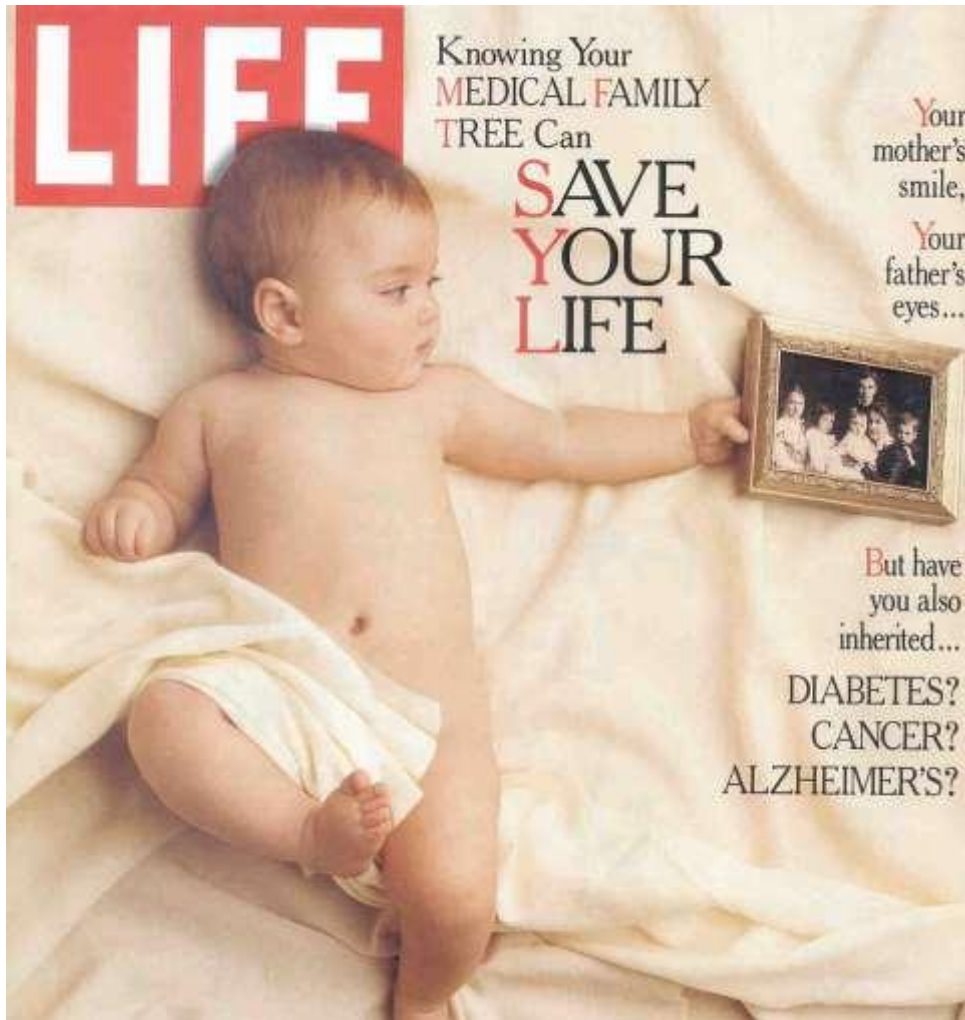


Single-Gene Inheritance

Importance of Family History



- Understanding the past is the key to predicting the future.

OBJECTIVES

- Construct and interpret pedigrees using standard nomenclature
- Describe the general features of Mendelian patterns of single gene inheritance.
- Identify the mode of inheritance of traits discussed in lecture.
- Describe aspects of phenotypic expression, using traits discussed in lecture as examples.
- Understand basic concepts of probability.
- Recognize the pattern of inheritance of a trait segregating in a family.
- Apply basic concepts of probability and principles of Mendelian inheritance to calculate the probabilities that offspring of specified mating types will be affected and unaffected.

Concept 14.3: Inheritance patterns are often more complex than predicted by simple Mendelian genetics

- The relationship between genotype and phenotype is rarely as simple as in the pea plant characters Mendel studied
- Many heritable characters are not determined by only one gene with two alleles
- However, the basic principles of segregation and independent assortment apply even to more complex patterns of inheritance

Extending Mendelian Genetics for a Single Gene

- Inheritance of characters by a single gene may deviate from simple Mendelian patterns in the following situations:
 - When alleles are not completely dominant or recessive
 - When a gene has more than two alleles
 - When a gene produces multiple phenotypes

Degrees of Dominance

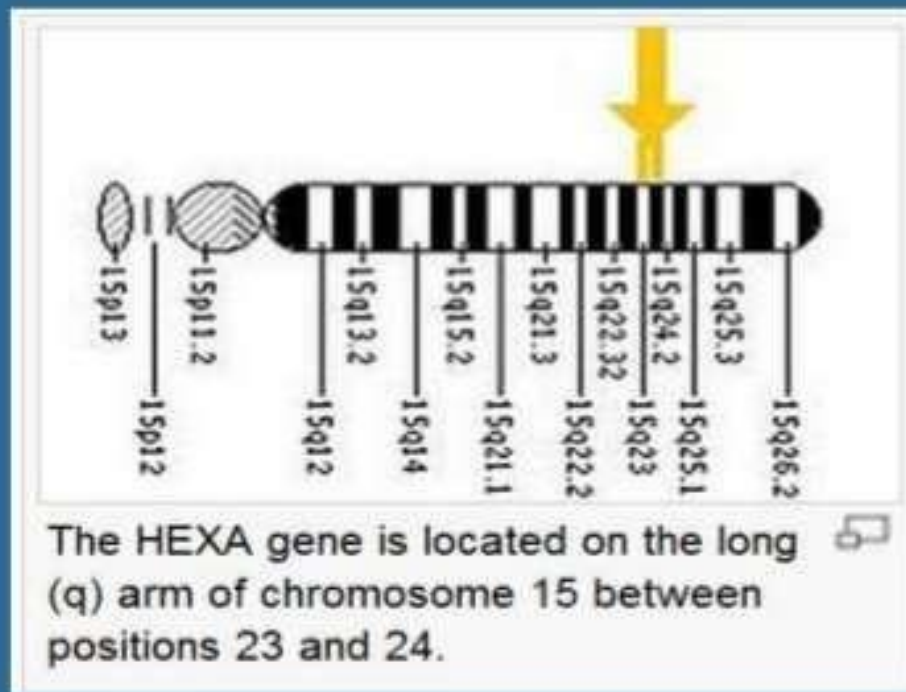
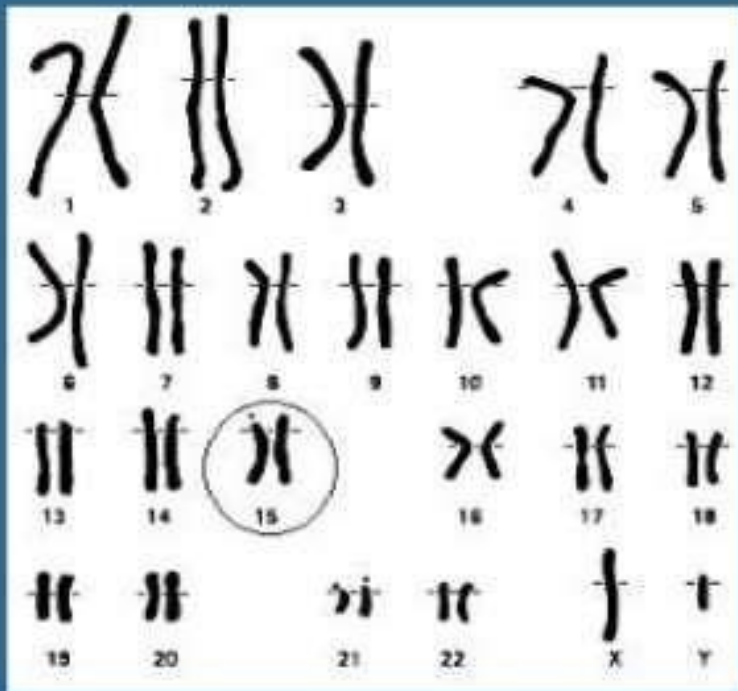
- **Complete dominance** occurs when phenotypes of the heterozygote and dominant homozygote are identical
- In **incomplete dominance**, the phenotype of F_1 hybrids is somewhere between the phenotypes of the two parental varieties
- In **codominance**, two dominant alleles affect the phenotype in separate, distinguishable ways

The Relation Between Dominance and Phenotype

- A dominant allele does not subdue a recessive allele; alleles don't interact that way
- Alleles are simply variations in a gene's nucleotide sequence
- For any character, dominance/recessiveness relationships of alleles depend on the level at which we examine the phenotype

Causes of Tay-Sachs

The disease is caused by **mutations on chromosome 15 in the HEX A gene**, which produces a lack of hexosaminidase A.



Tay Sach's features:

TAY SACHS

- **T**esting recommended
- **A**utosomal recessive
- **Y**oung death (<4 yrs.)
- **S**pot in macula (cherry red spots)
- **A**shkenazi Jews
- **C**NS degeneration
- **H**ex A deficiency
- **S**torage disease



MENDELIAN GENETICS AND HUMANS

Human genetic disorders

Tay Sachs Disease

Inheritance Pattern:

-Autosomal recessive

Physical Effects:

-Nerve cells destroyed in brain and spinal cord

-Symptoms appear 3-6 months after birth

-Loss of motor control and atrophy of muscles, seizures

-Death



Autosomal Recessive Disorders

- Tay-Sachs Disease
 - Usually occurs in Jewish people
 - Symptoms
 - Development slows at age 4 to 8 months
 - Neurological and Psychomotor impairment
 - Child gradually becomes blind and helpless, seizures, paralyzed, death by age 3 – 4 years old
 - Caused by gene on chromosome 15 → caused buildup of nonfunctional lysosomes in neurons

- **Tay-Sachs disease** is fatal; a dysfunctional enzyme causes an accumulation of lipids in the brain
 - At the *organismal* level, the allele is recessive
 - At the *biochemical* level, the phenotype (i.e., the enzyme activity level) is incompletely dominant
 - At the *molecular* level, the alleles are codominant

Frequency of Dominant Alleles

- Dominant alleles are not necessarily more common in populations than recessive alleles
- For example, Polydactyly one baby out of 400 in the United States is born with extra fingers or toes



- The allele for this unusual trait is dominant to the allele for the more common trait of five digits per appendage
- In this example, the recessive allele is far more prevalent than the population's dominant allele

Multiple Alleles

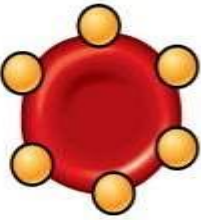
- Most genes exist in populations in more than two allelic forms
- For example, the four phenotypes of the ABO blood group in humans are determined by three alleles for the enzyme (I) that attaches A or B carbohydrates to red blood cells: I^A , I^B , and i .
- The enzyme encoded by the I^A allele adds the A carbohydrate, whereas the enzyme encoded by the I^B allele adds the B carbohydrate; the enzyme encoded by the i allele adds neither

Figure 14.11

(a) The three alleles for the ABO blood groups and their carbohydrates

Allele	I^A	I^B	i
Carbohydrate	A 	B 	none

(b) Blood group genotypes and phenotypes

Genotype	$I^A I^A$ or $I^A i$	$I^B I^B$ or $I^B i$	$I^A I^B$	ii
Red blood cell appearance				
Phenotype (blood group)	A	B	AB	O

Pleiotropy

- Most genes have multiple phenotypic effects, a property called **pleiotropy**
- For example, pleiotropic alleles are responsible for the multiple symptoms of certain hereditary diseases, such as cystic fibrosis and sickle-cell disease

A Organs affected by cystic fibrosis

Sinuses:
sinusitis (infection)

Lungs: thick, sticky mucus buildup, bacterial infection, and widened airways

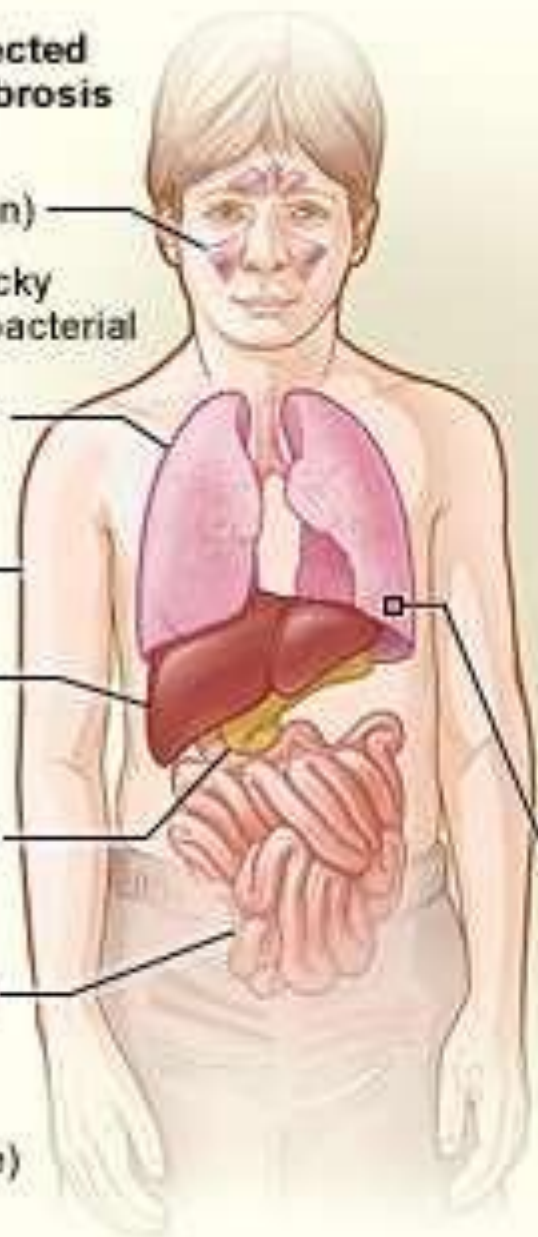
Skin: sweat glands produce salty sweat.

Liver: blocked biliary ducts

Pancreas:
blocked pancreatic ducts

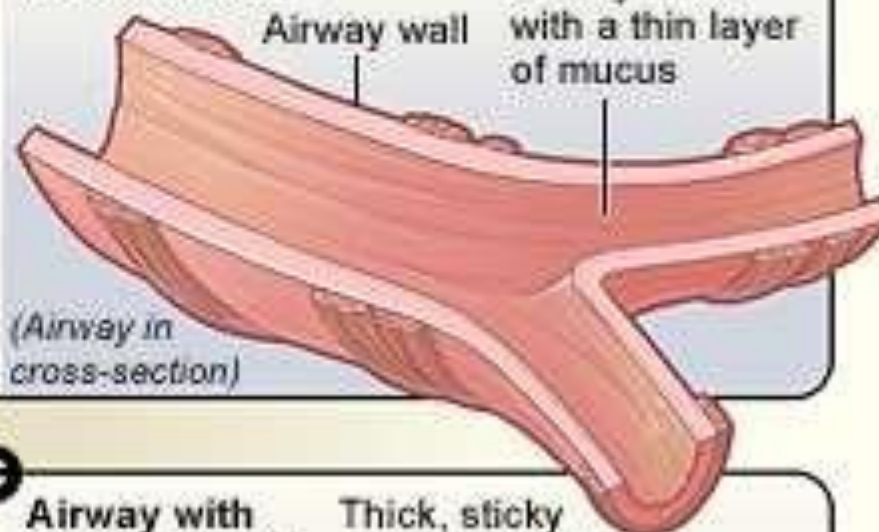
Intestines:
cannot fully absorb nutrients

Reproductive organs:
(male and female) complications



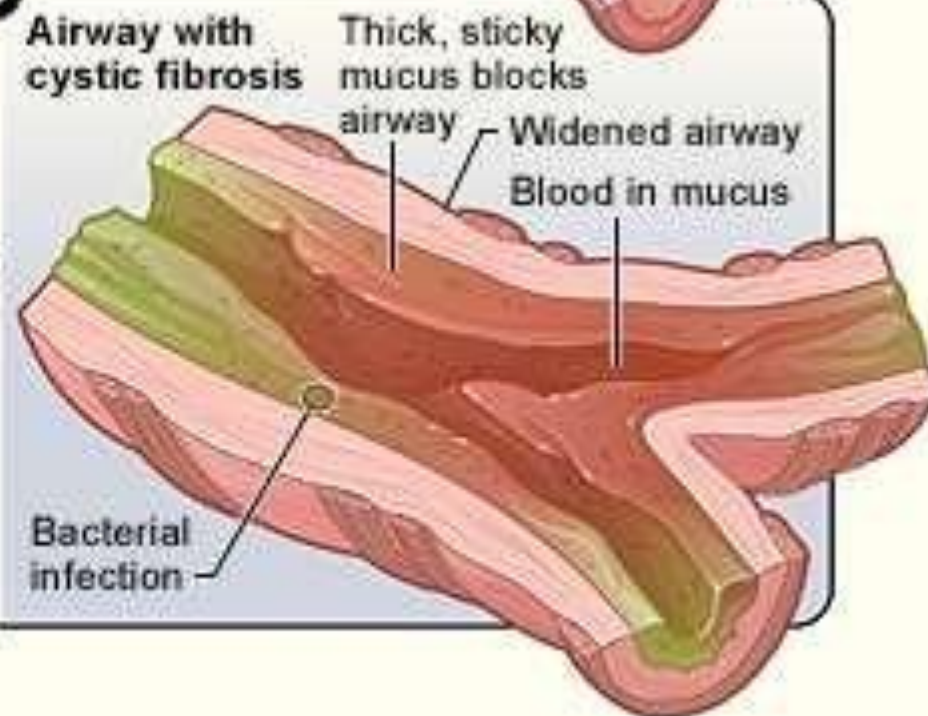
B

Normal airway



C

Airway with cystic fibrosis



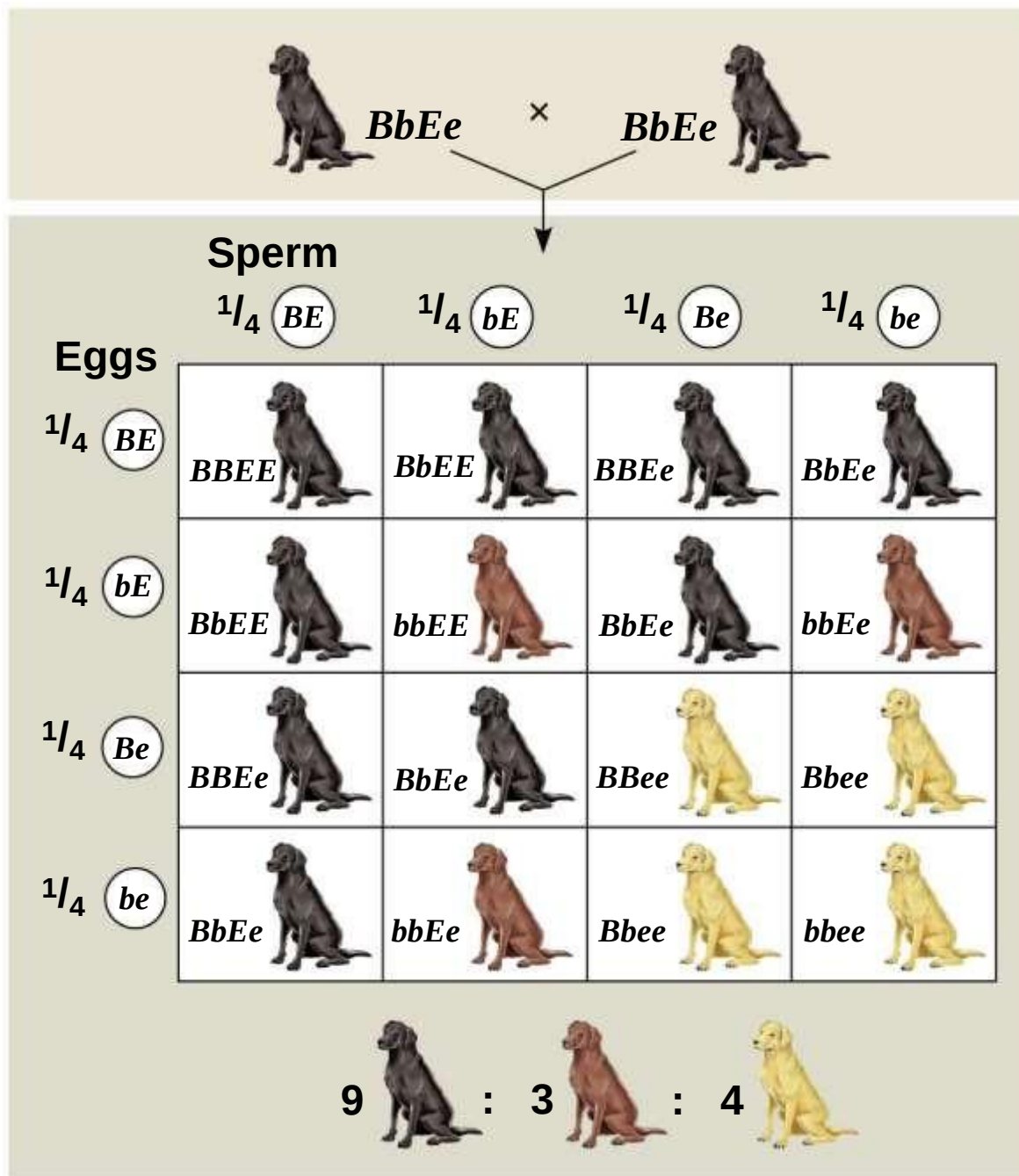
Extending Mendelian Genetics for Two or More Genes

- Some traits may be determined by two or more genes

Epistasis

- In **epistasis**, a gene at one locus alters the phenotypic expression of a gene at a second locus
- For example, in Labrador retrievers and many other mammals, coat color depends on two genes
- One gene determines the pigment color (with alleles *B* for black and *b* for brown)
- The other gene (with alleles *C* for color and *c* for no color) determines whether the pigment will be deposited in the hair

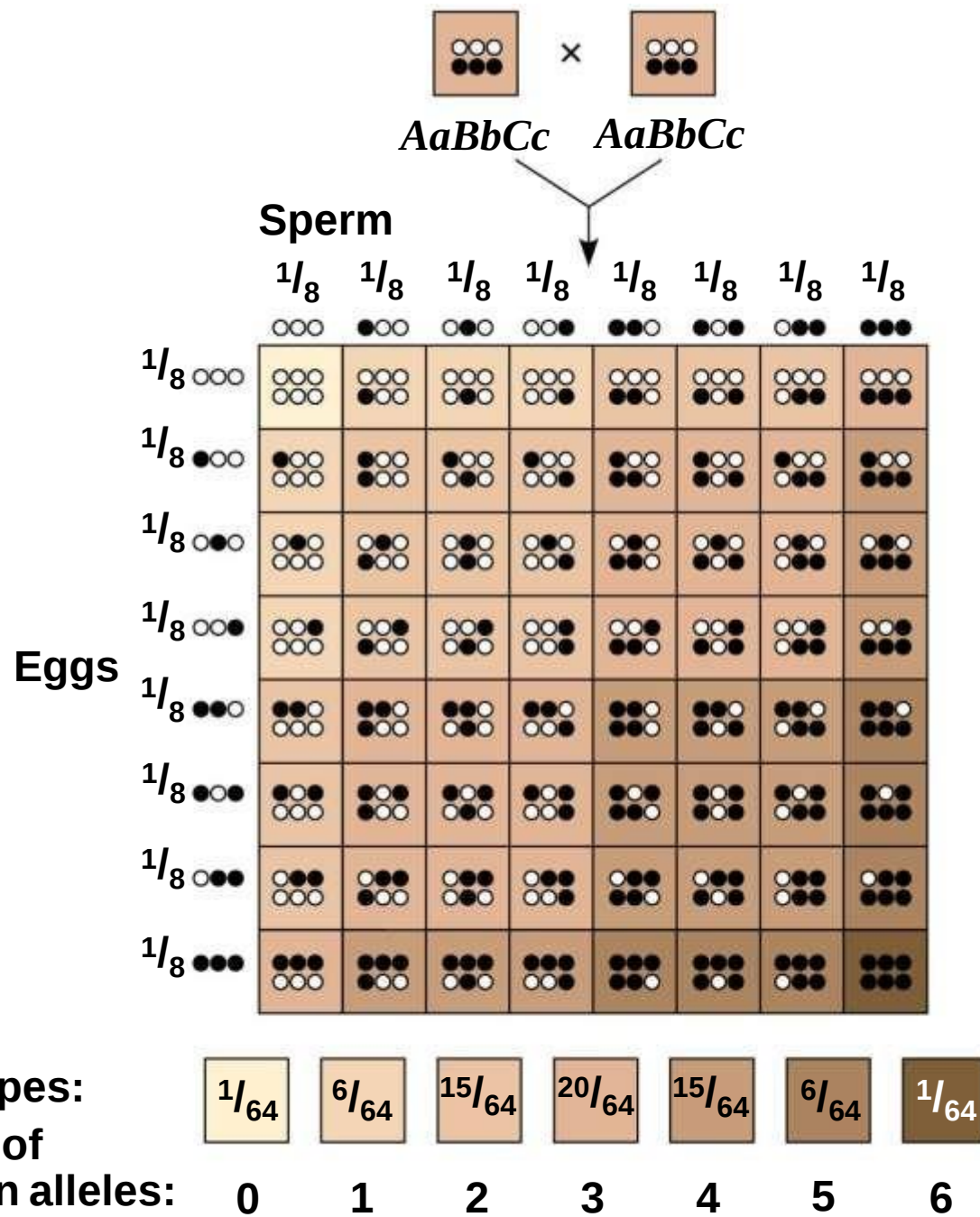
Figure 14.12



Polygenic Inheritance

- **Quantitative characters** are those that vary in the population along a continuum
- Quantitative variation usually indicates **polygenic inheritance**, an additive effect of two or more genes on a single phenotype
- Skin color in humans is an example of polygenic inheritance

Figure 14.13



Nature and Nurture: The Environmental Impact on Phenotype

- Another departure from Mendelian genetics arises when the phenotype for a character depends on environment as well as genotype
- The **norm of reaction** is the phenotypic range of a genotype influenced by the environment
- For example, hydrangea flowers of the same genotype range from blue-violet to pink, depending on soil acidity

- Norms of reaction are generally broadest for polygenic characters
- Such characters are called **multifactorial** because genetic and environmental factors collectively influence phenotype

Integrating a Mendelian View of Heredity and Variation

- An organism's phenotype includes its physical appearance, internal anatomy, physiology, and behavior
- An organism's phenotype reflects its overall genotype and unique environmental history

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

Concept 14.4: Many human traits follow Mendelian patterns of inheritance

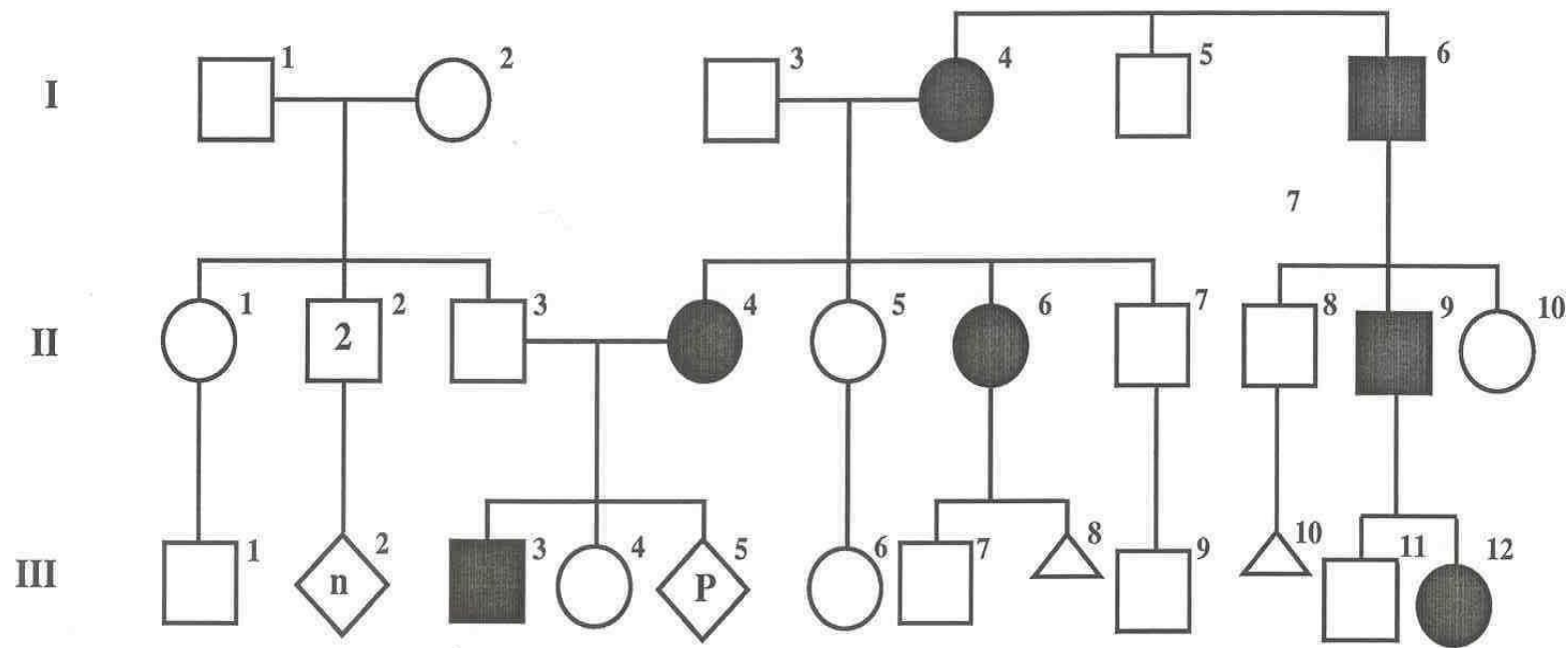
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Sample Pedigree



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		

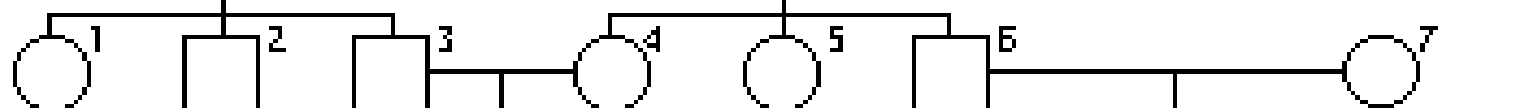
A **pedigree** is a concise summary of the medical family history; it is the symbolic language of clinical genetics and human genetics research.

- 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.

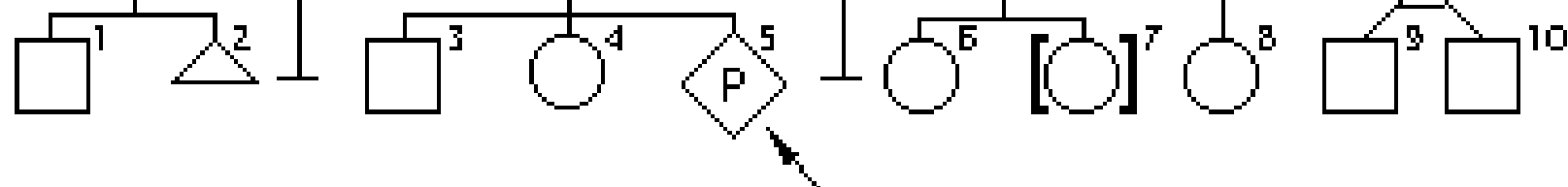
I



II



III



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

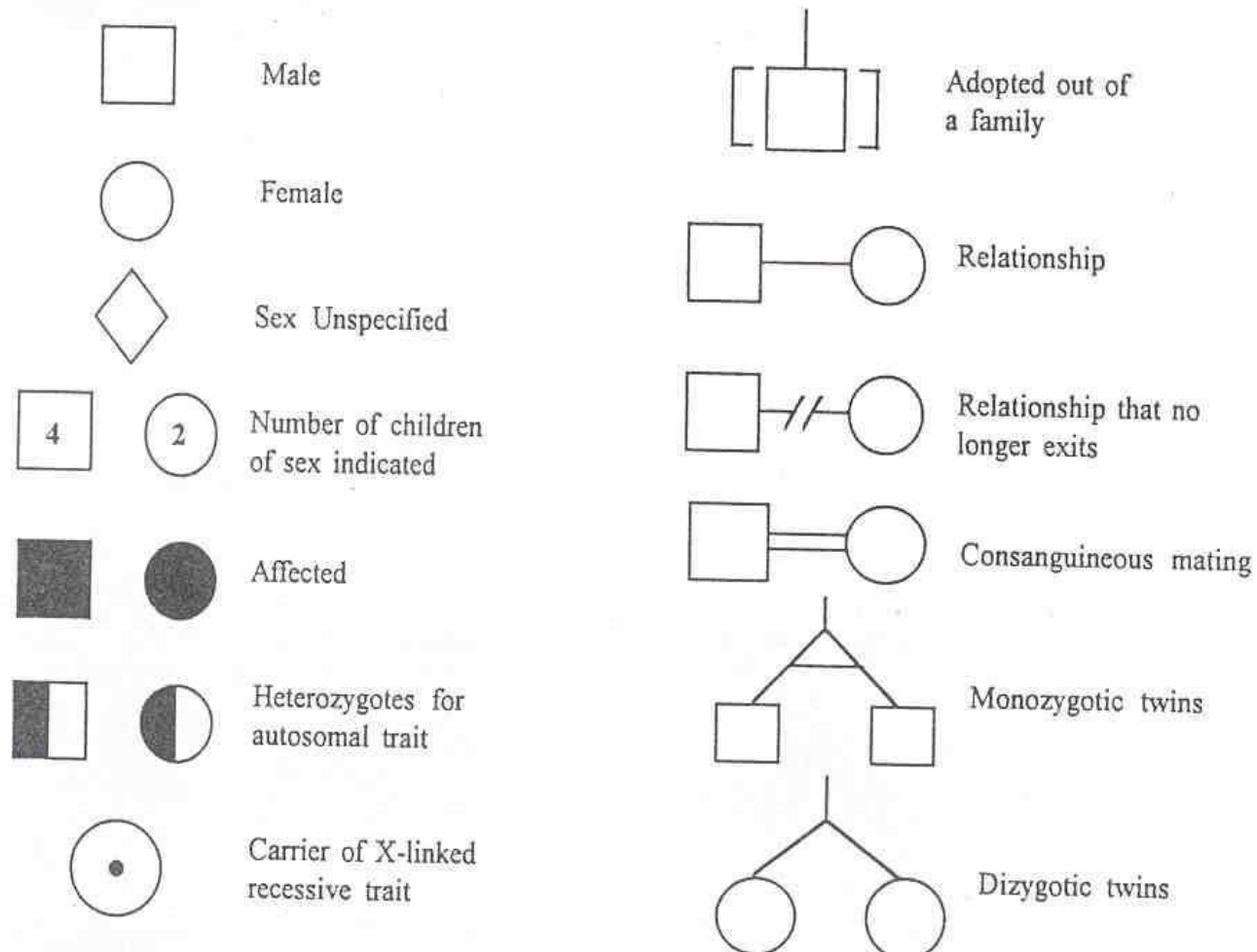
- The proband is an affected individual coming to medical attention independently of other
- family members. The proband is designated with an arrow in the pedigree, and there may be more than one proband per family.

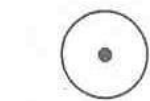
Medical status and results of genetic evaluation/testing of family members

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

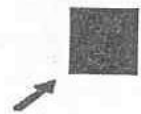
PEDIGREE NOMENCLATURE

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

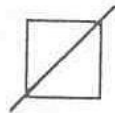




Carrier of X-linked recessive trait



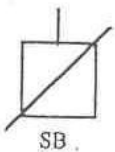
Proband



Deceased individual



Pregnancy



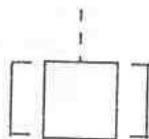
Stillbirth



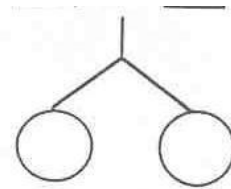
Spontaneous abortion (SAB)



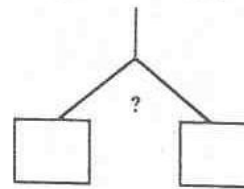
Termination of pregnancy (TOP)



Adopted into a family

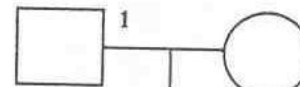


Dizygotic twins



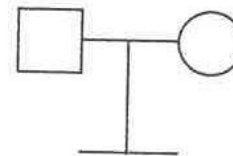
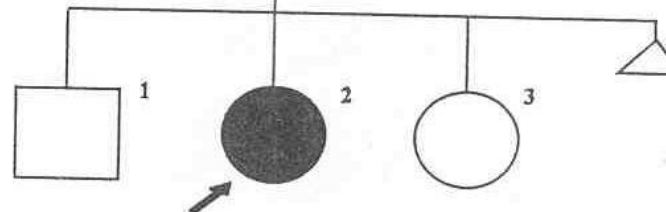
Twins of unknown zygosity

I

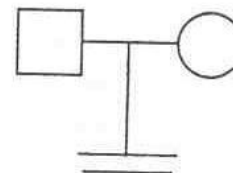


Numbering individuals in pedigrees

II



No offspring by choice or reason unknown



Infertility

The Gene is the Unit of Inheritance

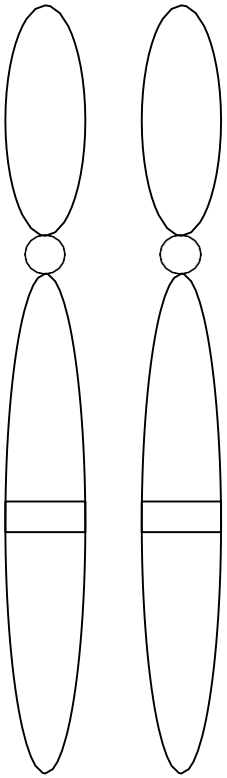
The location of a gene on a chromosome is its **locus**.

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

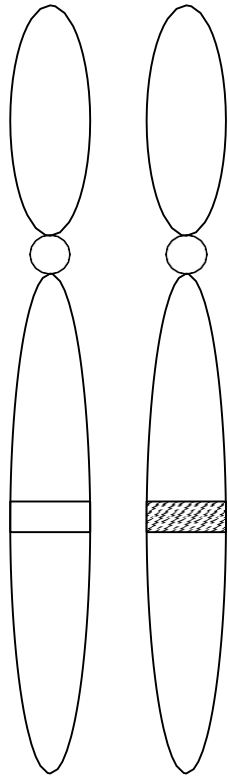
If both alleles are identical, then the individual is **homozygous** at the locus. Homozygosity may refer to the presence of two normal or two mutant alleles.

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**.



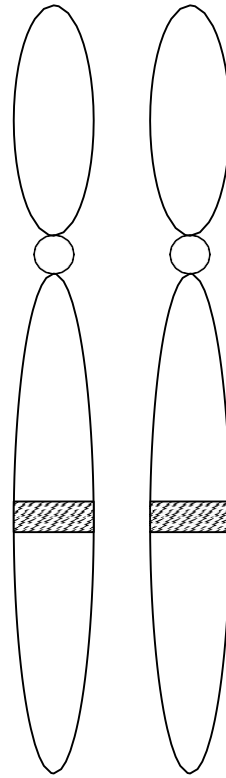
A A

homozygote
A allele



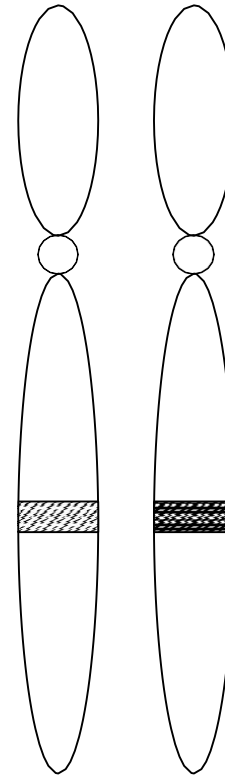
A a

heterozygote



a a

homozygote
a allele



a1 a2

compound
heterozygote

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.

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.

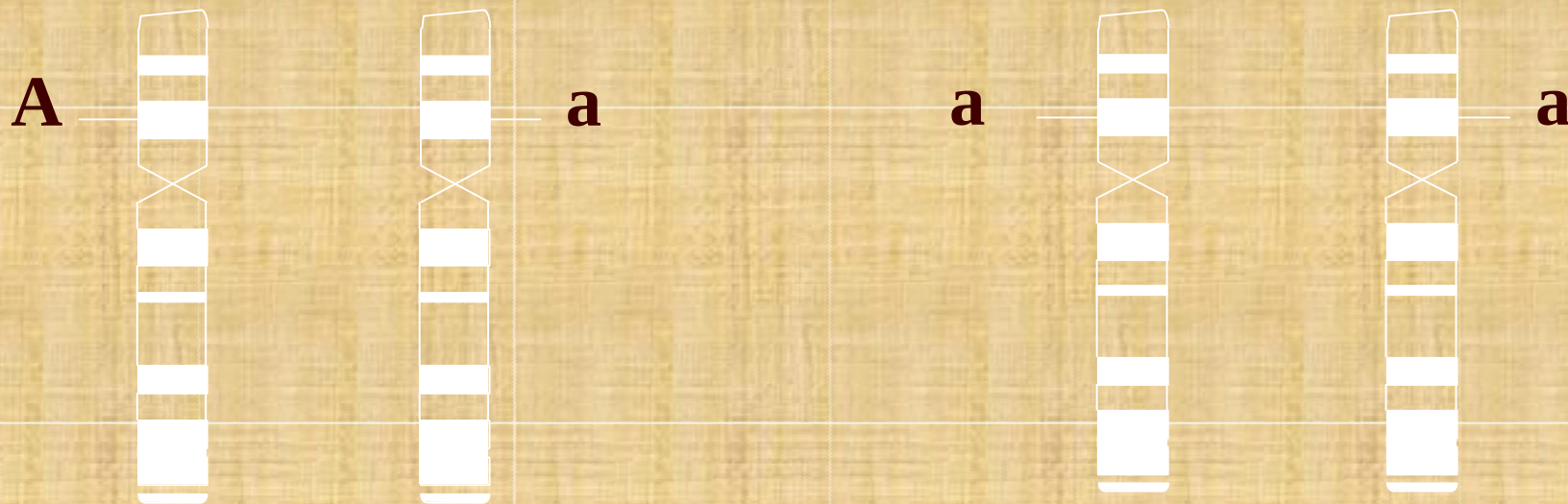
Dominant and Recessive Inheritance

- 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.
- **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., $XaXa$.

Types of Genetic Disease

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

Examples and Features of Autosomal Dominant Inheritance



**Affected
individual**

**Unaffected
individual**

**A=mutant allele
a=normal allele**

Examples

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

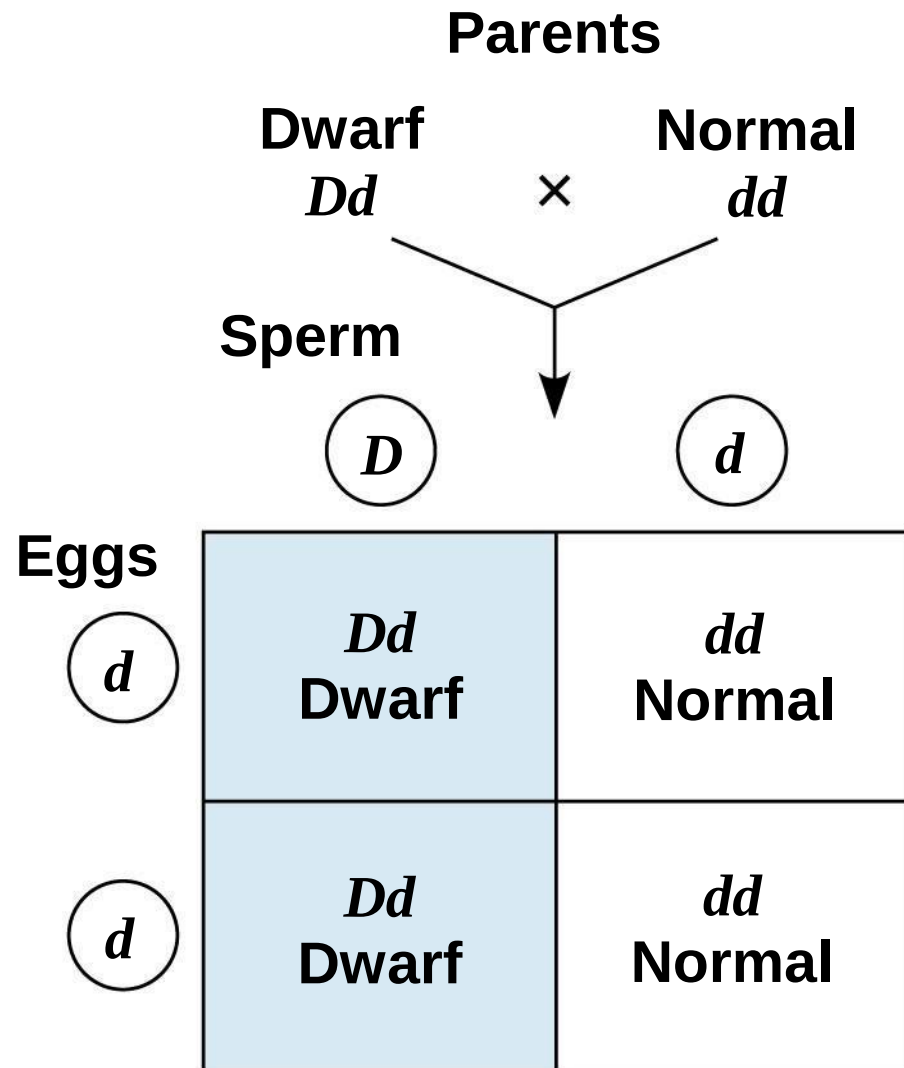
DISEASE	CLINICAL FEATURES
Note: Key aspects of phenotypic expression or inheritance features are bolded <u>Autosomal Dominant</u>	
HUNTINGTON DISEASE	Progressive loss of brain neurons, dementia, loss of motor control Affects 1/20,000 persons of European descent Late onset, typically between 30-40 years, 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 Megaloccephaly Lordosis & Kyphosis 80% new mutations Increased mutations with increasing paternal age

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



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Achondroplasia

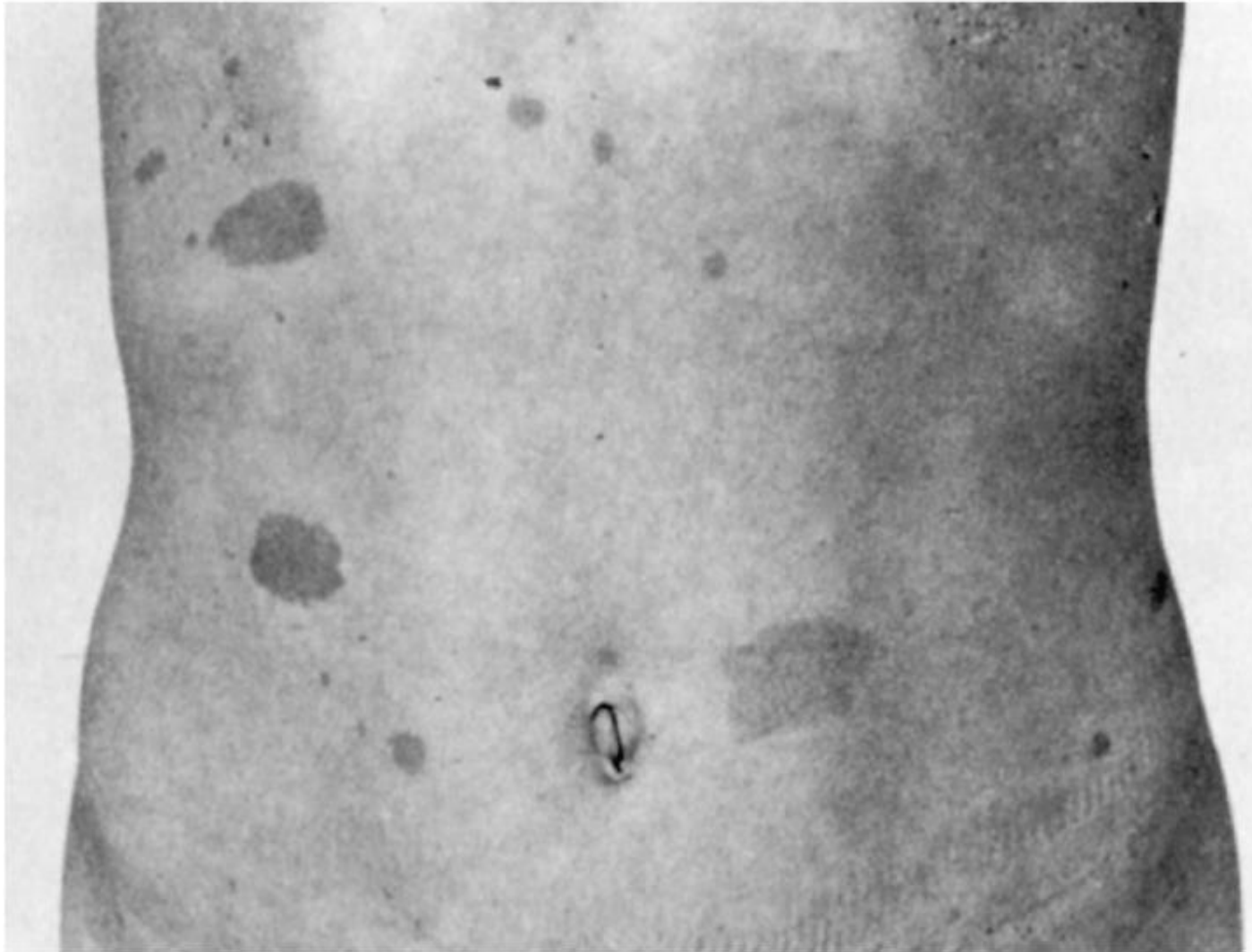


From www.hopkinsmedicine.org



From www.sciencemuseum.org.uk

Neurofibromatosis Type 1



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Neurofibromatosis Type 1



Neurofibromatosis Type 1

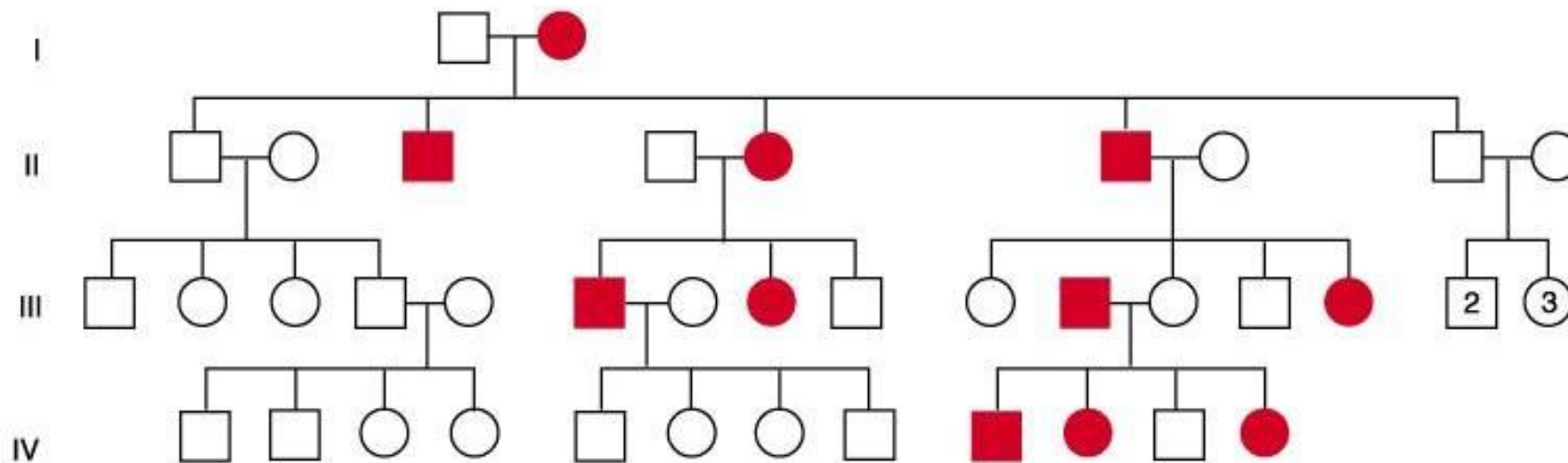


Fig. 121-3. — Recklinghausen neurofibromatosis.

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 Pedigree



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Autosomal Dominant Inheritance

(Affected Father)

Parental Gametes

	A	a
a	Aa	aa
a	Aa	aa

Maternal Gametes

1Aa: 1aa
A = mutant, a = normal

Transmission probabilities and the use of the Punnett square

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

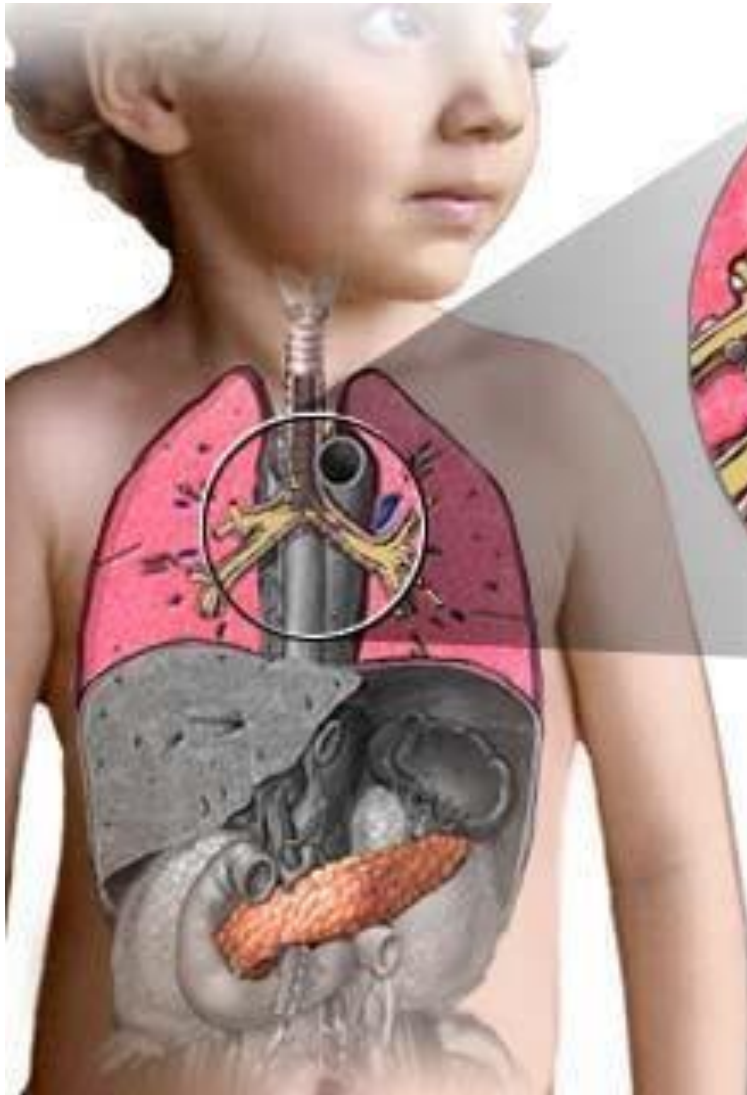
Autosomal Recessive

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 <u>Vasocclusive crisis (pain)</u> Increased risk for infection Higher frequency in those of African descent Heterozygote advantage

Cystic Fibrosis

- **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)



Cystic fibrosis is a hereditary disorder characterized by lung congestion and infection and malabsorption of nutrients by the pancreas

 ADAM.

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

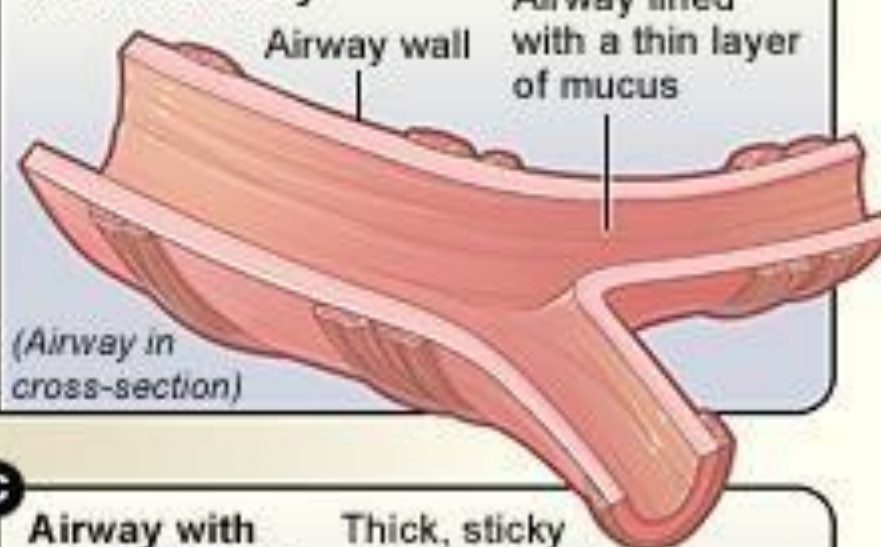
Intestines: cannot fully absorb nutrients

Reproductive organs: (male and female) complications



B

Normal airway



(Airway in cross-section)

C

Airway with cystic fibrosis

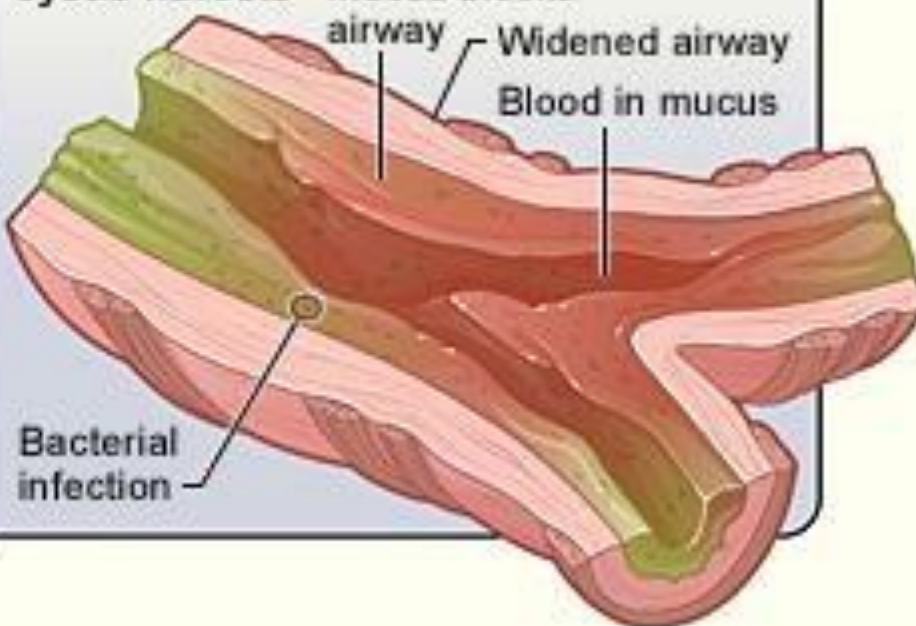
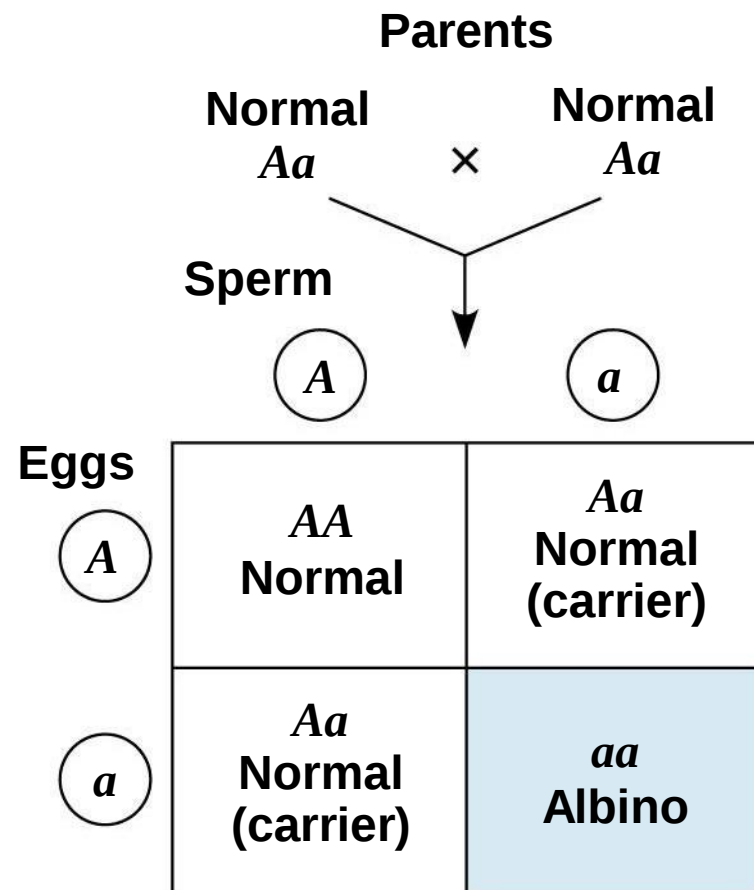


Figure 14.16



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- 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
- 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 defective hepatic enzyme phenylalanine hydroxylase (PAH) .
 - Necessary to metabolize the amino acid phenylalanine ('Phe') to the amino acid tyrosine
-

Symptoms

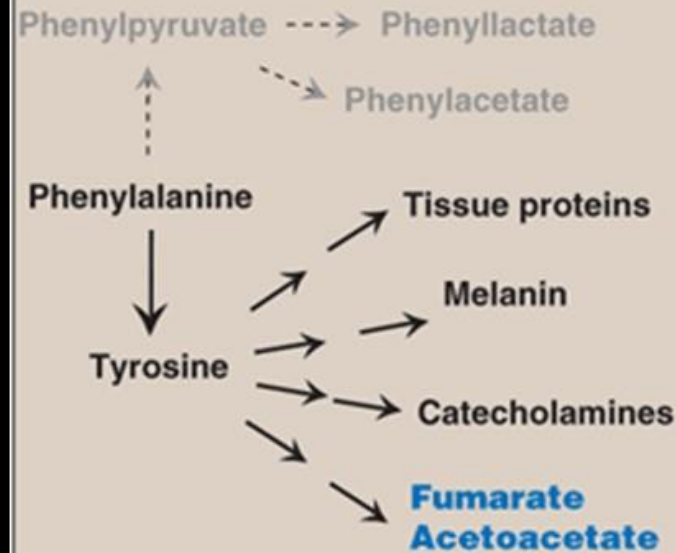
- Elevated phenylalanine, phenylpyruvate, phenyllactate and phenylacetate in blood and urine (musty odor of urine).

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

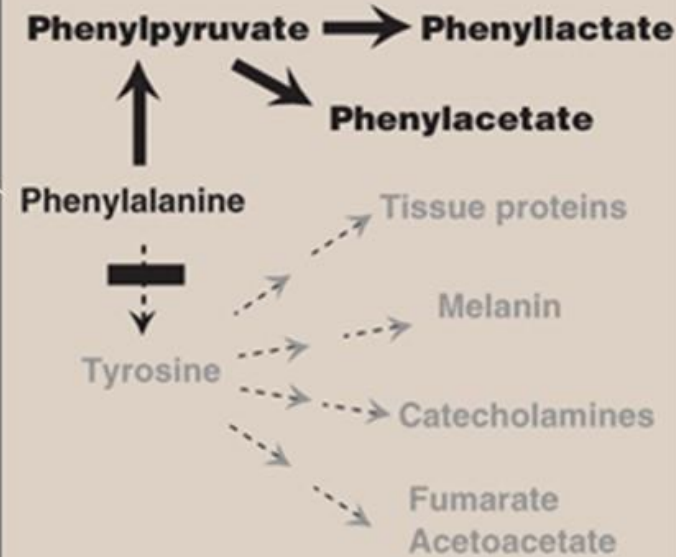
- Hypopigmentation** (light skin, hair, blue eyes) due to reduced melanin production.

NO COMPLETE LOSS OF PIGMENT B/C
WILL STILL HAVE SOME TYROSINE FROM DIET

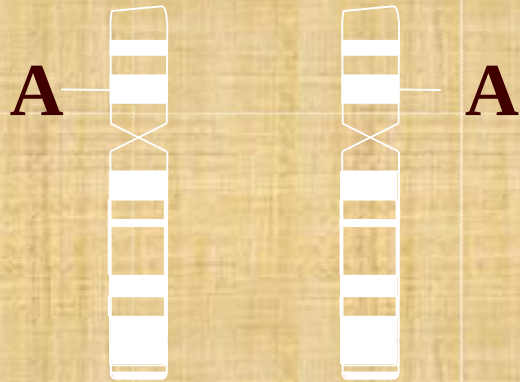
Normal



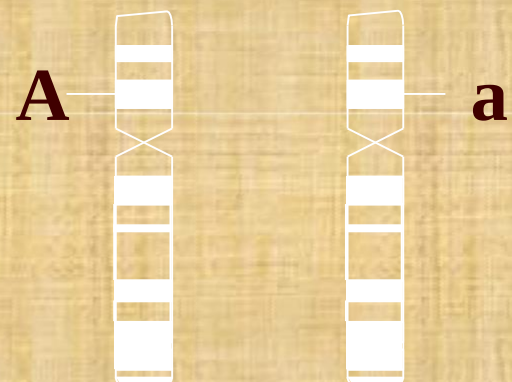
Phenylketonuria



Autosomal Recessive

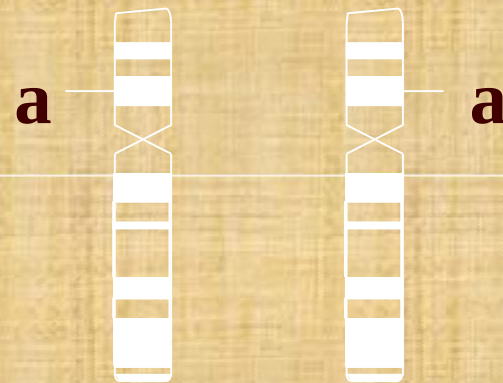


Unaffected, not a carrier



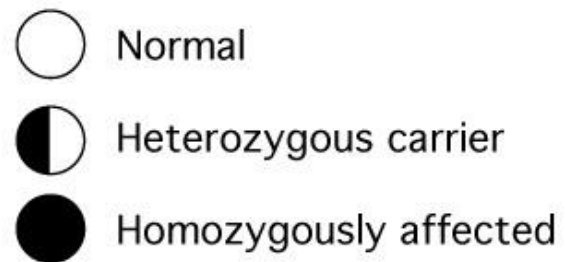
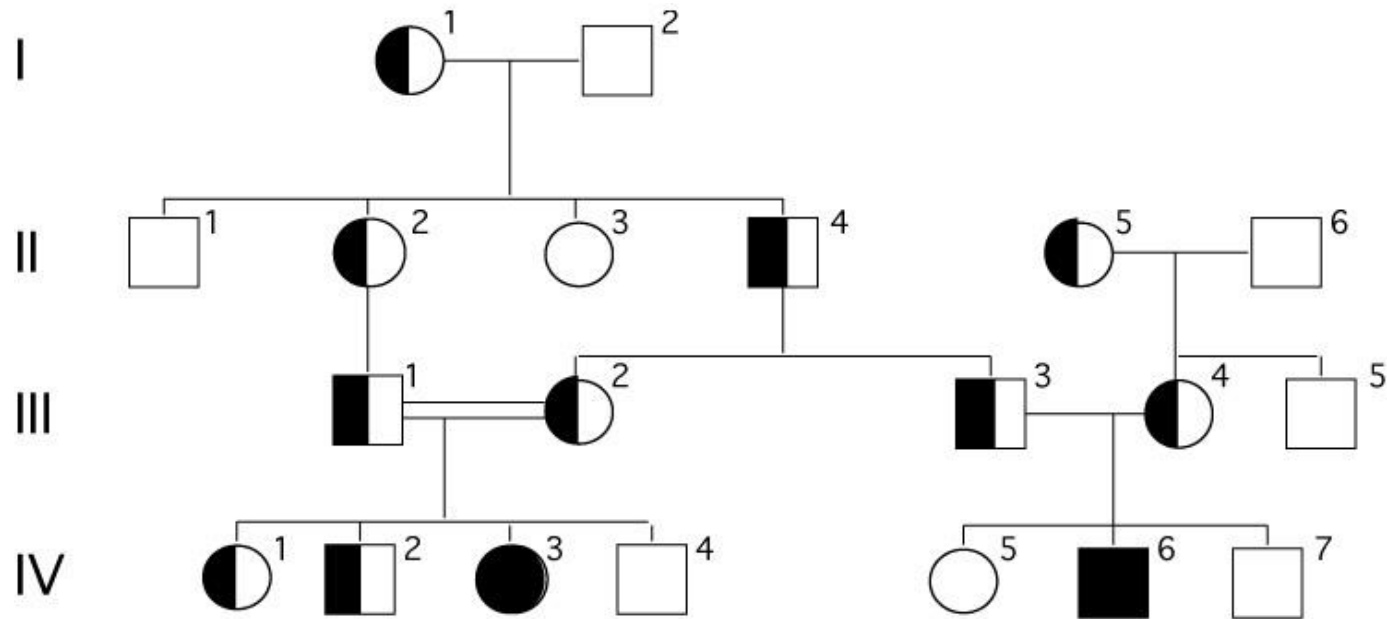
Carrier, unaffected

A=normal allele
a=mutant allele

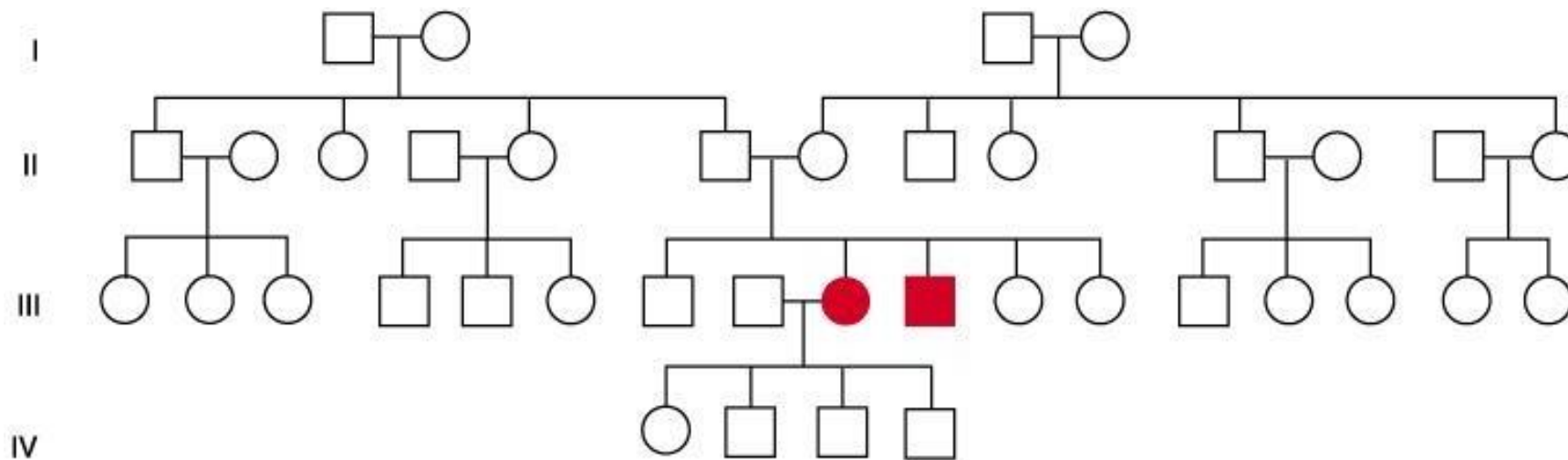


Affected

Autosomal Recessive Pedigree



Autosomal Recessive Pedigree



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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

Transmission probabilities and use of the Punnett square

If both parents are carriers ($Aa \times Aa$) then there is

25% chance that the child will have the disorder (aa)

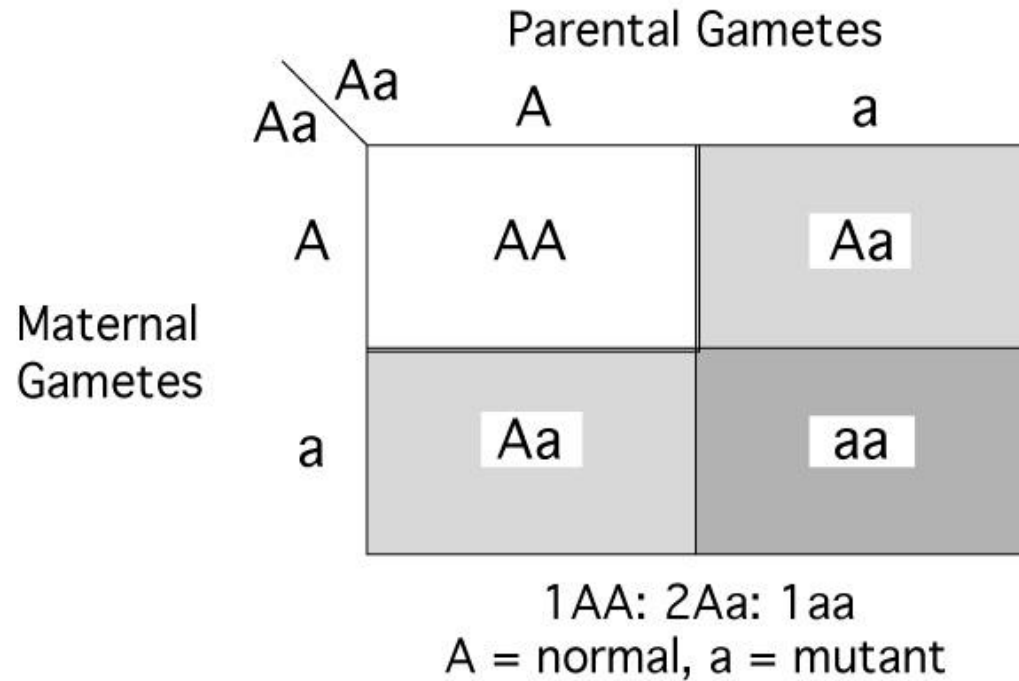
50% chance that the child will be a carrier (Aa), and

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.

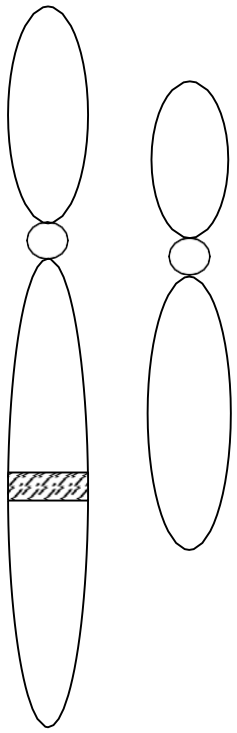
Autosomal Recessive Inheritance

(Both Parents Carriers)

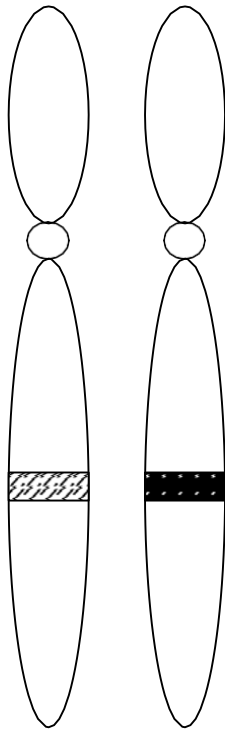


Affected homozygotes are commonly the offspring of two heterozygote carriers.

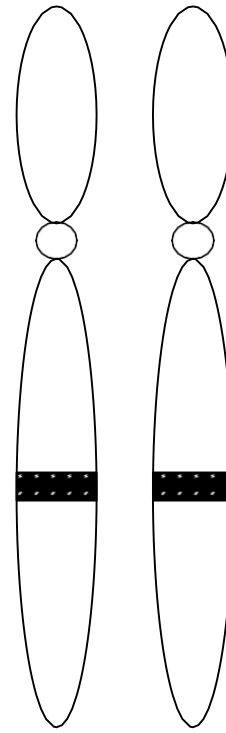
Sex Linkage and X-Inactivation



$X^A Y$



$X^A X^a$



$X^a X^a$

Dosage compensation

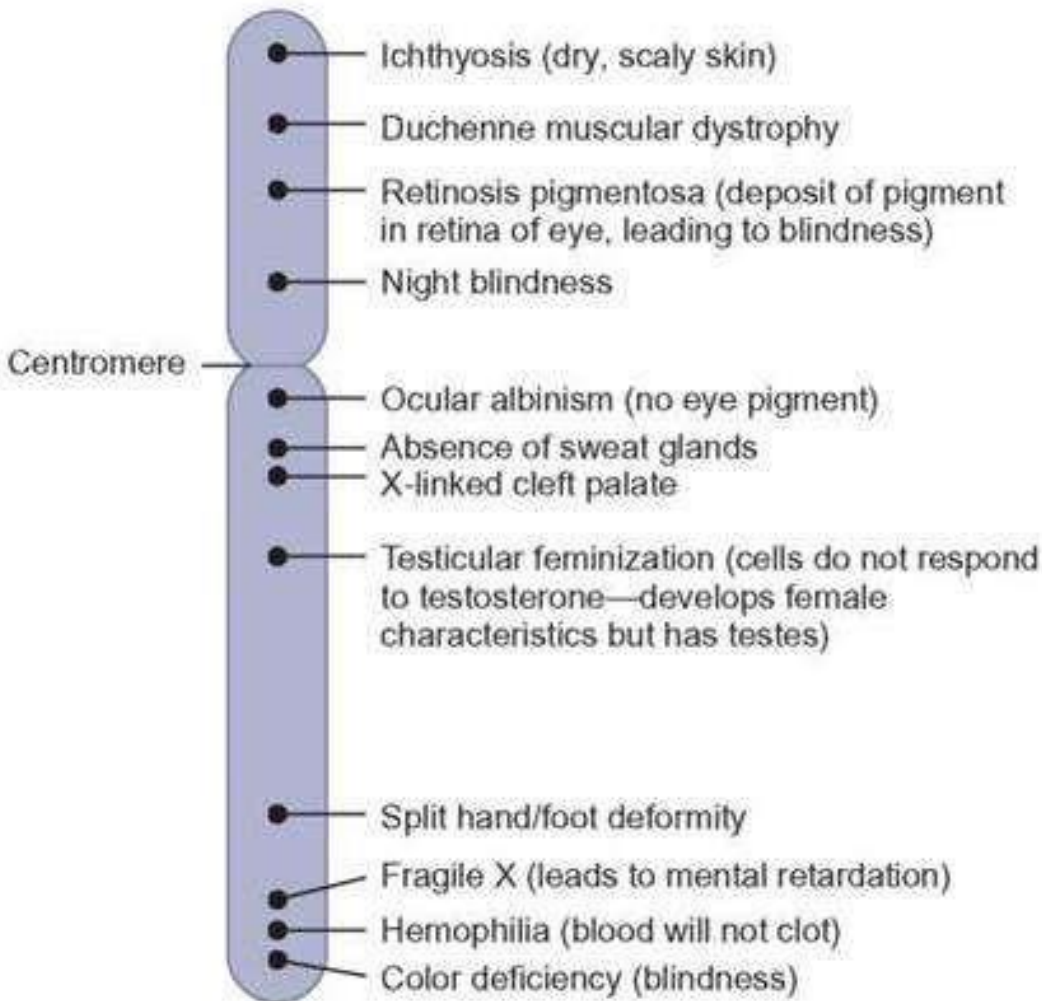
1. For autosomal traits, two doses lead to a normal phenotype, while one dose or more than two doses often have clinical significance
2. For X-linked traits two doses in females and one dose in males both lead to a normal phenotype

X-inactivation in females allows compensation for this difference in dosage for X-linked traits

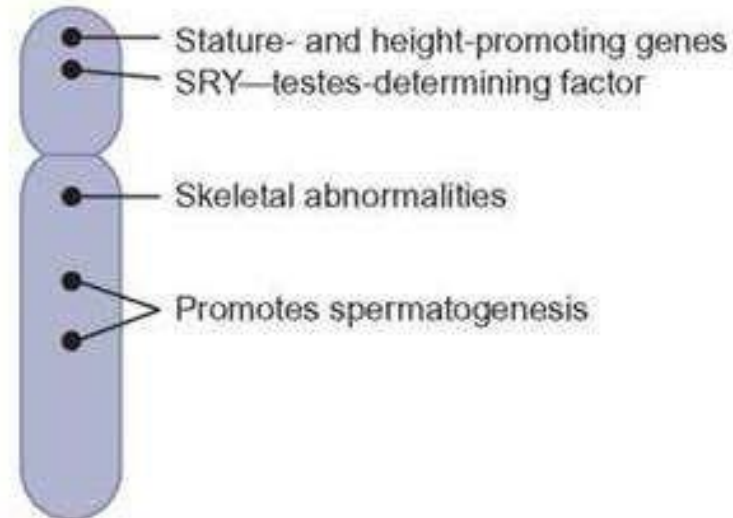
- Lyon hypothesis
- In early embryonic life (3-7 days after fertilization) one X chromosome is inactivated. The inactive X chromosome is condensed in a Barr body.
- Inactivation of the maternal or paternal X chromosome is random, but once it occurs, the same X will be inactive in all descendants of a particular cell.
- Some genes on the inactive X chromosome remain active, i.e., escape inactivation. These include the genes in the pseudoautosomal region that have matching genes on the Y chromosome, genes outside the pseudoautosomal region that have related copies on the Y chromosomes, and others.

X-Inactivation

- Allows dosage compensation between males and females for genes on the X chromosome
- In females, early in embryonic life, one of the X chromosomes is inactivated
- The process is random and clonal
- Some genes escape X-inactivation



X chromosome



Y chromosome

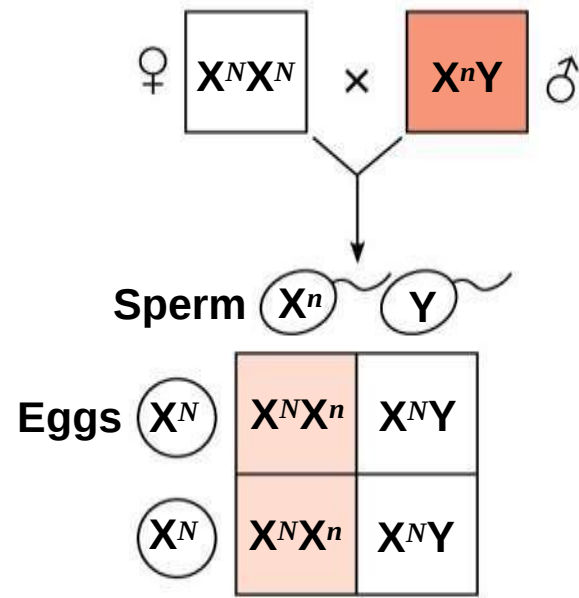
- A gene that is located on either sex chromosome is called a **sex-linked gene**
- Genes on the Y chromosome are called Y-linked genes; there are **few** of these
- Genes on the X chromosome are called **X-linked genes**

Inheritance of X-Linked Genes

- X chromosome have genes for many characters **unrelated** to sex, whereas the Y chromosome mainly encodes genes **related** to sex determination

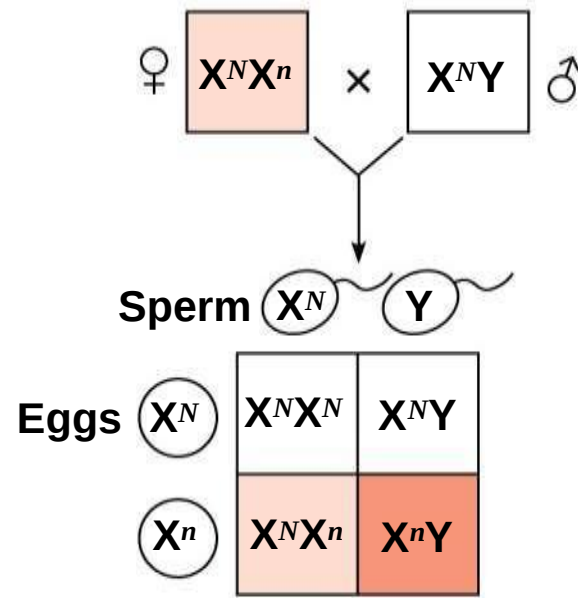
- X-linked genes follow specific patterns of inheritance
- For a recessive X-linked trait to be expressed
 - A female needs two copies of the allele (**homozygous**)
 - A male needs only one copy of the allele (**hemizygous**)
- X-linked recessive disorders are much **more** common in males than in females

Figure 15.7

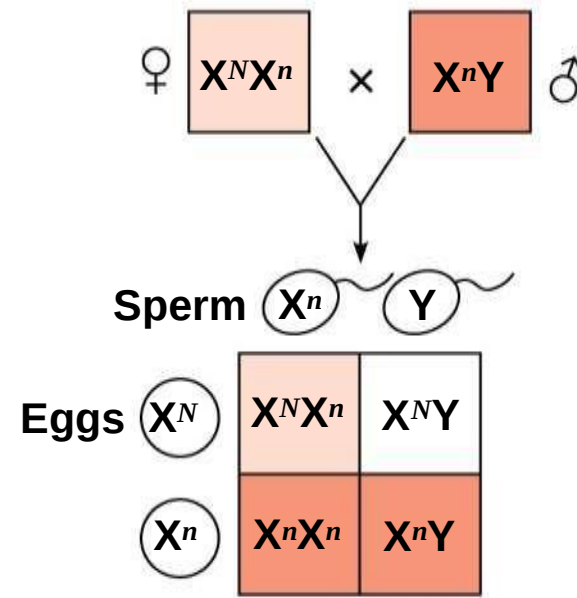


(a)

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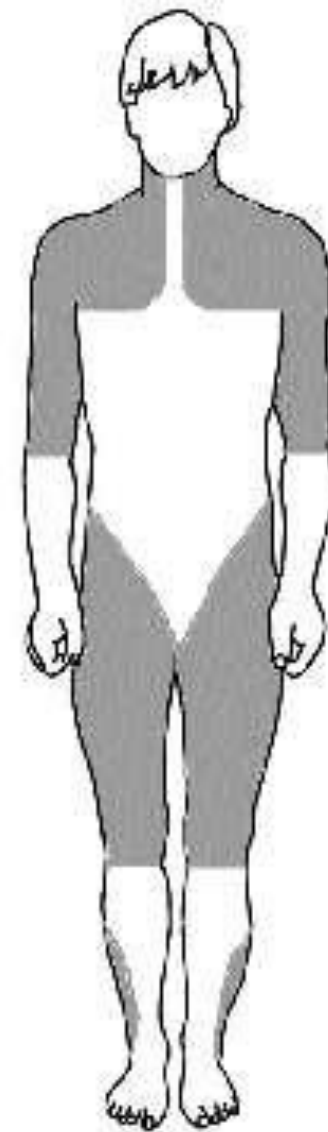


(b)



(c)

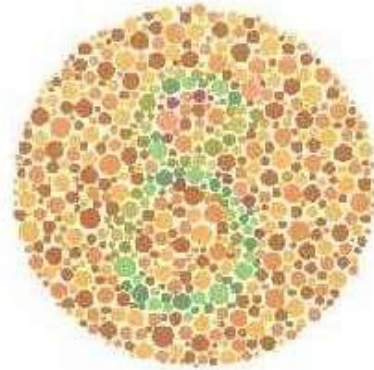
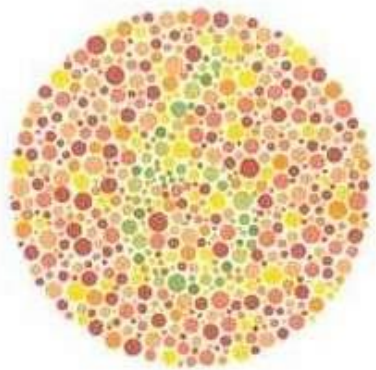
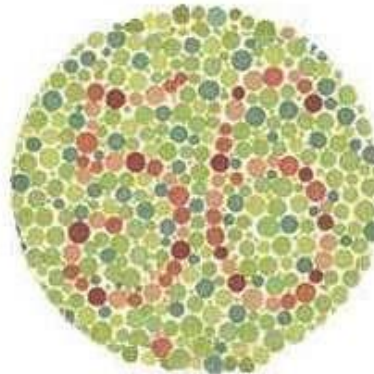
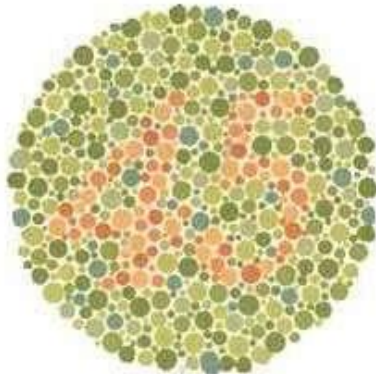
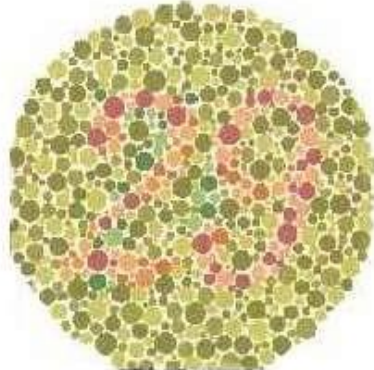
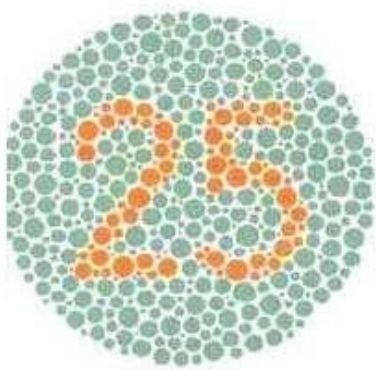
- Some disorders caused by recessive alleles on the X chromosome in humans
 - Color blindness (mostly X-linked) (**Red-green color blindness**)
 - **Duchenne muscular dystrophy**
(**dystrophy** muscle weakness and loss of muscle tissue)
 - **Hemophilia**



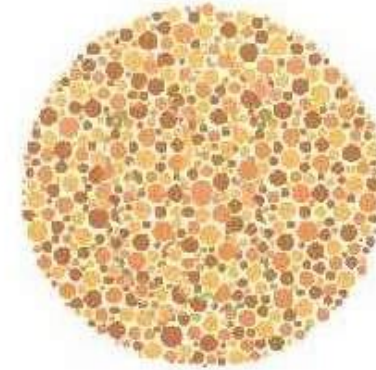
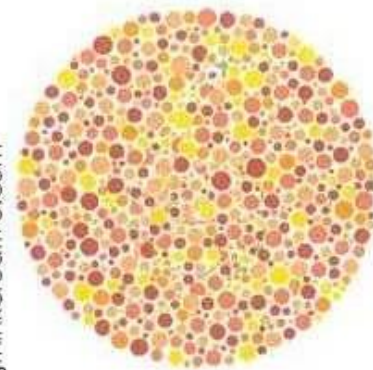
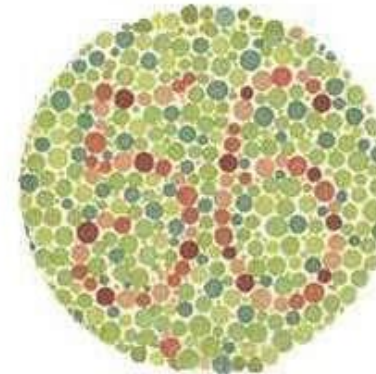
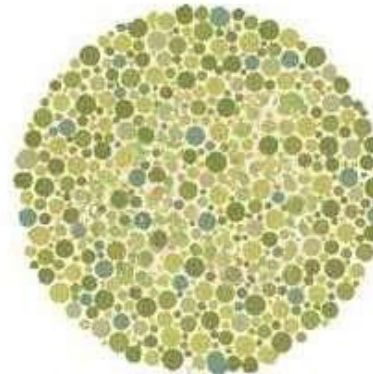
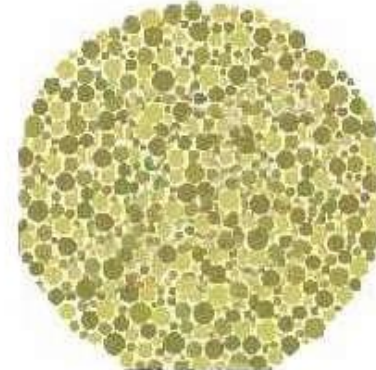
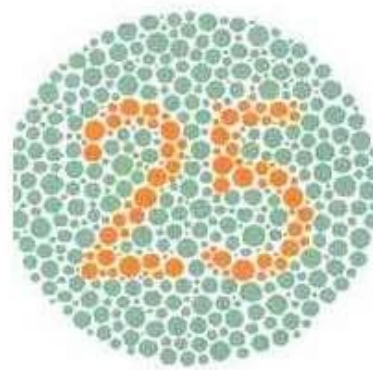
Duchenne and
Becker Types

Ishihara Test For Color Blindness

What People With Regular Vision See

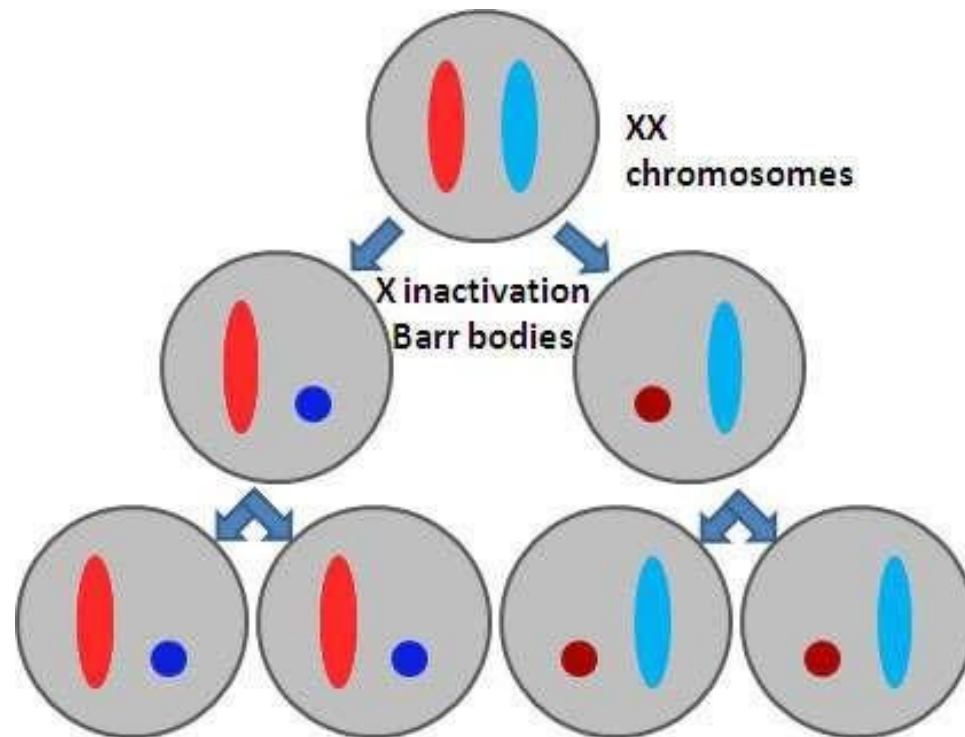


What Red-Green Color Blind People See



X Inactivation in Female Mammals

- In mammalian females, one of the two X chromosomes in each cell is randomly inactivated during embryonic development
- The inactive X condenses into a **Barr body**
- If a female is heterozygous for a particular gene located on the X chromosome, she will be a mosaic for that character



Examples and Features of X-Linked Recessive Inheritance

Examples:

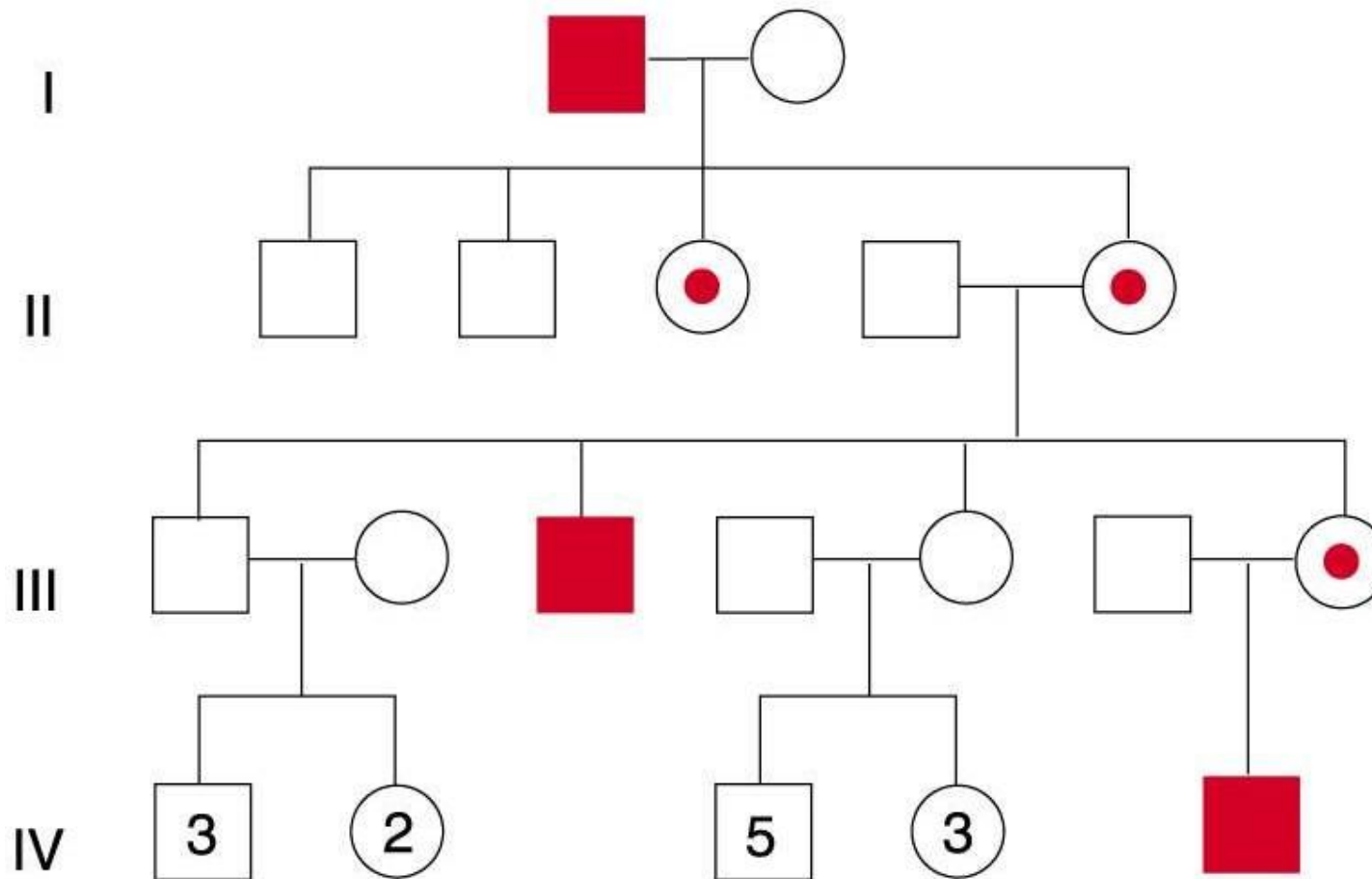
<u>X-Linked Recessive</u>	
HEMOPHILIA A	Coagulation disorder Prolonged bleeding Easy bruising Hemorrhage Various mutations & very heterogeneous
DUCHENNE MUSCULAR DYSTROPHY	Progressive muscle weakness Death typically in 2nd or 3rd decade 30% cases due to new mutation Allelic heterogeneity (Becker MD)

Duchenne muscular dystrophy



Figure 1.4. A 15-year-old boy with Duchenne muscular dystrophy

X-Linked Recessive Pedigree



Features of X-Linked Recessive Inheritance

1. Diagonal inheritance – affected males related through females of the maternal line
2. Absence of male-to-male transmission
3. Incidence of trait much higher in males than females
4. Full expression in hemizygous males
5. No or mild expression in carrier females due to X-inactivation

Transmission probabilities and use of the Punnett square

1. A son never inherits the disorder from his father.
2. All daughters of a male with the disorder are obligate carriers.
3. Sons of carrier females have a 50% chance of inheriting the disorder.
4. Daughters of carrier females have a 50% chance of being carriers too.

X-Linked Recessive Inheritance

(Affected Father)

		Paternal Gametes	
		X^a	Y
Maternal Gametes	X^A	$X^A X^a$	$X^A Y$
	X^A	$X^A X^a$	$X^A Y$

A = normal, a = mutant

1 carrier female : 1 normal male

X-Linked Recessive Inheritance

(Carrier Mother)

		Paternal Gametes	
		X^A	Y
Maternal Gametes	X^A	$X^A X^A$	$X^A Y$
	X^a	$X^A X^a$	$X^a Y$

A = normal, a = mutant

1 normal female : 1 carrier female : 1 normal male : 1 affected male

Examples and Features of X-Linked Dominant Inheritance

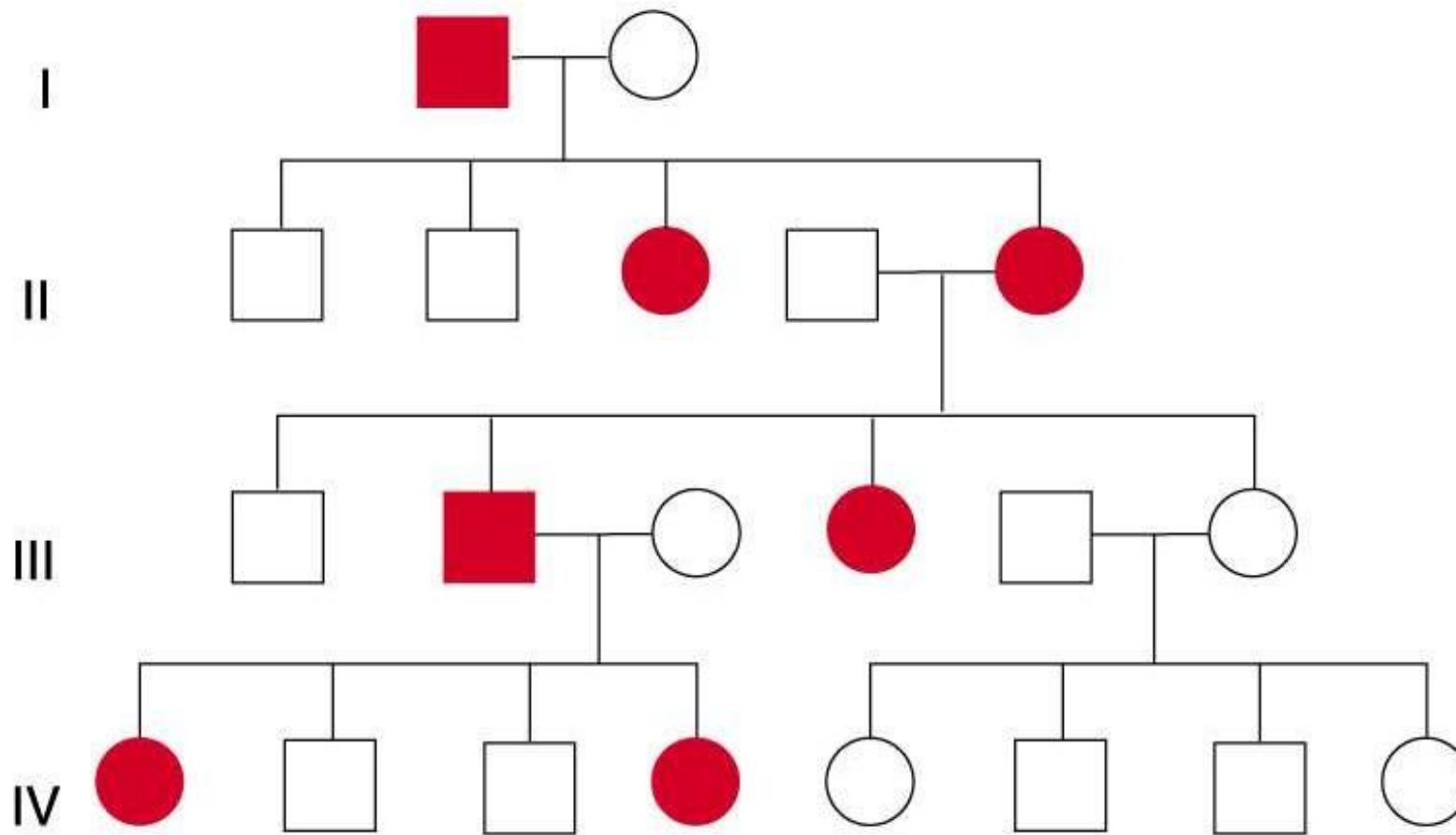


X-linked Dominant

VITAMIN D RESISTANT
RICKETS

Rickets
Short stature
Low serum phosphate
Less severe in heterozygous females

X-Linked Dominant Pedigree



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Features of X-Linked Dominant Inheritance

1. Twice as many females with the disorder as males
2. Absence of male-to-male transmission
3. Males with the disorder transmit it to all daughters and no sons
4. Females usually have more mild and variable expression due to X-inactivation
5. Few disorders classified as X-linked dominant

Transmission probabilities and use of the Punnett square

1. A son never inherits the disorder from his father
2. All daughters of male with the disorder will also have the disorder
3. Sons of affected females have a 50% chance of inheriting the disorder
4. Daughters of affected females also have a 50% chance of inheriting the disorder
5. Can distinguish between autosomal and X-linked dominant by looking at offspring of affected males

X-Linked Dominant Inheritance

(Affected Mother)

		Paternal Gametes	
		X^a	Y
Maternal Gametes	X^A	$X^A X^a$	$X^A Y$
	X^a	$X^a X^a$	$X^a Y$

A = mutant, a = normal

1 normal female : 1 normal male : 1 affected female : 1 affected male

Phenotypic Expression

1. Penetrance
2. Expressivity
3. Variable age of onset
4. Pleiotropy
5. Genetic heterogeneity
6. Sex-limited
7. Sex-influenced

Penetrance

- **Penetrance** refers to the all or none expression of a mutant genotype. It usually refers to dominant traits in heterozygotes, and means that even though an individual has inherited the mutant allele, there may be no expression of the phenotype. If a condition is expressed in less than 100 % of persons who have one copy of the mutant allele, it is said to have reduced penetrance.

If a condition/feature is expressed in less than 100% of individuals who carry the responsible allele, then it is said to have reduced penetrance

- The probability of expression of the phenotype given the genotype
- Term used for dominant conditions

Reduced Penetrance

Retinoblastoma, a malignant eye tumor. About 10% of individuals who transmit the mutant allele are unaffected. Therefore, the mutant allele is 90% penetrant.



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Retinoblastoma

Reduced Penetrance

Waardenburg syndrome, a congenital sensorineural deafness, heterochromia, displacement of the inner canthi, white forelock, and other features. Since only about 20% of people with Waardenburg syndrome are deaf, this shows reduced penetrance of this feature of this syndrome



B

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Deafness in Waardenburg syndrome

Variable Expressivity

- The extent to which a trait is expressed
- If expression ranges from mild to severe then it is said to have variable expressivity
- However, it is never completely unexpressed
 - Eg. Neurofibromatosis & myotonic dystrophy

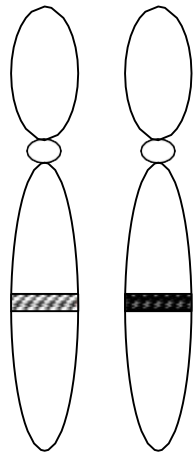
Variable age of onset & pleiotropy

Variable age of onset refers to the variation in the time to phenotypic expression of mutant gene (s). Example: the onset of Huntington disease is typically in the 40's, however, age of onset may range from the 20's to 60's.

A mutant gene is said to be **pleiotropic** when it produces a wide range of phenotypic effects. Example: Marfan syndrome involves the skeletal, cardiovascular, and ocular systems.

Genetic heterogeneity

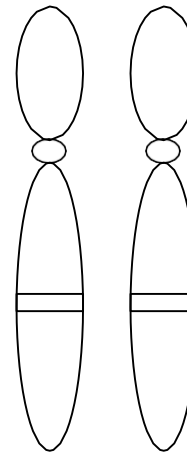
allelic heterogeneity



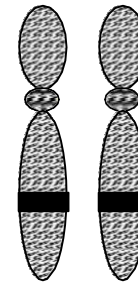
a1 a2

At the CF locus on 7q
a1 = Δ F508 allele
a2 = S549R allele

locus heterogeneity



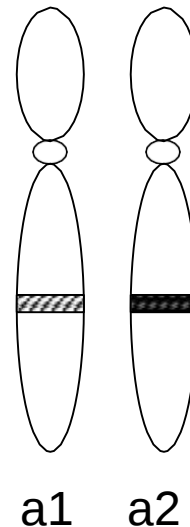
PAX3 on 2q
Auto dom HL



GJB2 on 13q
Auto rec HL

Genetic heterogeneity

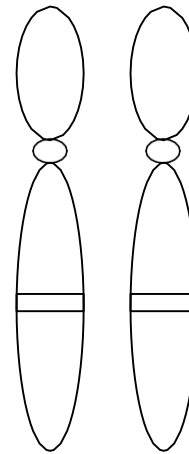
Allelic heterogeneity refers to two or more different mutant alleles at the same genetic locus (Example: Duchenne and (the less severe) Becker muscular dystrophy; cystic fibrosis).



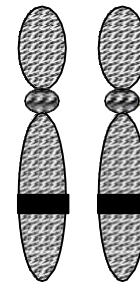
At the CF locus on 7q
a1 = Δ F508 allele
a2 = S549R allele

Genetic heterogeneity

Locus heterogeneity is when mutations at two different genetic loci result in similar phenotypes (Example: congenital deafness). In some cases, the mode of inheritance of the disorders can vary

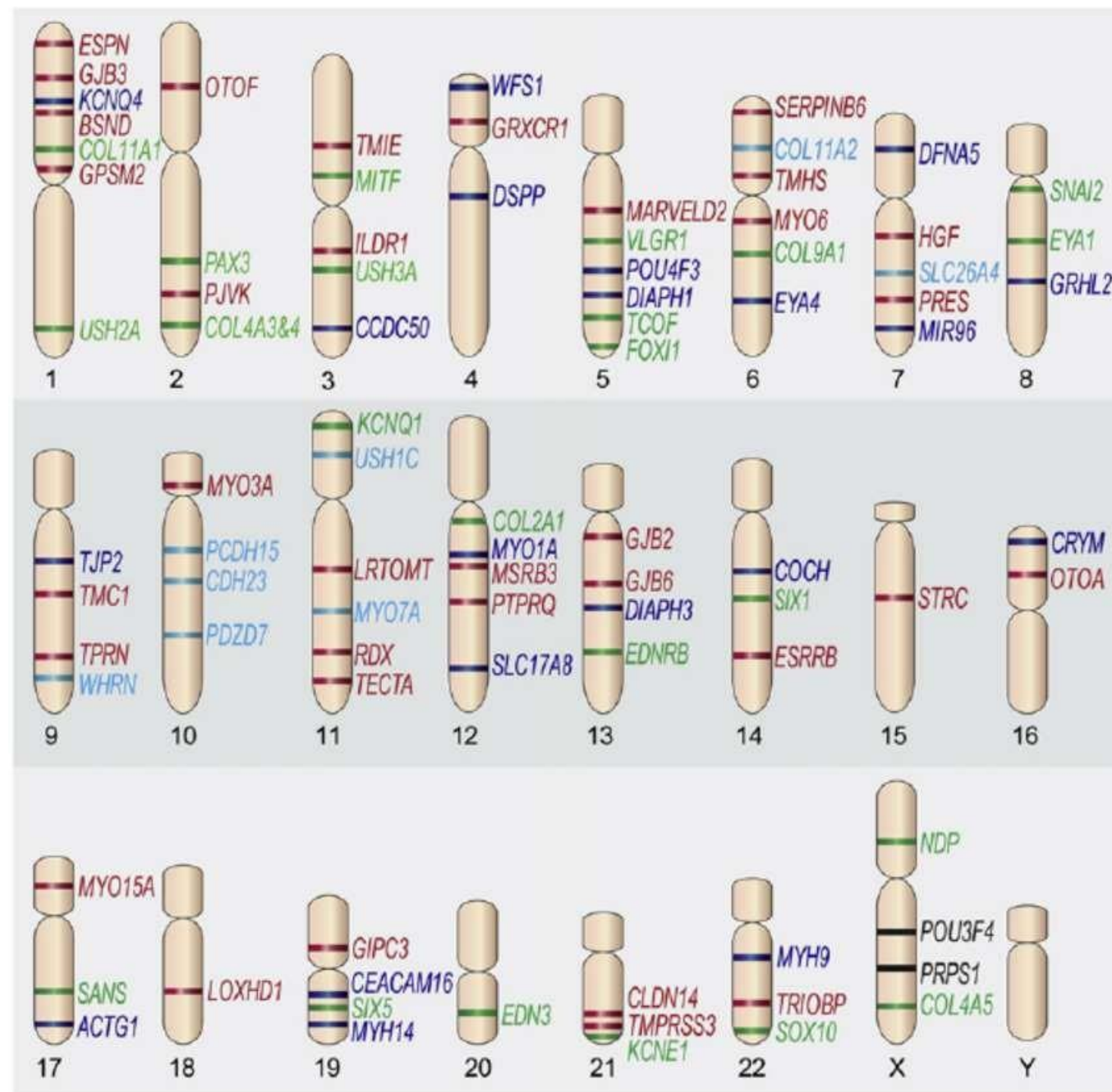


PAX3 on 2q
Auto dom HL



GJB2 on 13q
Auto rec HL

— Autosomal recessive
 — Autosomal dominant
 — X-linked
 — Syndromic
 — SHL & NSHL



Sex-limited & Sex-influenced

- refers to a phenotype that is autosomally transmitted but expressed only in one sex. Example: Autosomal dominant male precocious puberty.
- **Sex-influenced** refers to autosomally inherited traits that are expressed differently, in either degree or frequency, in males and females. Example: hemochromatosis (autosomal recessive disorder of increased absorption of dietary iron) is more commonly found in males due to lower dietary intake and menstruation in females.

- *Some disorders do not follow Mendelian patterns of inheritance.*
- *These disorders are clearly genetic (inherited) and their inheritance is classified as non-Mendelian.*
- *We now understand why some of these disorders do not follow Mendelian patterns and examples include: **mitochondrial inheritance, unstable trinucleotide repeats, and imprinting.***