Genetics & molecular biology

◉ Sheet ○ Slide

Number:	- 22
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Autosomal dominant inheritance

❖ Description :

One mutant allele is enough to manifest the clinical features, 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 (both are affected if we talk about a disease) where A=dominant allele. In practice, if the heterozygote expresses the trait, then the trait isclassified as dominant . So, AA &Aa both will be affected while aa will be normal.

❖ examples :

- ✓ Familial hypercholesterolemia
- ✓ Huntington disease
- ✓ Neurofibromatosis type I (NF1)
- ✓ Myotonic dystrophy
- ✓ Marfan syndrome
- ✓ Achondoplasia

Please don't worry about the number of pages . It is a very interesting & easy sheet ,so DON'T skip it.

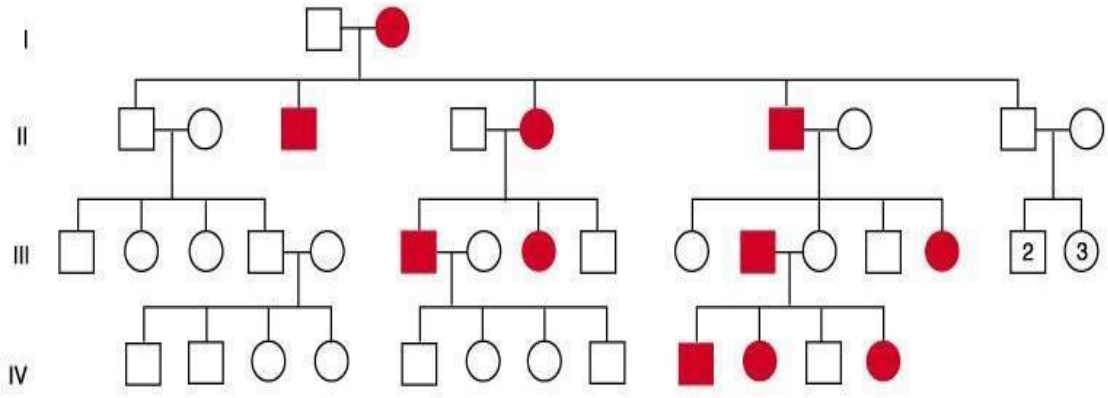
BEST OF LUCK (^_^)...

❖ Features :

- ✓ Vertical transmission: direct transmission from grandparent to parent to child withoutskipping generations.
- ✓ Both sexes are affected in almost 1:1 ratio.
- ✓ Both sexes may transmit the trait (affected mother and affected father can transmit the trait to their daughters and sons).
- ✓ May see variable expressivity (severity) and variable ages of onset.
- ✓ Homozygous individuals are usually more seriously affected (have a more severe disease) than heterozygous individuals, fortunately homozygous for autosomal dominant traits are less common than heterozygous.(when you see an individual affected with autosomal dominant disease , your first assumption should be that this individual is heterozygous not homozygous mutant they could be homozygous mutant but most probably heterozygous
- ✓ May be due to new mutations and this is the challenging feature.

- ✓ Gene product is usually a structural (non-enzymatic) protein, as structural proteins are usually defective when one of the allelic products is non-functional; enzymes usually require both allelic products to be non-functional to produce a mutant phenotype.

❖ Pedigree :



Autosomal recessive disorders

❖ Description :

Many genetic disorders are inherited in an autosomal recessive mannerand they range from relatively mild to life-threatening . For an individual to be affected they must have a homozygous mutant genotype, while the one that has a heterozygous genotype is known as a carrier and is phenotypically normal. Most individuals with recessive disorders are born to carrier parents.

❖ Examples :

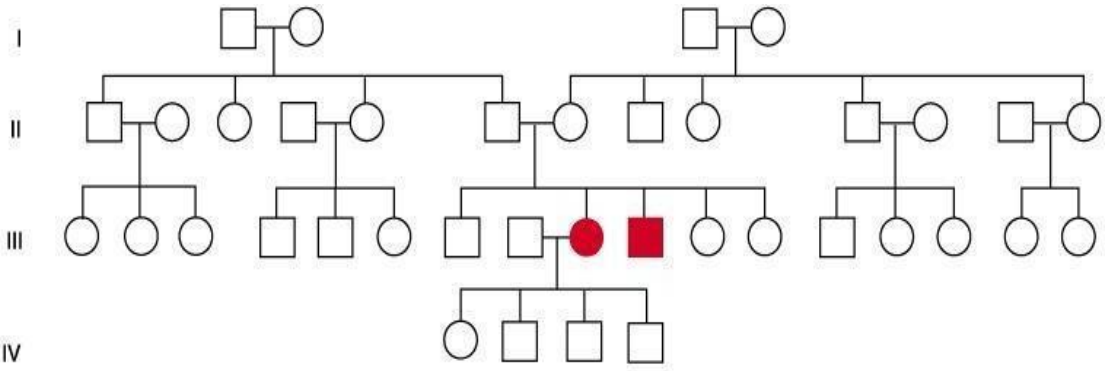
- ✓ Tay sachs
- ✓ albinism

- ✓ Cystic fibrosis
- ✓ PKU
- ✓ Sickle cell anaemia
- ✓ Most inborn errors of metabolism

❖ Features :

- ✓ Horizontal transmission: affected individuals are usually within thesame generation,AR isskipping generations.
- ✓ Both sexes are affected in 1:1 ratio and may equally transmit the mutant allele.
- ✓ Consanguineous mating (mating between close relatives)increases the chance of mating of two carriers of the same rare allele, and because of that most societies and cultures have laws against marriages between close relatives, BUT recent studies show that the chance of recessive disorders is the same whether it's close relatives' marriage or nonrelatives' marriage EXCEPT if there is a disease running in the family.
- ✓ Gene product is usually an enzymatic protein.

❖ Pedigree :



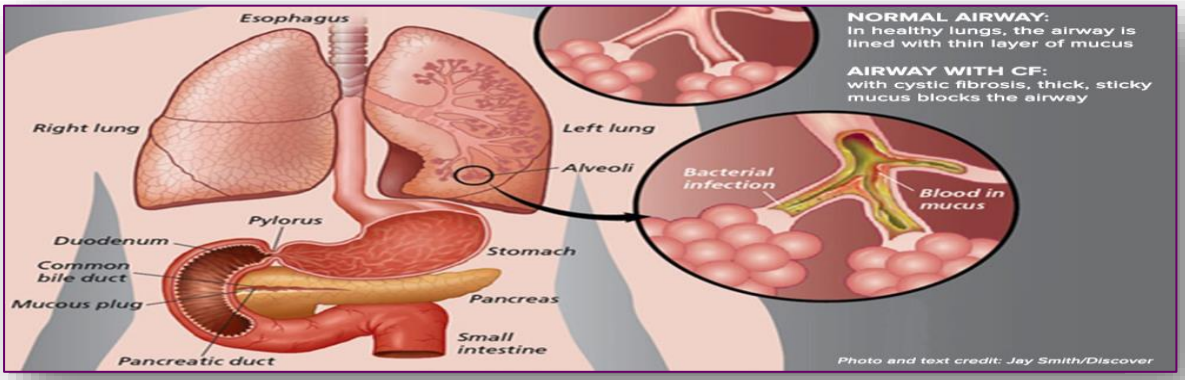
1. Sickle cell disease

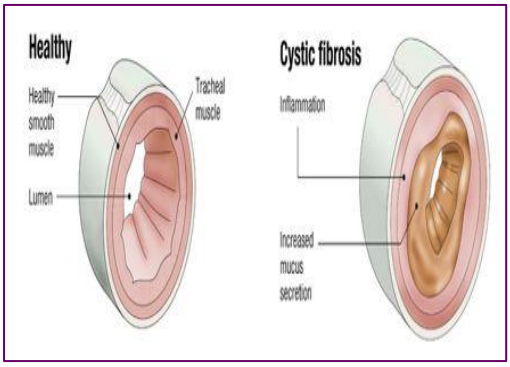
Affects one out of 400 African-Americans .The disease is caused by the substitution of a single amino acid (glutamic acid is substituted by valine) in the haemoglobin protein (especially in the beta subunit) in red blood

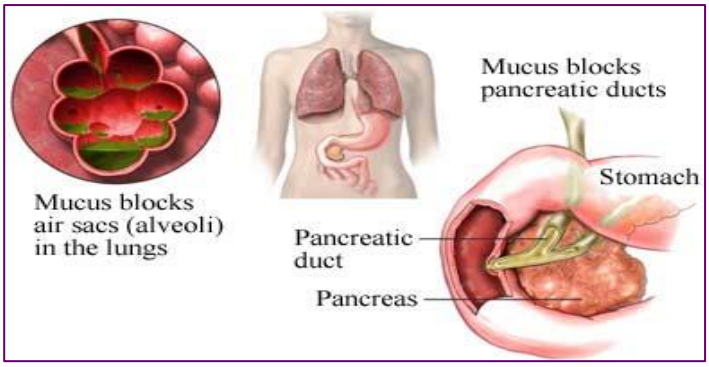
cells.In homozygous individuals, all haemoglobin is abnormal (sickle cell) while heterozygotes (said to have sickle-cell trait) are usually healthy but may suffer from some symptoms. About one out of ten African Americans has sickle cell trait, an unusually high frequency of an allele with detrimental effects in homozygotes.Heterozygotes are less susceptible to the malaria parasite (infection), so there is an advantage to being heterozygous.Sickled RBCs are poor oxygen carrier and they aggregate causing blockage of blood vessels (vaso-occlusive crisis). Also those sickled RBCs are destroyed by the spleen resulting in anaemia. Other symptoms include physical weakness, failure to thrive, pain, increased risk of infections, organ damage, and even paralysis.

2- Cystic fibrosis

Is the most common lethal genetic disease in the United States, striking one out of every 2500 people of European descent (European Caucasians). The Cystic fibrosis allele results in defective or absent Chloride transport channels in plasma membranes leading to a build-up of chloride ions outside the cell.Symptoms include mucus build-up in some internal organs(pancreatic ducts , air sacs of the lungs [alveoli]...) and abnormal absorption of nutrients in the small intestines and because of that it is a chronic progressive pulmonary disease with pancreatic insufficiency and elevated chloride sweat.

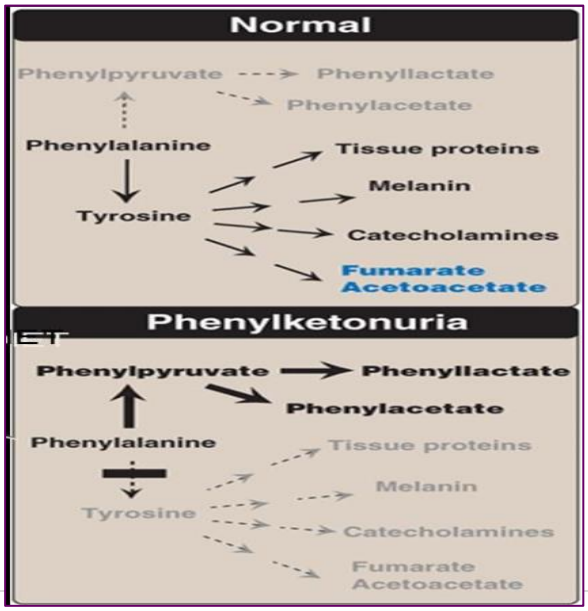






3-Phenylketonuria (PKU)

Inborn error of metabolism, caused by deficiency in phenylalanine hydroxylase enzyme - PAH - (responsible for metabolism of phenylalanine and converts it to tyrosine) which will result in increased phenylalanine in blood, which will be converted to phenyl pyruvate, phenyllactate and phenylacetate, which will result in musty odor secretions (sweat, urine). Other symptoms include neurologic disorders (mental retardation ,seizures, tremors ,microcephaly), due to reduced production of catecholamines (epinephrine , norepinephrine and dopamine).Also hypopigmentation (light hair and skin , blue eyes) due to reduced melanin production –not complete loss of pigmentation because tyrosine can be obtained from diet. Treatment is by phenylalanine restriction.



4-Albinism

A recessive condition characterized by a lack of pigmentation in skin, hair and eyes due to defect in the enzyme tyrosinase, so they are more prone to skin cancers.

5- Tay-sachs disease

One of the lysosomal storage disease as a result of mutations on the chromosome 15 in the HEX A gene which produce a lack of Hexoaminidase A (since this mutation causes under expression of this gene).
Consequences: Hexoaminidase A is important for lipid metabolism so mutations will lead to non-functional lysosomes (contain hydrolytic enzymes) and accumulation of lipids in the neurons. symptoms usually appear after several months from birth, these symptoms include loss of motor control, blindness, seizures and paralysis and they usually die after a few years from birth.

***Features: are in its spelling*:**

T ...Testing recommended.

A...Autosomal recessive (so one mutant allele isn't enough to cause the disease and the person is a carrier in this case) .

Y...Young death

S...Spots in macula (cherry red spots).

A... Ashkenazi Jews (usually occur in them).

C...CNS degeneration .

H... HEX A deficiency.

S...storage disease.

NOTE: Don't forget the degree of dominance in TAY-SACHS at the organismal , biochemical & molecular (DNA expression) levels...

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

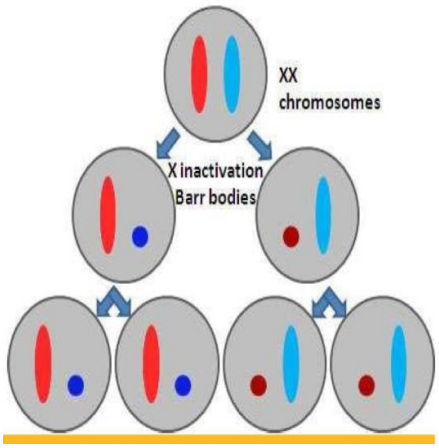
X chromosome inactivation

we all know that we must control the amount of proteins in our cells and if we don't there will be a problem (remember BCR-ABL story where the protein by itself was normal but the quantity of the protein was normal) . This is what we call Dosage compensation (Lyon hypothesis) which says:

- For autosomal traits, two doses lead to a normal phenotype, while one dose or more than two doses often have clinical significance.

- For X-linked traits two doses in females and one dose in males both lead to a normal phenotype.

-females and only females during first week of fertilization (3-7days after fertilization) each cell randomly and individually decides to inactivate one X-chromosome (either maternal or paternal).



-once the cell decides to inactive the maternal or the paternal X-chromosome all the descendants of the mitosis of that cell should have the same X-chromosome inactive.

-how the inactivation occur ?

By condensation (barr body) where it can't be exposed to the enzymes.

Note : you can see the inactive X-chromosome condensed under the microscope during interphase.

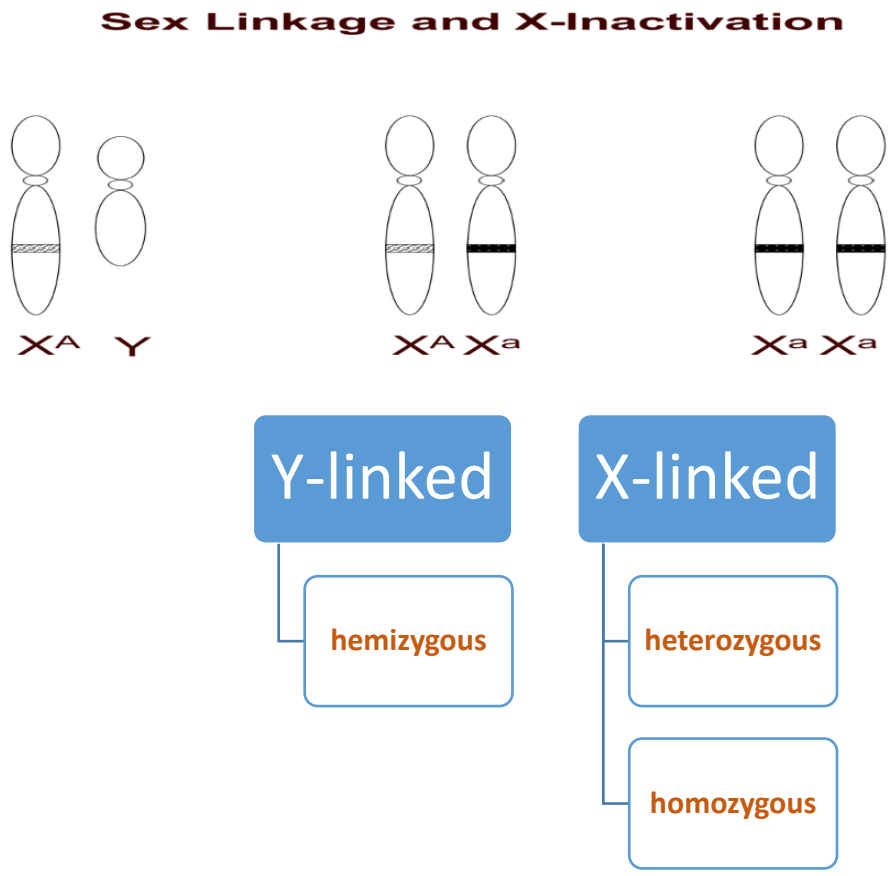
-the X-chromosome inactivation continue during female life , that's how we compensate the dose in males and females :

Male: have only one X-chromosome

Female: each cell in her body express only one X-chromosome.

-Some genes on the inactive X chromosome remain active, they 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.

Sex linkage



Sex-linked genes: genes that are physically located on either sex chromosome:

Note: don't confuse with sex-limited and sex-influence

-located on Y chromosome-> Y-linked genes (few genes only).

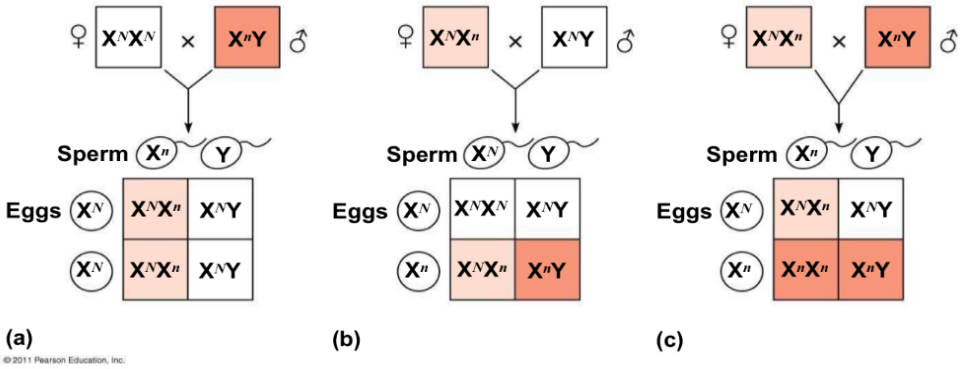
-located on X chromosome -> X-linked genes.

- The X chromosome has genes for many characters unrelated to sex, whereas the Y chromosome mainly encodes genes related to sex determination.

- Sex-linked genes follow a specific pattern of inheritance.

1-X-linked recessive disorders : much more common in males than in females because females need two copies of the allele to be affected (homozygous) since they have two X chromosomes, while males need one copy of the allele to be affected (hemizygous), since they have one X chromosome only.

-Sex-linked disorders are less common than autosomal disorder.



probabilities in inheritance of X-linked recessive traits-

XNY-> normal male, XnY->affected male.

XNXN-> normal female, XNXn-> carrier female (called mosaic), XnXn-> affected female.

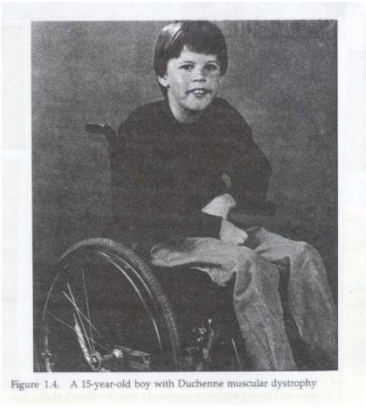


Figure 1.4. A 15-year-old boy with Duchenne muscular dystrophy

- Examples on X-linked recessive disorders :

A) Color blindness: it has many types, but the most common type is red-green color blindness(X-linked recessive).

B) Duchenne muscular dystrophy: dystrophy means

muscle weakness and loss of muscle tissue; mutation in the DMD gene which is carried on the X chromosome can cause two types of muscular dystrophy:

Note: both Duchenne muscular dystrophy and Becker muscular dystrophy result from the same mutation, but Duchenne is more severe than

-less severe -> Becker.

-more severe -> Duchenne.

D) hemophilia.

X-Linked Recessive	
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)**

-features of X-linked recessive inheritance:

1. Diagonal inheritance – affected males related through females of the maternal line (affected father transmits the mutant gene to his daughters only–since he gives Y for the son and X for the girl – while affected mother transmit the mutant gent to her sons and daughters).

2. Absence of male-to-male transmission (a son never inherits the disorder from his father).

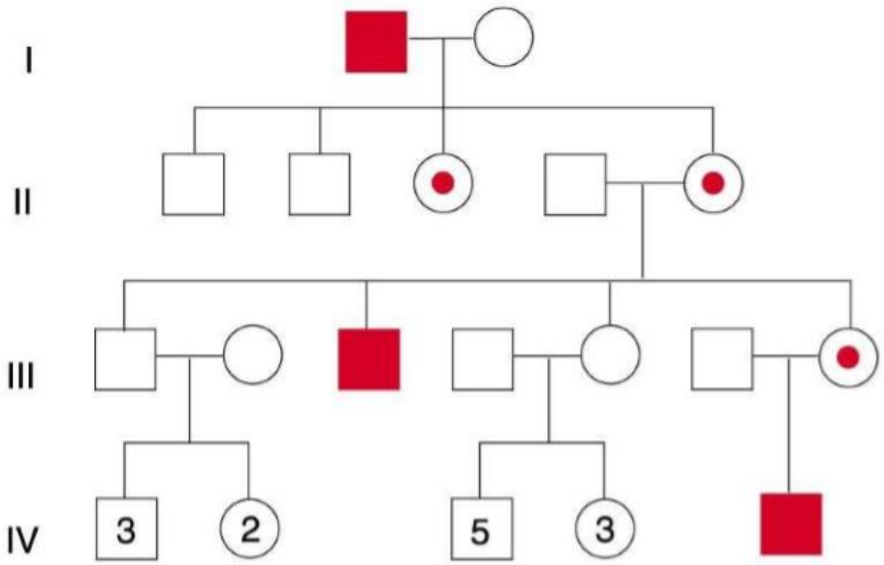
3. Incidence of trait much higher in males than females.

4. Full expression in hemizygous males.

5. No or mild expression in carrier females due to X-inactivation (clinically normal though they have some Features of the disease).

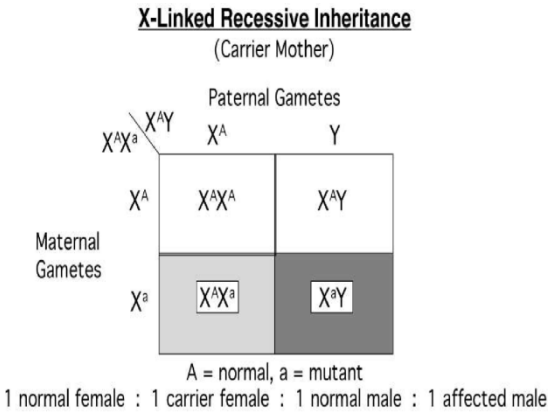
6. females only affected if they are homozygous mutant.

X-linked recessive pedigree



Notice:

1- The father is affected.
2- because the disease is recessive we have skipping generation.
3- All daughters of a male with the disorder are obligate carriers.
4- Sons of carrier females have a 50% chance of inheriting the disorder.
5- Daughters of carrier females have a 50% chance of being carriers too.
6- A son never inherits the disorder from his father.
7- Male : female →2 : 1



x-linked dominant disorders

- they are very rare diseases.

- they are disorders in which the mutation will be inherited dominantly and a mutation in one gene is enough to manifest the disease .

- an example on this disease is vitamin D resistant rickets .

features of vitamin D resistant rickets:

-Rickets

-Short stature

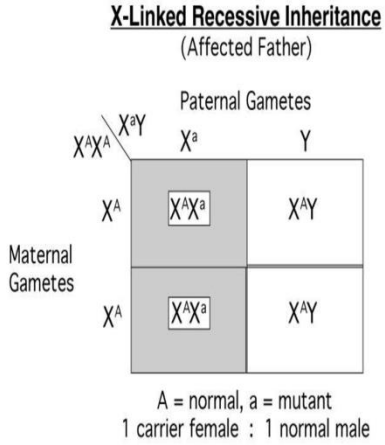
-Low serum phosphate

-Less sever in heterozygous female

Now we will talk about X-Linked dominant disorders features:

* Twice as many affected females as for males , this is normal because female has twice as much of a chance of receiving the disease (they receive 2 chromosomes).

*female will be affected but the severity in female is less than in male because of X inactivation.

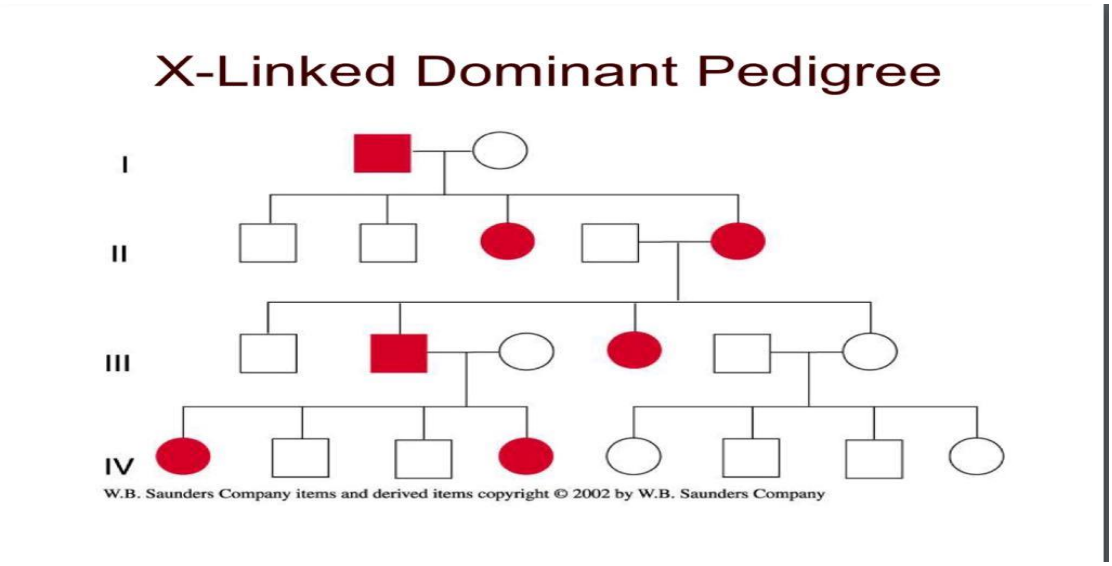


*very rare , just few disorders are classified as X-Linked dominant.

* Like any dominant, every generation is affected and there are no carriers either you are affected or not.

*there is no male to male transmission * which means that the affected male all of

his daughters will be affected but not the sons . whereas the mother will transmit the mutated gene to both males and females.



2 important notes :

1 – if the father is affected and one of his daughters escape the disease it is not an x-linked dominant disorder , it looks like x-linked dominant disorder but is not .

2 – in autosomal dominant or x-linked dominant disorders we assume heterozygous genotype for the affected individuals , it may be homozygous but my first assumption is heterozygous genotype.

Now will discuss somePhenotypic Expressions:

Penetrance

it is refers to all or none expression of a mutant genotype .

we talked previously that in dominant disorders one mutant allele is enough to manifest the clinical features , but in some patients in some diseases will not manifest the clinical features (there is no expression of the phenotype) , although they have mutant allele , in another words they have mutant allele but they are normal .

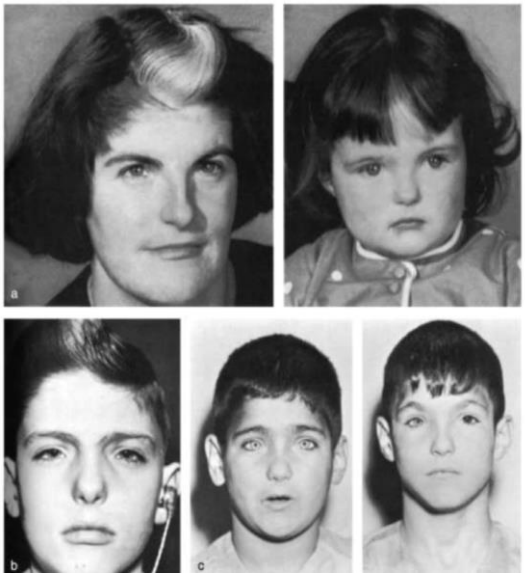
note that not all patients only percentage of them .

to understand more read this example :

RB or retinoblastoma is an autosomal dominant disorder which cause tumor in retina . 90% of the patients will manifest the disease and 10% of them will not show any clinical symptoms of RB disease .

Reduce penetrance:a condition that is expressed in less than 100 % of persons who have one copy of the mutant allele.

Full penetrance: a condition that is expressed in 100% of persons who have one copy of the mutant allele.



Another example on reduced penetrance is waldenbur gsyndrome , which is congenital sensoneural deafness , in this disease 20% of patients will manifest hearing loss and 80% will not . (high penetrance) .

The main features of waldenburg syndrome is :

- heterochromia which means that each eye has a different colour .

- displacement of the inner canthi.

- white forelock.

Some information

- syndromic disorders → more than one affected tissue , like Ascher syndrome manifest deafness and blindness (more than one clinical feature) .

- nonsyndromic disorders → one affected tissue , like hearing loss only without any clinical features .

- hearing loss is one of two types :

1 - conductive hearing loss in which the problem happens to the middle ear ossicles or the outer ear .

2- sensorineuralhearing loss in which the damage affects the inner ear.

Now we will talk about anotherPhenotypic Expressions:

Variable Expressivity

The extent to which a trait is expressed.

In this case there is a disease but the severity of clinical symptoms differ from one patient to another although the disease results from the same mutation on the same gene. in another word the expression differs and ranges from mild to severe , it is not completely unexpressed (the disease is present). Examples:Neurofibromatosis &myotonic dystrophy (weakness in muscles).

Variable age of onset

refers to the variation in the time tophenotypic expression of mutant gene (s). Example: the onsetof Huntington disease is typically in the 40's, however, age ofonset 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. (from slide).

Genetic heterogeneity

-there is 2 types

1 – allelic heterogeneity

2 – locus heterogeneity

- allelic heterogeneity: refers to two or more differentmutant alleles at the same genetic locus (Example:Duchenne and (the less severe) Becker musculardystrophy; cystic fibrosis).

FOR example : cystic fibrosis is a disease which results from a mutation In CFTR gene , but there is more than one type of mutations could happen to this gene and all of them will cause cystic fibrosis , to clarify , a deletion in phenyl alanine amino acid at the 508th position on the protein can cause cystic fibrosis as well as a substitution mutation on the same gene can result in the same disease which is cystic fibrosis .

- note that the mutations on the same gene on the same location .

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

For instance, in chromosome 2 q arm there is agene called PAX3, if its mutated it causes hearloss in chromosome 13 q arm there is anothergene called GJB2, if its mutated it also causeshear loss, here we have locus heterogeneity asthe resulting clinical feature (hearing loss) is the same even if the location of the mutation differs.

Sex – limited disorders:

– refers to a phenotype that is autosomallytransmittedbut expressed only in one sex. Example: Autosomaldominant male precocious puberty.

Autosomal dominant male precocious puberty which is an Autosomal dominant disease that cause primary sexual organ maturity for males before the age of puberty , now if the same mutation presents in female the disease will not appear (limited only to one sex).

Sex-influenced

refers to autosomally inherited traitsthat are expressed differently, in either degree orfrequency, in males and females. Example:

hemochromatosis which is an autosomal recessive disorder of

increased absorption of dietary iron and it is morecommonly found in males due to lower dietary intakeand menstruation in females.

Good luck