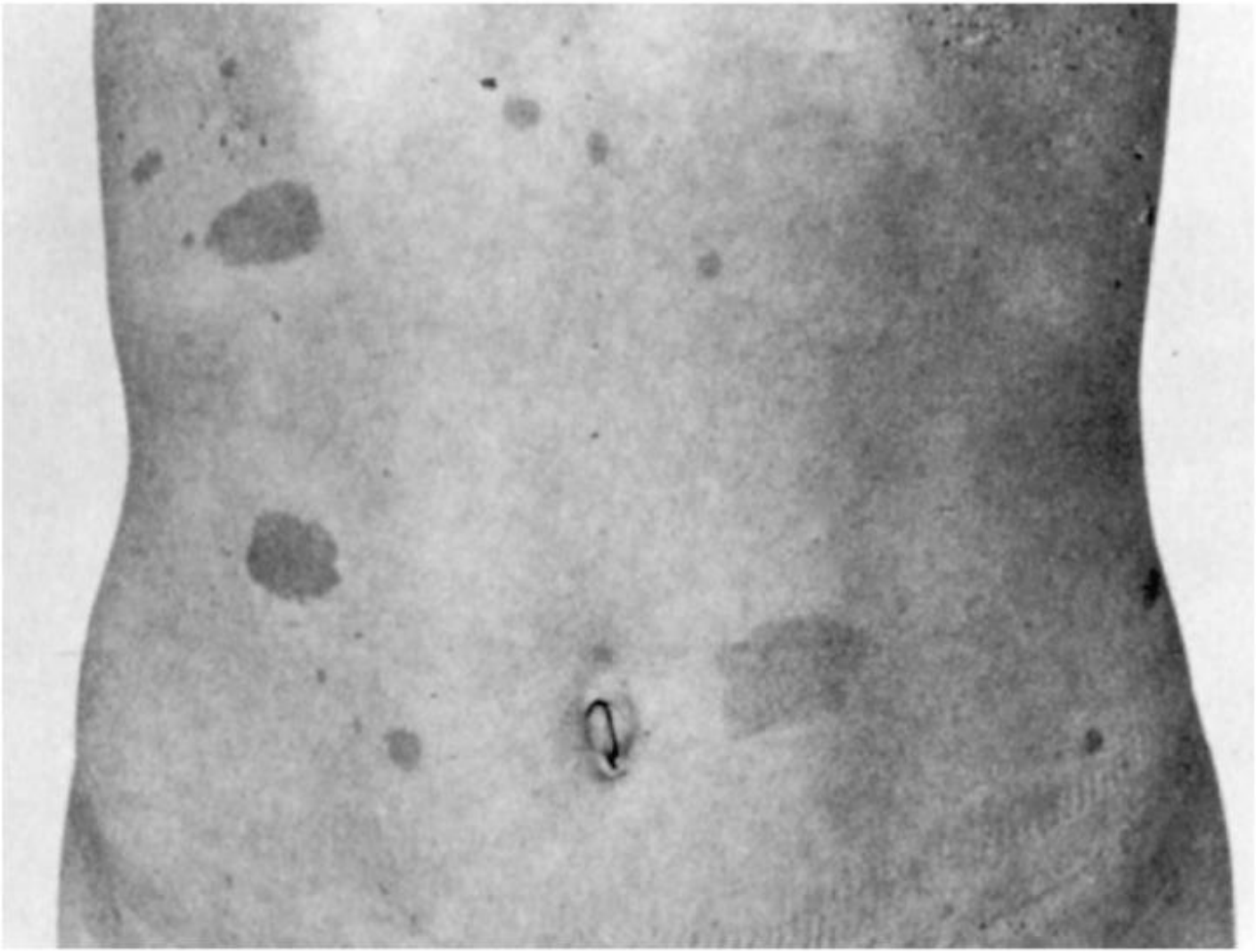


Achondroplasia

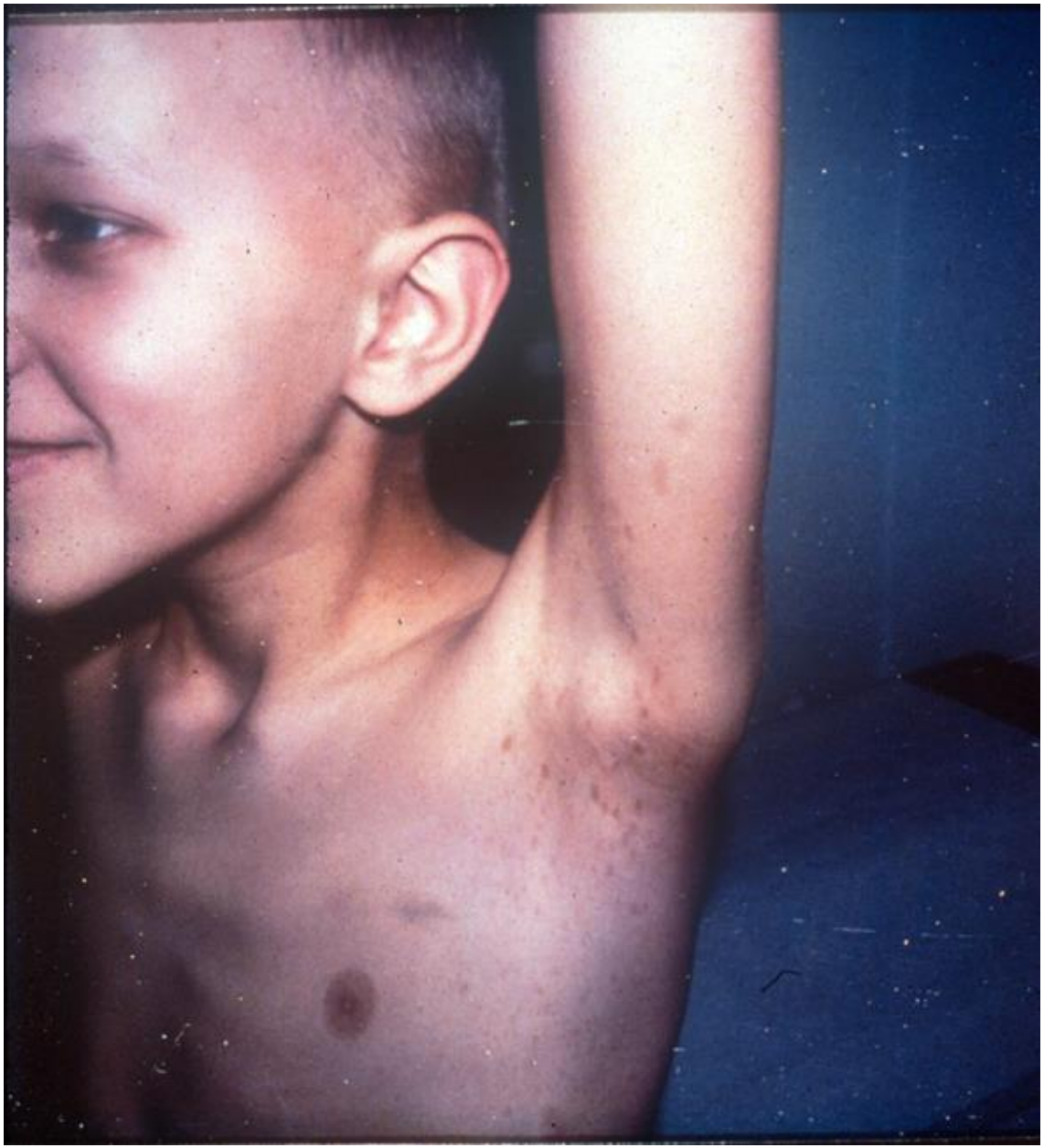
From www.hopkinsmedicine.org

From www.sciencemuseum.org.uk

Neurofibromatosis Type 1



Neurofibromatosis Type 1



Neurofibromatosis Type 1

Severe

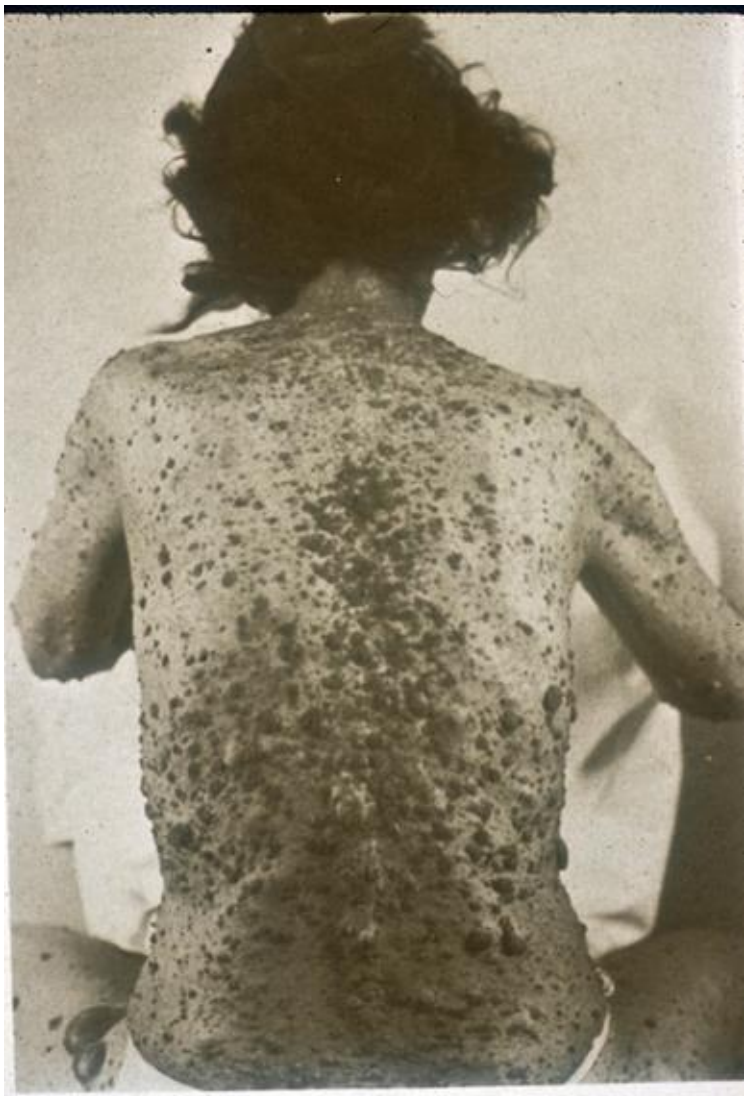
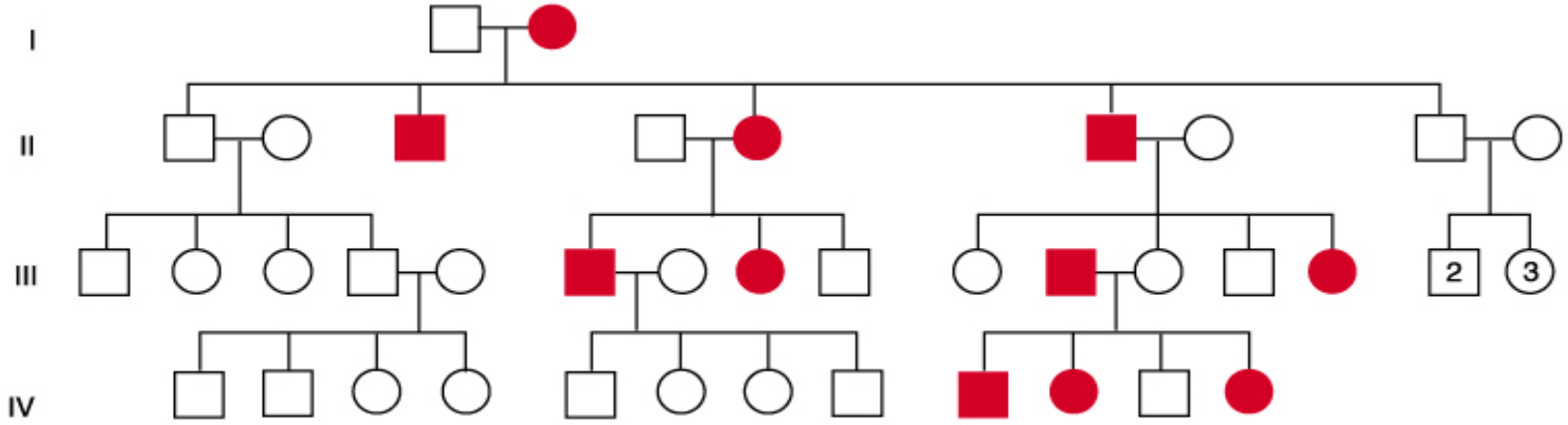


Fig. 121-3.—Recklinghausen neurofibromatosis.

الحمد لله الذي عافانا مما ابتلى به غيرنا وفضلنا على كثير من خلقه تفضيلاً

Autosomal Dominant Pedigree



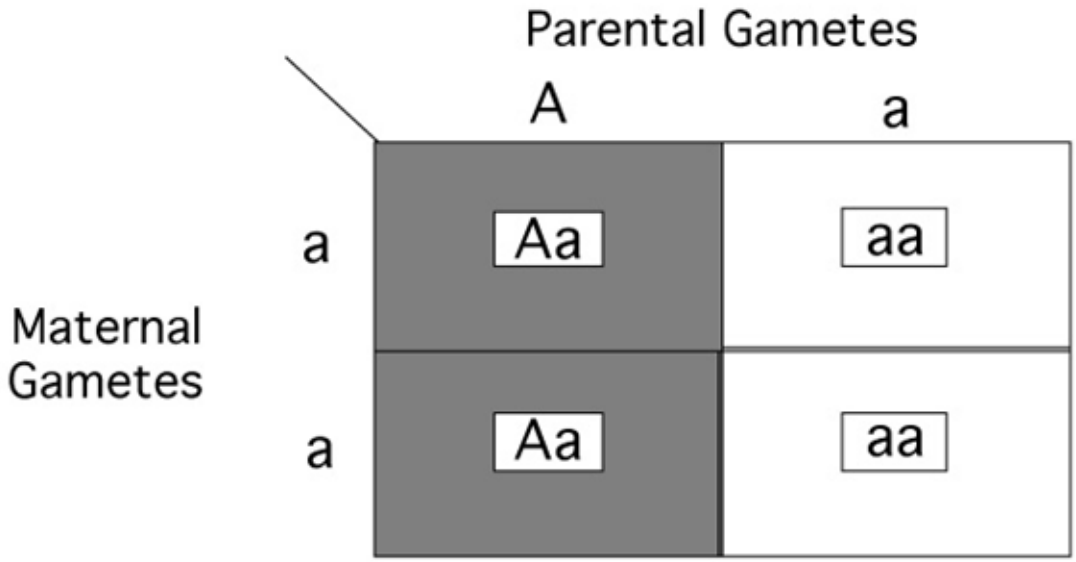
- **Vertical transmission** means that affected individuals appear in **every generation**, with direct transmission of the mutation from grandparents to parents and then to offspring.
- Because the disorder is autosomal, the **male-to-female ratio is approximately 1:1,** meaning that males and females are affected at similar frequencies.
- Another feature of autosomal dominant diseases is that both sexes can transmit the trait. This occurs because the gene is located on an autosome rather than a sex chromosome.
- This principle also applies to autosomal recessive diseases. **Either parent can transmit the mutant allele equally to sons and daughters, regardless of sex.**
- ***Zygosity*** is determined by genetic testing; however, as a general rule in autosomal dominant disorders, affected individuals are **assumed to be heterozygous unless proven otherwise.**

Features of Autosomal Dominant Inheritance

1. Vertical transmission – direct transmission from grandparent to parent to child without skipping generations
2. Both sexes affected in 1:1 ratio
3. Both sexes may transmit the trait
4. Heterozygotes much more common than homozygotes
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
8. Gene product is usually a structural (non-enzymatic) protein

Autosomal Dominant Inheritance

(Affected Father)



1Aa: 1aa

A = mutant, a = normal

Transmission probabilities and the use of the Punnett square

The mutant allele is dominant

1. 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.

Examples and Features of Autosomal Recessive Inheritance

Recessively Inherited Disorders

- Many genetic disorders are inherited in a recessive manner
- These range from relatively mild to life-threatening

Examples

- cystic fibrosis
- sickle cell anemia
- Tay-Sachs disease
- Phenylketonuria
- most inborn errors of metabolism

The Behavior of Recessive Alleles

- Recessively inherited disorders show up only in individuals homozygous for the allele
- **Carriers** are heterozygous individuals who carry the recessive allele but are phenotypically normal; most individuals with recessive disorders are born to carrier parents
- **Albinism** is a recessive condition characterized by a lack of pigmentation in skin and hair and eyes

Recessive diseases show different prevalence rates among different populations.

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

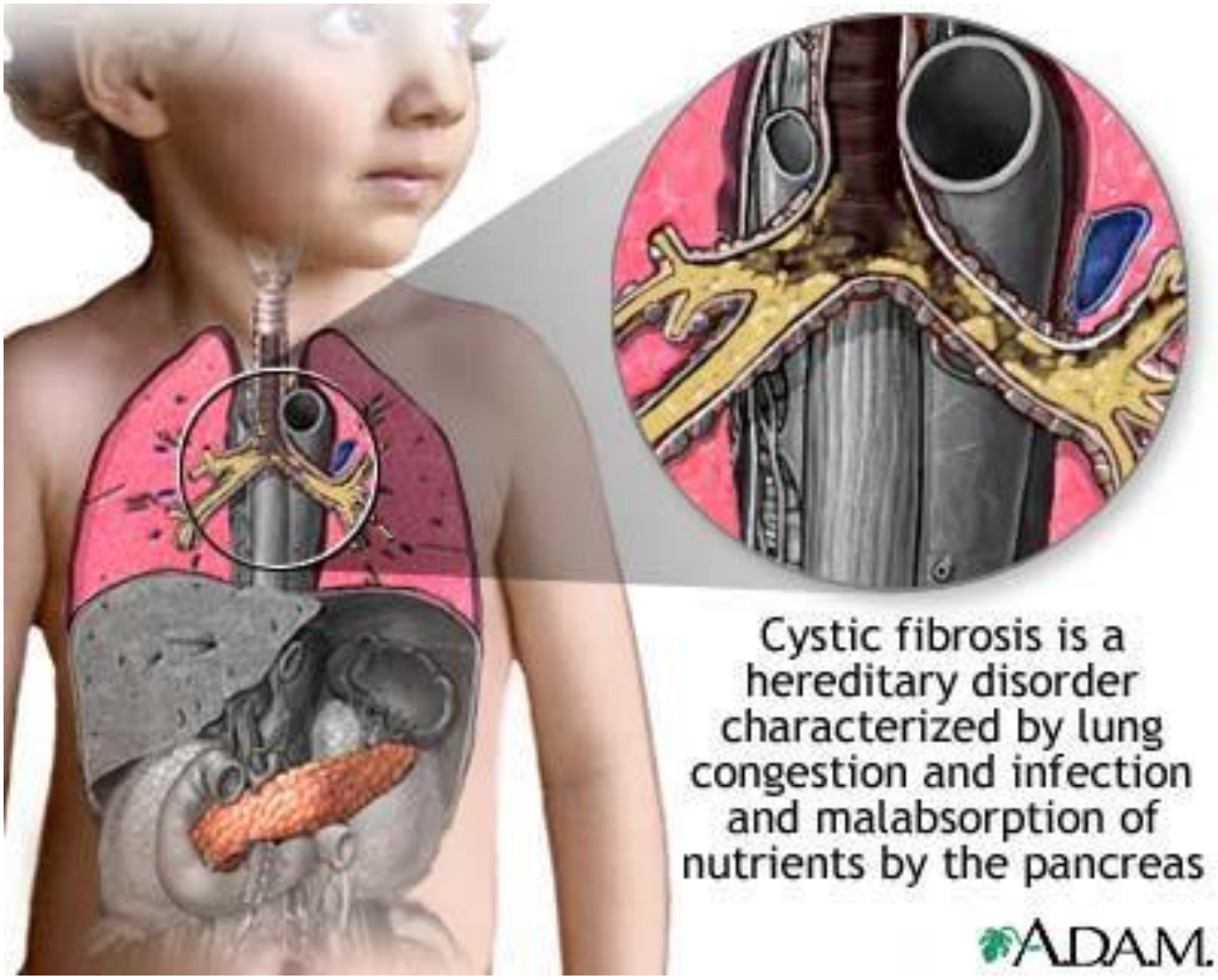
- It affects red blood cells, causing an abnormal sickle shape.
- Since structure dictates function, loss of normal structure leads to loss of normal function.
- As a result, affected individuals have impaired oxygen transport by red blood cells.

Cystic Fibrosis

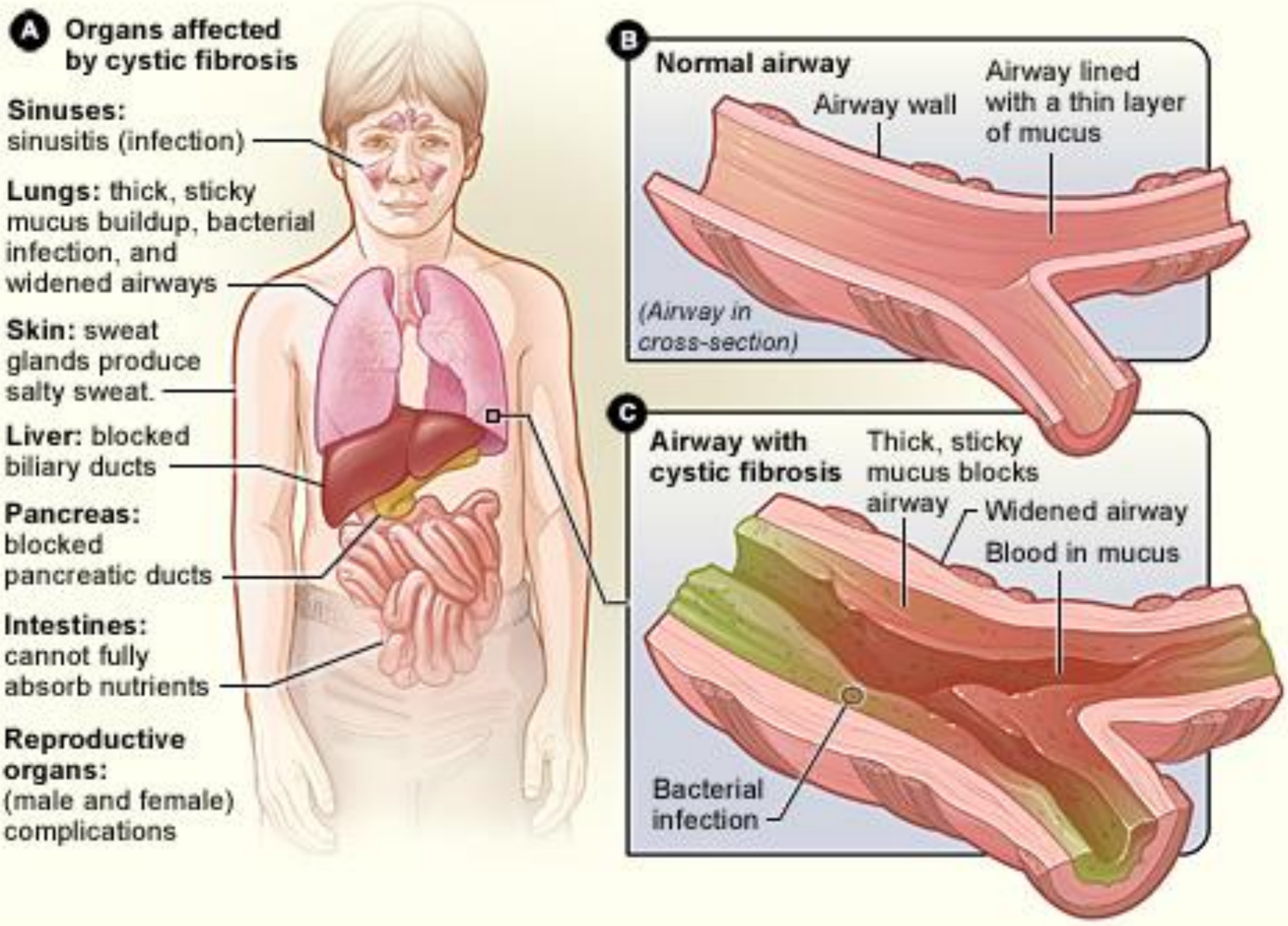
Explained earlier

- **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

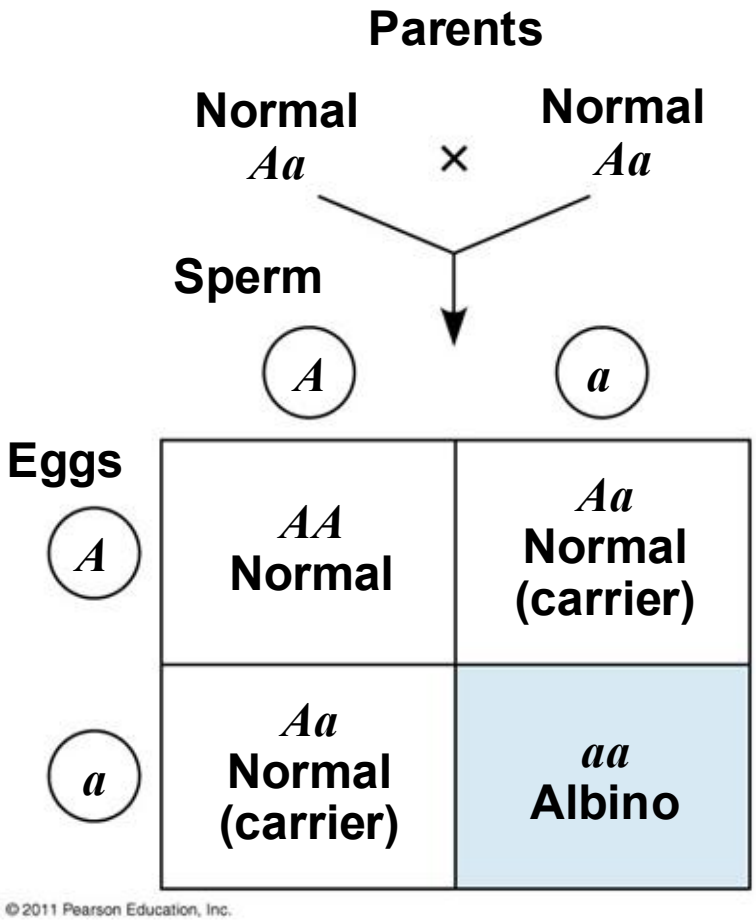
Cystic fibrosis (CF)



Photos from
www.cff.org


A
Organs affected by cystic fibrosis
Sinuses: sinusitis (infection)
Lungs: thick, sticky mucus buildup, bacterial infection, and widened airways
Skin: sweat glands produce salty sweat.
Liver: blocked biliary ducts
Pancreas: blocked pancreatic ducts
Intestines: cannot fully absorb nutrients
Reproductive organs: (male and female) complications
B
Normal airway
Airway wall
Airway lined with a thin layer of mucus
(Airway in cross-section)
C
Airway with cystic fibrosis
Thick, sticky mucus blocks airway
Widened airway
Blood in mucus
Bacterial infection

- **Albinism** is characterized by lack of pigmentation affecting the hair, skin, and eyes. The blue color of the eye represents absence of pigmentation.



- If both parents are carriers (heterozygous), then 50% of the gametes (eggs and sperms) will carry the mutant allele.
- ✓ Among the offspring:
  - ❑ 25% will be homozygous normal.
  - ❑ 50% will be heterozygous carriers (clinically normal).
  - ❑ 25% will be homozygous mutant and affected with albinism.

- If a recessive allele that causes a disease is rare, then the chance of two carriers meeting and mating is low
- **Consanguineous matings** (i.e., matings between close relatives) increase the chance of mating between two carriers of the same rare allele

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- Most societies and cultures have laws or taboos against marriages between close relatives

Sickle-Cell Disease: A Genetic Disorder with Evolutionary Implications

- **Sickle-cell disease** 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

Sickle Cell Anemia

Phenylketonuria

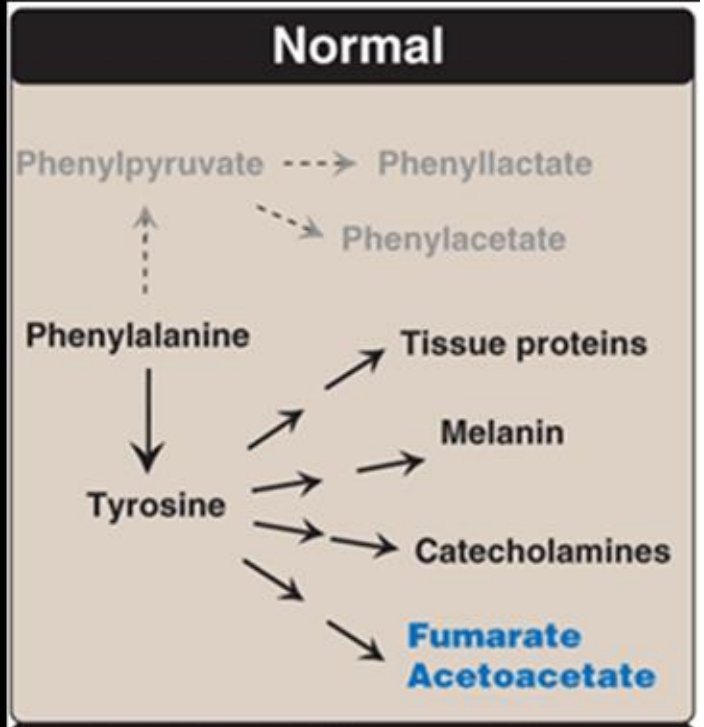
- PKU is an inherited disorder that increases the levels of phenylalanine in the blood
- Due to defictive hepatic enzyme phenylalanine hydroxylase (PAH) .
- Necessary to metabolize the amino acid phenylalanine ('Phe') to the amino acid tyrosine

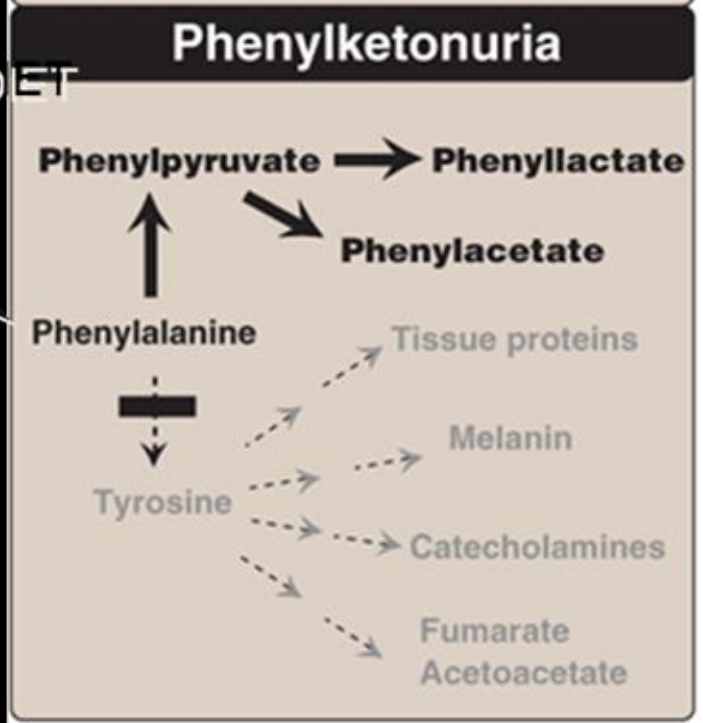
Symptoms

- Elevated phenylalanine, phenylpyruvate, phenyllactate and phenylacetate in blood and urine **(musty odor of urine).**

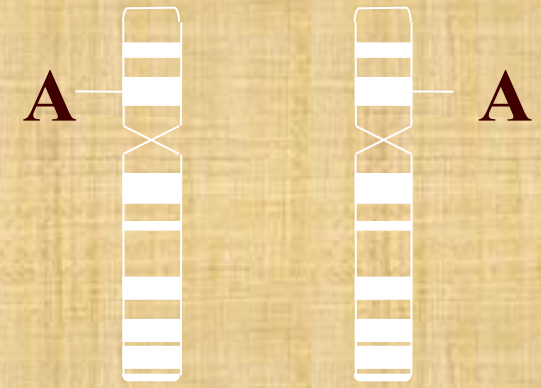
- **Neurological problems** (mental retardation, seizures, tremors, microcephaly etc) due to reduced production of catecholamines.

- **Hypopigmentation** (light skin, hair, blue eyes) due to reduced melatonin production. NO COMPLETE LOSS OF PIGMENT B/C WILL STILL HAVE SOME TYROSINE FROM DIET

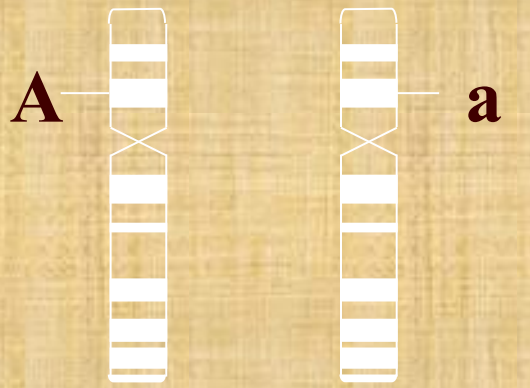




Autosomal Recessive

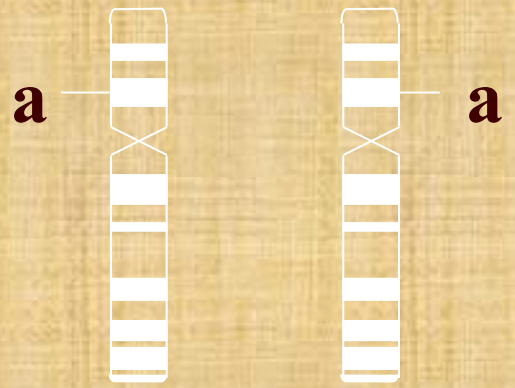


Unaffected, not a carrier



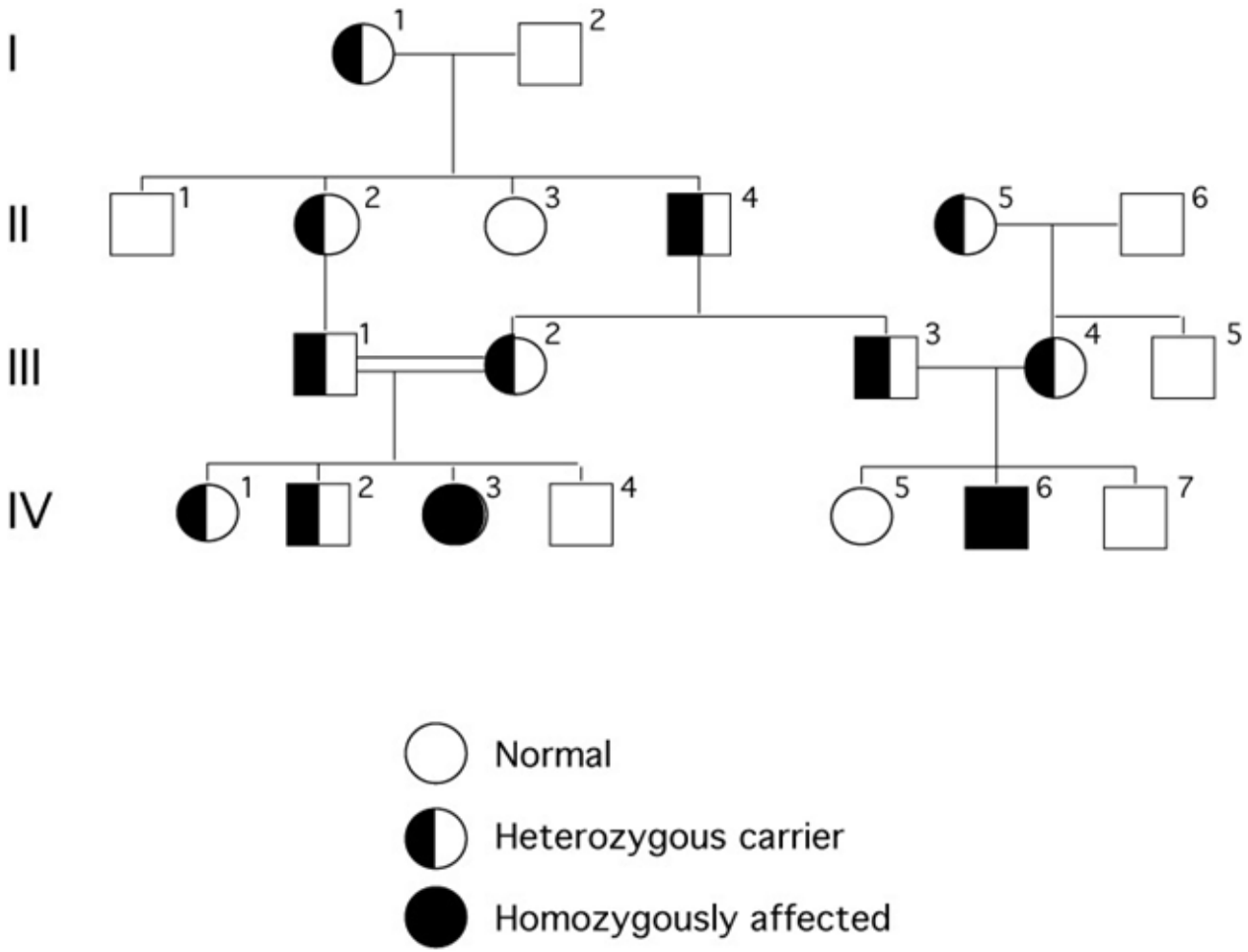
Carrier, unaffected

A=normal allele
a=mutant allele



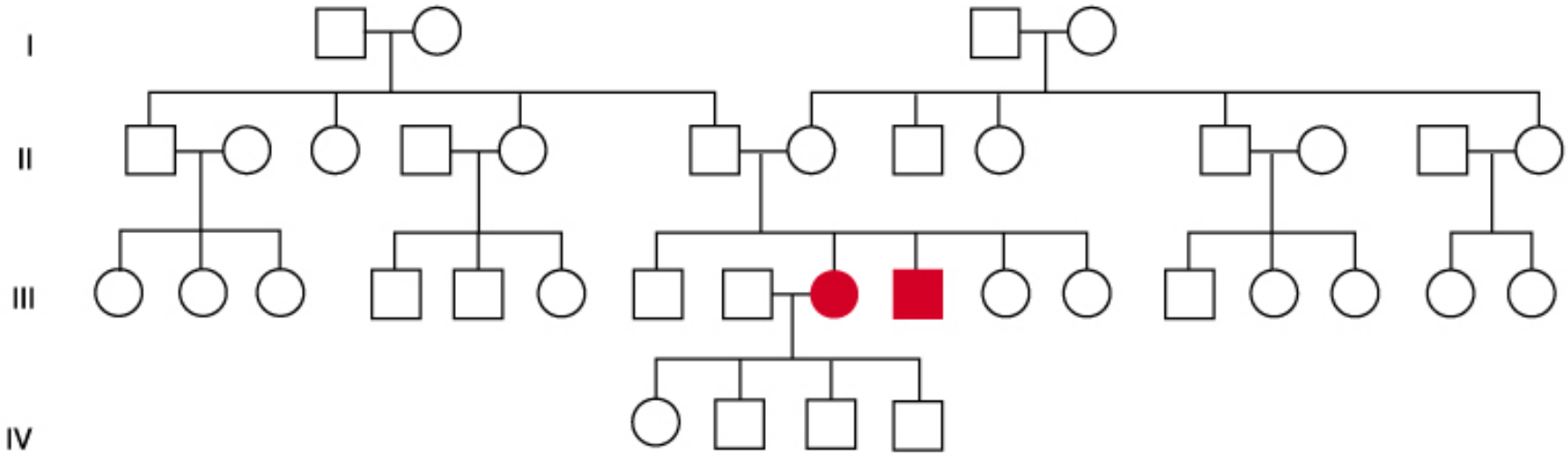
Affected

Autosomal Recessive Pedigree



- A female (1) transmitted the mutation to both her son and her daughter.
- The son (4) and the daughter (2) each had children, who are cousins.
- These cousins married, and both were carriers of the mutation.
- Their offspring included one affected individual, two unaffected carrier individuals and one normal individual.

Autosomal Recessive Pedigree



- Unlike autosomal dominant pedigrees, affected individuals do **NOT** necessarily appear in every generation (skipping generations).
- ✓ This pattern is not considered vertical transmission; rather, it represents **horizontal transmission.**

Features of Autosomal Recessive Inheritance

1. Horizontal transmission – affected individuals usually within the same sibship or generation
2. Both sexes affected in 1:1 ratio
3. Both sexes may equally transmit the mutant allele
4. May observe consanguinity
5. Gene product is usually an **enzymatic protein**

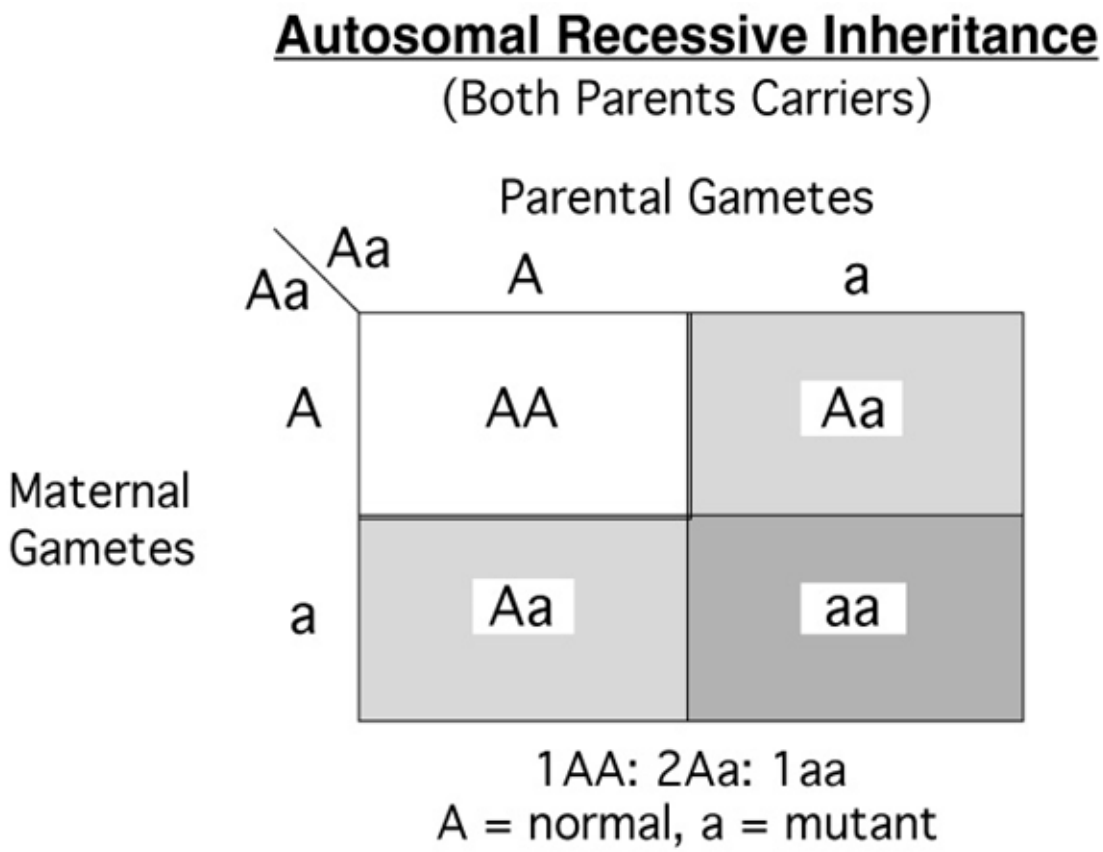
- In autosomal dominant diseases, the gene product is usually a **structural protein,** whereas in recessive diseases, the gene product is typically an **enzyme**.

Transmission probabilities and use of the Punnett square

If both parents are carriers (Aa x Aa) then there is

- 25% chance that the child will have the disorder (aa)
- 50% chance that the child will be a carrier (Aa), and
- 25% chance that the child will be neither affected nor a carrier (AA).

Thus the chance that an unaffected child of carrier parents is also a carrier is two in three.



Affected homozygotes are commonly the offspring of two heterozygote carriers.

Please click here and let me know if there's any mistake.
Good Luck ☺