Genetics & molecular biology

◉ Sheet ○ Slide

Number:	21
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Last time we talked about Tay-sachs disease, and we said that the Dominance (complete, incomplete, codominance) is not s.th that is straight forward, rather it is more complicated, as it depends on the level we are talking about (genetic level, biochemical level or genotypic level).

Frequency of dominant alleles

The mutant(disease causing) allele is not always recessive.

It`s not necessary to say that dominant alleles are more common than recessive alleles in a population, for example polydactyly (**Dominant allele**) is **less common** than the normal trait \ 5 digits per appendage\ (**recessive allele**).

There is no correlation between the prevalence of dominant or recessive allele in the population.

- For instance, one baby out of 400 in the United States is born with extra fingers or toes, (so the recessive allele is more common).

Multiple Alleles

Looking at the individual level, each individual has only two alleles for each trait, **however**, most genes exist in populations in more than two allelic forms.

For example, **Blood type** in humans is determined by the type of carbohydrate represented on red blood cells, so we have **3 alleles** controlling Blood type (on the population level):

- A carbohydrates: I^A
- B carbohydrates: I^B
- No carbohydrates: i

Allele I^A produces antigen **A**
Allele I^B produces antigen **B**
Allele **i** produces **no** antigen.

Genotypes	Phenotypes (blood types)
$I^A I^A$	A
$I^A I^B$	AB
$I^A i$	A
$I^B I^B$	B
$I^B i$	B
ii	O

*BUT only two alleles control Blood type in each individual.

Pleiotropy (pleiotropic genes)

Means that:

A single gene ⟶ has multiple phenotypic effects (**pleiotropic genes**)

• For example, **pleiotropic alleles** are responsible for the **multiple symptoms** of certain hereditary diseases, such as Cystic fibrosis and Sickle-cell disease.

Cystic fibrosis ⟶ CFTR (mutated gene) ⟶ coding for abnormal chloride channels (membrane protein) ⟶ causing accumulation of chloride and mucus outside the cells (in the lumen) ⟶ causing problems and increasing the risk of bacterial infections.

Symptoms: sinusitis, salty sweat (high chloride concentration)

– sweat is used to diagnose CF -, accumulation of thick sticky mucus in the lungs (more prone to infections), blocks the pancreatic duct (hindering it's function), blockage of liver and bile ducts, decrease level of absorption from small intestine, complications in reproductive organs.

* Most genes have multiple phenotypic effect therefore most genes have pleiotropic.

Epistasis

A gene at one locus ⟶ alters phenotypic expression of a gene at a second locus

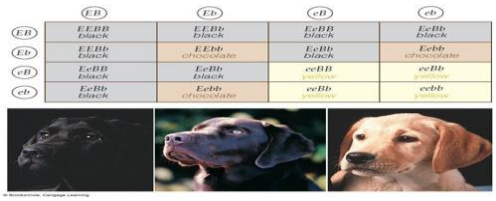
•A simple example, the coat colour in mammals (dogs) depends on two genes

• One gene determines the pigment colour: - B (black, dominant)

-b (brown, recessive)

• The other gene determines whether the pigment will be deposited in the hair: -E: for colour

-e: for no colour (so 'ee' will prevent both black and brown from manifesting).



So we say that (E, e) gene has an epistatic effect on (B, b) gene.

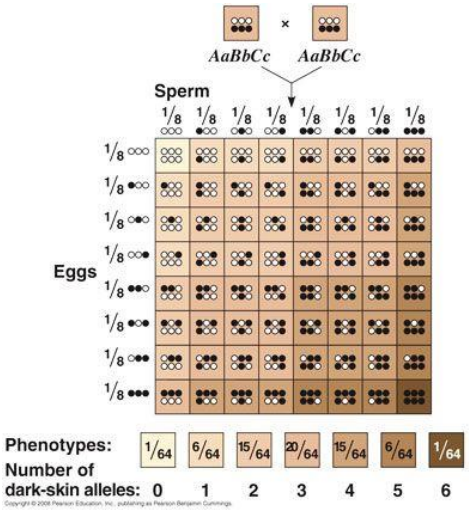
Polygenic Inheritance

One phenotype ⟶ *is influenced by more than one gene* (multiple mutations are needed to develop the disease).

*Actually, the common genetic diseases are polygenetic, for example, Diabetes, CVD, cancer, depression and epilepsy.

• Quantitative variation ⟶ 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.



Assuming that skin color is controlled by 3 different genes (6 alleles)

So this will give us a spectrum of colors rather than two specific ones.

A polygenic trait has a **normal distribution** among a population (a continuous variable)

Nature and Nurture: The Environmental Impact on Phenotype

 # Multifactorial: The phenotype ⟶ is affected by more than one factor (*genetic predispositions and environmental factors*).

- For example, if someone has a predisposition for developing lung cancer, with smoking (environmental factor) he might increase the risk of developing lung cancer. (without smoking the cancer might not develop or might be less aggressive).

- So genetic and environmental factors collectively influence phenotype.
- Norms of reaction are generally broadest for polygenic characters.

- Example from the slides, hydrangea flowers of the same genotype range from blue-violet to pink, depending on soil.

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

• Phenotype includes: physical appearance, internal anatomy, physiology, and behavior, also the phenotype reflects the organism's overall genotype and unique environmental history.

Pedigree Analysis

• **A pedigree**: is a family tree that describes the interrelationships of parents and children across generations (concise summary of the medical family history).

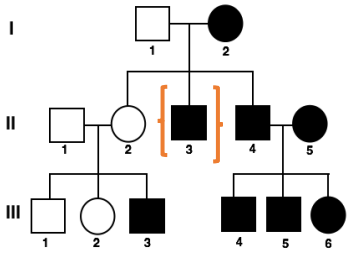
•**A pedigree** is used to trace and describe Inheritance patterns of particular traits

• **Pedigrees** can also be used to make predictions about future offspring.

IN THE EXAM, we are expected to read the given pedigree and to figure out the mode of inheritance.

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, proband, imprinting, trinucleotide repeat.



1. Each horizontal line is a generation.
2. Use Roman numbers to identify **generations**.
3. Use Arabic numbers to identify **individuals** within a generation.
4. List siblings from oldest to youngest, from left to right.
5. Male partner is usually placed to the left of the female partner.
   - Is individual (2,3) a female or a male?
   - Answer: MALE

In a pedigree we:

. Record full name, current age and date of birth, or age at death for each individual.

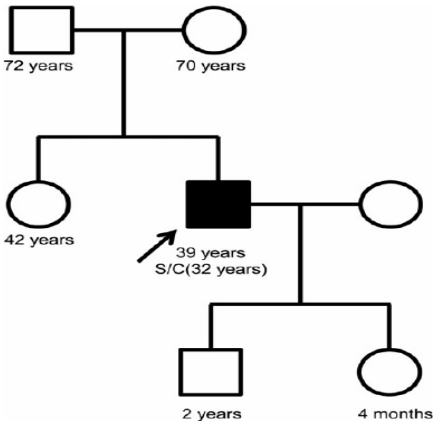
. Record race and ethnic origin of each individual.

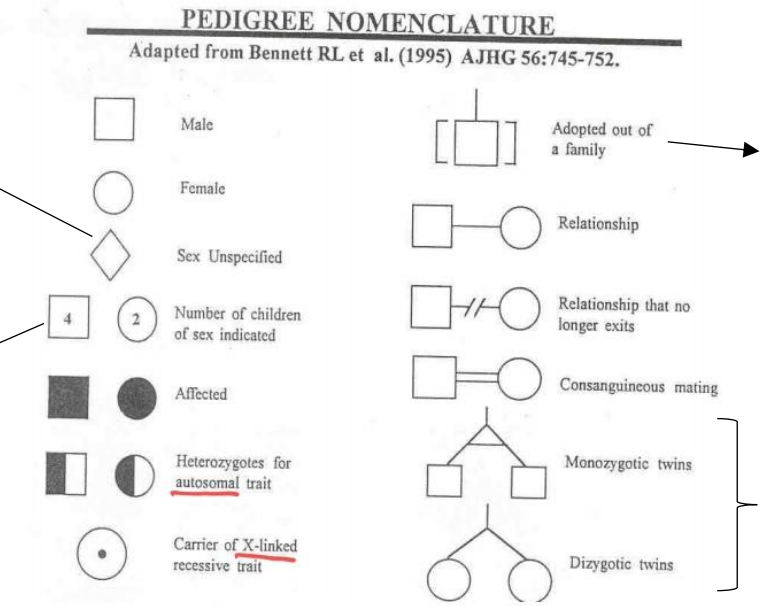
. Note health problems and/or cause of death for each individual.

. There are appropriate symbols to use for both adoption and assisted reproductive technologies.

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

- Shading or fill (hatches, dots, etc.) is used to denote medical status or symptoms of individuals. * A – - key/legend is used to define meanings.
- Results of an evaluation (E) are recorded below the symbol.





Not a third sex, either male or female only, but simply unknown.

4 males

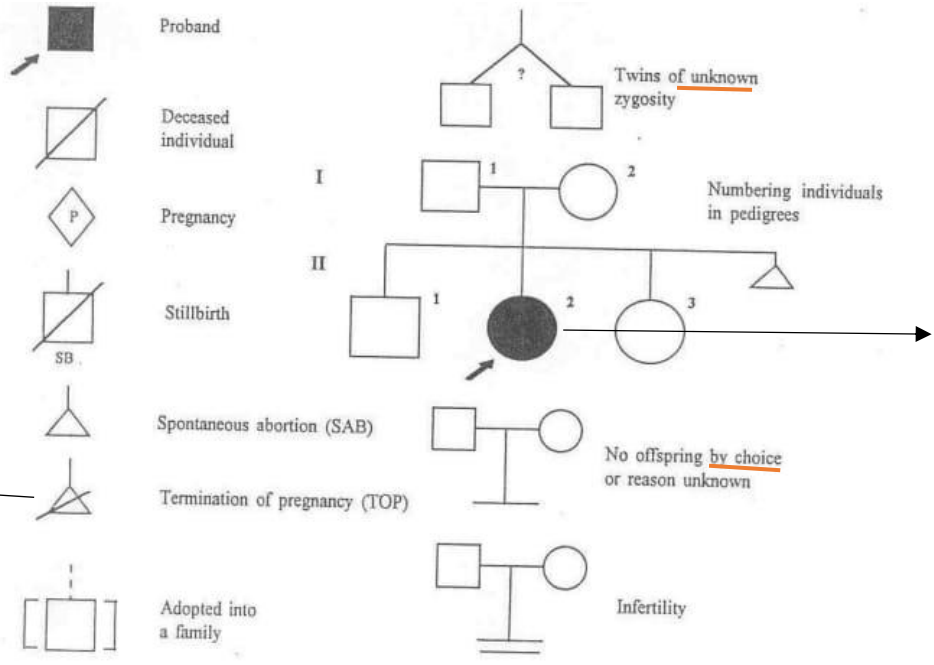
2 female

Avoid repetition.

Brackets and a **continuous line** ---The biological child of the family but he lived in another environment. Adapted outside the family. This affect the multifactorial phenotypes, like depression, bipolar disorder, schizophrenia.

Monozygotic: identical

Dizygotic: non identical (genetically like siblings)



Proband: is the individual who brings the family to clinical attention.

Usually the proband is the affected individual but not necessary

For example, if you not affected, but you told the doctor about your affected brother, in this case you are the proband. Also proband is the point of connection who gives information about the family.

The family chose to terminate the pregnancy.

Brackets and a **discontinues line**, the member is not the biological child of the family, but he grew up with them.

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** 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 (AA) or two mutant alleles(aa).

- 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 *(a1 a2)***.

For example, one allele has a missense mutation, and the other has a nonsense mutation. And the individual is affected as the homozygous mutant.

(a,a) <- both alleles have the same mutation.

(a1,a2)<- alleles carry different mutations.

Dominant Inheritance

– *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, if a disease is inherited in an autosomal dominant way only one mutant allele is needed for the individual to be affected(The dominant allele causes the disease)

There is **no carrier** in dominant inheritance, only affected or not affected.

Examples (autosomal dominant diseases)

• familial hypercholesterolemia • Huntington disease • neurofibromatosis type I (NF1) • myotonic dystrophy • MARFAN syndrome • achondroplasia

(The doctor chose these diseases in order to explain criterions of autosomal dominant inheritance, so the features applied to all autosomal dominant diseases).

NOTE: Key aspects of phenotypic dominant inheritance features are underlined.

1- Huntington disease is a (neurodegenerative: worsen with time) progressive brain **disorder** that causes loss of brain neurons (damage to basal ganglia), dementia, loss of cognition and motor control.

- Late -onset, usually appears in a person's (30s - 40s), so the patient is clinically normal until his late 30s, when he starts to stumble, and loses control, and this gradually progressing disease will eventually cause death (4-5) years after onset.

2- Myotonic dystrophy is a long term genetic disorder that affects muscle function (weakness of the muscles).

- Symptoms include gradually worsening muscle loss and weakness, facial weakness and cataracts.
- Variable onset (the age of onset varies among patients).
- Variable expressivity (different intensities among patients).

3- Neurofibromatosis type 1 is a condition characterized by:

- Skin hyperpigmentation (Ca-fe-au-lait spots).
- *Peripheral nerve tumors*.
- Benign growth on the iris (lisch nodules).
- High mutation rate.
- Variable expressivity {different degrees of severity} (a prime example that shows this feature).

4- **Familial hypercholesterolemia**: caused by a mutation in cell`s LDL receptors making the body unable to remove (LDL, or bad) cholesterol from the blood, results in arteriosclerosis, xanthomas and coronary heart disease (CHD).

- Homozygous mutated (AA): CHD develops at childhood (more severe).
- Heterozygous (Aa): CHD in middle age (later onset, one mutated allele).

5- **MARFAN syndrome:** is a genetic disorder of the connective tissue.

- Tall stature, long limbs.
- Narrow faces, high long palate.
- Dislocated lenses, myopia(can't see far objects).
- Aortic aneurysm (rupture): high pressure, weak connective tissue that can't withstand this pressure, causes rupture and internal hemorrhage (not easily diagnosed, which increases the risk of aortic aneurysm).
- Variable expressivity.
- Pleiotropy: one gene mutation, multiple phenotypes (involving musculoskeletal system, vision, cardiovascular system).

6- **Achondroplasia**(most common form of dwarfism).

- Short-limb dwarfism.
- Megalocephaly.
- Lordosis & Kyphosis.
- Increased mutations with increasing paternal age.
- 80% new mutations. (spontaneous, acquired, not inherited mutations, parents do not carry this mutation it occurs at some point before or at the embryonic development).

Some slides the doctor did not mention in the lecture, but said to have a look at:

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