# Genetic Disorders

Dr.K.Aruldoss

Assistant professor

Periyar Govt Arts College cuddalore

# Brief History

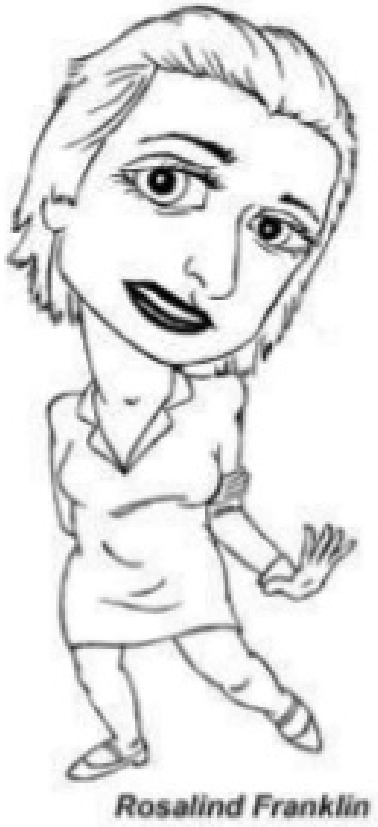
- **First there was Gregor Mendel, a monk who studied inherited characteristics. This was followed by Francis crick and James Watson who unraveled the DNA molecule. This has led us to understanding the human genome sequence**

# Gregor Mendel

- **1866**
- **Gregor Mendel published the results of his investigations of the inheritance of "factors" in pea plants.**

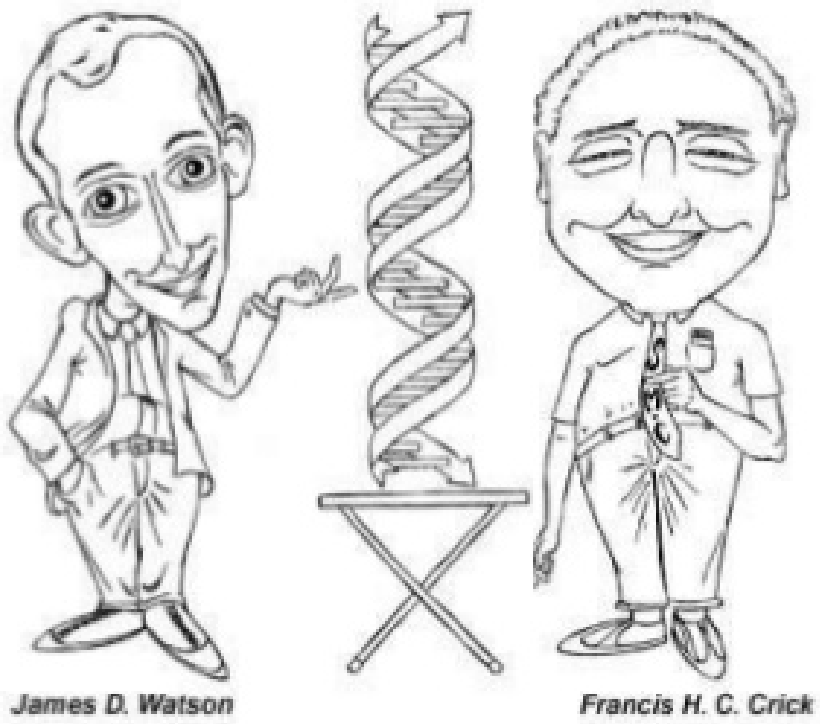
Gregor Mendel

# Rosalind Franklin




- **1950's.**
- **Maurice Wilkins (1916- ), Rosalind Franklin (1920-1957), Francis H. C. Crick (1916- ) of Britain and James D. Watson (1928- ) of the U.S. Discover chemical structure of DNA, starting a new branch of science--molecular biology. .**

# Watson and Crick




- **Watson and Crick made a model of the DNA molecule and proved that genes determine heredity**

# Arthur Kornberg

Arthur Kornberg

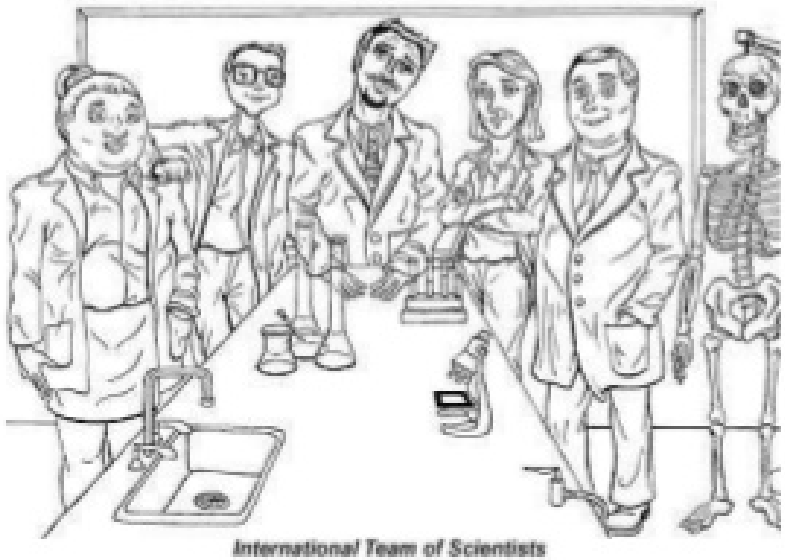
- **1957**
- **Arthur Kornberg (1918- ) of the U.S. produced DNA in a test tube.**

# Barbara McClintock

Barbara McClintock

- **1983**
- **Barbara McClintock (1902-1992) of the U.S. was awarded the Nobel Prize for her discovery that genes are able to change position on chromosomes.**

# DNA Fingerprinting



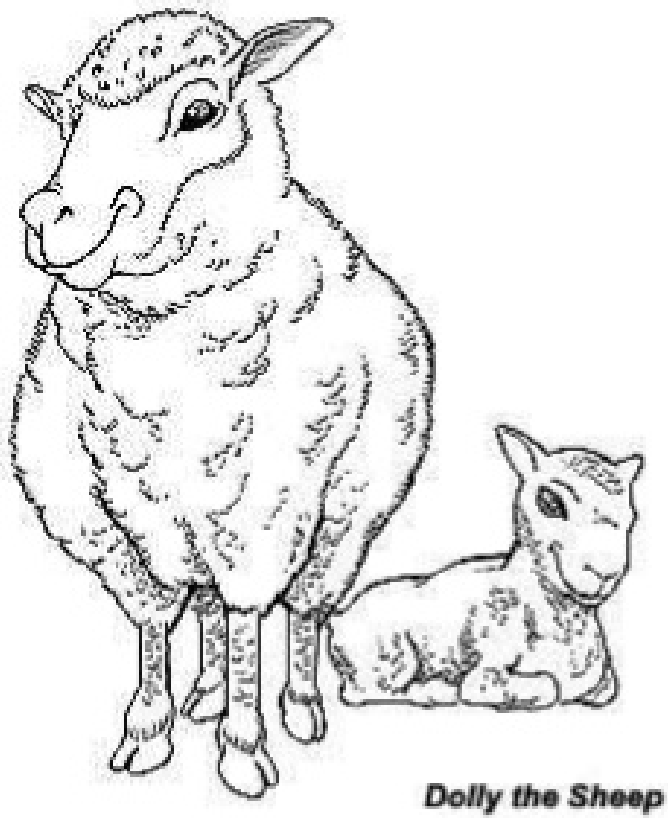
*International Team of Scientists*

- **The late 1980's.**
- **An international team of scientists began the project to map the human genome.**
- **The first crime conviction based on DNA fingerprinting, in Portland Oregon.**

# Gene Therapy


- **1990.**
- **Gene therapy was used on patients for the first time.**

# Cloning Begins



*Dolly the Sheep*

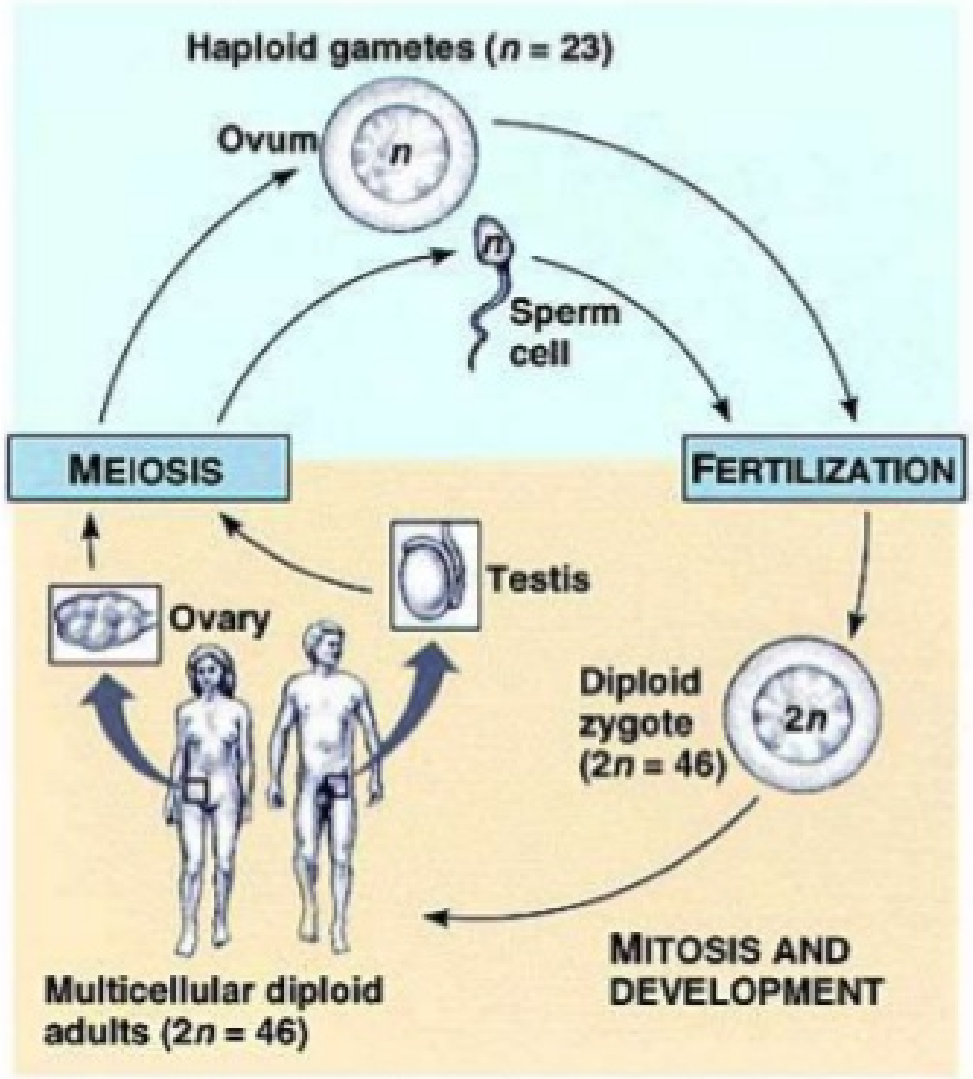
- **1997.**
- **Dolly the sheep - the first adult animal clone.**

# Human Genome Project

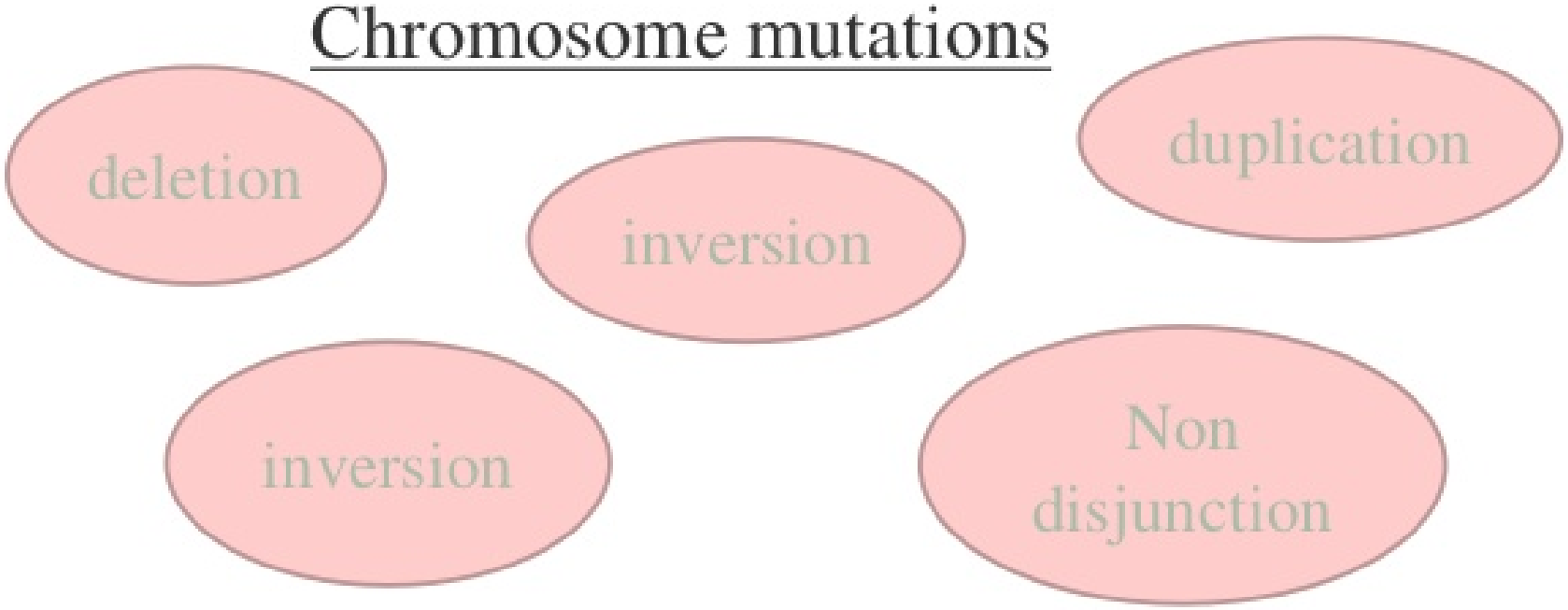
- **.. Imagine a world in which we will be able to treat diseases by altering our very genes, giving us new ones if ours are non-functional, changing bad genes for good ones. For the first time in our existence, we are closer to understanding just what we are. We now have the tools to make the whole world better through science , the science of the human genome.**

# Genetic Disorders

Figure 12.3 The human life cycle

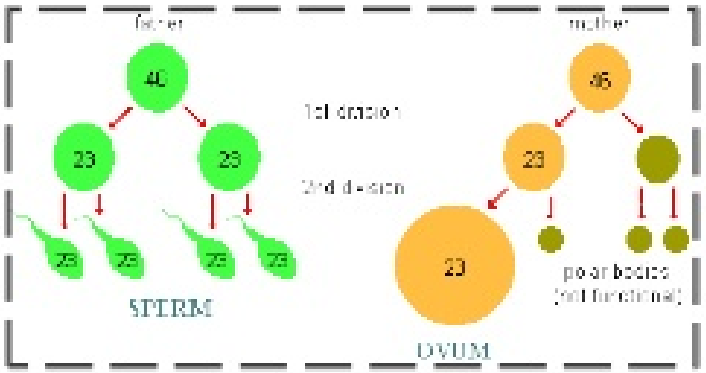


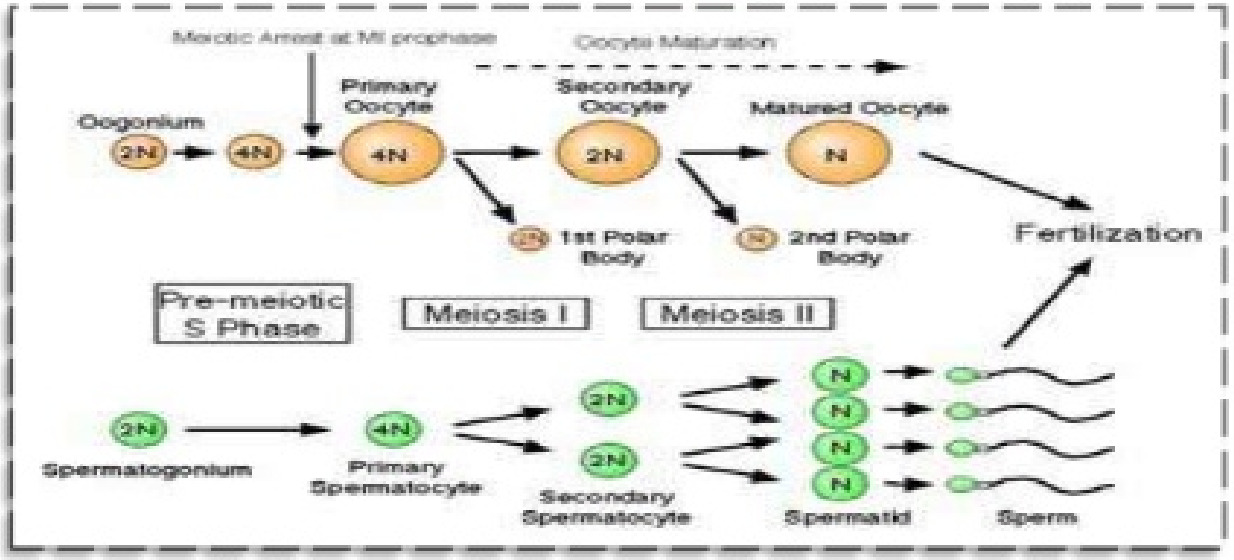
- Chromosomes :
- - sex chromosomes
- - autosomes



# Mutations

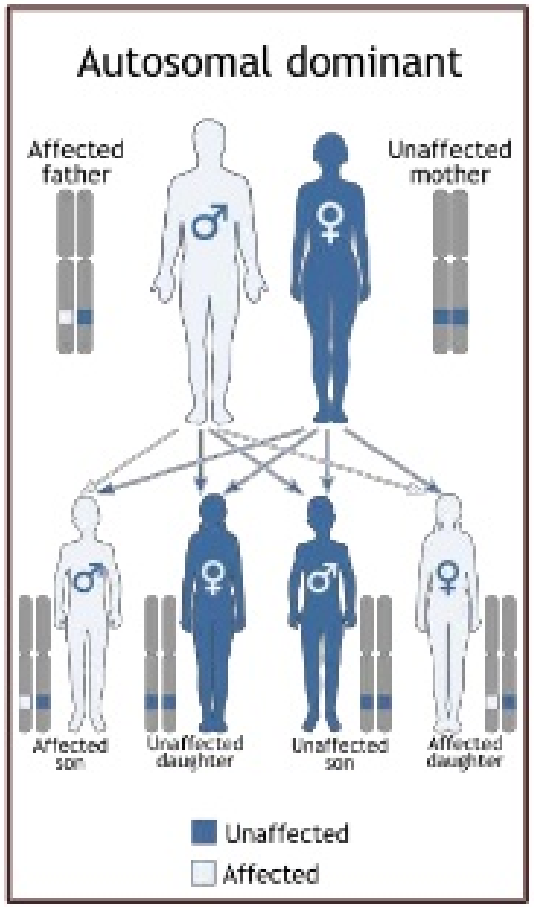
- Gene mutations can be either inherited from a parent or acquired. A hereditary mutation is a mistake that is present in the DNA of virtually all body cells. Hereditary mutations are also called *germ line* mutations because the gene change exists in the reproductive cells and can be passed from generation to generation, from parent to newborn. Moreover, the mutation is copied every time body cells divide

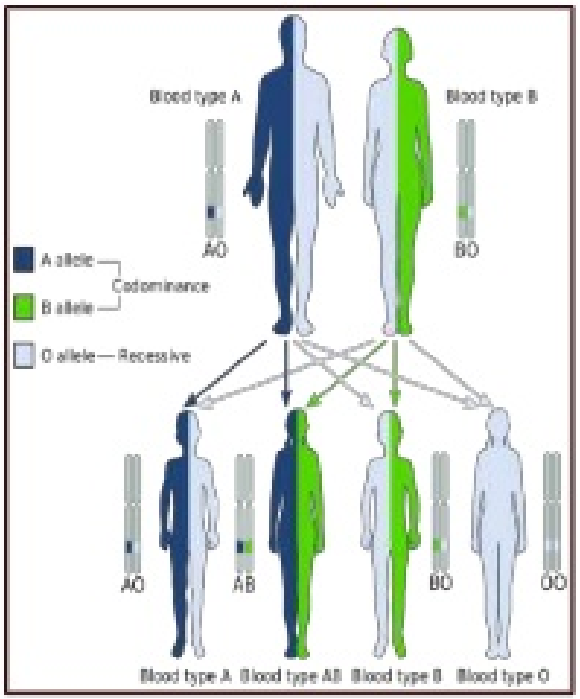

father
mother
46
1st division
23
23
2nd division
23
23
23
23
23
SPERM
polar bodies
(all functional)
OVUM

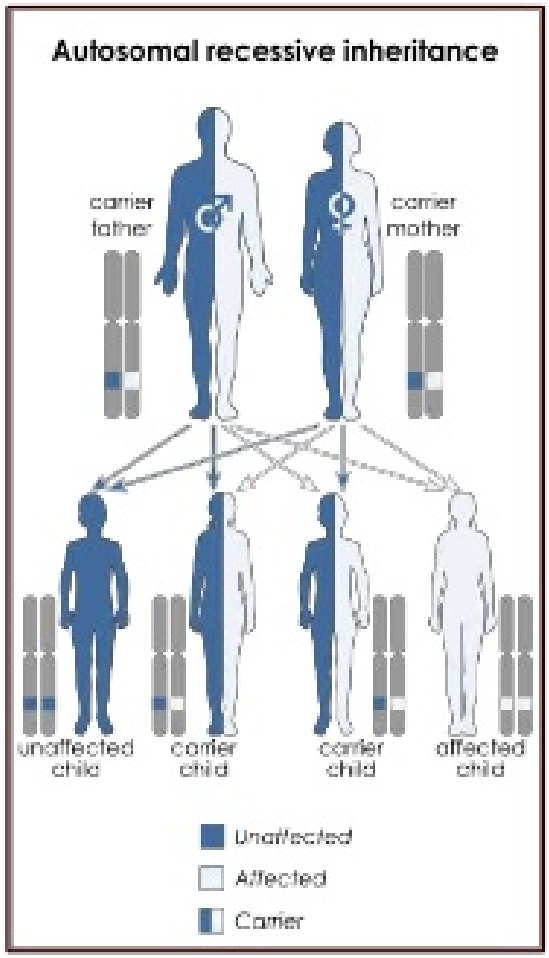

Meiotic Arrest at MI prophase
Oocyte Maturation
Oogonium
2N
4N
Primary Oocyte
4N
Secondary Oocyte
2N
Matured Oocyte
N
1st Polar Body
2nd Polar Body
Fertilization
Pre-meiotic S Phase
Meiosis I
Meiosis II
2N
Spermatogonium
4N
Primary Spermatocyte
2N
2N
Secondary Spermatocyte
N
N
N
N
Spermatid
Sperm

- Mutations occur all the time in every cell in the body. Each cell, however, has the remarkable ability to recognize mistakes and fix them before it passes them along to its descendants. But a cell's DNA repair mechanisms can fail, or be overwhelmed, or become less efficient with age. Over time, mistakes can accumulate.

# Dominance


Autosomal dominant
Affected father
Unaffected mother
Affected son
Unaffected daughter
Unaffected son
Affected daughter
Unaffected
Affected

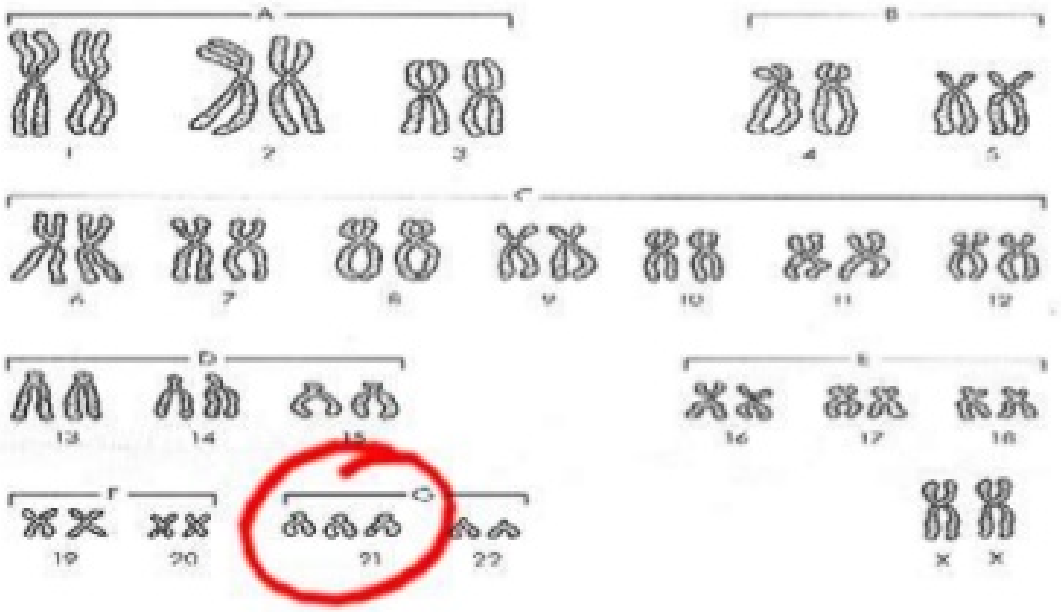

Blood type A
Blood type B
AO
BO
A allele
B allele
Codominance
O allele — Recessive
AO
AB
BO
OO
Blood type A
Blood type AB
Blood type B
Blood type O


Autosomal recessive inheritance
carrier father
carrier mother
unaffected child
carrier child
carrier child
affected child
Unaffected
Affected
Carrier

# #1- Down's Syndrome

- Caused by non-disjunction of the 21st chromosome.
- This means that the individual has a trisomy (3 – 2lst chromosomes).

# Down's Syndrome or Trisomy 21

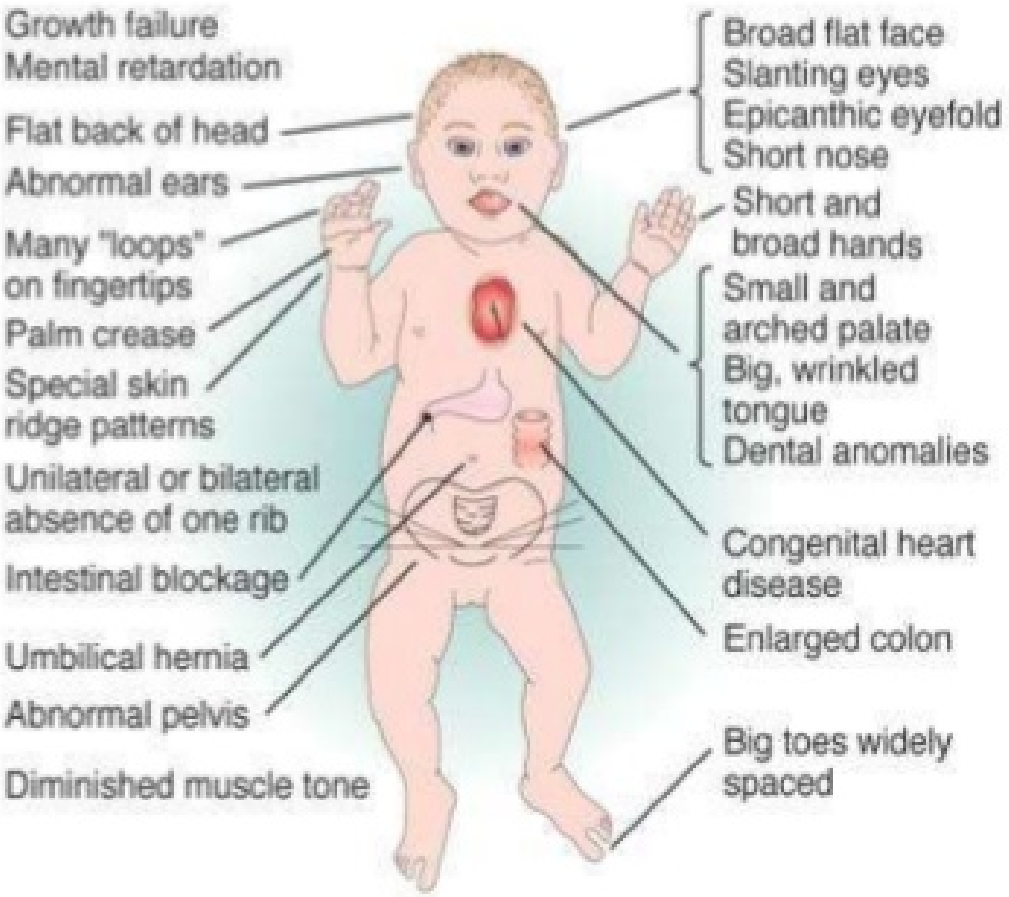


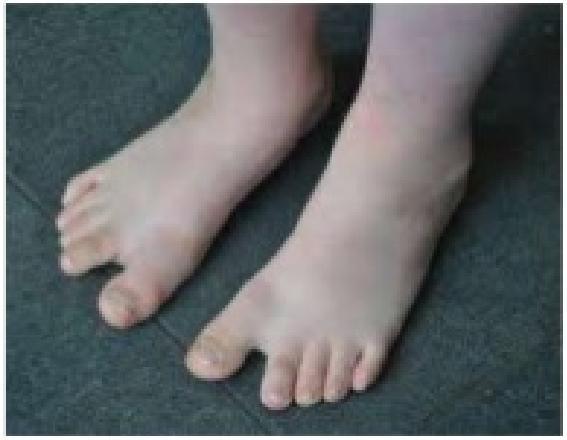
# Symptoms of Down Syndrome

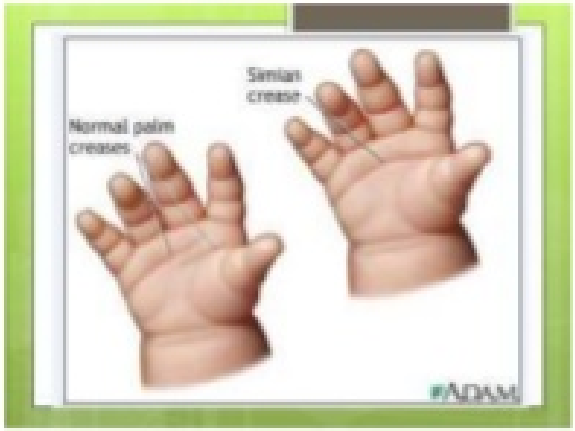
- Upward slant to eyes.
- Small ears that fold over at the top.
- Small, flattened nose.
- Small mouth, making tongue appear large.
- Short neck.
- Small hands with short fingers.

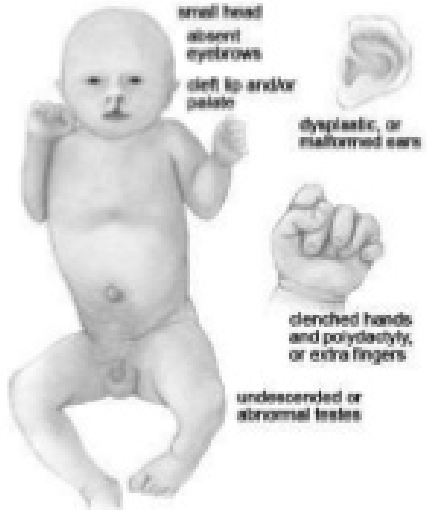
# Symptoms of Down Syndrome

- Low muscle tone.
- Single deep crease across center of palm.
- Looseness of joints.
- Small skin folds at the inner corners of the eyes.
- Excessive space between first and second toe.
- In addition, down syndrome always involves some degree of mental retardation, from mild to severe. In most cases, the mental retardation is mild to moderate.


Growth failure
Mental retardation
Flat back of head
Abnormal ears
Many "loops" on fingertips
Palm crease
Special skin ridge patterns
Unilateral or bilateral absence of one rib
Intestinal blockage
Umbilical hernia
Abnormal pelvis
Diminished muscle tone
Broad flat face
Slanting eyes
Epicanthic eyefold
Short nose
Short and broad hands
Small and arched palate
Big, wrinkled tongue
Dental anomalies
Congenital heart disease
Enlarged colon
Big toes widely spaced




Simian crease
Normal palm creases


small head
absent eyebrows
cleft lip and/or palate
dysplastic, or malformed ears
clenched hands and polydactyly, or extra fingers
undescended or abnormal testes

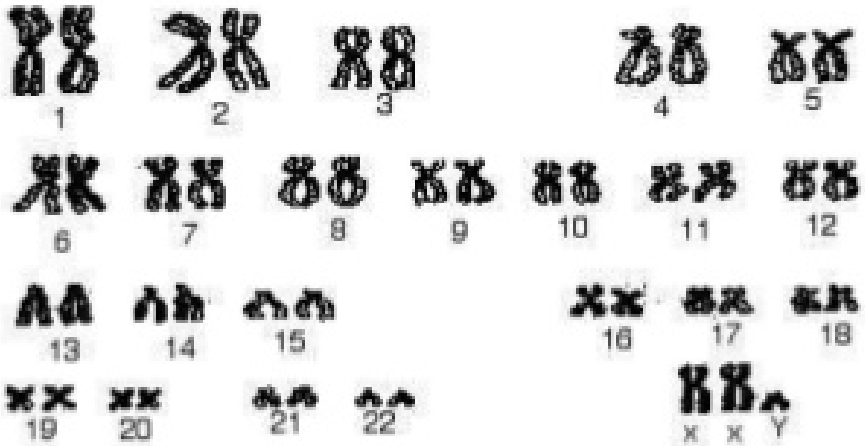
# #2 - Kleinfelter's syndrome

(or Klinefleter's)

- Disorder occurring due to nondisjunction of the X chromosome.
- The Sperm containing both X and Y combines with an egg containing the X, results in a male child.
- The egg may contribute the extra X chromosome.

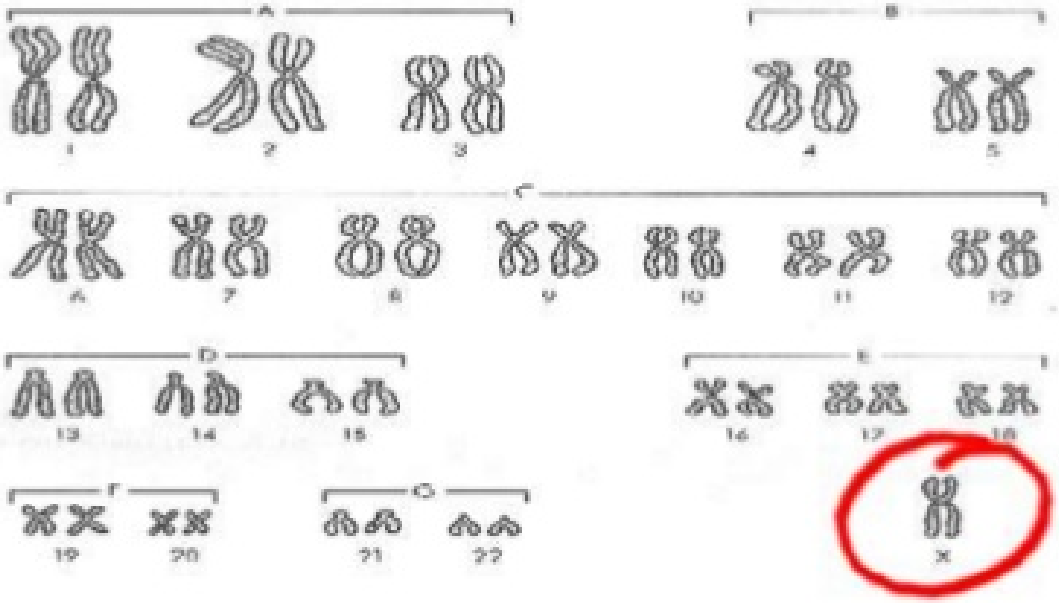
# XXY

- **Males with some development of breast tissue normally seen in females.**
- **Little body hair is present, and such person are typically tall, have small testes.**
- **Infertility results from absent sperm.**
- **Evidence of mental retardation may or may not be present.**


1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
X X Y

- Treatment with testosterone has to start at puberty , around the age of 12 years,
- increasing levels of testosterone by therapy is maintaining normal levels of estradiol, FSH and LH

# Turner's Syndrome

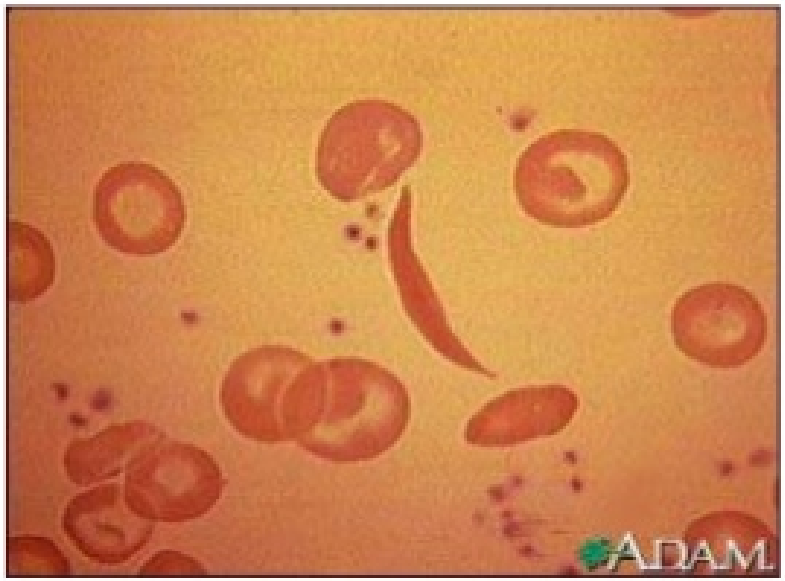


Deletion or partial deletion of X chromosome

# ttt :

- **Growth hormone.** Growth hormone therapy is recommended for most girls with Turner syndrome . Growth hormone treatment is usually given several times a week as injections of **Somatropin** (Humatrope, Genotropin, Saizen, others
- **Estrogen therapy.** Most girls with Turner syndrome need to start estrogen and related hormone therapy in order to begin puberty and achieve adult sexual development

# #4 - Sickle Cell Anemia

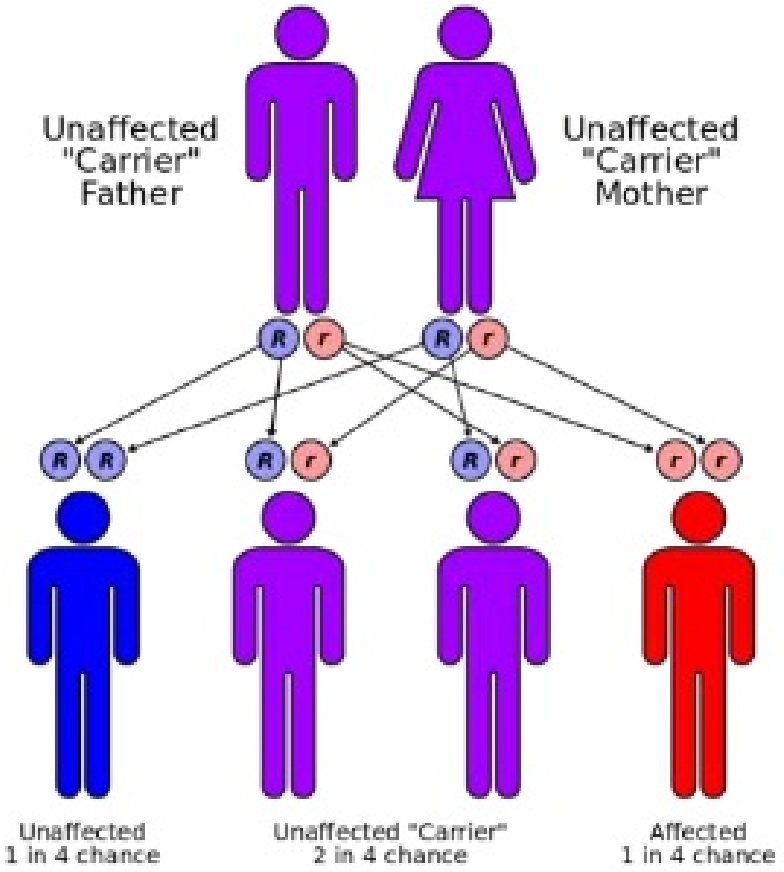


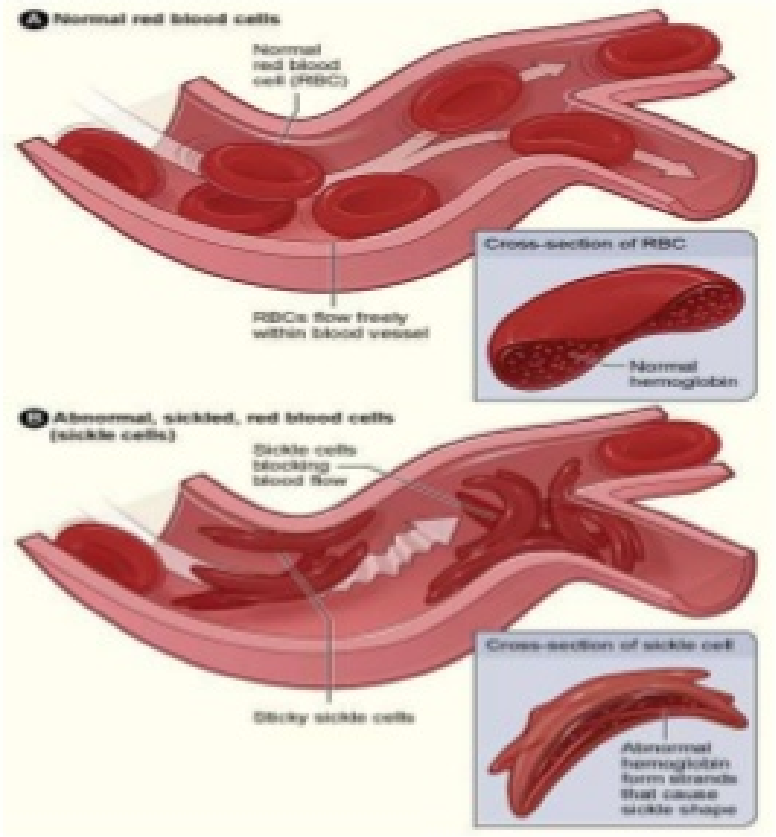

- An inherited, chronic disease in which the red blood cells, normally disc-shaped, become crescent shaped. As a result, they function abnormally and cause small blood clots. These clots give rise to recurrent painful episodes called "sickle cell pain crises".

- Formed by abnormal Hb genes aquired from carrier parents
- Carrier has only one affected copy of Hb gene

# Sickle Cell

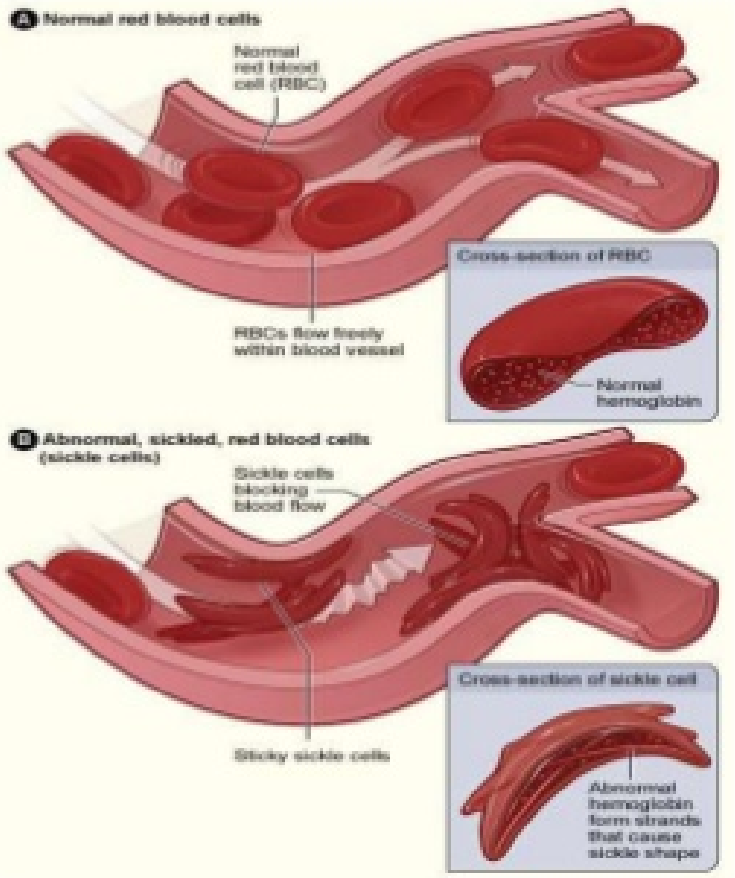
- **Sickle cell disease is most commonly found in African American populations. This disease was discovered over 80 years ago, but has not been given the attention it deserves.**




A Normal red blood cells
Normal red blood cell (RBC)
RBCs flow freely within blood vessel
Cross-section of RBC
Normal hemoglobin
B Abnormal, sickled, red blood cells (sickle cells)
Sickle cells blocking blood flow
Sticky sickle cells
Cross-section of sickle cell
Abnormal hemoglobin form strands that cause sickle shape

# Complications

- Increased risk of severe bacterial infections due to loss of functioning spleen tissue
- Silent stroke
- Stroke
- Pripism and infarction of the penis[
- excessive bilirubinproduction and precipitation due to prolonged haemolysis.
- Chronic renal failure due to sickle-cell nephropathy
- Osteomyelitis
- Pulmonary hypertension
- Leg ulcers
- eye proplems ( proliferative retinopathy, vitreous haemorrhages )

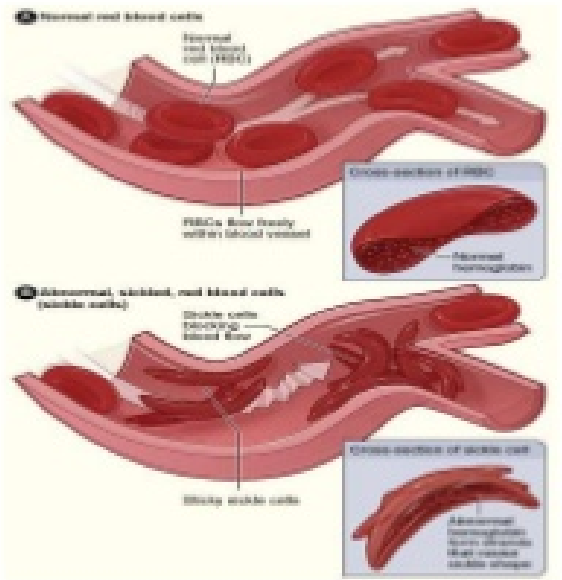

A Normal red blood cells
Normal red blood cell (RBC)
RBCs flow freely within blood vessel
Cross-section of RBC
Normal hemoglobin
B Abnormal, sickled, red blood cells (sickle cells)
Sickle cells blocking blood flow
Sticky sickle cells
Cross-section of sickle cell
Abnormal hemoglobin form strands that cause sickle shape

PLZ Donate !!! U could save them

## Ttt:

- **Folic acid ( 1 gm life time )**
- **penicillin ( 5y )**
- If living in malarial countries should receive **anti-malarial chemoprophylaxis** for life.
- Vaso-occlusive crisis **: Opioids , NSAID .**
- Acute chest crisis : **oxygen supplementation for hypoxia , blood transfusion or exchange transfusion.**

- **Transfusion therapy :** Blood transfusions are often used in the management of sickle-cell disease in acute cases by adding normal red blood cells . reduces the risk of recurrent stroke and additional silent strokes



- **Bone marrow transplants .**

# #5 - Von Willebrand disease :

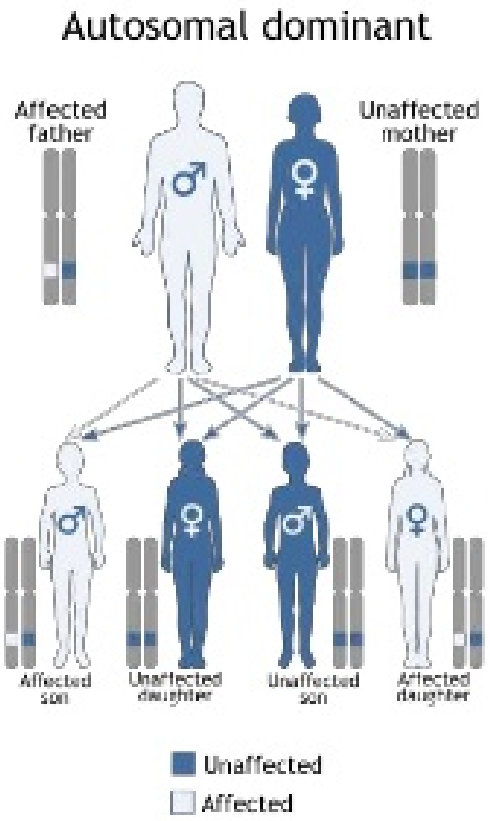
- the most common hereditary coagulation abnormality described in humans, although it can also be acquired as a result of other medical conditions ( auto antibodies ) .
- arises from a qualitative or quantitative deficiency of von Willebrand factor (vWF), a multimeric protein that is required for platelet adhesion

- three forms of vWD: hereditary, acquired, and pseudo or platelet type

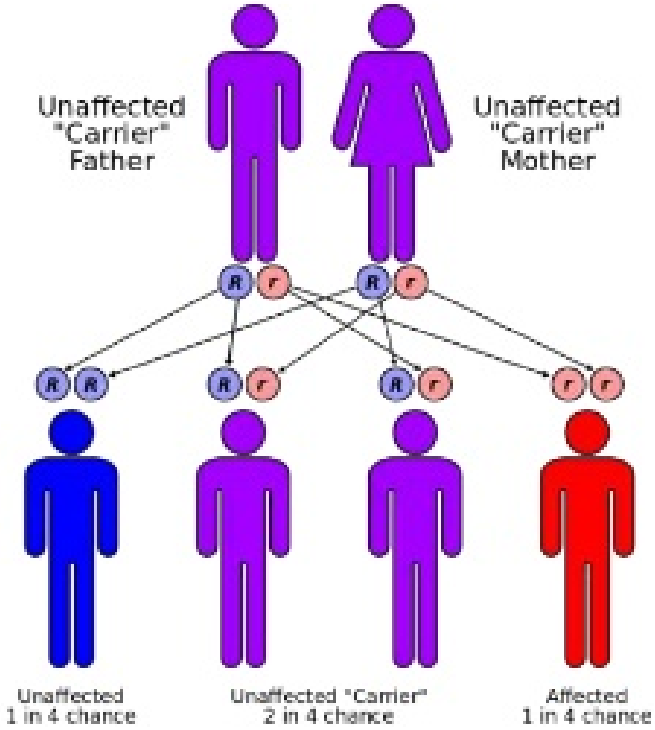
- There are three types of hereditary vWD: vWD Type I ( most common ) , vWD Type II, and vWD Type III

- Within the three inherited types of vWD there are various subtypes 2a , 2b , 2m , 2n

# Type 1,2




# Type 3

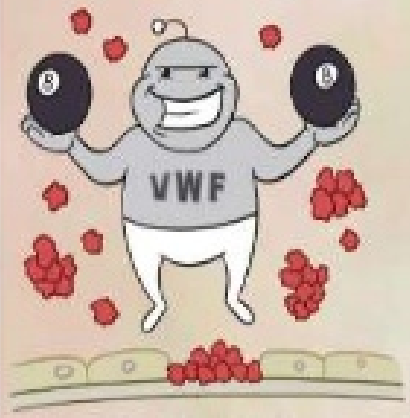


- The prevalence of vWD is about 1 in 100 individuals.[1] However the majority of these people do not have symptoms. The prevalence of clinically significant cases is 1 per 10,000
- most forms are rather mild, they are detected more often in women, whose bleeding tendency shows during menstruation

# VON WILLEBRAND DISEASE

MOST COMMON INHERITED BLEEDING DISORDER

VON WILLEBRAND FACTOR (VWF)
ACTS AS A CARRIER PROTEIN
FOR FACTOR VIII IN PLASMA




VWF ALSO HELPS WITH PLATELET
AGGREGATION AND ADHESION
TO DAMAGED ENDOTHELIUM


**TYPE 1**: DEFICIENCY OF VWF
(MOST COMMON TYPE)

TREATMENT: DESMOPRESSIN
OR CRYOPRECIPITATE

PATIENTS MAY PRESENT WITH MUCOCUTANEOUS BLEEDING
(E.G., EPISTAXIS, EASY BRUISING, MENORRHAGIA, GI BLEEDING)


**TYPE 2**: ABNORMAL
AND DYSFUNCTIONAL VWF


**TYPE 3**: VWF IS ABSENT

TREATMENT: FACTOR VIII CONCENTRATE
OR CRYOPRECIPITATE

www.medonic.com

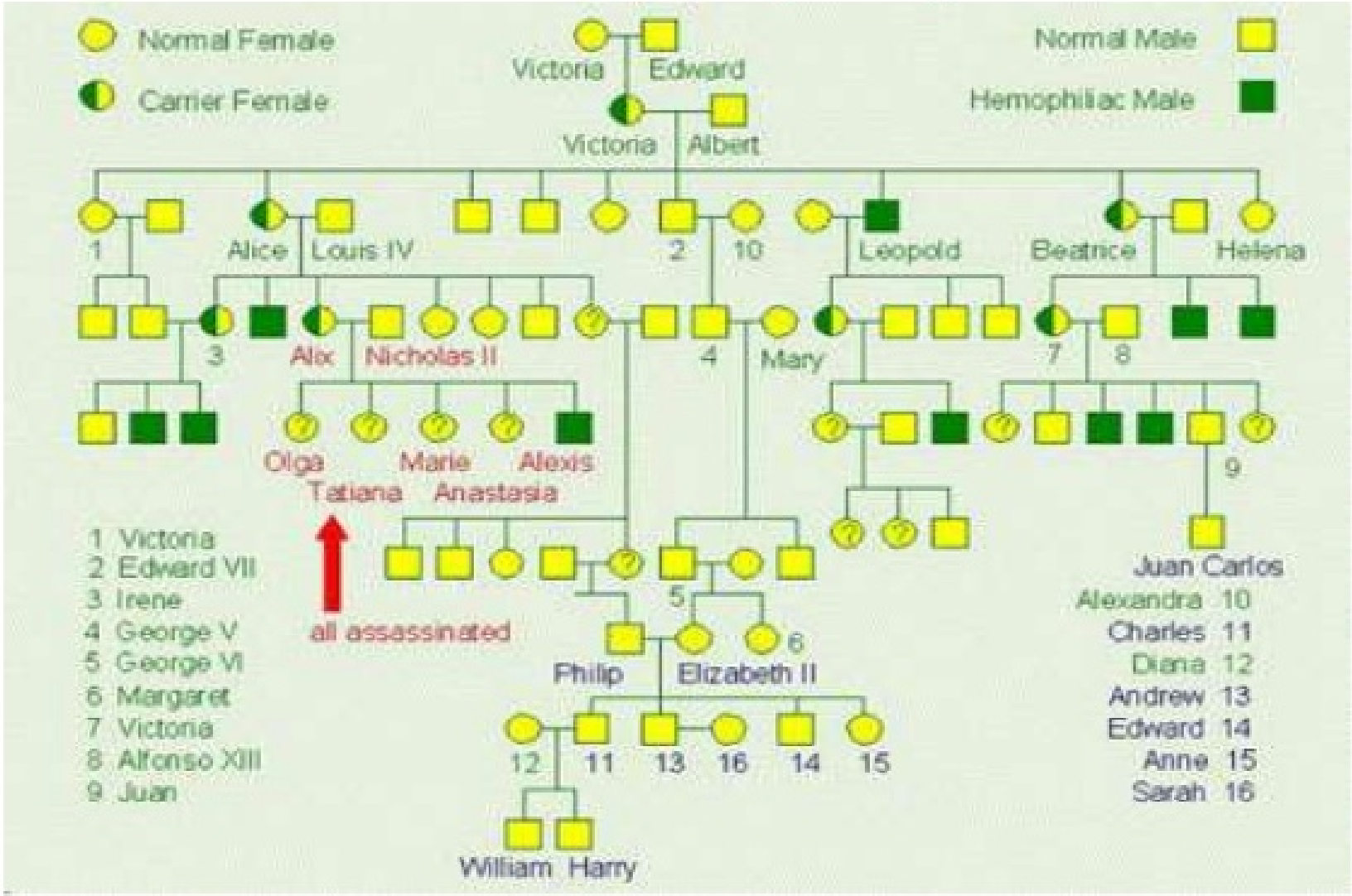
## ttts

- Topical thrombin JMI and Topical Tisseel VH for wounds
- antifibrinolytic agents (Tranexamic acid ) for clinical haemorrhage
- Blood transfusions for anemia and hypovolemia
- Desmopressin (DDAVP) . Type 1,2a

# # 6 - Hemophilia, the royal disease

- Hemophilia is the oldest known hereditary bleeding disorder.
- Caused by a recessive gene on the X chromosome.
- There are about 20,000 hemophilia patients in the United States.
- One can bleed to death with small cuts.
- The severity of hemophilia is related to the amount of the clotting factor in the blood. About 70% of hemophilia patients have less than one percent of the normal amount and, thus, have severe hemophilia.
- Factor VIII deficiency
- Less prevelance in female

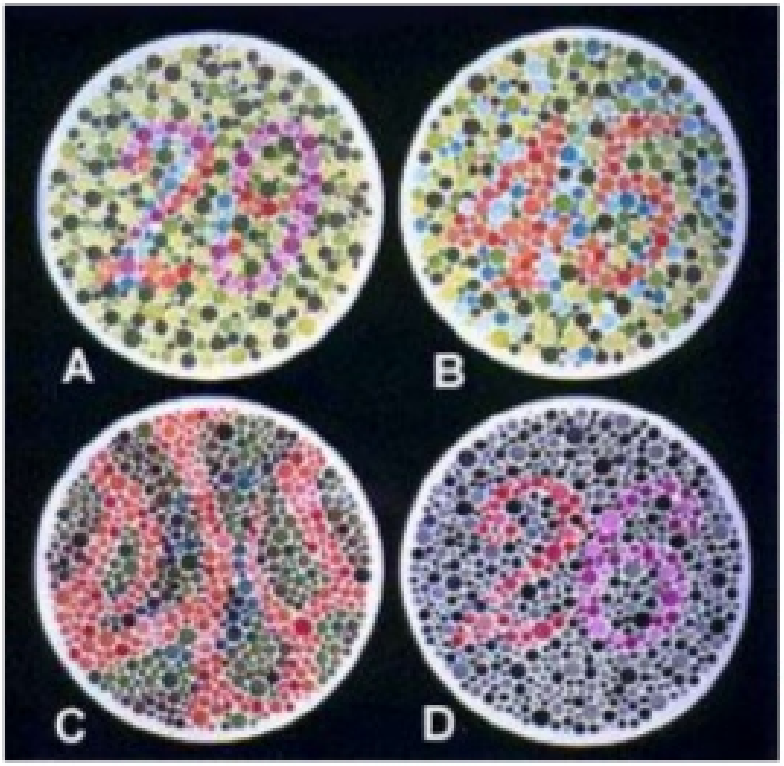
# X-linked Inheritance pedigree chart



## Ttt :

- Factor VIII concentrate
- Xyntha ( anti hemolytic )
- Gene therapy
- Preventive excersices
- Alternative therapy ( hypnosis )
- Avoid hymolytic drugs ( Asprin , heparin , …. )

# #7 - Color Blindness




- Cause: x-linked recessive
- 1/10 males have, 1/100 females have.
- Individuals are unable to distinguish shades of red-green.
- Are you color blind?

# Monochromacy :

- (and thus the person views everything as if it were on a black and white television)

  - ***Rod monochromacy :*** exceedingly rare, nonprogressive inability to distinguish any colors as a result of absent or nonfunctioning retinal cones

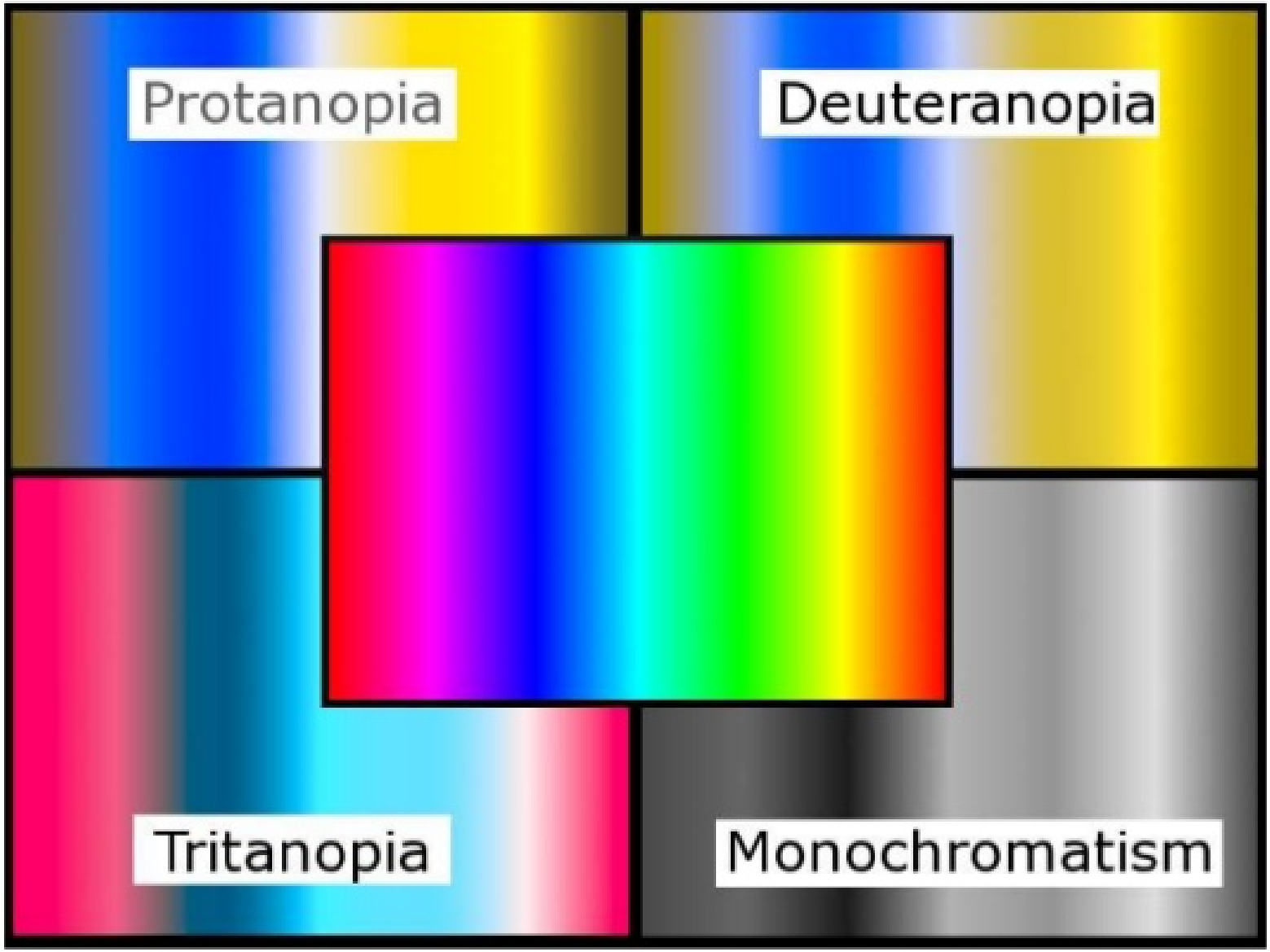
  - ***Cone monochromacy :*** a rare total color blindness that is accompanied by relatively normal vision, electroretinogram, and electrooculogram

# Dichromacy :

- moderately severe color vision defect in which one of the three basic color mechanisms is absent or not functioning
- Dichromacy occurs when one of the cone pigments is missing and color is reduced to two dimensions
- "first" (*prout*:referring to the red photoreceptors), "second" (*deuter-*, the green), or "third" (*trit-*, the blue) photoreceptors are affected.

- Protanopia : perceive light wavelengths from 400 to 650 nm so no pure red !
- Deuteranopia : the green retinal photoreceptors are absent
- Tritanopia : total absence of blue retinal receptors. Blues appear greenish, yellows and oranges appear pinkish .

- Protanopia : perceive light wavelengths from 400 to 650 nm so no pure red !
- Deuteranopia : the green retinal photoreceptors are absent
- Tritanopia : total absence of blue retinal receptors. Blues appear greenish, yellows and oranges appear pinkish .


Protanopia
Deuteranopia
Tritanopia
Monochromatism

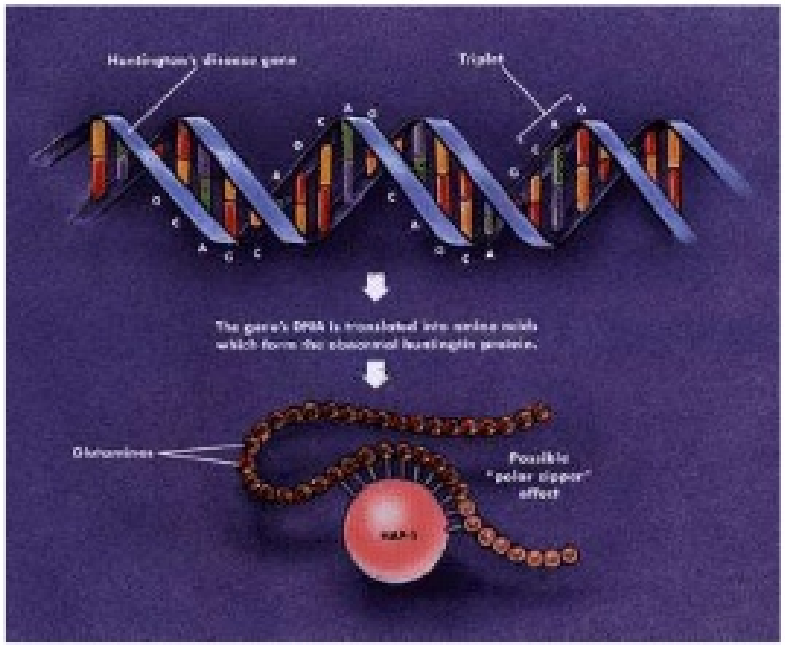
# Trichromacy :

- Protanomaly : altered spectral sensitivity of red retinal receptors so poor red–green hue discrimination .
- Deuteranomaly : shift in the green retinal receptors , the most common type of color vision deficiency, mildly affecting red–green hue discrimination 5% of Eu. Males.
- Tritanomaly : rare, hereditary color vision deficiency affecting blue–green and yellow–red/pink hue discrimination

# #8 - Huntington's Disease

- Huntington's disease (HD) is an inherited, degenerative brain disorder which results in an eventual loss of both mental and physical control. The disease is also known as Huntington's chorea. Chorea means "dance-like movements" and refers to the uncontrolled motions often associated with the disease.

# Huntington's



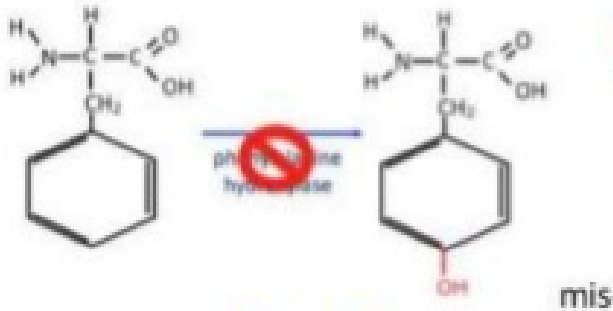

- Looking back at the pedigree chart is Huntington's dominant or recessive?
- Scientists have discovered that the abnormal protein produced by the Huntington's disease gene, which contains an elongated stretch of amino acids called glutamines, binds more tightly to HAP-1 than the normal protein does.

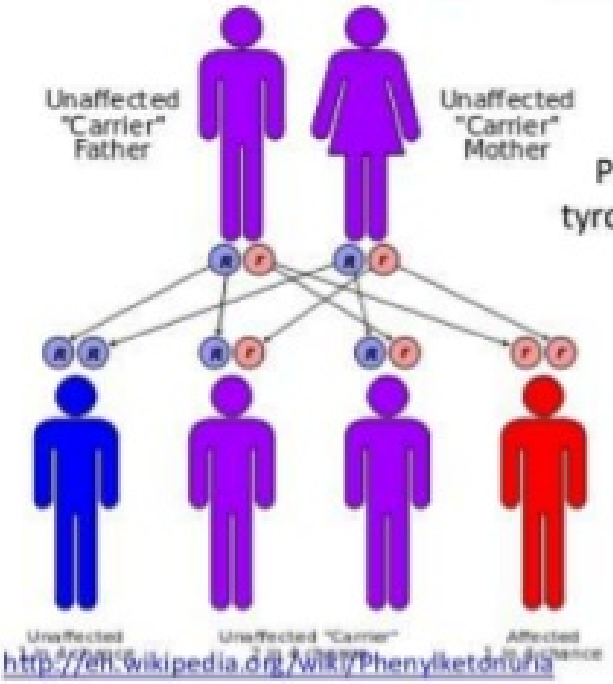
# # 9 - Phenylketonuria or PKU

People with PKU cannot consume any product that contains aspartame.

PKU is a metabolic disorder that results when the PKU gene is inherited from both parents (recessive or dominant? Monogenic or chromosomal?)

- inborn error of metabolism involving impaired metabolism of phenylalanine, one of the amino acids. Phenylketonuria is caused by absent or virtually absent phenylalanine hydroxylase (PAH) enzyme activity.






http://en.wikipedia.org/wiki/Phenylketonuria

# Phenylketonuria (PKU)

*Inherited, progressive, degenerative.*

## Cause

Autosomal recessive, disease-causing allele: mis-sense base-substitution mutation on the gene for the enzyme ***phenylalanine hydroxylase***.

## Result

Phenylalanine (Phe) cannot be metabolised into tyrosine. Phe builds up in the brain, and competes with other amino-acids related to transport.

## Effect

Mental development is retarded.

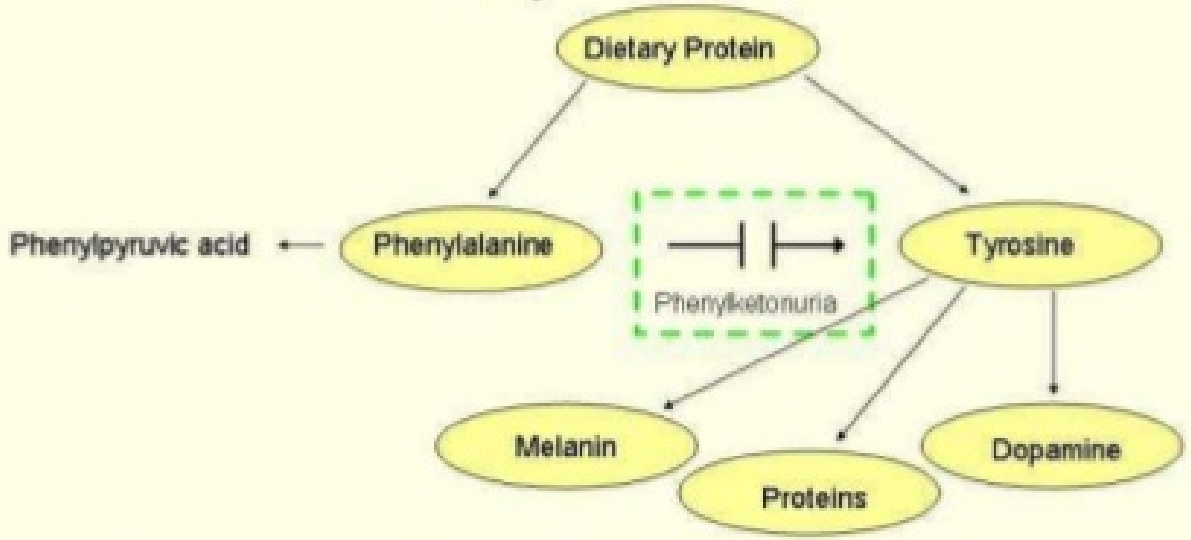
## Detection

Heel-prick (Guthrie test) of newborns to test concentration of Phe and Phe:Tyr ratio.

# PKU

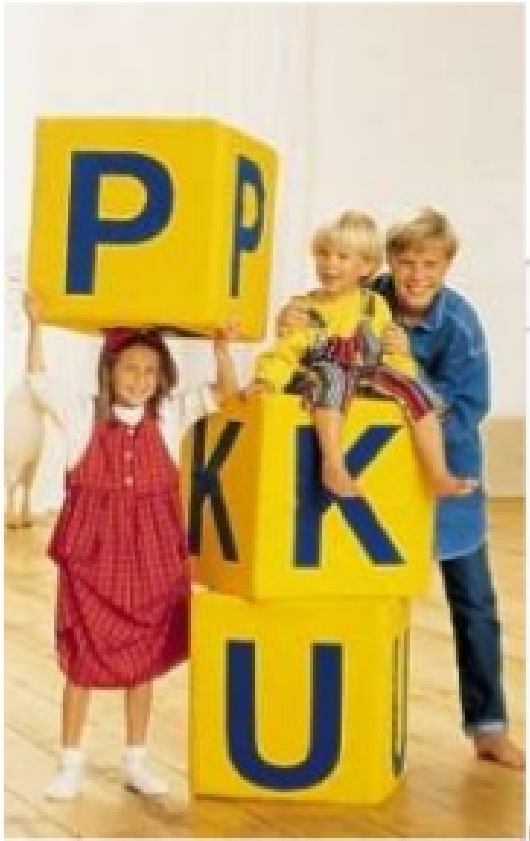
- Phenylalanine is an essential amino acid and is found in nearly all foods which contain protein, dairy products, nuts, beans, tofu… etc.
- A low protein diet must be followed.
- Brain damage can result if the diet is not followed causing mental retardation…and mousy body odor (phenylacetic acid is in sweat).

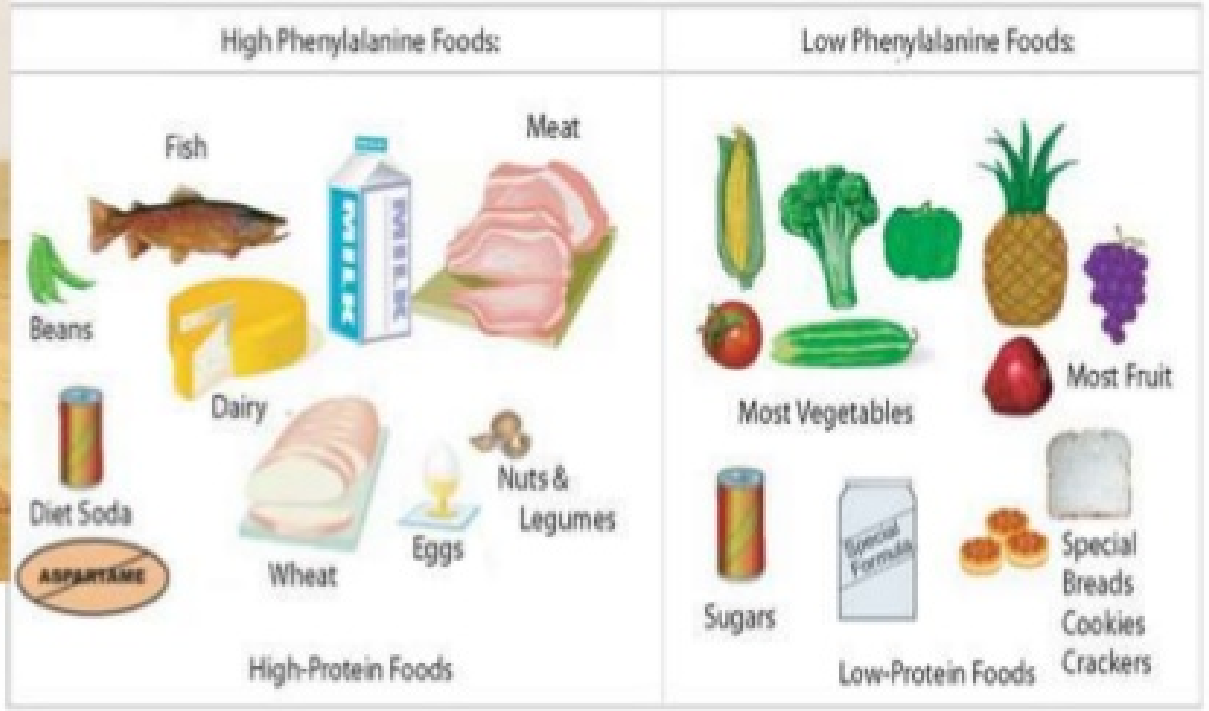
# Phenylketonuria




- Lack of phenylalanine hydroxylase blocks the transformation of phenylalanine into tyrosine
- Unmetabolized phenylalanine is shunted into the pathway that leads to the formation of phenylketones
- Excess phenylalanine also inhibits the formation of melanin from tyrosine

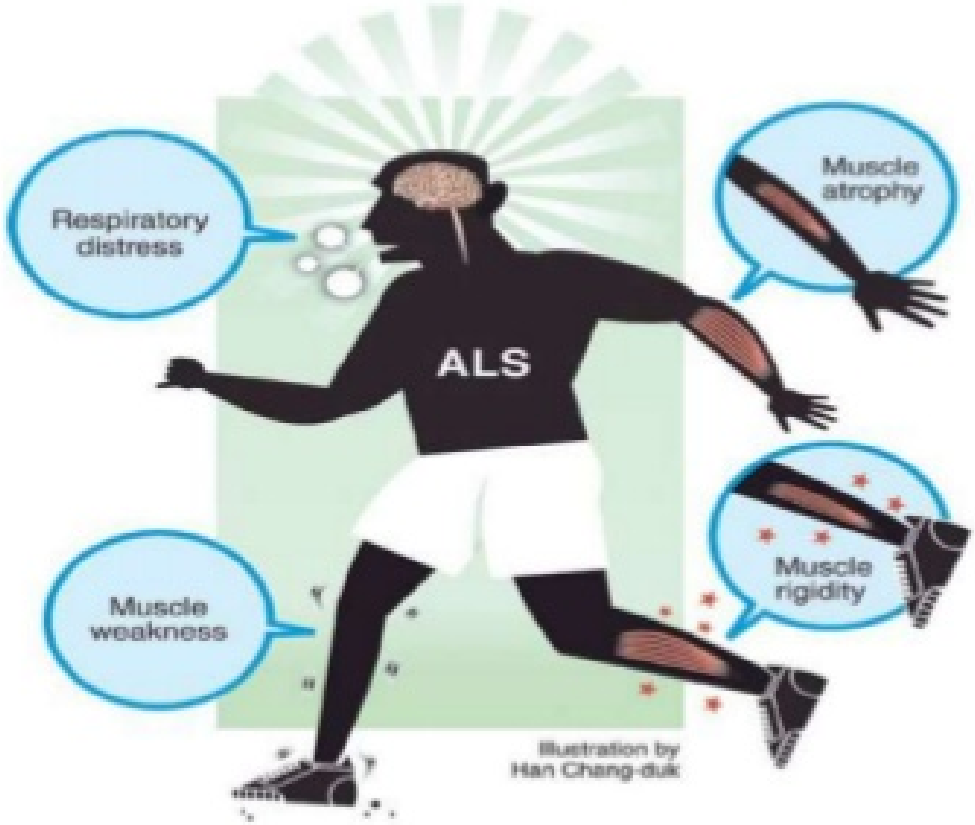
# Phenylalanine.
## Free diet



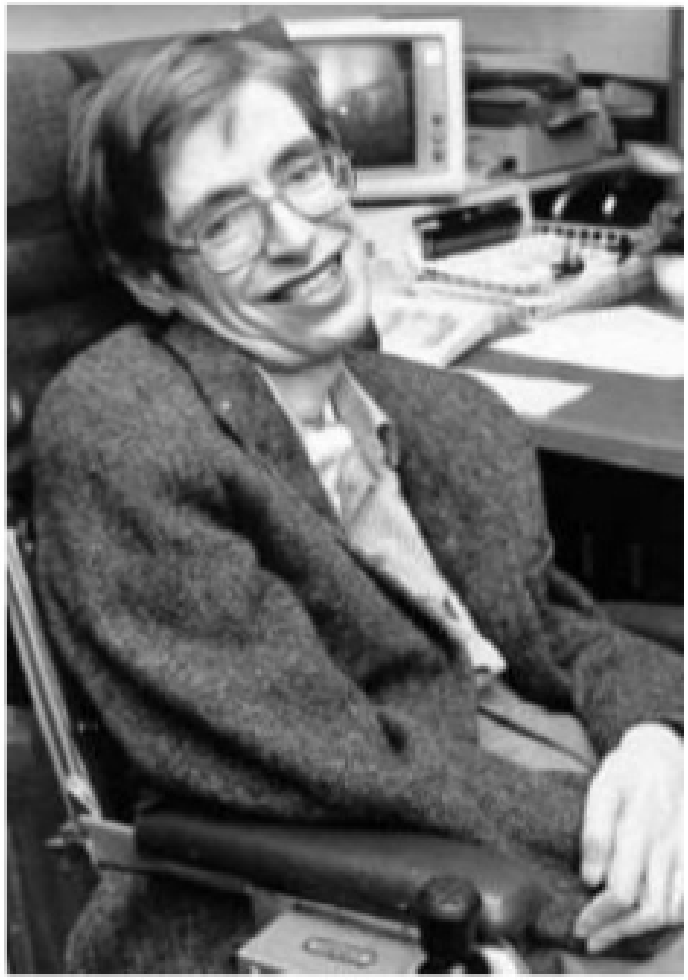



# # 10 - ALS
# (Amyotrophic Lateral Sclerosis, or Lou Gehrig's disease)

- Autosomal
- Dominant



# Stephen Hawking ??!!!



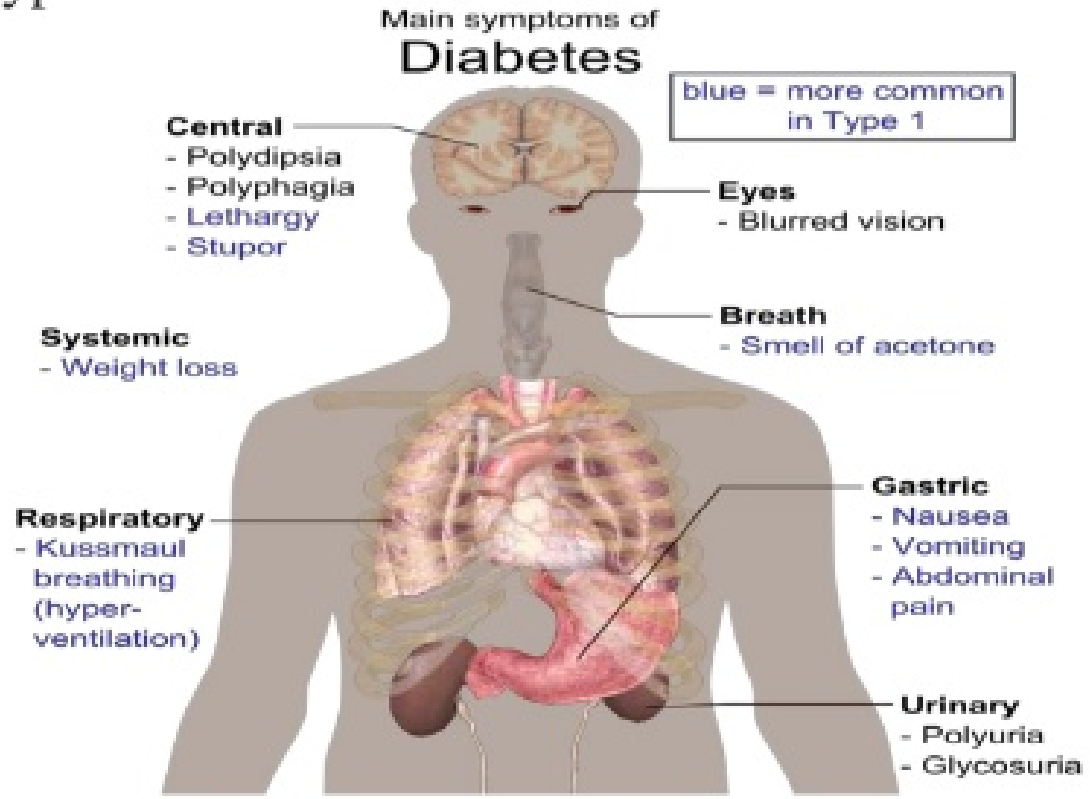
the fourth cosmology theor y by union of general theory of relativity and quantum mechanics

The theory of every thing . 2014 movie

- the disease strikes people between the ages of 40 and 70, and as many as 30,000 Americans have the disease at any given time
- This monogenic mutation is believed to make a defective protein that is toxic to motor nerve cells.
- A common first symptom is a painless weakness in a hand, foot, arm or leg, other early symptoms include speech swallowing or walking difficulty

# Diabetes

- Type 1 reveals itself in childhood with polygenic disorders , Type 2 can be made worse from excessive lifestyle



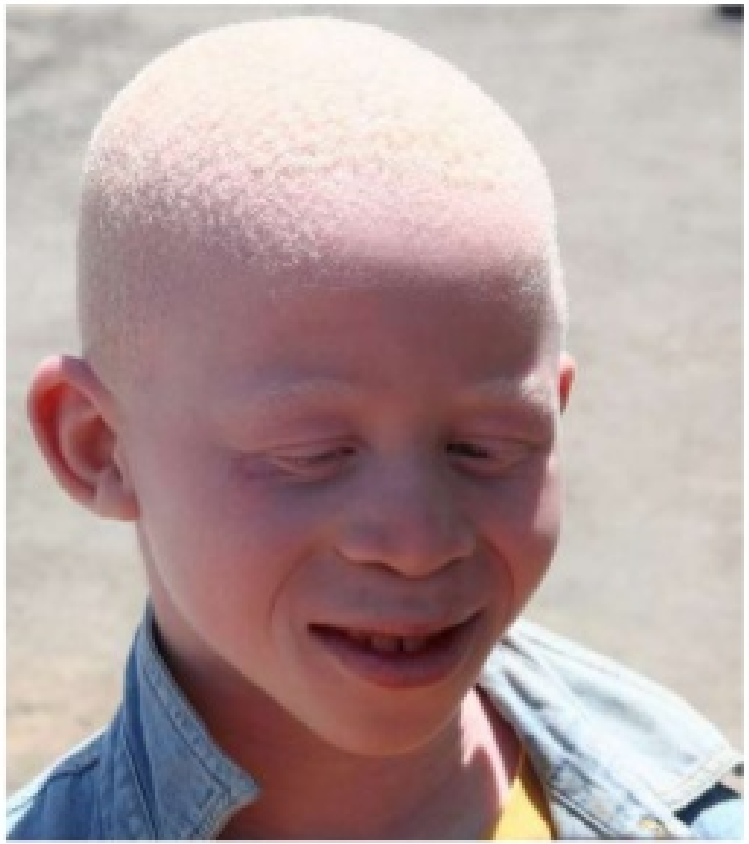
- Warning signs of diabetes :
  - Extreme thirst
  - Blurry vision from time to time
  - Frequent urination
  - Unusual fatigue or drowsiness
  - Unexplained weight loss

  - Diabetes is the leading cause of kidney failure, blindness, and amputation in adults, and can also lead to heart disease.

# #12 - Albinism

- Patients are unable to produce skin or eye pigments, and thus are light-sensitive
- congenital disorder characterized by the complete or partial absence of pigment in the skin, hair and eyes due to absence or defect of tyrosinase which is a copper-containing enzyme involved in the production of melanin
- Autosomal recessive

- no cure for Albinism , just be away from sun and regularly visit the dermatologist , dark glasses and dark contact lenses



# # 13 - Achondroplasia

# Achondroplasia (a.k.a. dwarfism)

- Monogenic, autosomal
  - Carriers express genes , so it is recessive

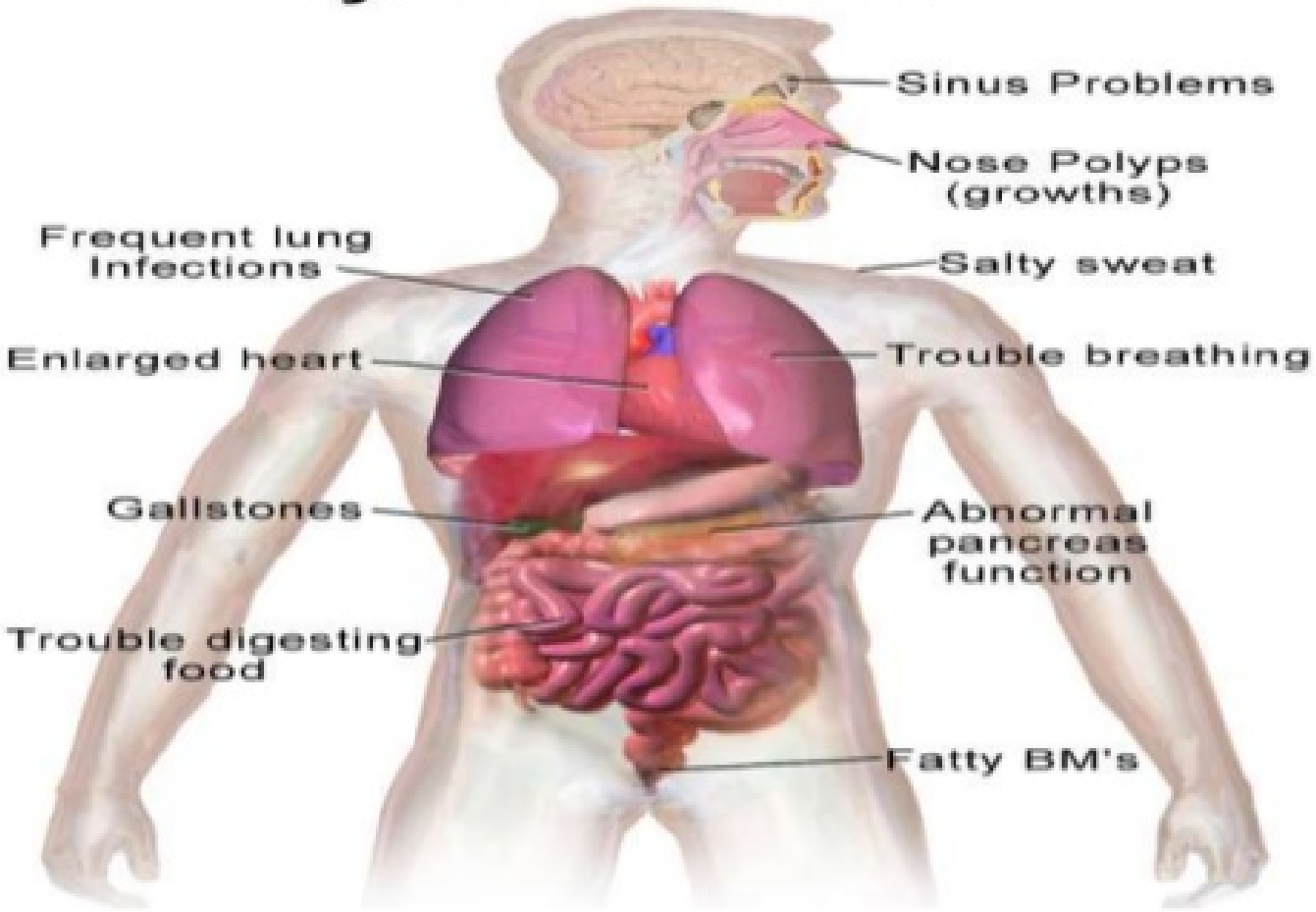
  - Ttt:

  *GH , thyroid injection*

# # 16 - Cystic Fibrosis (CF)

- Monogenic autosomal recessive ( by carriers )
- Cause:  deletion of only 3 bases on chromosome 7
- Fluid in lungs, potential respiratory failure
- Common among Caucasians…1 in 20 are carriers

# Health Problems with Cystic Fibrosis



# # 17 - Muscular Dystrophy

- **What Is Muscular Dystrophy?**
  **Muscular dystrophy** is a disease in which the muscles of the body get weaker and weaker and slowly stop working because of a lack of a certain protein
- Can be passed on by one or both parents, depending on the form of MD (therefore is autosomal both dominant and recessive)

# Very rare genetic disorders

- Cri du chat ( deletion chromosome #5 )
- Prader willi syndrome ( chromosome #15 )
- #18 Q deletion syndrome
- Hereditary hemochromatosis
- Marfen syndrome

# I'm So Tired

THANX a lot