GENETICS

Modified no. 9

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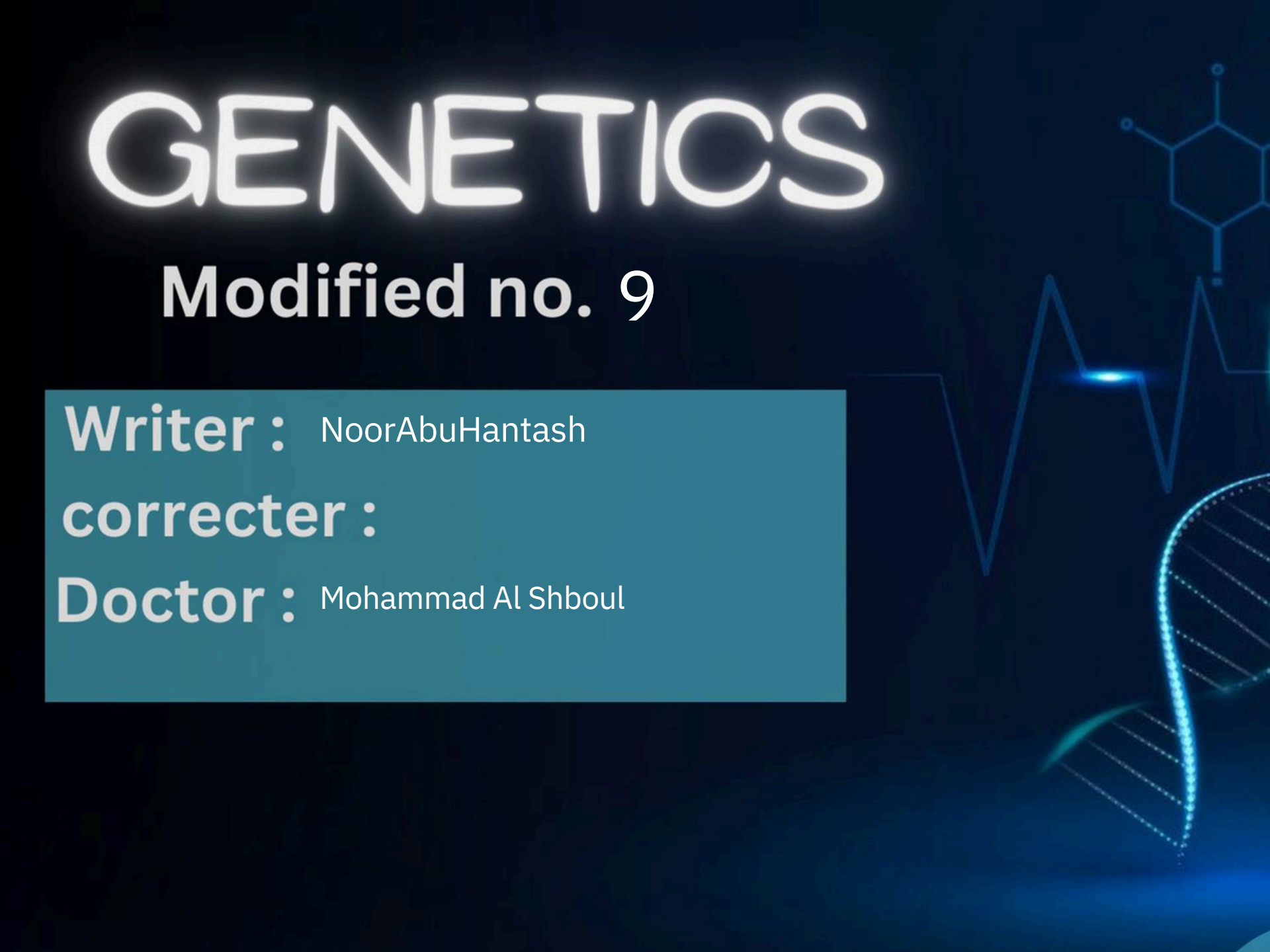


Extensions of & Deviations from Mendelian Genetic Principles

Lecture 6

-as you know, the gene that controls a trait has 2 alleles(maternal and paternal)

Extensions of Mendelian Principles can alter expected Mendelian ratios

- Multiple alleles level
- Codominance
- Incomplete dominance
- Polygenics
- Environmental effects

In general population, there are some traits have more than 2 alleles, however only 2 of them are present at the organismal

Multigenes can cause a disease, …

Like: diet, wethear,…affect the gene expression

Introduction

- **Mendelian inheritance** describes inheritance patterns that obey two laws
  - **–Law of segregation.**
  - **– Law of independent assortment.**

The allelesfortheSAMEgenearesegregatedin gametogenesis

Alleles for DIFFERENT genes are assorted independently

- **Simple Mendelian inheritance** involves
  - –A single gene with two different alleles.
  - –Alleles display a simple dominant/recessive relationship.

Some phenotypic variation poses a challenge to Mendelian analysis

- There are human characteristics that **don't** follow Mendel's rules

Explanations for some traits:

No definitively **dominant** or **recessive** *allele* •The level of protein expression,

•The sex of the individual,Sex limited vs sex influenced

•More than two alleles exist,

•Multiple genes involved,ABO blood group

•Gene-environment interactions.

Why wecan'texplainthe difference in the clinical featuresof 2brothers with same mutation locus??
Though they are different in intensity and onset of symptoms,…

Has epigeneticimpact

- There are many ways in which two ***alleles*** of a single **gene** may govern the outcome of a trait.
- Table describes several different patterns of Mendelian inheritance.

TABLE 4.1

Different Types of Mendelian Inheritance Patterns

What will be mentioned in the lecis what required

Type	Description
Simple Mendelian	**Inheritance:** This term is commonly applied to the inheritance of alleles that obey Mendel's laws and follow a strict dominant/recessive relationship. In chapter 4, we will see that some genes can be found in three or more alleles, making the relationship more complex. **Molecular:** 50% of the protein normally encoded by two copies of the dominant allele is sufficient to produce the dominant trait.
X linked	**Inheritance:** It involves the inheritance of genes that are located on the X chromosome. In mammals and fruit flies, males are hemizygous for X-linked genes while females have two copies. **Molecular:** If a pair of X-linked alleles shows a simple dominant/recessive relationship, 50% of the protein encoded by two copies of the dominant allele is sufficient to produce the dominant trait (in the female).
Lethal alleles	**Inheritance:** An allele that has the potential of causing the death of an organism. **Molecular:** Lethal alleles are most commonly loss-of-function alleles that encode proteins that are necessary for survival. In rare cases, the alleles may be in nonessential genes that change a protein to function with abnormal and detrimental consequences.
Incomplete dominance	**Inheritance:** This pattern occurs when the heterozygote has a phenotype that is intermediate between either corresponding homozygote. For example, a plant produced from a cross between red-flowered and white-flowered parents will have pink flowers. **Molecular:** 50% of the protein encoded by two copies of the normal (i.e., wild-type) allele is not sufficient to produce the normal trait.
Codominance	**Inheritance:** This pattern occurs when the heterozygote expresses both alleles simultaneously. For example, in blood typing, an individual carrying the *A* and *B* alleles will have an AB blood type. **Molecular:** The codominant alleles encode proteins that function slightly differently from each other, and the function of each protein, in the heterozygote, affects the phenotype uniquely.
Overdominance	**Inheritance:** This pattern occurs when the heterozygote has a trait that is more beneficial than either homozygote. **Molecular:** Three common ways that heterozygotes may have benefits include: their cells may be resistant to infection by microorganisms, they may produce protein dimers with enhanced function, or they may produce proteins that function under a wider range of conditions.
Incomplete penetrance	**Inheritance:** This pattern occurs when a dominant phenotype is not expressed even though an individual carries a dominant allele. An example is an individual who carries the polydactyly allele but has a normal number of fingers and toes. **Molecular:** Even though a dominant gene may be present, the protein encoded by the gene may not exert its effects. This can be due to environmental influences or due to other genes that may encode proteins that counteract the effects of the protein encoded by the (seemingly) dominant allele.
Sex-influenced inheritance	**Inheritance:** This pattern refers to the impact of sex on the phenotype of the individual. Some alleles are recessive in one sex and dominant in the opposite sex. An example would be baldness in humans. **Molecular:** Sex hormones may regulate the molecular expression of genes. This can have an impact on the phenotypic effects of alleles.
Sex-limited inheritance	**Inheritance:** This refers to traits that occur in only one of the two sexes. An example would be breast development in mammals. **Molecular:** Sex hormones may regulate the molecular expression of genes. This can have an impact on the phenotypic effects of alleles. In this case, sex hormones that are primarily produced in only one sex are essential to produce a particular phenotype.

1. inheritance pattern of single genes

- Prevalent ***alleles*** in a population are termed **wild-type *alleles***

  –These typically encode proteins that

  - **Function normally.**
    - **Are made in the right amounts.**

- ***Alleles*** that have been altered by **mutation** are termed **mutant alleles**

– These tend to be **rare** in natural populations.

Mutation vs polymorphism
-mutationrepresents less than or Equal to 1% of pop (very rare), it is the cause of the disease
-polymorphism occurs in more than 1% of pop, it gives variable characteristics but not diseases, like Antibiotics resistance
-every person differs in 4.5 million polymorphisms

1. inheritance pattern of single genes

- Genetic diseases are caused by **mutant *alleles***.
- In many human genetic diseases , the **recessive *allele*** contains a mutation.
  – This prevents the ***allele*** from producing a fully functional **protein**

Recessive means it needs 2 mutant, recessive alleles to cause the disease

Not required

TABLE 4.2

Examples of Recessive Human Diseases

Disease	Protein That Is Produced by the Normal Gene*	Description
Phenylketonuria	Phenylalanine hydroxylase	Inability to metabolize phenylalanine. The disease can be prevented by a phenylalanine-free diet. If the diet is not followed early in life, symptoms can develop, including severe mental retardation and physical degeneration.
Albinism	Tyrosinase	Lack of pigmentation in the skin, eyes, and hair.
Tay-Sachs disease	Hexosaminidase A	Defect in lipid metabolism. Leads to paralysis, blindness, and early death.
Sandhoff disease	Hexosaminidase B	Defect in lipid metabolism. Muscle weakness in infancy, early blindness, and progressive mental and motor deterioration.
Cystic fibrosis	Chloride transporter	Inability to regulate ion balance across epithelial cells. Leads to production of thick lung mucus and chronic lung infections.
Lesch-Nyhan syndrome	Hypoxanthine-guanine phosphoribosyl transferase	Inability to metabolize purines, which are bases found in DNA and RNA. Leads to self-mutilation behavior, poor motor skills, and usually mental retardation and kidney failure.

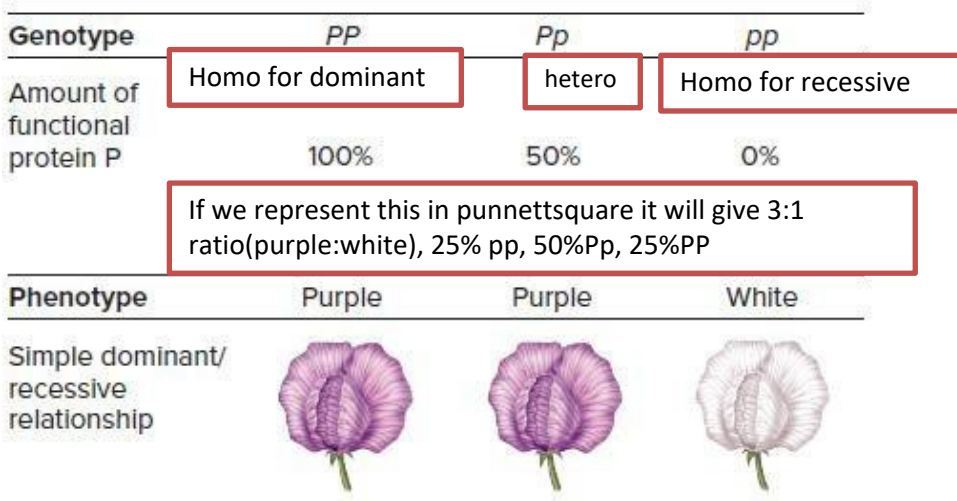
*Individuals who exhibit the disease are homozygous (or hemizygous) for a recessive allele that results in a defect in the amount or function of the normal protein.

Inheritance pattern of single genes

- In a simple dominant/recessive relationship, the recessive allele DOES NOT affect the phenotype of the heterozygote.
  - So how can the wild-type phenotype of the heterozygote be explained?

- A completely dominant allele creates the full phenotype by one of two methods:Homozygous either for wild-type alleles or mutant alleles
  - It produces half the amount of protein found in a homozygous dominant individual, but that is sufficient to produce the full phenotype. These genes are haplosufficient
  - Expression of the one active allele may be upregulated, generating protein levels adequate to produce the full phenotype

FIGURE A comparison of protein levels among homozygous (*PP* or *pp*) and heterozygous (*Pp*) genotypes.
Genes→Traits In a simple dominant/recessive relationship, 50% of the protein coded by one copy of the dominant allele in the heterozygote is sufficient to produce the wild-type phenotype, in this case, purple flowers. A complete lack of the functional protein results in white flowers.



Degrees of Dominance

- Complete dominance occurs when phenotypes of the heterozygote and dominant homozygote are identical

  The dominant allele completely masks the recessive allele, and both heterozygous and homozygous for wild type allele have the same phenotype, PP=Pp=purple flowers

- In incomplete dominance when the phenotype of the heterozygote is intermediate (falls within the range) between the phenotypes of the two homozygotes.

  Incomplete= gives an **in**termediate trait between the recessive and dominant, ex: purple and white crossing gives pink flowers, more applied to the blended theory before Mendel's laws

- In codominance, two dominant alleles affect the phenotype in separate, distinguishable ways

  - Both alleles make a product, producing a combined phenotype:

    P, and p are expressed equally

Incomplete Dominance

- In incomplete dominance, the recessive allele is not expressed, and the dominant allele produces only enough product for an intermediate phenotype

•Example: Flower color in four-o'clock plant is an example of incomplete dominance

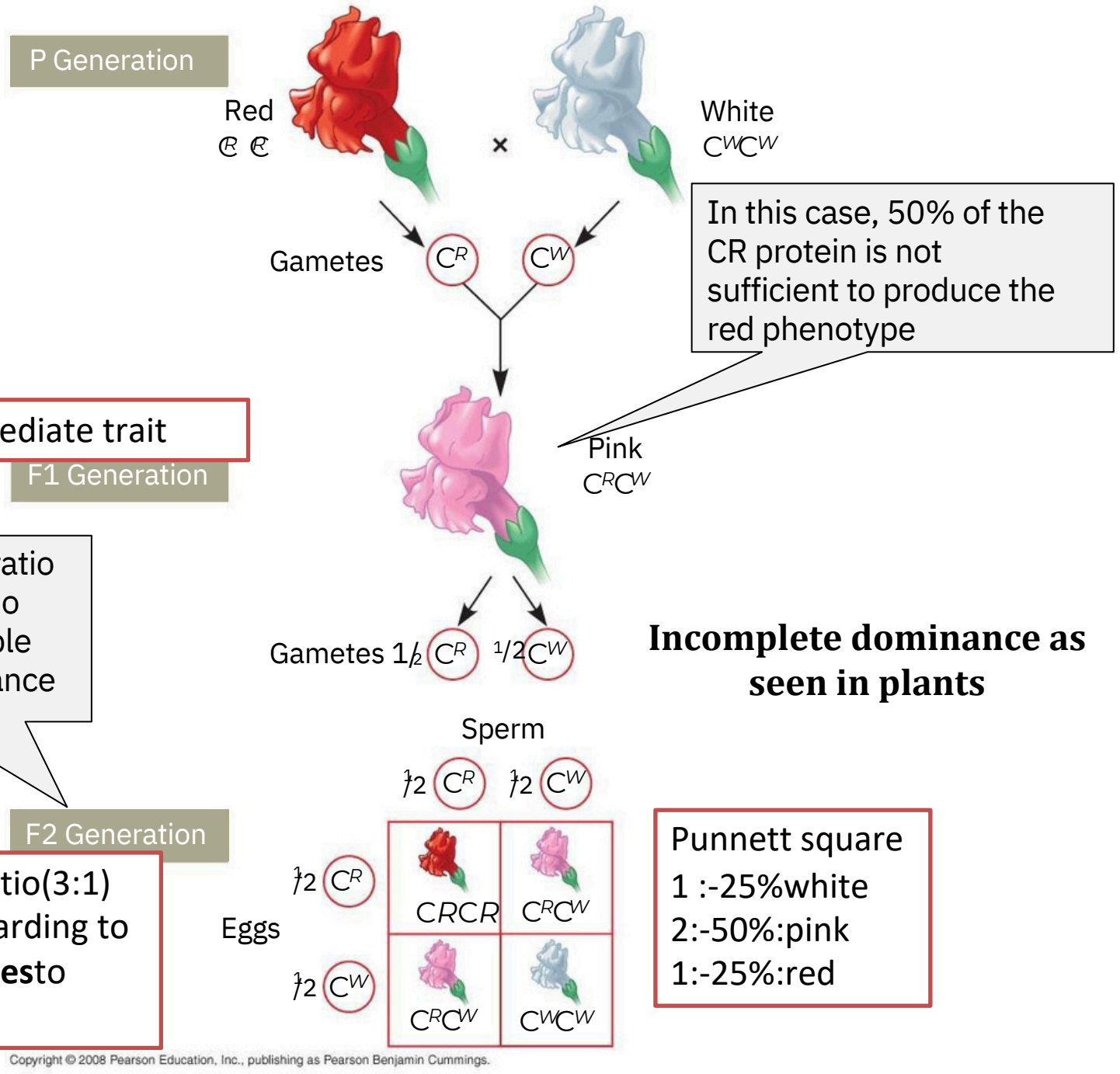
–Two alleles

•*CR* = wild-type allele for red flower color

•*CW* = allele for white flower colorrecessive

Crosses of pure-breeding red with pure-breeding white results in all pink F1 progeny

Fig. 14-10-3



Incomplete dominance

- Themost well-studied example of incomplete dominance in humans occurs in the genes for curly hair.
- Inheriting a gene for curly hair from one parent and a gene for straight hair from the other parent will give a hair texture that is a blend of the two, wavy hair.

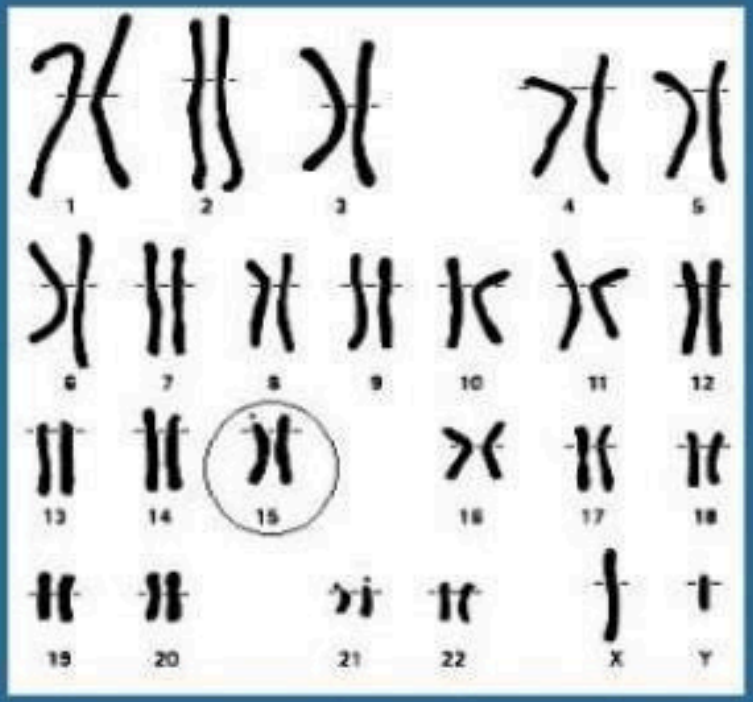
Homozygous Straight	Heterozygous	Homozygous Curly
hh	Hh	HH

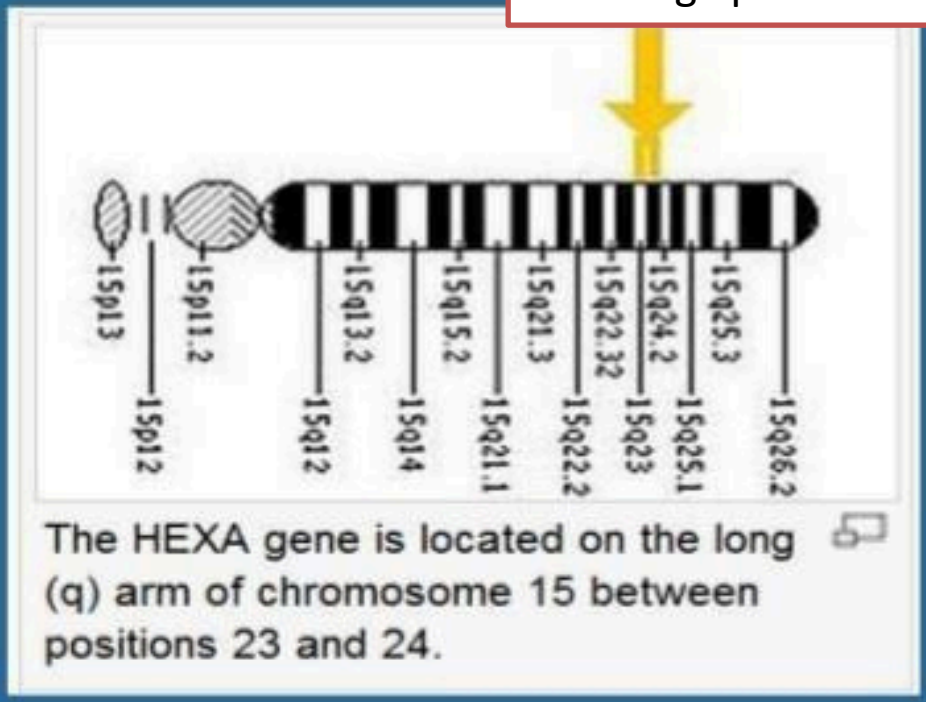
Causes of Tay-Sachs

How to differentiate between enzyme and protein of humans in writing:
Genes arewritten in italic: like :*HEX A, proteins are straight HEX A*

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

This enzyme is important in breaking lipids





The HEXA gene is located on the long (q) arm of chromosome 15 between positions 23 and 24.

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

PATIENTS DIE EARLY IN LIFE BETWEEN 2-4 YRS, due to accumulation of the lipid, also they have severe hypotonia

MENDELIAN GENETICS AND HUMANS

Human genetic disorders

Tay Sachs Disease

Inheritance Pattern:

-Autosomal recessive

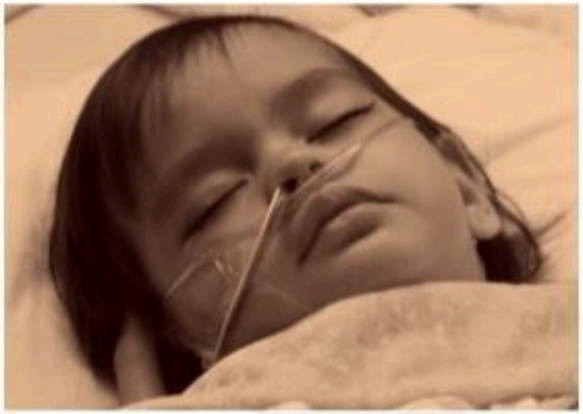
Physical Effects:

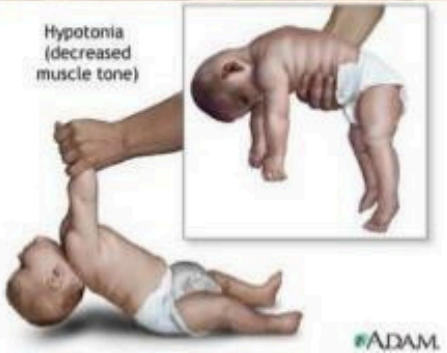
-Nerve cells destroyed in brain and spinal cord

-Symptoms appear 3-6 months after birth

-Loss of motor control and atrophy of muscles, seizures

-Death





- **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

-at the organismal levelthe phenotype is determined by the dominant allele, meaning it needs both recessive alleles to have the disease
-atthebiochemical level, the activity of the normal genotype expression for the protein is higher than homozygous for the dominant which is also higher than the hetero
-atthe molecular level,itiscodominance,meaningboththeallele types are present(If it is hetero), P and p both exist at the molecular level before the expression
-noteifthequestionaskedaboutthetypeofdominance without determining the level, we would consider it at the organismal level

examples

- Human examples of *recessive lethal alleles*:
  - **Hemophilia:** results from an X-linked recessive allele and is lethal if untreated.

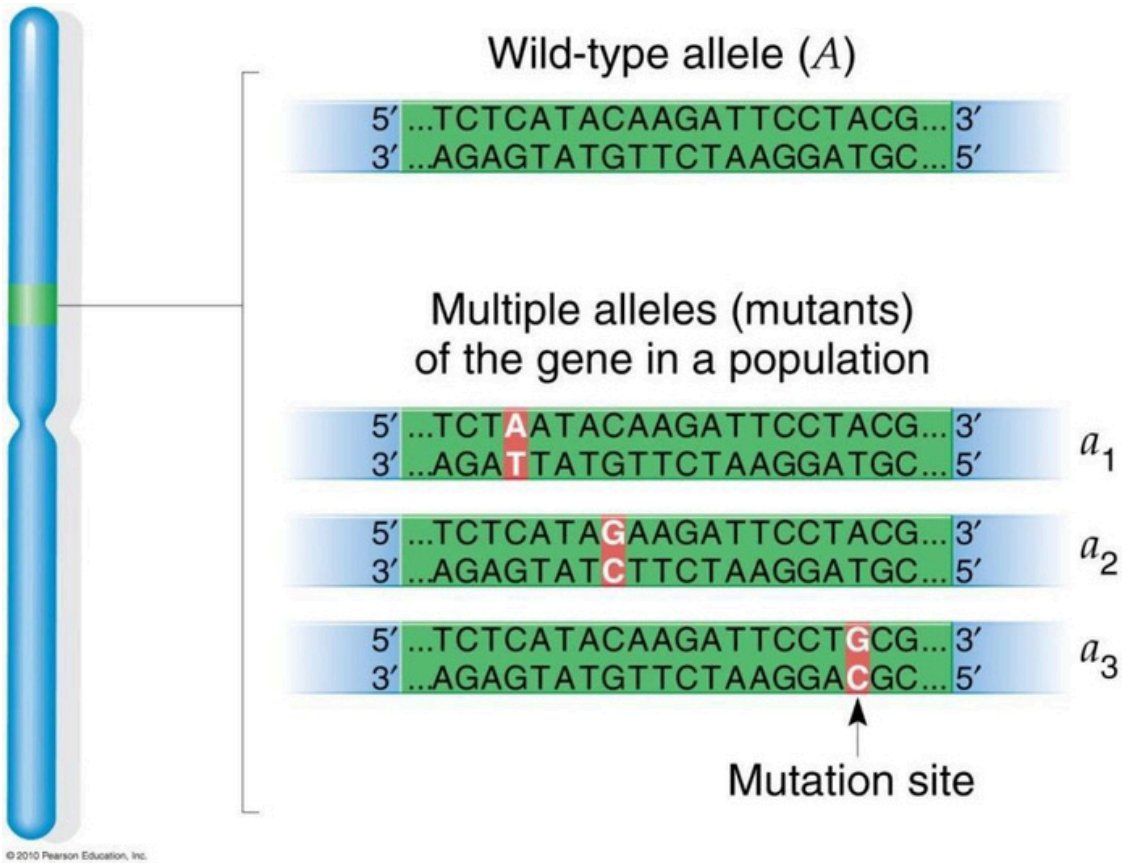
Deficiency in either factor 8(hem A) or factor 9(hem B)
-itismoredangerousinchildren,duetofrequentfalling down
-wetreat it by giving the deficient factors

A *dominant lethal gene* causes **Huntington disease**, characterized by progressive central nervous system degeneration. The phenotype is not expressed until individuals are in their 30's. Dominant lethals are rare, since death before reproduction would eliminate the gene from the pool

-the dominant allele what causes the lethality, and if we test these patients, they will be heterozygous
-This heterozygosity causes death, indicating that homozygosity for the lethal allele will be more lethal, preventing it from spreading by reproduction and being a genotype for the population
-sodominantlethalhomozygous is very rare(they die very early after birth, unable to reproduce)

Multiple Alleles

- Although a gene only exists in two forms in an individual (alleles), many forms exist in a population (polymorphisms)



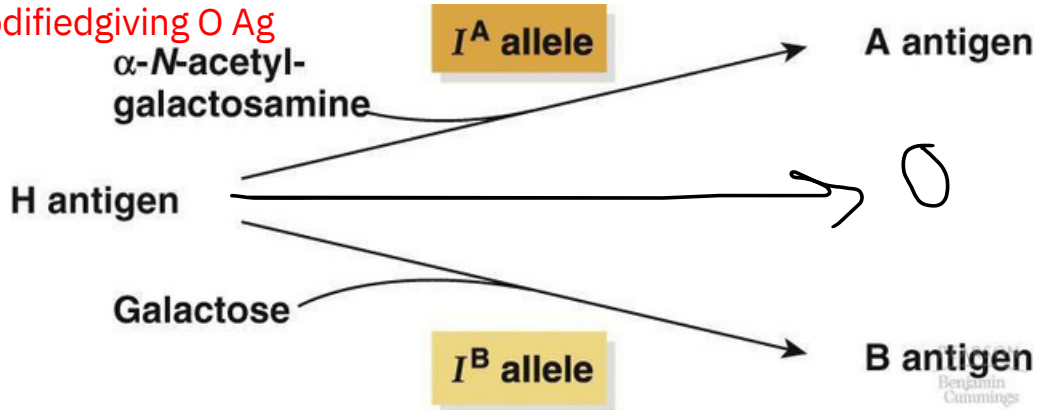
Multiple Alleles

- The **ABO blood group** provides another example of multiple alleles.
- It is determined by the type of antigen present on the surface of red blood cells.
  - Antigens are substances that are recognized by antibodies produced by the immune system

- There are three different types of antigens found on red blood
  - **Antigen A**, which is controlled by **allele I^A**
  - ***I* Antigen B**, which is controlled by I^B
  - **allele *I* Antigen O**, which is controlled by **allele *i***

Biochemistry of ABO Red Blood Cell grouping

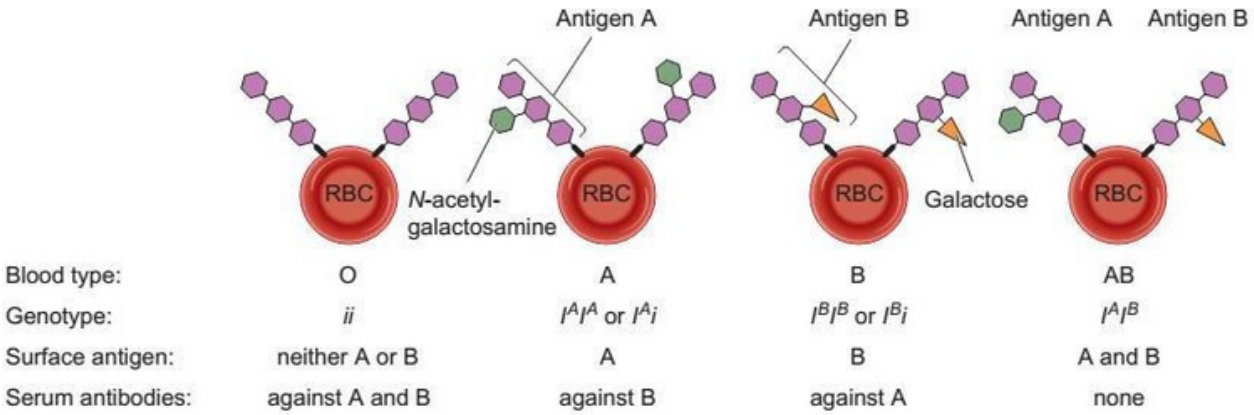
- The ABO locus produces RBC antigens by encoding glycosyltransferases, which add sugars to polysaccharides on membrane glycolipid molecules (the H antigen)
- Activity of the *IA* gene product, α-N-acetylgalactosamyl transferase, converts the H antigen to the A antigen
- Activity of the *IB* gene product, α-D-galactosyltransferase, converts the H antigen to the B antigen
- Neither enzyme is present in an *i/i* individual, and so the H antigen remains unmodifiedgiving O Ag
  - so O Ag is H Ag without modifications



Multiple Alleles

With 4 phenotypes : A
B
AB
O

- Allele ***i*** is recessive to both ***IA*** and ***IB***
- Alleles ***IA*** and ***IB*** are **codominant**
  – They are both expressed in a **heterozygous** individual



- A given gene may have more than two alleles, or multiple alleles; e.g. the series of alleles is denoted ***IA***, ***IB and i***. However, each person carries only two of the alternatives ***IA IA , IB IB , IA IB , IA i, IB i, ii.***
- allele is not inherently dominant or recessive; its dominance or recessiveness is always relative to a second allele.

Genotypes	Corresponding Phenotypes: Type(s) of Molecule on Cell
I^AI^A I^Ai	A
I^BI^B I^Bi	B
I^AI^B	AB
ii	O

-Can a child with an A blood group mother and a B blood group father have an O blood group?
Yes,themotherhasIAi,and the fatherhasIBi, sothe childwillhaveiigenotype with O phenotype

Pleiotropy

- Most genes have multiple phenotypic effects, a property called pleiotropy, syndromic not isolated cases
- For example, pleiotropic alleles are responsible for the multiple symptoms of certain hereditary diseases, such as cystic fibrosis
- Pleiotropy occurs for several reasons, including the following:
  - The expression of a single gene can affect cell function in more than one way. For example, a defect in a microtubule protein may affect cell division and cell movement.
  - A gene may be expressed in different cell types in a multicellular organism.
  - A gene may be expressed only at a specific stage of development.

Also, there are isolated cases, meaning mutation in a gene will affect that organ only and other systems are normal like mutation in retinal genes causes blindness only

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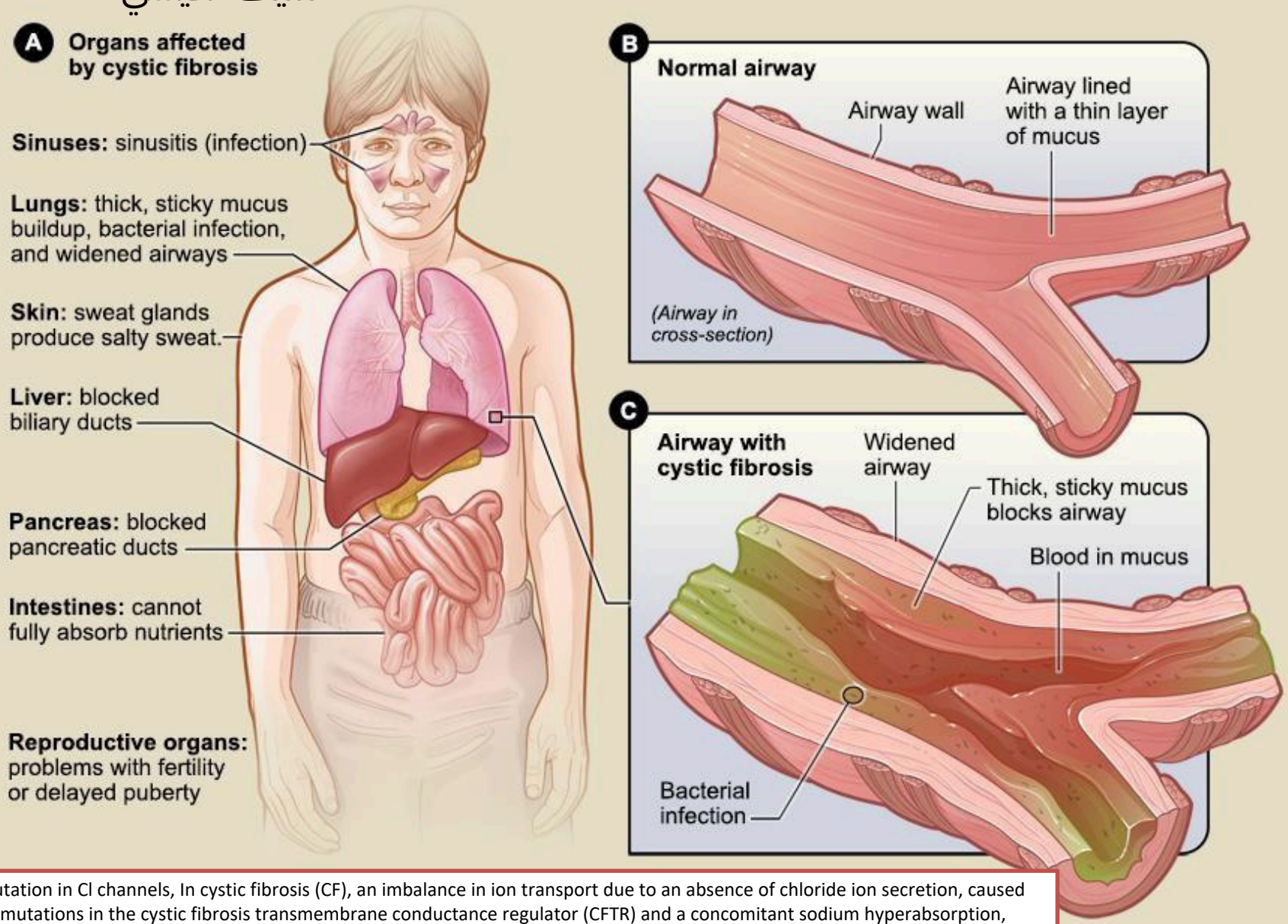


Mutation in Cl channels, In cystic fibrosis (CF), an imbalance in ion transport due to an absence of chloride ion secretion, caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) and a concomitant sodium hyperabsorption, caused by dysregulation of the epithelial sodium channel (ENaC), results in mucus stasis and dehydration which predisposes the lungs to cycles of chronic infection and inflammation leading to lung function decline.

Summary of different dominance relationships

The phenotype of the heterozygote defines the dominance relationship of two alleles

Complete dominance:

Hybrid resembles one of the two parents

Incomplete dominance: Hybrid resembles neither parent

Codominance: Hybrid shows traits from both parents

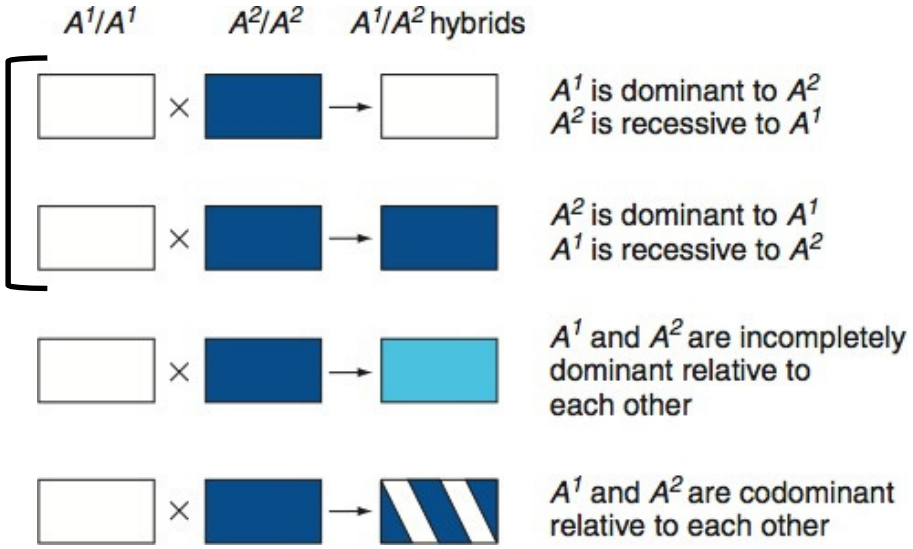


Figure 3.2

Overdominance

Overdominance	**Inheritance:** This pattern occurs when the heterozygote has a trait that is more beneficial than either homozygote. **Molecular:** Three common ways that heterozygotes may have benefits include: their cells may be resistant to infection by microorganisms, they may produce protein dimers with enhanced function, or they may produce proteins that function under a wider range of conditions.

- **Overdominance** is the phenomenon in which a **heterozygote** is more vigorous than both of the corresponding **homozygotes**.
  - It is also called **heterozygote advantage.**
  - Example = *Sickle-cell anemia*

Autosomal recessive disorder

–Affected individuals produce abnormal form of hemoglobin

–Two alleles

- ***HbA*** ➔ Encodes the **normal** hemoglobin, **hemoglobin A**
- ***HbS*** ➔ Encodes the **abnormal** hemoglobin, **hemoglobin S**

HbAHbA: normal: but whengets infected with plasmodium, the disease appears
HbAHbS: carrier: but shows resistance to plasmodium by impeding its life cycle which occurs in RBCs, they aren't preferable for replication anymore.
HbSHbS: sickled
-hence, homo HBS will die from SCD, and homo HBA will suffer from malaria, the hetero is preferable by showing its resistance

Overdominance

- ***HbSHbS*** individuals have red blood cells that deform into a sickle shape under conditions of low oxygen tension.
  - This has two major complications

1. Sickling phenomenon greatly shortens the life span of the red blood cells
   - Anemia results
2. Odd-shaped cells clump
   - Partial or complete blocks in capillary circulation

  - Thus, affected individuals tend to have a shorter life span than unaffected ones

Overdominance

- The *sickle cell* ***allele*** has been found at a fairly high frequency in parts of Africa where malaria is found…!!!

  –How come?

- Malaria is caused by a protozoan, ***Plasmodium***

  –This parasite undergoes its life cycle in two main parts

  •One inside the *Anopheles* mosquito

  •The other inside **red blood** cells

  –Red blood cells of **heterozygotes**, are likely to rupture when infected by *Pasmodium sp*.

  - This **prevents** the propagation of the parasite

- Therefore, ***HbAHbS*** individuals are "**better**" than

  – ***HbAHbA***, because they **do not** suffer from sickle cell anemia

  – ***HbSHbS***, because they are more resistant to malaria

Overdominance

- At the molecular level, overdominance is due to two alleles that produce slightly different proteins.

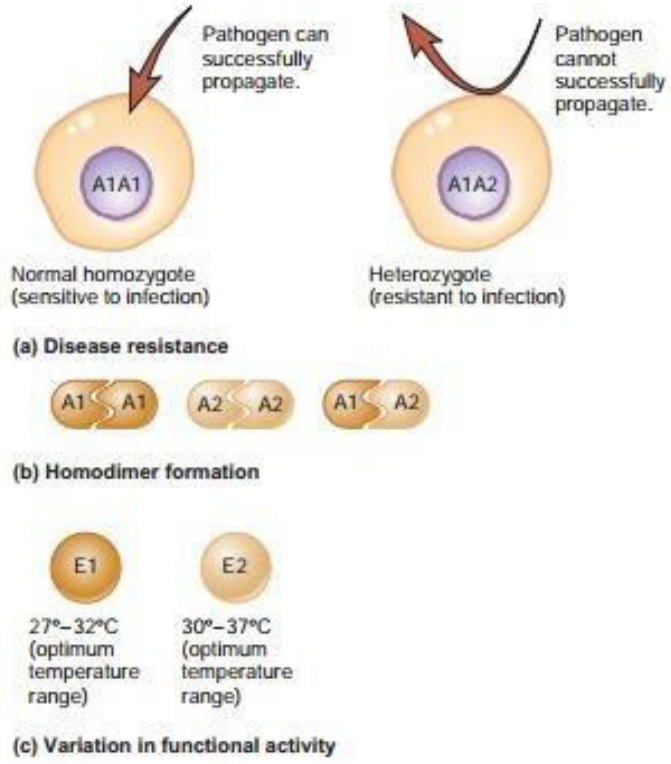
- **But how** can these two protein variants produce a favorable phenotype in the heterozygote?

- Well, there are **three possible explanations** for **overdominance** at the molecular/cellular level

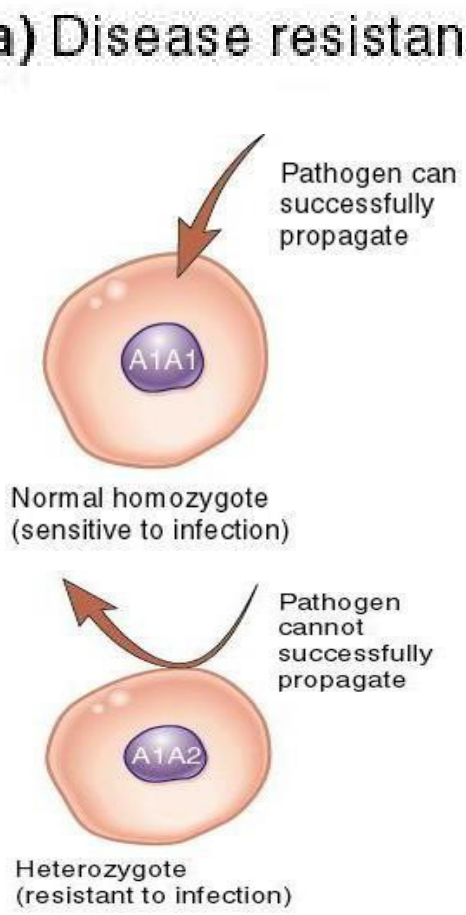
  a.Disease resistance

  b.Homodimer formation

  c.Variation in functional activity



- A microorganism will infect a cell if certain cellular proteins function optimally.
  - **Heterozygotes** have one altered copy of the gene.
  - Therefore, they have slightly reduced protein function.
  - This reduced function is **not enough** to cause serious side effects
  - Examples include
    But it is **enough to prevent infections.**
    - Sickle-cell anemia and
    - malaria Tay-Sachs disease
      - Heterozygotes are resistant to tuberculosis



This review considers available evidence for mechanisms of conferred adaptive advantages in the face of specific infectious diseases. In short, we explore a number of genetic conditions, which carry some benefits in adverse circumstances including exposure to infectious agents. The examples discussed are conditions known to result in resistance to a specific infectious disease, or have been proposed as being associated with resistance to various infectious diseases. These infectious disease–genetic disorder pairings include malaria and hemoglobinopathies, cholera and cystic fibrosis, tuberculosis and Tay-Sachs disease, mycotic abortions and phenylketonuria, infection by enveloped viruses and disorders of glycosylation, infection by filoviruses and Niemann–Pick C1 disease, as well as rabies and myasthenia gravis. We also discuss two genetic conditions that

•Some proteins function as **homodimers**

–Composed of two different subunits

–Encoded by two ***alleles*** of the same gene.

•***A1A1*** homozygotes

–Make only **A1A1 homodimers**

■

A2A2 homozygotes

■

Make only **A2A2 homodimers**

■

***A1A2* heterozygotes**

■

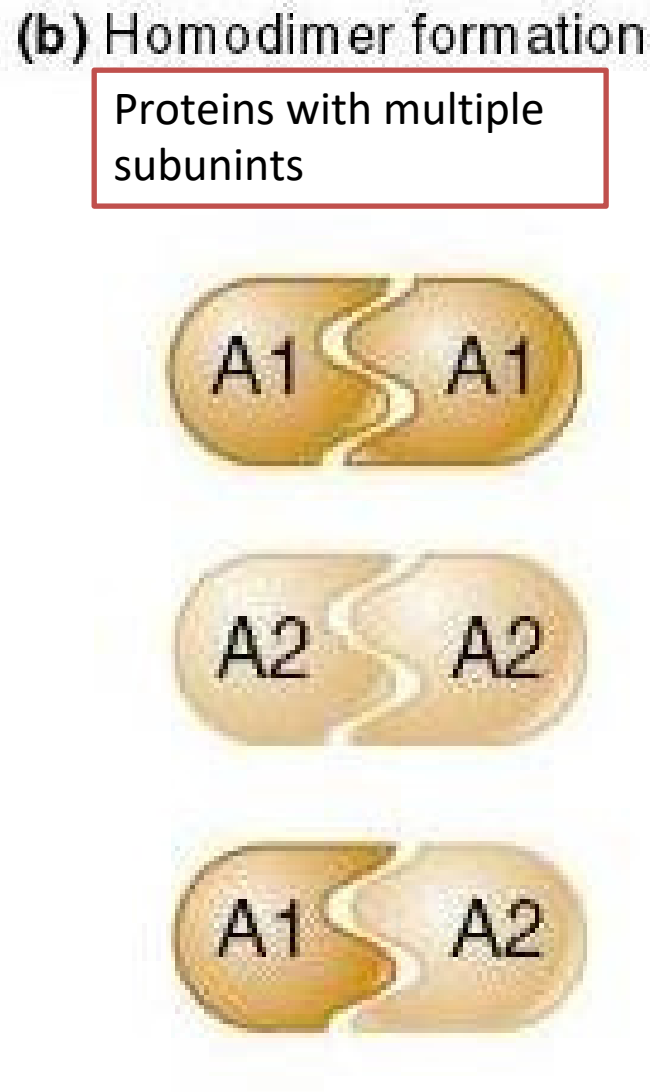
Make **A1A1** and **A2A2** heterodimers and **A1A2** homodimers

■

For some proteins, the **A1A2 heterodimer** may have better functional activity

■

Giving the **heterozygote superior**



(c) Variation in functional activity

- A gene, ***E***, encodes a metabolic ***enzyme***
- Allele ***E1*** encodes an ***enzyme*** that functions better at **lower** temperatures.
- Allele ***E2*** encodes an enzyme that functions better at **higher** temperatures

27°–32°C (optimum temperature range)

30°–37°C (optimum temperature range)

- ***E1E2*** heterozygotes produce **both** enzymes.
- Therefore they have an advantage under a wider temperature range than both ***E1E1*** and ***E2E2*** homozygotes

Combination of wide range of Temp

The same genotype does not always produce the same phenotype

Each patientis a separate case

- In all of the traits discussed so far, the relationship between a specific genotype and its corresponding phenotype has been absolute

- Phenotypic variation for some traits can occur because of: •Differences in penetrance and/or expressivity
  - •Effects of modifier genes
  - •Effects of environment
  - Pure chance

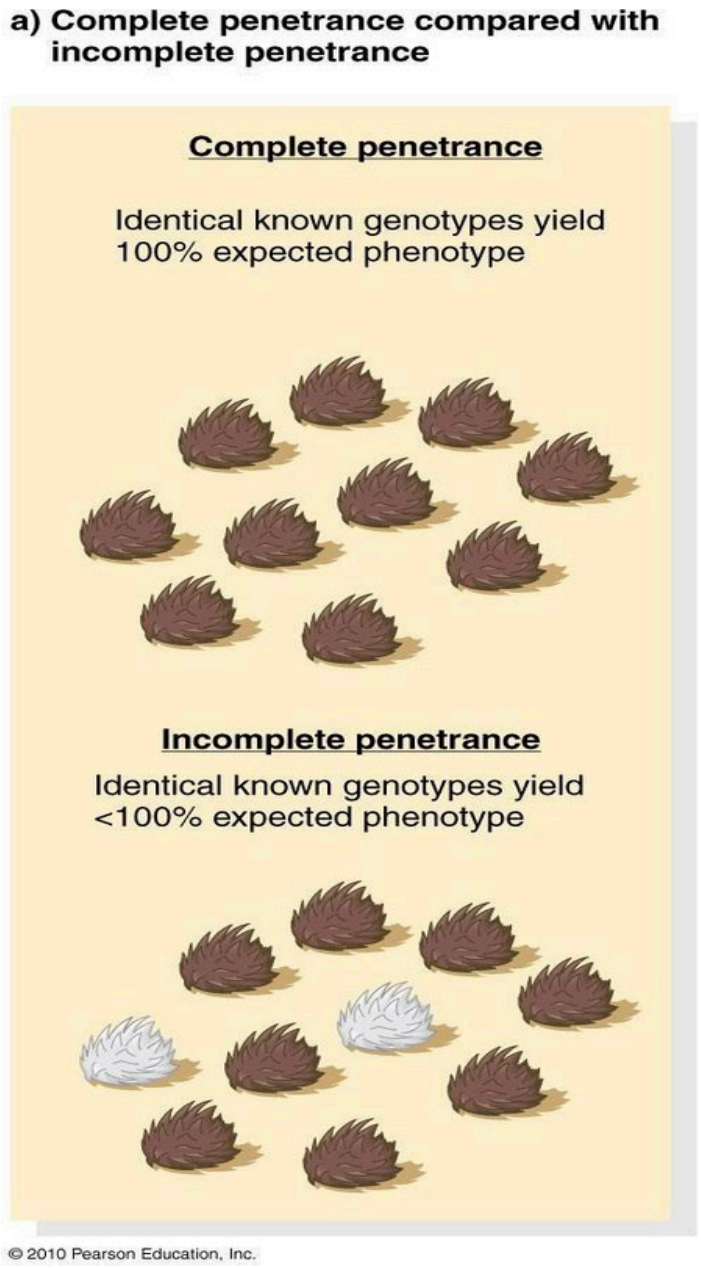
Penetrance vs expressivity - https://youtu.be/L2TNAilLqpI?si=FtzKBlfji-LaGyVp

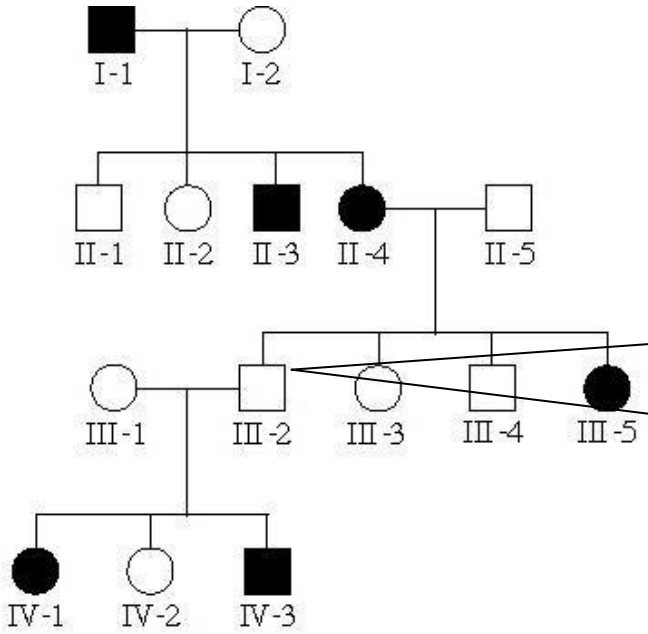
Incomplete Penetrance

- Penetrance is the percentage of a population with a particular genotype that shows the expected phenotype
- The term indicates that a dominant *allele* does not always "penetrate " into the phenotype of the individual.
  - –Can be complete (100%) or incomplete (e.g. penetrance of retinoblastoma is 75%)
  - –Incomplete penetrance, where an individual may carry a particular genotype but may not express the corresponding phenotype.
  - –In any particular individual, the trait is either penetrant or not
- The measure of penetrance is described at the population level.
  - –If 60% of heterozygotes carrying a dominant *allele* exhibit the trait *allele*, the trait is 60% penetrant.
  - – -if 60% has the mutation, the penetrance is 60%

Incomplete Penetrance

- Example = *Polydactyly*
  - –Autosomal dominant trait.
  - –Affected individuals have additional fingers and/or toes
  - –A single copy of the *polydactyly allele* isusually sufficient to causethis condition.Normally foundallele
  - –In somecases, however, individuals carry the dominant *allele* but do not exhibit the trait





In F3 2 children have polydactyly despite their parents don't have, indicating that they are carriersand the allele is incompletely penetrated

Inherited the polydactyly allele from his mother and passed it on to a daughter and son

Does not exhibit the trait himself even though he is a heterozygote

Brachydactyly is a congenital condition that leads to shortened fingers or toes due to unusually short bones1234. It is typically inherited as an autosomal dominant trait involving abnormal or absent development of one or more phalanges, metacarpals, or metatarsals1. There are different types of brachydactyly, based on which bones are shortened23. For most people, brachydactyly will not affect how they live their lives3.

- Human examples include:
  - Brachydactyly involves abnormalities of the fingers, and shows 50–80% penetrance
  - Many cancer genes are thought to have low penetrance, making them harder to identify and characterize

Phenotype often depends on penetrance and/or expressivity

Penetrance is the percentage of a population with a particular genotype that shows the expected phenotype

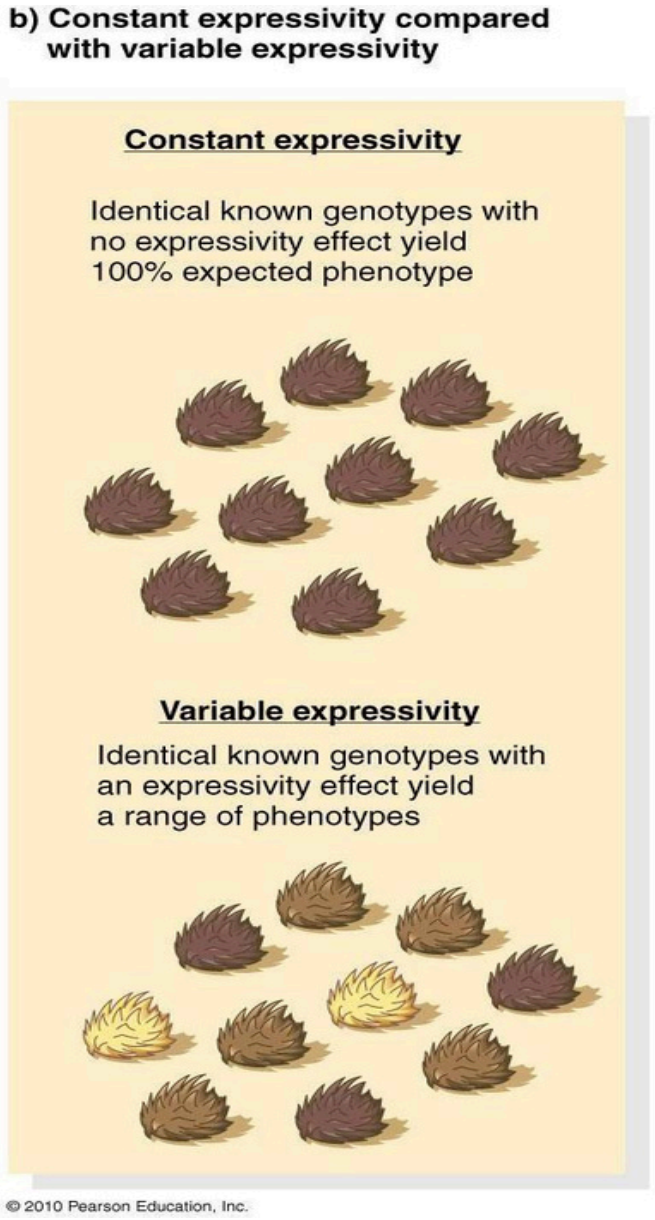
- Can be complete (100%) or incomplete (e.g. penetrance of retinoblastoma is 75%)

Expressivity is the degree or intensity with which a particular genotype is expressed in a phenotype

- Can be variable or unvarying

Expressivity

- Expressivity is the degree to which a trait is expressed.
- In the case of *polydactyly*, the number of digits can vary.
- For example, one individual may have an extra toe on only one foot, whereas a second individual may have extra digits on both the hands and feet.
  - A person with *several* extra digits has high expressivity . of this trait.
  - A person with a *single* extra digit has low expressivity .



- Some genes have both **incomplete penetrance** and **variable expressivity**
  - Neurofibromatosis is an autosomal dominant disorder with 50-80% penetrance and variable expressivity

It may cause cancer, affects nerves, or only pigmentation…

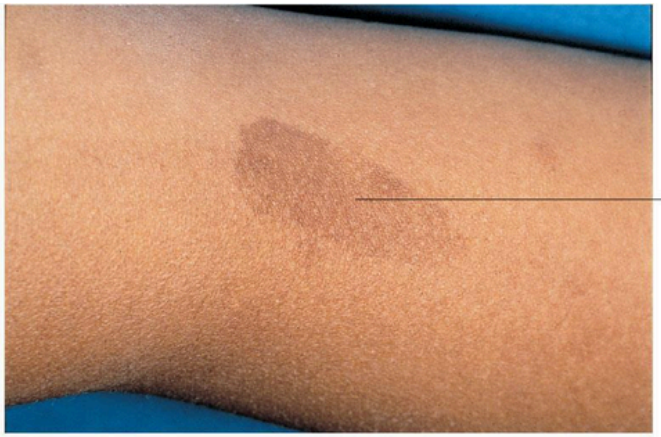
- Individuals with the disease show a wide range of phenotypes

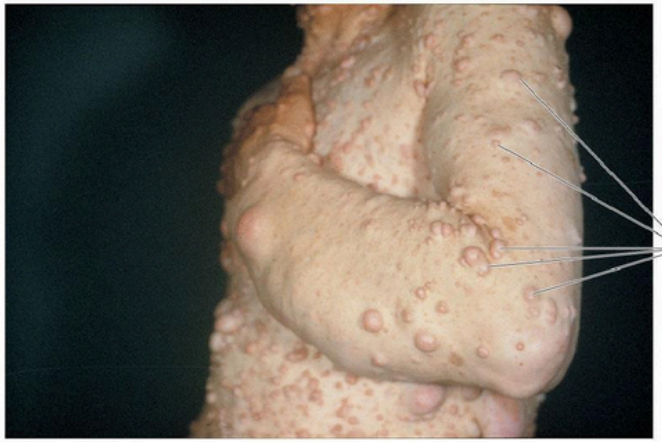
  Incomplete penetrance and variable expressivity complicate medical genetics and counseling

c) Incomplete penetrance with variable expressivity

Incomplete penetrance with variable expressivity

Identical known genotypes produce a broad range of phenotypes, due to varying degrees of gene activation and expression





Expressivity

- The molecular explanation of **expressivity** and **incomplete penetrance** may **not** always be understood.

- In most cases, the range of phenotypes is thought to be due to influences of the
  - **Environment**

  and/or

  - **Other genes**

For example, E148Q in familial Mediterranean fever can establish the disease in our regions considering it a mutation, while in west cold world, it is considered supportive

Modifier genes

Environment

- **Environmental** conditions may have a great impact on the phenotype of the individual
- Temperature is a common element of the environment that can affect phenotype

- Example 1
  - The **arctic fox** (Alopex lagopus) goes through two color phases.
  - During the **cold** winter, the arctic fox is primarily **white**, but in the warmer summer, it is mostly **brown**.
  - Such **temperature sensitive *alleles*** affecting fur color are found among many species of mammals.

Not required

- **Temperature** may alter the activity of enzymes so that they function normally at one temperature but are nonfunctional at another
- The Siamese phenotype occurs in cats homozygous for the recessive allele (c^s) of the albino (C) locus, which encodes a tyrosinase
- Tyrosinase is required in the melanin synthesis pathway. Activity of the tyrosinase encoded by c^s is temperature sensitive
  - Kittens are uniformly warm, and so stay light colored
  - As cats grow, extremities become cooler, and tyrosinase becomes active, allowing melanin to be made and fur on the points to become darker

Environment

- Example 2 = Phenylketonuria

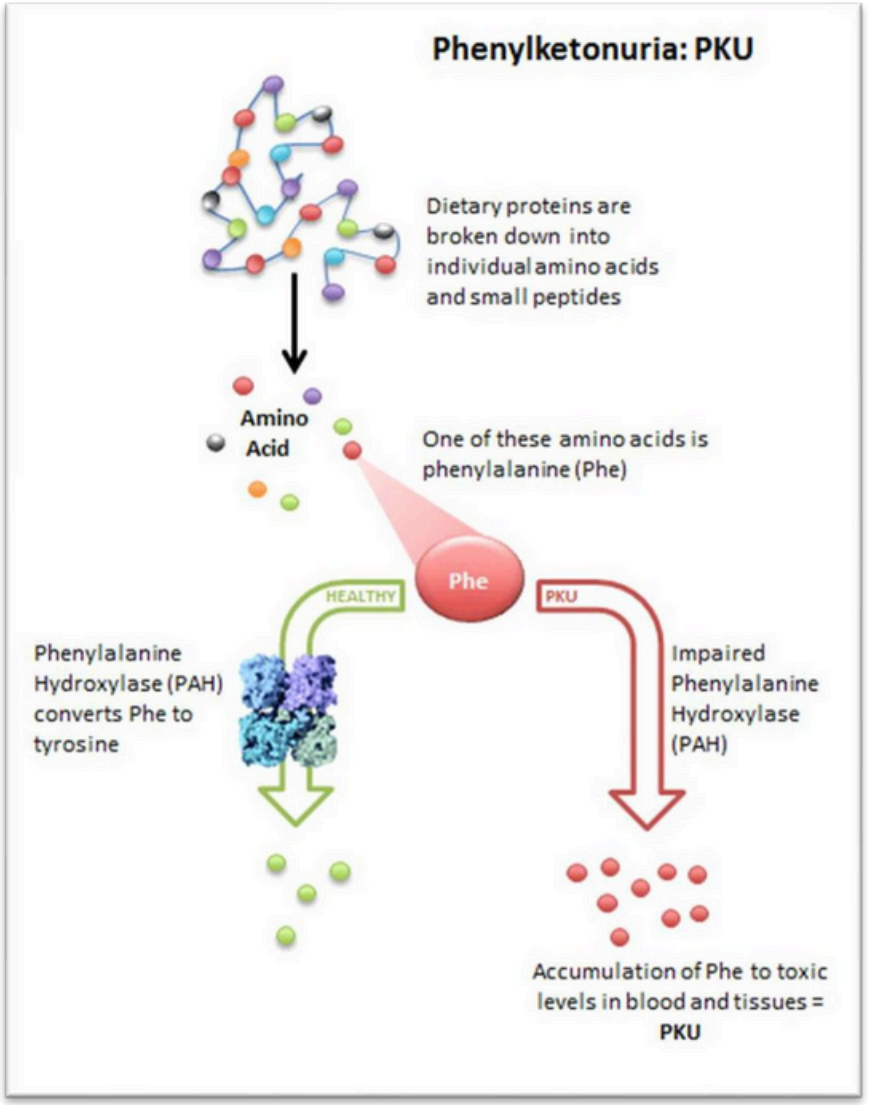
  –Autosomal recessive disorder in humans.

  –Caused by a defect in the gene that encodes the *enzyme phenylalanine hydroxylase*.

  –Affected individuals cannot metabolize *phenylalanine*.

  •*Phenylalanine* will thus accumulate in tissues especially brain

Especially if accumulation happens in brain, it should be early diagnosed



Environment

It ultimately causes a number of detrimental effects

- –Mental retardation
- –Delayed cognitive development
- –Psychiatric disorders: Behavioral, emotional and social problems
- –Neurological problems possibly leading to seizures
- – Hyperactivity
- –Bone density
- –Bad breath, urine odor, due to increase phenylalanine level
- –Light skin, blue eyes due to obstruction in phenylalanine transforming to melanin.

- Newborns are now routinely screened for **PKU**.
- Individuals with the disease are put on a strict dietary regimen.
- Their diet is essentially ***phenylalanine-free***.
- These individuals tend to develop normally
- Thus the **PKU** test prevents a great deal of human suffering
- Furthermore, it is cost-effective

Effects of the Environment

- Age of onset is an effect of the individual's internal environment. Different genes are expressed at different times during the life cycle, and programmed activation and inactivation of genes influences many traits
  - Human examples include:
    - Pattern baldness, appearing in males aged 20–30 years
    - Duchenne muscular dystrophy, appearing in children aged 2 to 5 years

Sex of the individual affects the expression of some autosomal genes

- Sex-limited traits can appear in one sex but not the other
  - Examples include:
    - Milk production in dairy cattle, where both sexes have milk genes, but only females express them
    - In human?
- Sex-influenced traits appear in both sexes, but the sexes show either a difference in frequency of occurrence or an altered relationship between genotype and phenotype
  - Examples include:
    - Pattern baldness, controlled by an autosomal gene that is dominant in males and recessive in females

Genotype	Phenotype in Females	Phenotype in Males
BB	bald	bald
Bb	non bald	bald
bb	non bald	bald

    - Cleft lip and palate (2:1 ratio of males to females)
    - Other? Gout, RA, SLE more common in females

Sex-limited and sex-influenced traits are not necessarily inherited on the X chromosome,itis mainly autosomallyinherited
-sex-limited traits appear only in one gender, switch on and off, like milk in cattle, beard in males, testes, and uterus,…
-sex-influencedtraitsexist inbothmales and females buttheirappearance andfeaturesare different
-ex: baldness, B is the dominant allele BBinmaleswillshowcomplete hairremovalwhile in females, it will show thin light hair
-alsoit could interfere with other health issues, if the female patient has an adrenal gland tumor, it will make her lose her hair but after the tumor excision, she will replace her hair back

A 10-year-old boy is brought to the emergency department for new swelling in his right leg. He has a history of lens dislocation and intellectual disability. Physical examination demonstrates moderate, pitting edema from his right calf to his right thigh and a normal left lower extremity. In addition, the patient has a caved-in appearing chest wall. He has no family members with similar conditions. Ultrasound reveals a deep venous thrombosis in his right femoral vein. Further genetic testing reveals a single missense mutation in the gene coding for cystathionine beta-synthase enzyme. Which of the following is the most likely explanation for this patient's genetic defect affecting multiple tissues?

- A. Dominant negative mutation
- B. Genetic linkage
- C. Incomplete penetrance
- D. Locus heterogeneity
- E. Pleiotropy
- F. Polyploidy
- G. Segregation

E

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