# Chromosomal and genetic disorders

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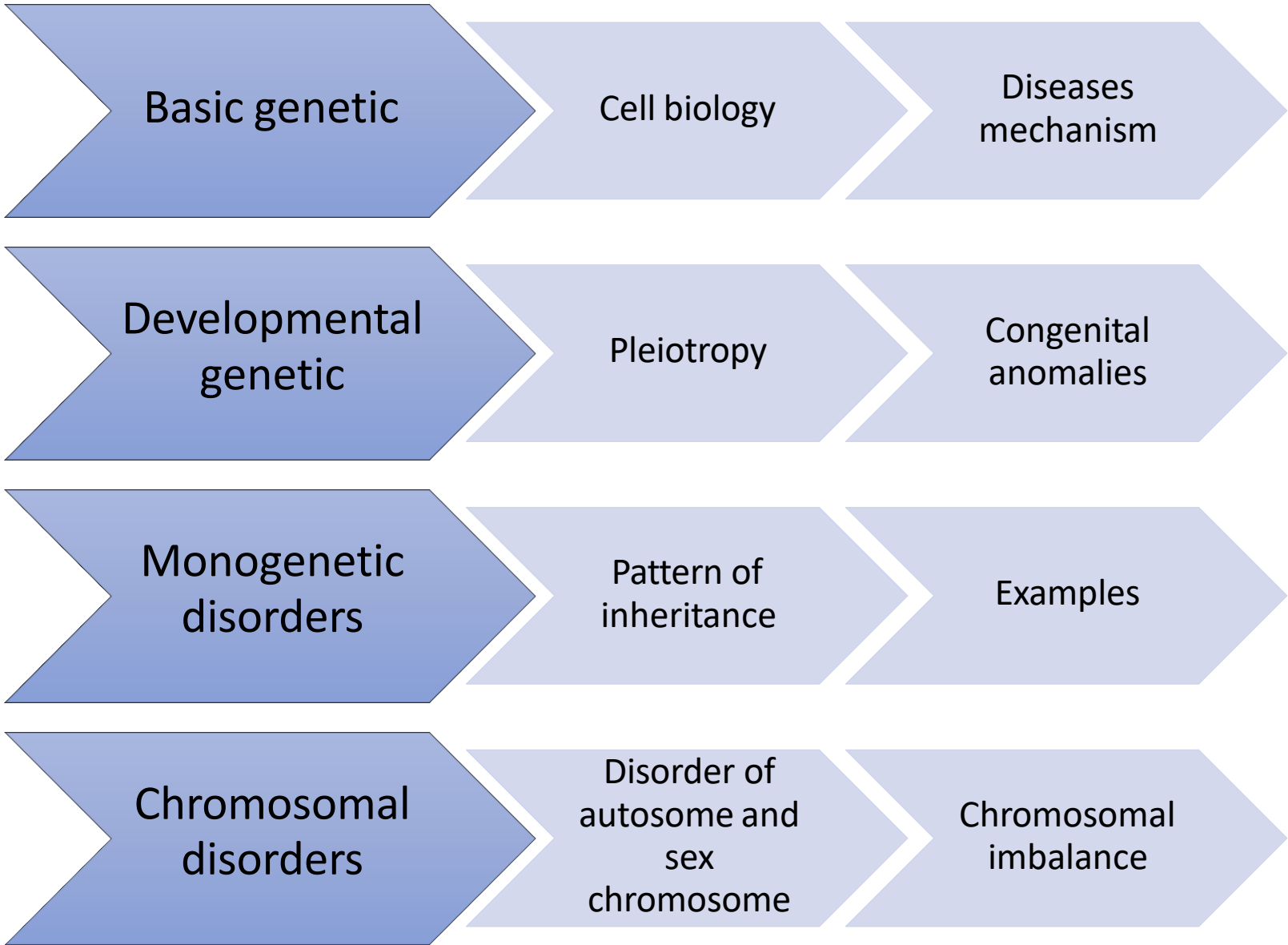
All genetics MCQ will be part of this presentation

# Outlines


Basic genetic
Cell biology
Diseases mechanism
Developmental genetic
Pleiotropy
Congenital anomalies
Monogenetic disorders
Pattern of inheritance
Examples
Chromosomal disorders
Disorder of autosome and sex chromosome
Chromosomal imbalance

# Basic genetic

- Cell biology and structure
- Mosaicism
- Imprinting
- X-inactivation

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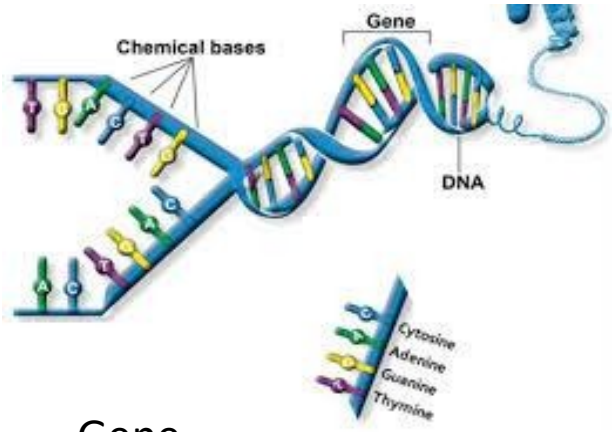


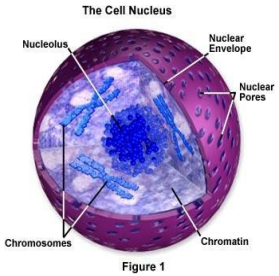

Gene

1) Starting from the human body generally, taking a cell (ex. Lymphocyte) and we look inside if we have any chromosomal issue either numerical, missing or extra chromosome it would be at this stage.
and the earlier stage the worse it'll present than when it's later (not always). That's because when we are missing or having an extra chromosome sometimes it's lethal. The commonest three unlethal are Down syndrome, Edward and Patau (very severe compared to Down syndrome and we can call them also lethal conditions)

2) and then if we have a problem with the segment of the chromosomes not the whole chromosomes is missing or duplicated, we have sometimes a part only a small segment of chromosomes which contains number of genes this segment

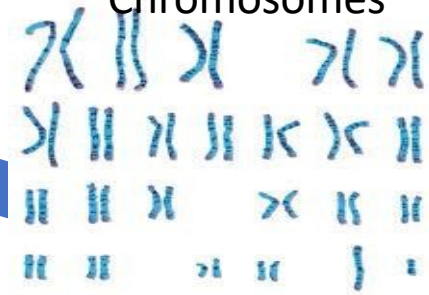
3) and then the monogenic disease will have a problem either with the exon or intron causing the gene to dysfunction. Exon is the coding area of the gene and the common mutation or the common variation in the exons causing dysfunction of the gene however many of the variants are in the intronic place or promoter area which cause also dysfunction of the gene.

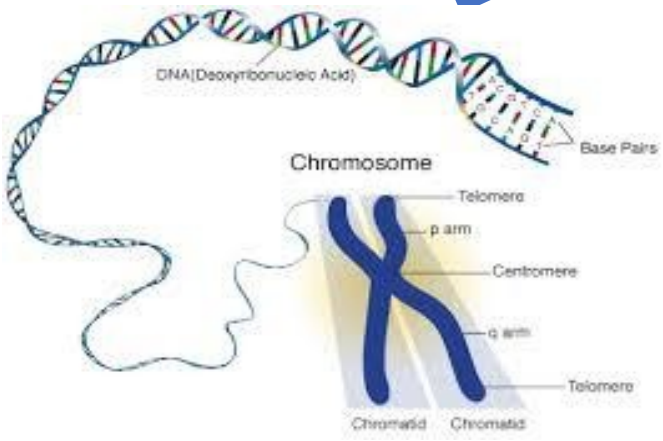
cell




Nucleus

1 Chromosomes



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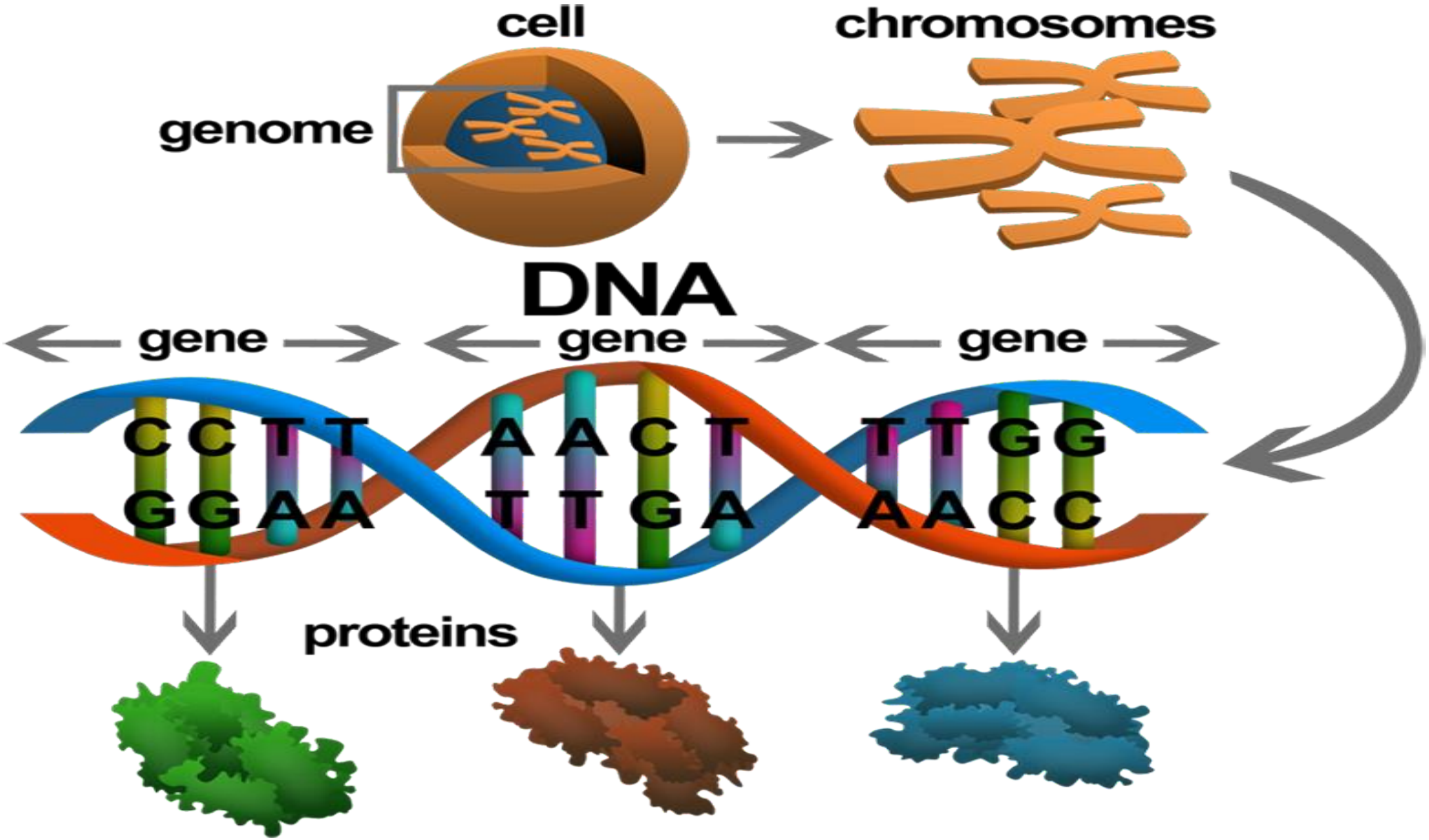

cell
chromosomes
genome
DNA
gene
gene
gene
C C T T
G G A A
A A C T
T T G A
T T G G
A A C C
proteins

very useful in dermatology and oncology.

# Mosaicism

- Is the presence in an individual or a tissue of at least two cell lineages that differ genetically but are derived from a single zygote.

Defect is post-zygotically, causing 2 or more cell lineages

- **Types** :
- Pure Confined placental mosaicism.

There's normal cell line the fetus with no mosaicism, and there's an extra added cell line which is confined to the placenta

- Pure Somatic mosaicism –segmental mosaicism.

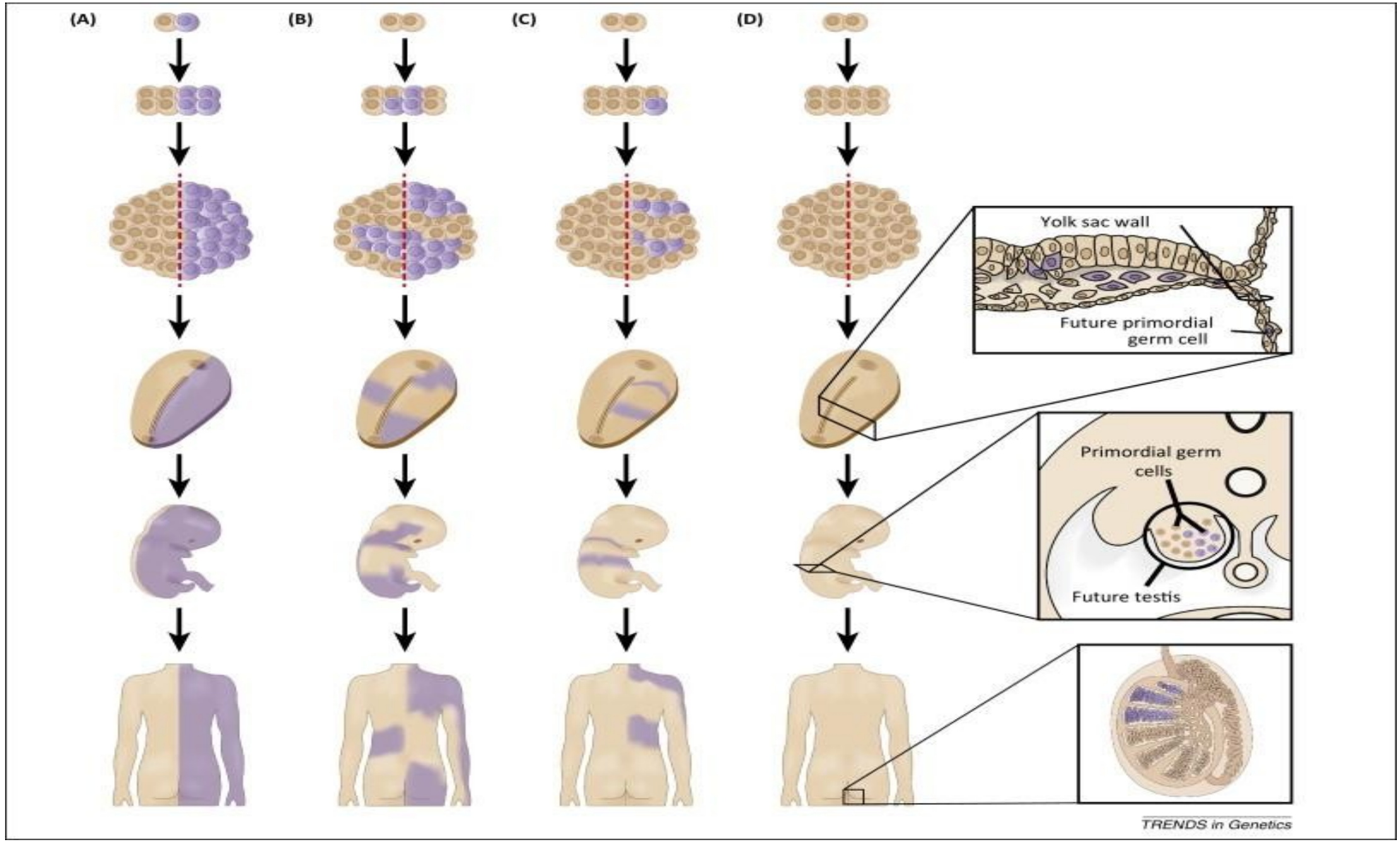
Very common in skin lesions, when there's a part of skin completely normal and the other is completely abnormal, it happens symmetrical where half of the body is affected with skin lesion the other is normal

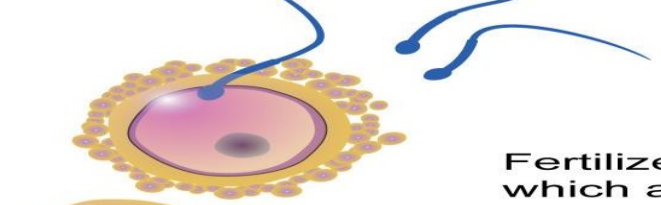
- Pure Germline mosaicism.

When we have the other cell line within the ova or sperm, its hard to detect, can be only detected when we have repeated affected children from completely healthy parents

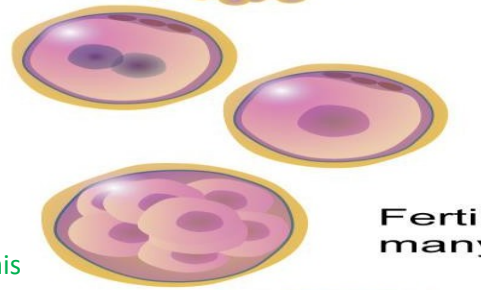
- Gonosomal mosaicism.

When its in the germ cell + somatic cell


(A)
(B)
(C)
(D)
Yolk sac wall
Future primordial germ cell
Primordial germ cells
Future testis
TRENDS in Genetics



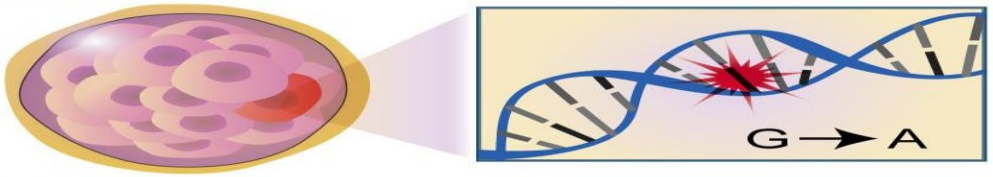
Fertilized egg from which all body cells arise



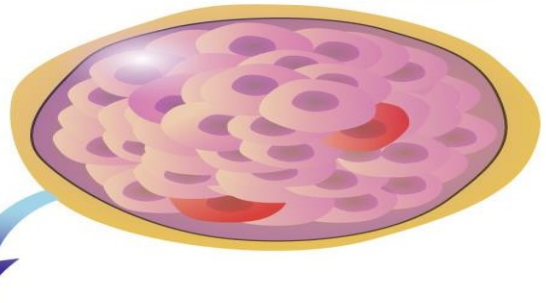
Fertilized egg divides into many cells to form an embryo

The mutation starts from this cell, after this colonies of this cell carry the same mutation

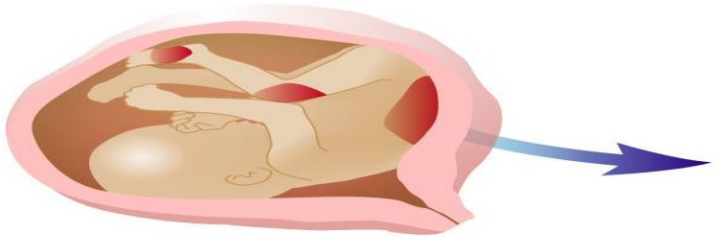
As the cells continue to divide, the DNA in one of the cells becomes altered




The AKT1 gene in one of the cells changes - where the DNA code should have a "G," it has an "A" instead



As the cells of the growing embryo continue to divide, the number of both the cells with a changed AKT1 gene and the cells with an unchanged AKT1 gene expand and contribute to the formation of organs and tissues



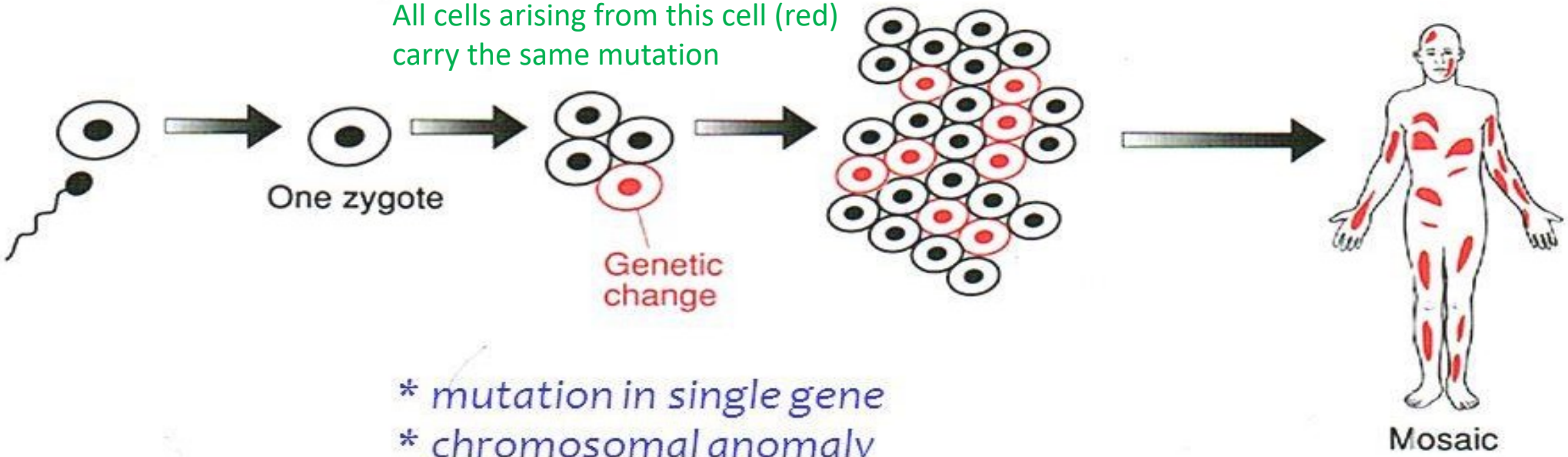
The developing baby has two types of cells. Some have the normal AKT1 gene and somehave the altered AKT1 gene

most types of cancer are mosaicism, and can happen in the liver, skin …

The parts of the body that developed from the cells with the altered AKT1 gene grow differently than normal cells. This is why the body parts of people with Proteus syndrome are unevenly affected.

# Mosaicism

All cells arising from this cell (red) carry the same mutation




* *mutation in single gene*
* *chromosomal anomaly*

The earlier the stage the more areas it'll cover

Mosaicism can be:

- **somatic** (ie in most body cells) or
- **gonadal** (confined solely to the gonads).

How can we discover the mosaicism if it's only in the gonad? as a clinician how can we see it? we will not go and take samples and test if they create mutation or not.
**In the offspring**, so usually it can happen with autosomal dominant, normal parents and we have one affected with OI type 2, ok we tell them it might be de Novo (the new mutation happened later), and tell them this is the likely one or it tell them it could be a mutation in germ cell in one of the parents. We say this in any counseling with dominant disease, new generation affected with the dominant disease. we will tell them commonly it's a denovo one and less likely to be germ cell mosaicism. sometimes we have a specific ratio for some diseases but not for all of them but we have to put the two possibilities. then we might have another child affected with the same disease parents both are healthy we could say that this mutation is carried by one of you in the germ cell, we don't know which one unless you divorce and remarry otherwise, we don't know which one of you because we cannot test the mutation in the germ cell

# Mosaicism

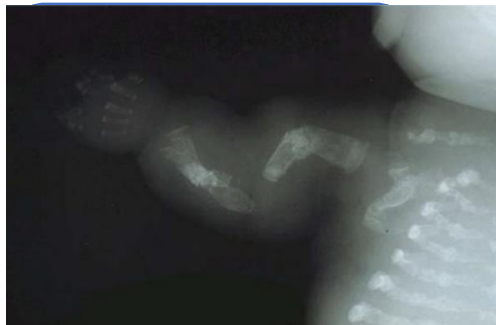
## Germ cell mosaicism

Osteogensis imperfecta type 2

OI II

Turner syndrome

DMD



## Somatic

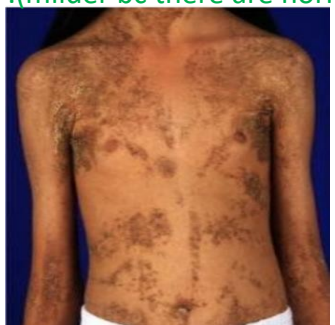
Most cancers are somatic

Cancer

Line of blaschko

Down syndrome

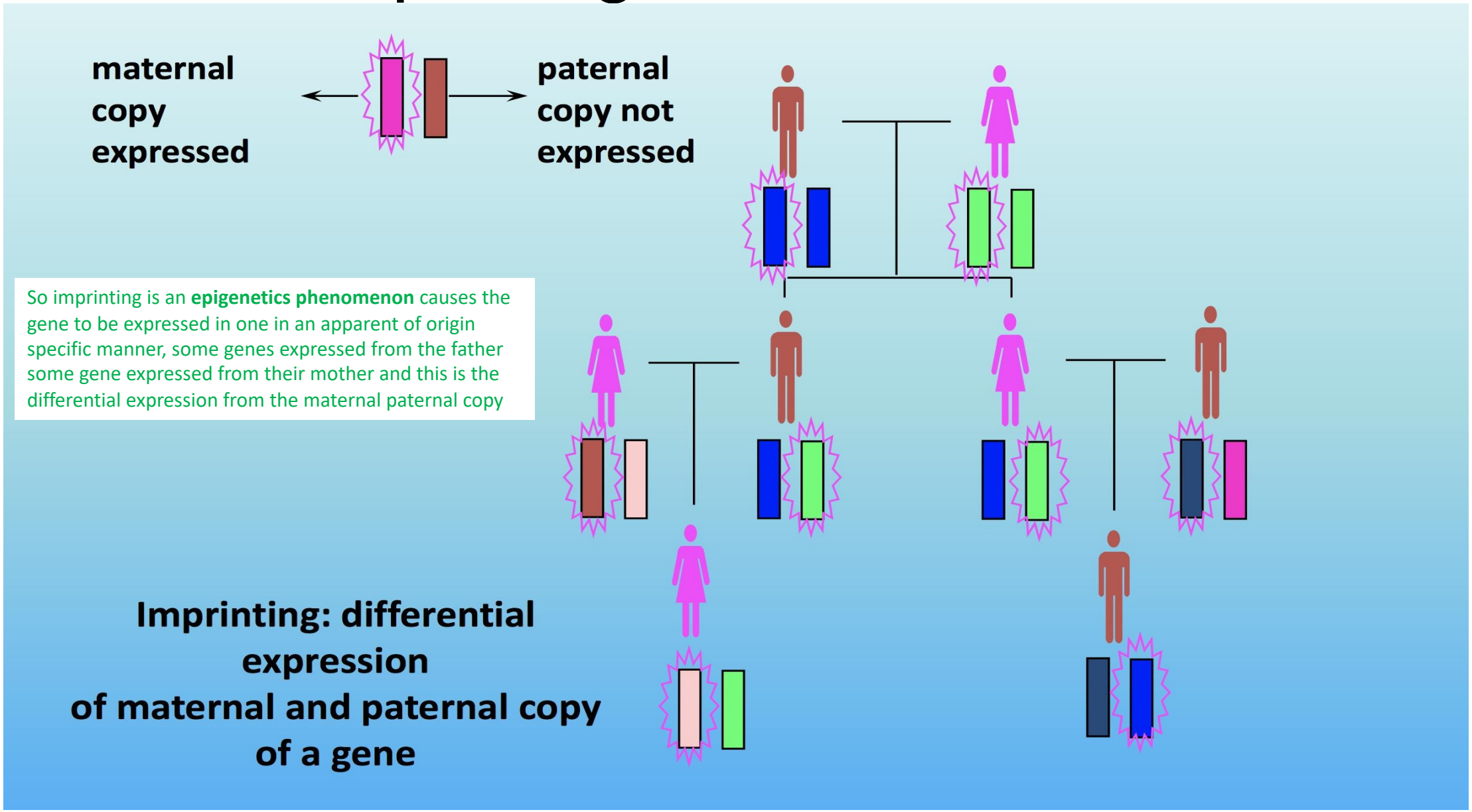
When down s. is mosaic only some cells carry the extra chromosome .(milder bc there are normal cells too)



## Gonosomal mosaicism

NF 2

# Genomic imprinting



Its another example of mosiacism

# X-inactivation

Also called x skewing

**There are many important genes on the X chromosome…**

**So, how can males, with only *one* X chromosome, and females, with *two* X chromosomes, not differ in the products encoded by most of these genes???**

Their genomic content are very simliar to this gene, meaning that the females don't have an extra genetic materials than males, and they are similar to males when they are expressed

**Explained by X-inactivation resulting in dosage compensation.**

One of the Xs is inactivated to make a dose compensation between males and females

# Lyon hypothesis

- **X-Inactivation occurs *early* in embryonic life.**

**~2 weeks after fertilization, at several hundred cell stage.**

**Note: The inactive X must become re-activated in the female's germ line so that each egg can receive an active X chromosome.**

One of them is inactivated in the female's human body and when she produce 2 eggs each will take an X, both of them should be active then inactivation will happen after fertilization

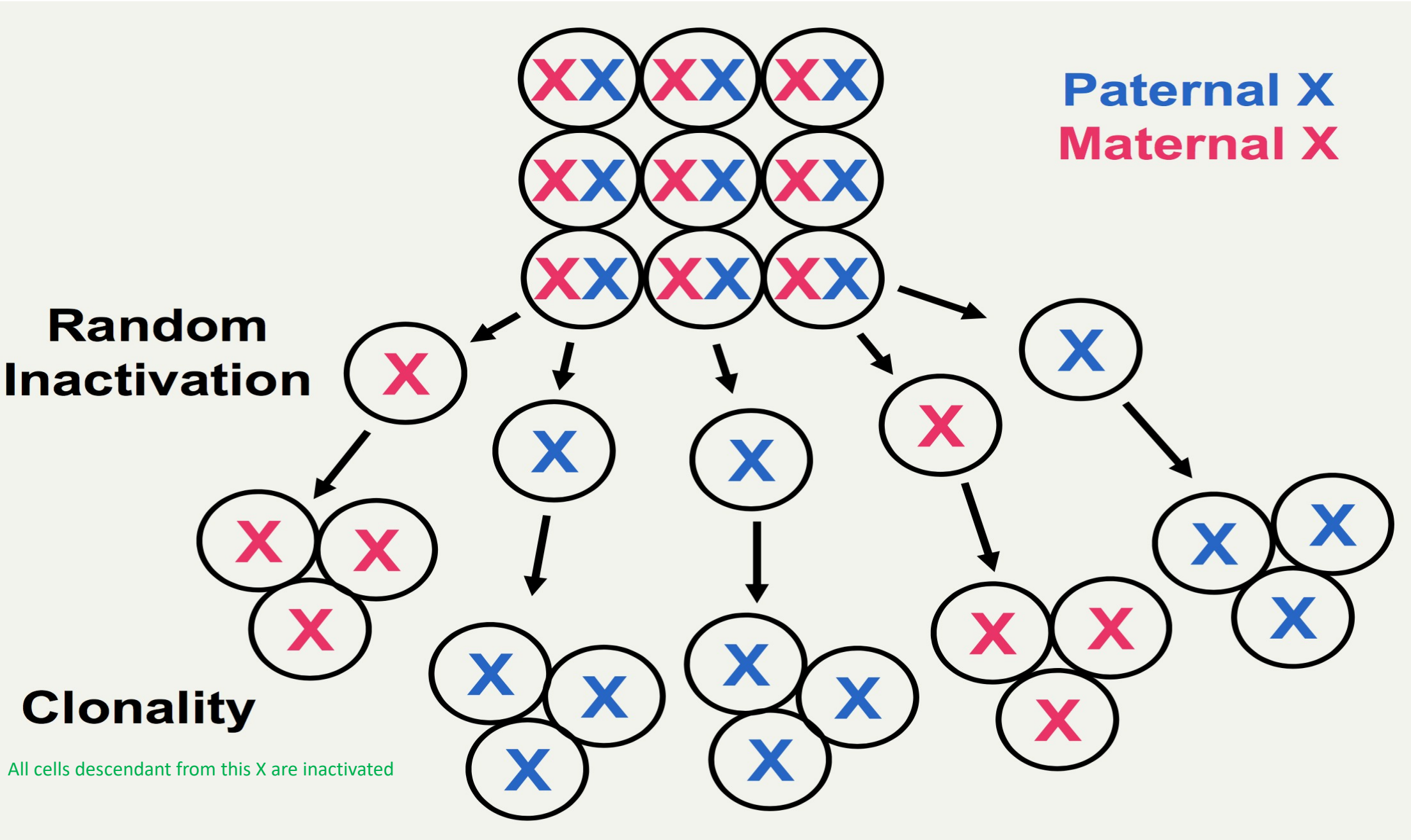
- **X-inactivation is *random*.**

**The inactive X may be either the paternal or the maternal X; with a mix of cells, females are mosaics for the X chromosome.**

It can also be random in the same tissue, where you'll find some cells with maternal active and some with the paternal active

- **X-inactivation is *clonal*.**

**After one X chromosome has become inactivated in a cell, all of that cell's descendants have the same inactive X.**


Paternal X
Maternal X
Random Inactivation
Clonality
All cells descendant from this X are inactivated

# Basis of diseases

Translocation(part of the chromosome travels and attaches to another prt of the chromosome.) Or inversion

Duplicate or missing in number

We look at it by karyotyping

- Chromosomal mutation ; structural or numerical

We look at it by microarray

- Sub-chromosomal mutation ; segmental deletion, duplications.

Unbalanced type of structural changes

- Single gene including dynamic mutation

Mendialian defect (monogenic)

- Imprinting disorders

epigenetics

- Complex genetic

Like in cancer and multifactorial disease like diabetes, schizophrenia where we have genes linked to the disease but not 100%

## Numerical chromosomal changes

Trisomy

3 copies of 1 chromosome

Monosomies

1 copy of the chromosome, most severe bc we haven't seen many cases

triploidy

3 copies of all chromosomes (lethal)

## Structural chromosomal changes

translocations

Inversions (balanced or unbalanced )

Unbalance= abnormal genetic dose
Balanced= complete dose only structural (shape) change

## Chromosomal imbalance

- **Wolf-Hirschhorn** — Missing Ch4
- **Williams** — Missing Ch7
- **Cri-du-Chat** — Missing Ch5
- **Beckwith-Wiedeman** — Missing Ch11
- **Smith-Magenis** — Missing Ch17
- **DiGeorge/VCFS** — Missing Ch22

## Imprinting disorders

Mostly affecting neurology and endocrine

Angelman syndrome

Prader willi syndrome

## Monogenic disease

Mendelian diseases

AD/AR/X-LINKED

## Complex diseases

Cancer

DM

Psychiatric illness

# Chromosomal disorders

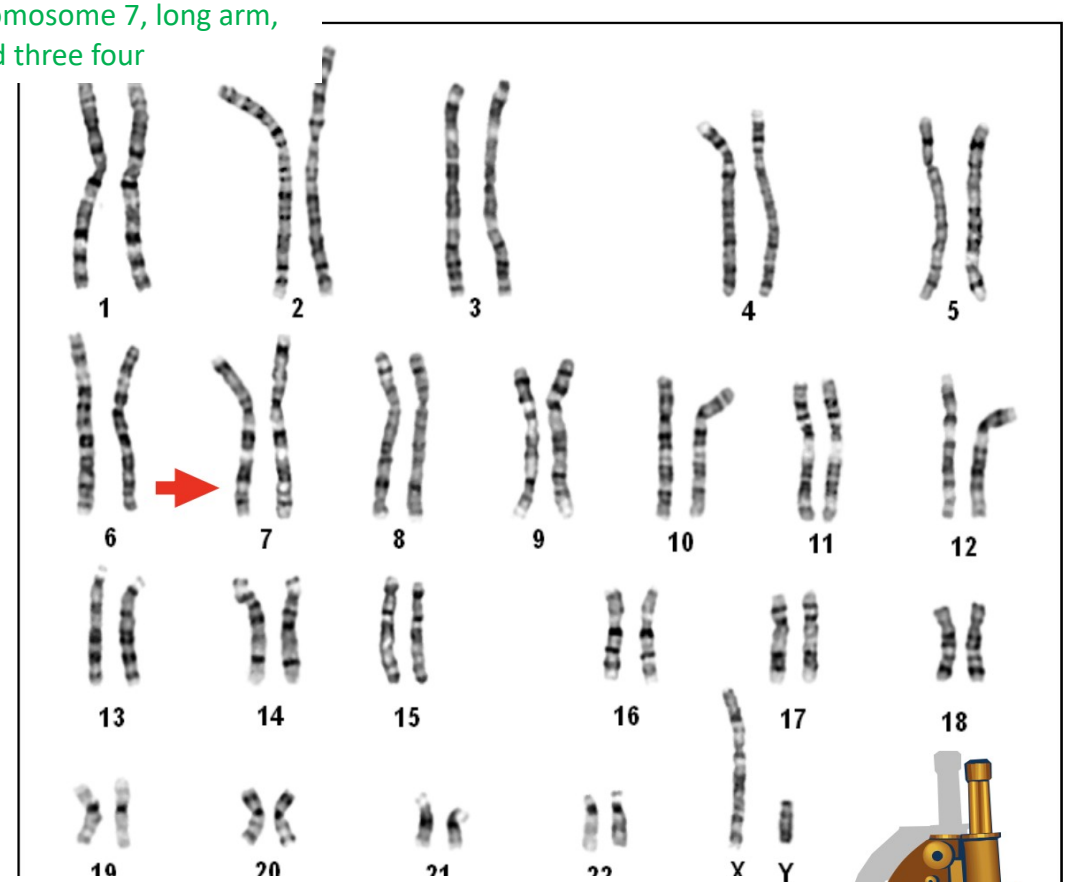
- **Molecular Cytogenetics Techniques**
- **Microdeletions/Microduplications**
- **Syndromes Recurrent Genomic Disorders**
- **X-Chromosome Abnormalities**

Karyotyping , the pattern here is G Banding

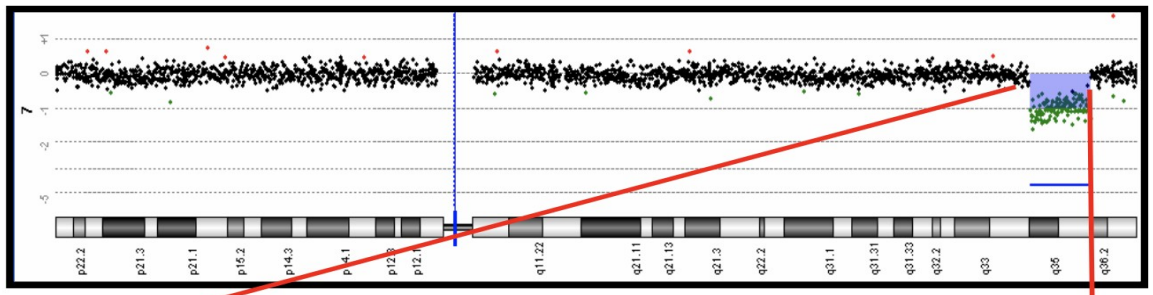
# G-band designation (subjective) vs. Array mapping (objective)

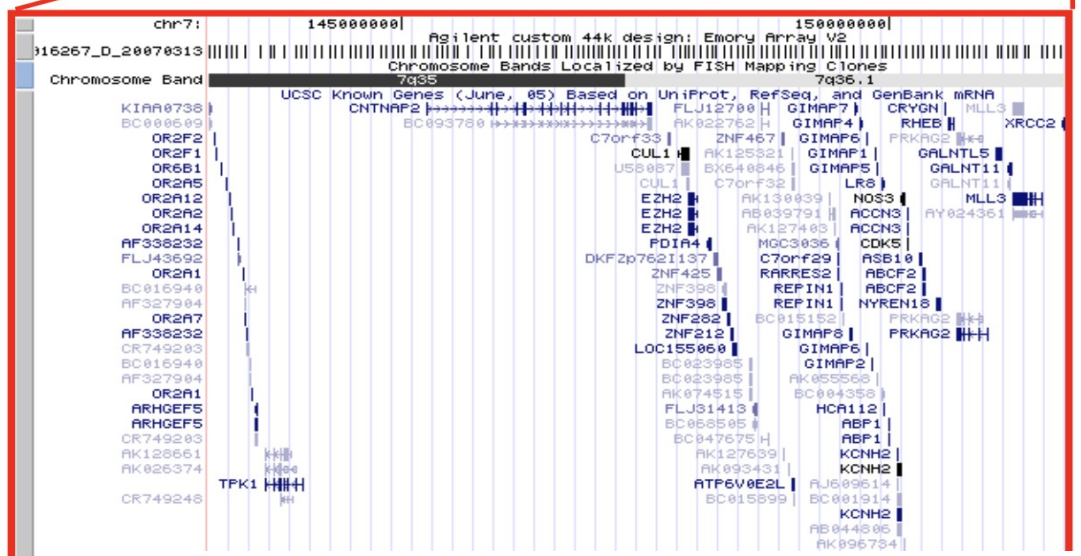
## 7q34 (+/- a band) → 7q35 – q36.1

Chromosome 7, long arm, band three four



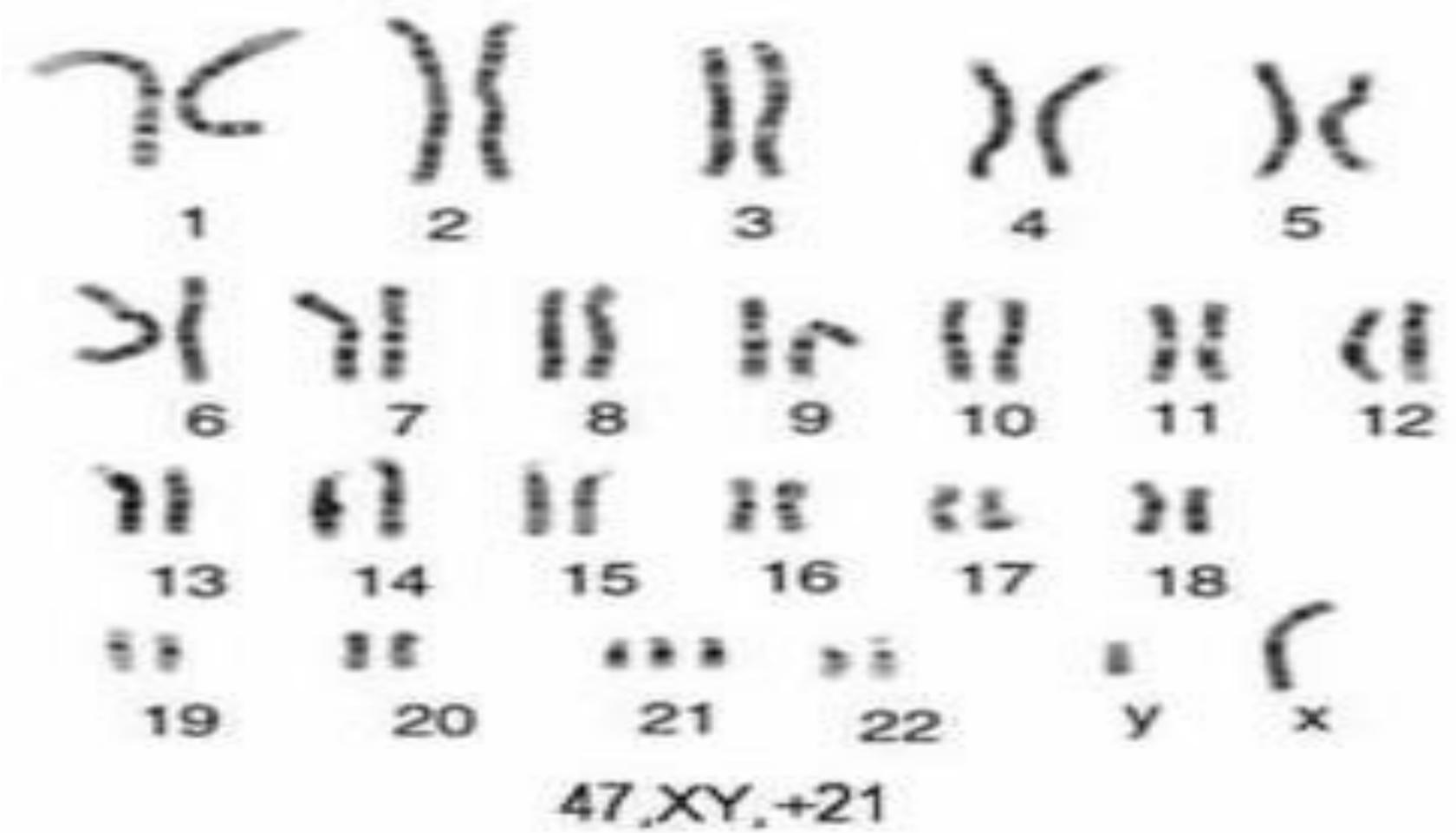

This view shows numerical and structural mutations (extra/missing , inversion/translocation, deletion/duplication “must be big enough to see by G banding)



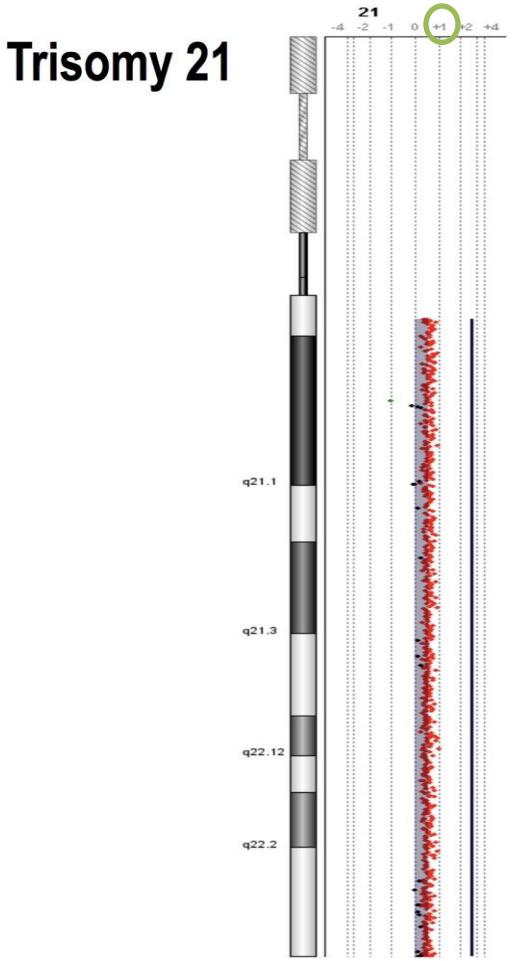



Microarray we look specifically at each chromosome and looking for how many copies we have 0=normal , -1=missing 1 copy, +1=extra 1 copy
Its easy to read complex to perform, its better done for deletion/duplication

# Trisomy 21 karyotyping vs CMA



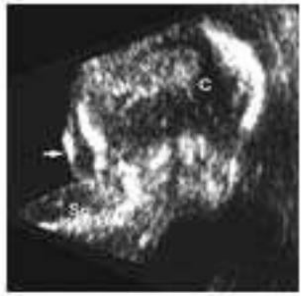

Micro array we can see the whole chromosome duplicated




Theres an extra copy of chromosome 21

We read it : 47 chromosomes, XY with extra chromosome 21

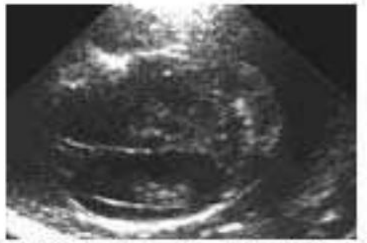
Can be seen at 12 weeks



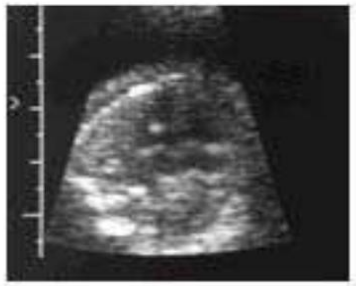
Nuchal Thickening

seen 11-12 weeks

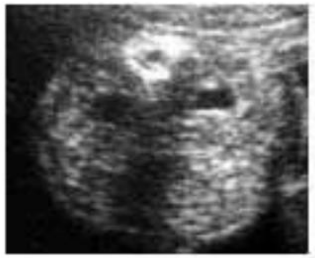
CNS manifestation



Mild Ventricular Dilatation

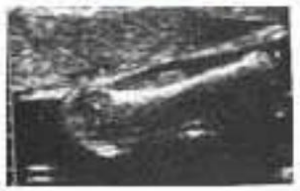


Echogenic Intracardiac Focus

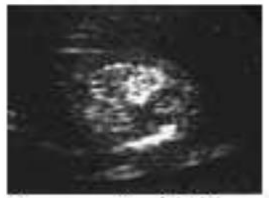


Pyelectasis

Renal dilatation



Shortened Limbs



Hyperechoic Bowel

# Trisomy 21

The prenatal testing for down s. could be a screening or diagnostic test, invasive or noninvasive, maternal or fetal sample. Based on situation, parents consent and budget we choose the test, if the mother is >35 with high risk of down s. we can give her option to do screening invasive (amniotic fluid sample 14-16 weeks , Chorionic villus sampling 11-13 weeks ) or noninvasive (maternal blood sample ”free fetal blood, BHCG, and other biomarkers), imp message: we shouldn’t take a medicolegal action (termination) based on the noninvasive methods, we should have a detailed diagnostic report

**Cytogenetic locus (loci)**: (21.22.1-22.2 has been called the DS critical region though there have been cases of duplication outside of this region who manifest DS

Testing using FISH takes 48 hours, we can either look for a specific loci, or we can also look for trisomy 13/18/21 using a genetic panel

**Inheritance**: 95% de novo, 5% due to Robertsonian translocation or isochromosome 21

Most imp here is cardiac, hypotonia and risk of cancer and leukemia in the future , facial features and short obese stature

**Clinical Features and Diagnostic Criteria**: mild-mod ID, hypotonia, growth delay, strabismus, adult cataracts, myopia, conductive HL, macroglossia, hypodontia, joint hyperflexibility, hypogenitalism, congenital heart defect, duodenal atresia, hirschprung, thyroid disease, early onset Alzheimers, transient myeloproliferation, ALL

Hyper laxity

**Clinical Tests**: prenatal US abnormalities detected in 50%, maternal serum screen: high free beta HCG, low PAPP-A,

Most of the time screening in utero, generally using karyotyping, array and FISH

**Molecular Tests**: maternal fetal free DNA testing, karyotype is diagnostic

MCQ question area!

**Disease Mechanism**: 90% due to maternal meiosis nondisjunction (¾ MI error, ¼ MII error)

However, there is 5% due to Robertsonian translocation or isochromosome 21

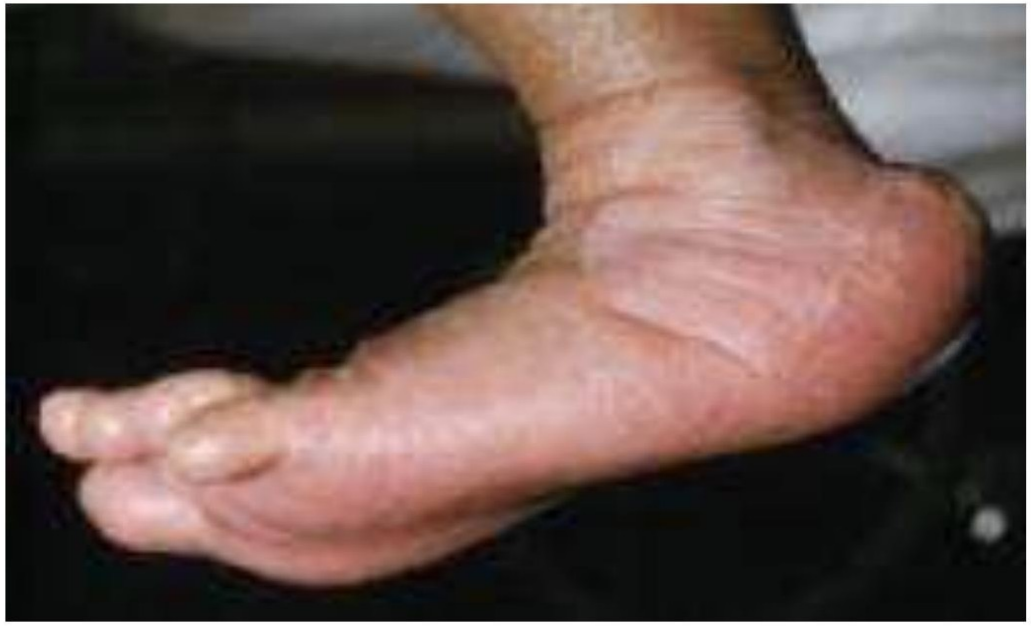
**Treatment/Prognosis**: Supportive care, overall life expectancy is reduced

Overlapping digits (clenched hand)

**Typical digit 2 over 3 and 5 over 4 of Trisomy 18**

Both are typical in trisomy 18 but can also be seen in other disorders

**Typical rocker bottom foot of Trisomy 18**

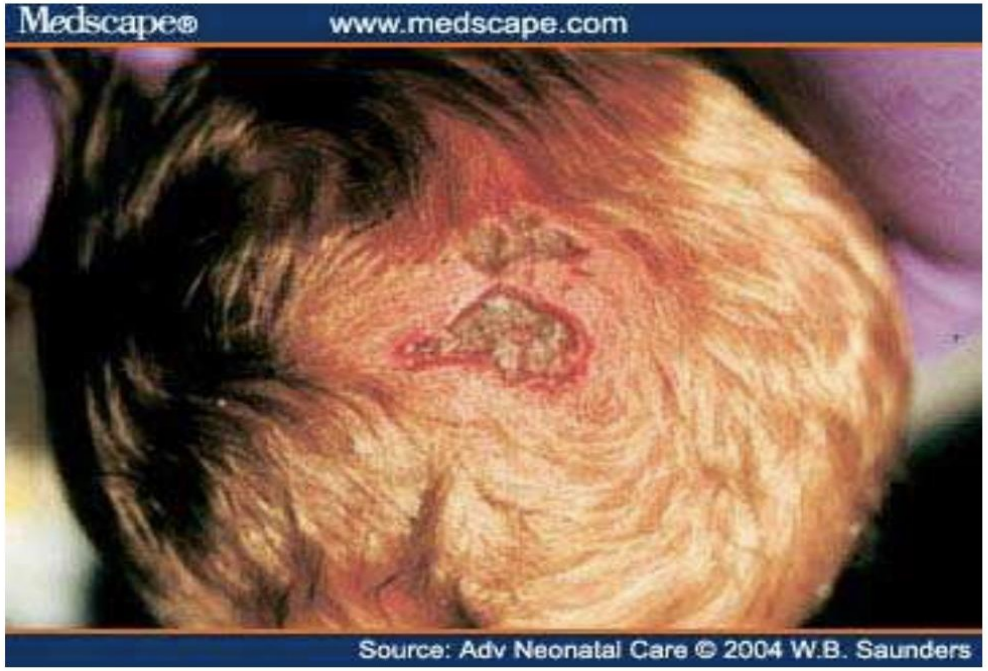


www.gfmer.ch/.../gendis

Most imp clenched hand, rocker bottom feet, cardiac VSD/ASD,

# Trisomy 18

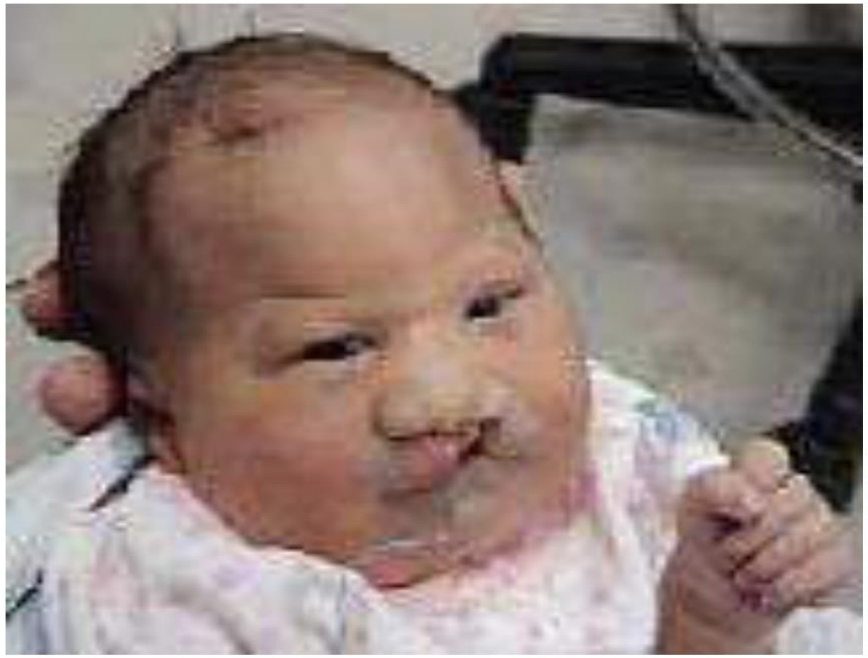
**Inheritance**: Less than 1% due to a translocation
**Clinical Features and Diagnostic Criteria**: clenched hand, fingers 2/5 overlap 3/4, IUGR, rocker bottom feet, micrognathia, prominent occiput, microphthalmia, VSD, ASD, PDA, generalized muscle spasm, renal anomalies, ID. Mosaic Tri 18 has variable but usually somewhat milder expression. Its imp to do MRI and cardiac testing to these patients
**Clinical Tests**: Echo, abdominal US. Maternal serum screen: low AFP, hCG, and UE3.
**Molecular Tests**: karytype is diagnostic
**Disease Mechanism**: Maternal nondysjunction (90%), mosaicism (10%)
That's why its allowed to terminated before نفخ الروح 19 weeks
**Treatment/Prognosis**: 50% die in first week, 90% die by one year




## Cutis Aplasia

Scalp deficiency

Cleft lip



www.prenatalpartnersforlife.org

HL: holoprosencephaly

# Trisomy 13

Major CNS presentation

**Inheritance**: 20% due to a translocation

**Clinical Features and Diagnostic Criteria**: The least common of the live born trisomy disorders. Holoprosencephaly, polydactyly, seizures, HL, microcephaly, midline CL/P, omphalocele, cardiac and renal anomalies, ID. Mosaic Tri 13: very broad phenotype from typical features of full trisomy to more mild ID and physical features and longer survival.

**Clinical Tests**: Brain MRI, EEG, audiogram, echo, renal US

**Molecular Tests**: Karyotype is diagnostic

We test by karyotyping, microarray , FISH and PCR

**Disease Mechanism**: 75% are due to maternal nondysjunction, 20% to a translocation, and 5% to mosaicism. Defect in fusion of the midline prechordial mesoderm in the first three weeks of gestation cause the major midline dysmorphic features.

**Treatment/Prognosis**: 44% die in the first month, >70% die within one year. Severe ID exists in all survivors.

Intellectual problem

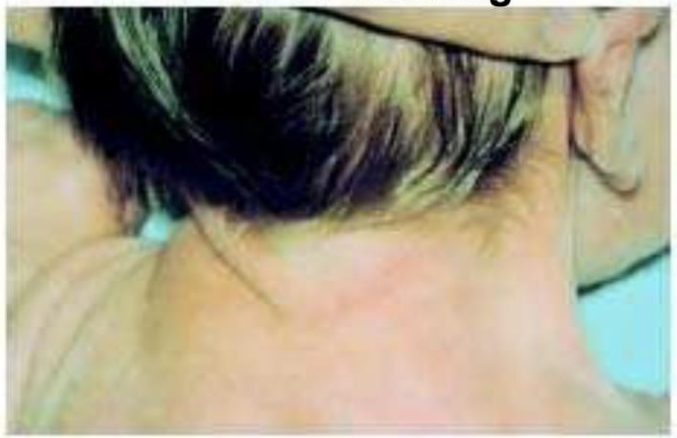
# Sex chromosome abnormalities

| Karyotype | incidence | name |
| --- | --- | --- |
| 45,X | (1/3000) | Turner syndrome |
| 47,XXX | (1/1000) | Trisomy X |
| 47,XXY | (1/1000) | Klinefelter syndrome |
| 47,XYY | (1/1500) | 47,XYY syndrome |

Phenotype: close to normal, obese and tall and subnormal intellectual , with no other problem even no fertility problems, bc the extra X will be inactivated

I put this beautiful girl just to show you that most of the turner will not be picked up early in life either in the post Natal with lymphoedema and cardiac issues or if they don't have, they will come later in life with pubertal issues like poor short stature, but they don't have a major distinctive features

**Low posterior hairline and neck webbing**



www.healthofchildren.com

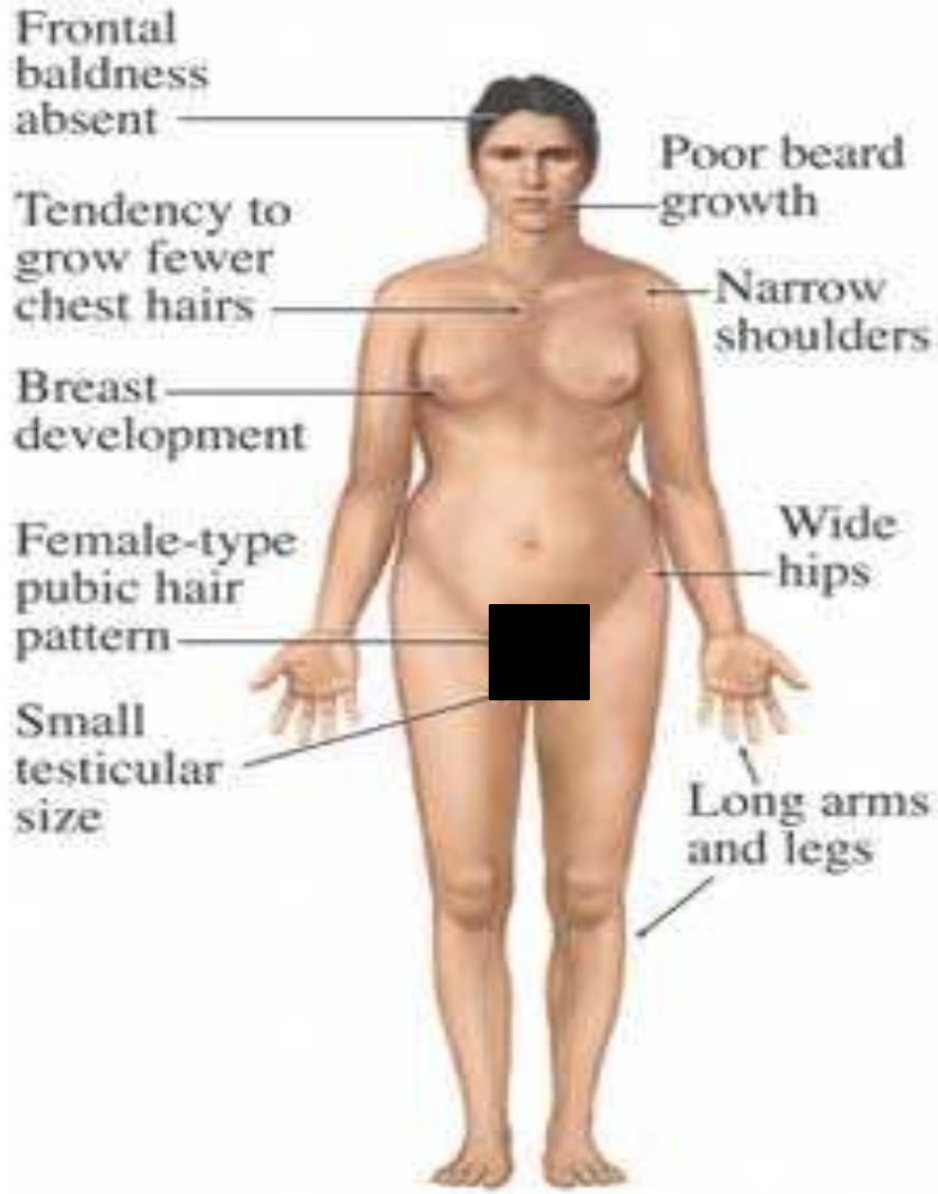
تباعد العينين

**Hypertelorism and low set ears**

Cardiac and hyperlipidemia in the future are the main issues

# Turner syndrome (monosomy X)

**Responsible genes**: X genes that escape inactivation, *SHOX*
**Proteins:** *SHOX:* Short stature homeobox protein
**Cytogenetic locus**: *SHOX:* Xpter-p22.32
**Inheritance**: sporadic There's no specific mode of inheritance
**Clinical Features and Diagnostic Criteria**: congenital lymphedema, growth failure, normal intelligence (10% sig delays), coarctation of the aorta, bicuspid aortic valve, HLHS, hyperlipidemia, gonadal dysgenesis (10% 45,X go into puberty), hypothyroidism, diabetes, strabismus, recurrent OM, SNHL, Crohns, renal malformation, osteoporosis.
**Clinical Tests**: echo, renal US, TFTs, GH testing, FISH SRY
**Molecular Tests**: Karyotype Or FISH
**Disease Mechanism**: *SHOX:* thought to act as a transcription regulator with many down-stream targets that modify growth and stature. SHOX protein has been id'ed in the growth plate from 12 weeks GA to late childhood. Growth H. for short stature, Hormone replacement for gonadal dysgenis
**Treatment/Prognosis**: GH, HRT, gonadectomy if Y chromosome mosaicism (risk for gonadoblastoma). Need lifelong cardiac follow-up, at risk for aortic dilation and dissection with bicuspid aortic valve.




health.yahoo.com/media/healthwise/nr551770

# Klinefelter syndrome

**Clinical Features and Diagnostic Criteria**: Tall stature, slightly delayed motor and language skills, inc learning probs, testosterone plateaus age 14, small fibrosed testes, azoospermia and infertility, gynecomastia, inc cholesterol, slightly inc risk of autoimmune disorders and mediastinal germ cell tumors (1% risk)

Not always

Most of the time fertility issues

**Clinical Tests**:

**Molecular Tests**: karyotype, at least one extra chromosome to a 46,XY Karyotype

And FISH

**Disease Mechanism**: 1st or 2nd meiotic division nondisjunction of either parent. Maternal>paternal origin. +AMA effect

Hormonal replacement therapy

**Treatment/Prognosis**: Testosterone in mid-late adolescence for bone density, secondary sex characteristic development, muscle mass, cholesterol, increase libido, improved energy. Can do testicular biopsy and use any retrieved sperm for ICSI (inc risk sex chrom abnormality so follow with PGD

They need some fertility techniques to help them reproduce

# Microdeletion/microduplication syndromes

Its complex bc more than 1 gene are involved, sometimes they're not related to each other CNS+ renal + CVS + skin….with no specific constellation of the phenotype

- **Complex phenotypes due to dosage imbalance of multiple, unrelated genes which happen to be contiguous on chromosome. In some cases, clinical syndrome defined before genetic basis known.**
- **Contiguous gene syndromes** Aneusomy means different number
- **Segmental aneusomy syndromes**
- **Genomic Disorders (subset mediated by segmental duplications – seg dup)**
- **Mechanisms include deletion, duplication, and UPD = any deviation from normal, biparental inheritance**

Some have a specific phenotype like DiGeorge, presentation is very specific to hypocalcemia, if you have a cardiac issue check immediately for DiGeorge also early in life XRAY may show thymus hypoplasia or aplasia

# DiGeorge syndrome/ VCFS/del(22)(q11.2)

- ~1/4,000 – most common mdel syndrome
- Thymus hypo/aplasia
  → cellular immunodeficiency
- Parathyroid hypo/aplasia → hypocalcemia
- DD, ID
- Cardiovascular:
  - Conotruncal heart defects, aortic arch defects
- Dysmorphic features: Facial dysmorphism
  - Micrognathia, ear anomalies, cleft palate, short palpebral fissures, short upper lip

22q pan 2

# del(22)(q11.2)

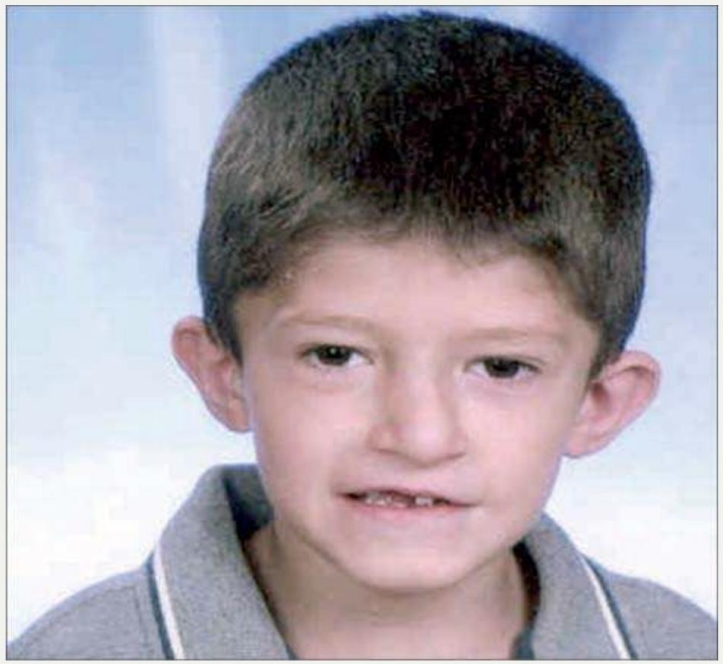
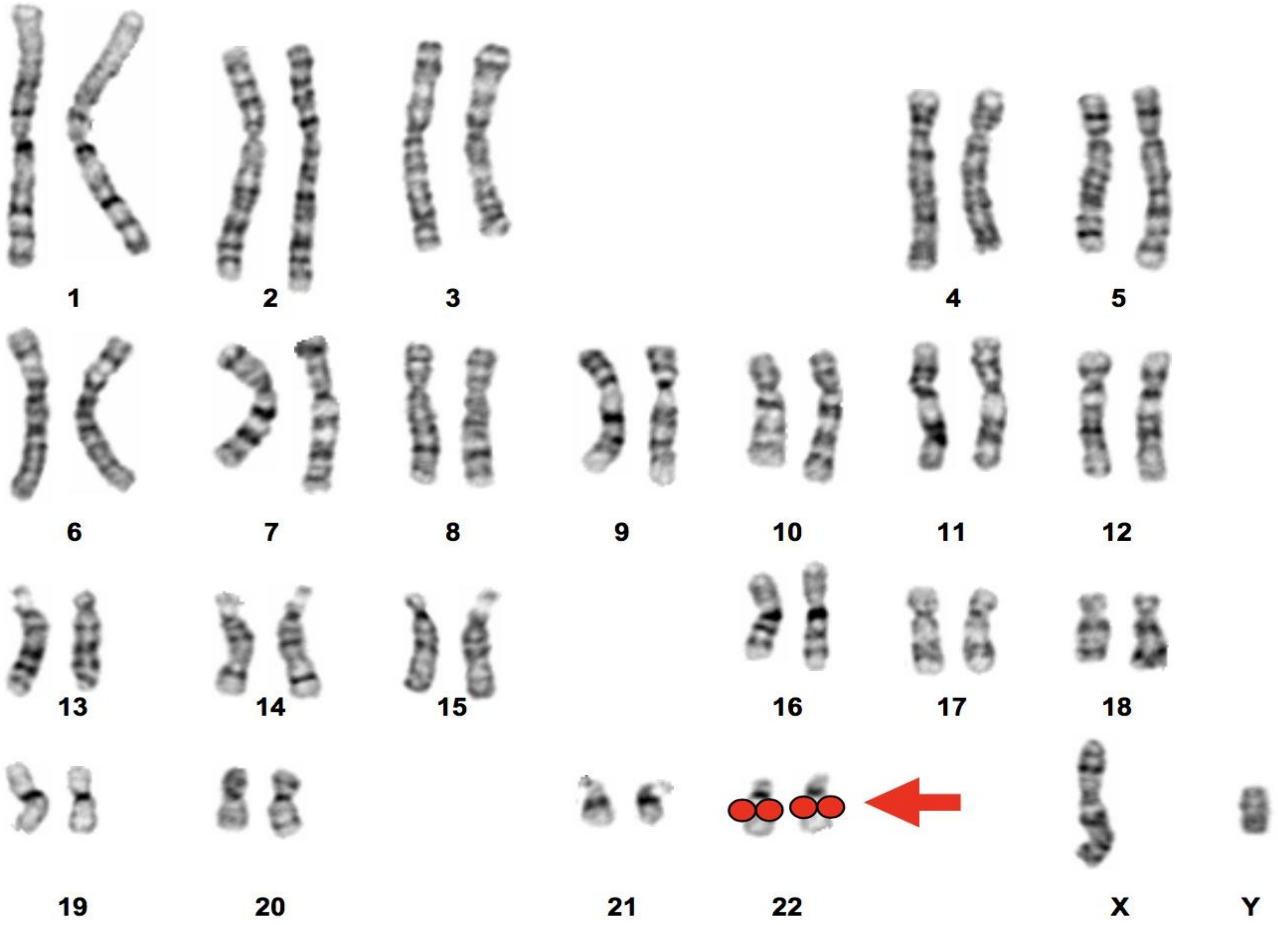


Image from www.thelancet.com

Image from www.pediastaff.com

## 22q Foundation - www.22q.org




**Resolution: Size of probe (~100 kb); but not equal across entire genome**

**Requires at least 500-600 evenly spaced DNA probes to match the power of the karyotype!!!**

We can't also see the deletion area through karyotyping bc its considered microdeletion

# Facial Features

**Microcephaly** Most imp
**Round face**
**Hypertelorism**
**Micrognathia** Small chin
**Epicanthal folds**
**Low-set ears**

Also severe intellectual disability

www.specialchild.com/archives/poster-child023

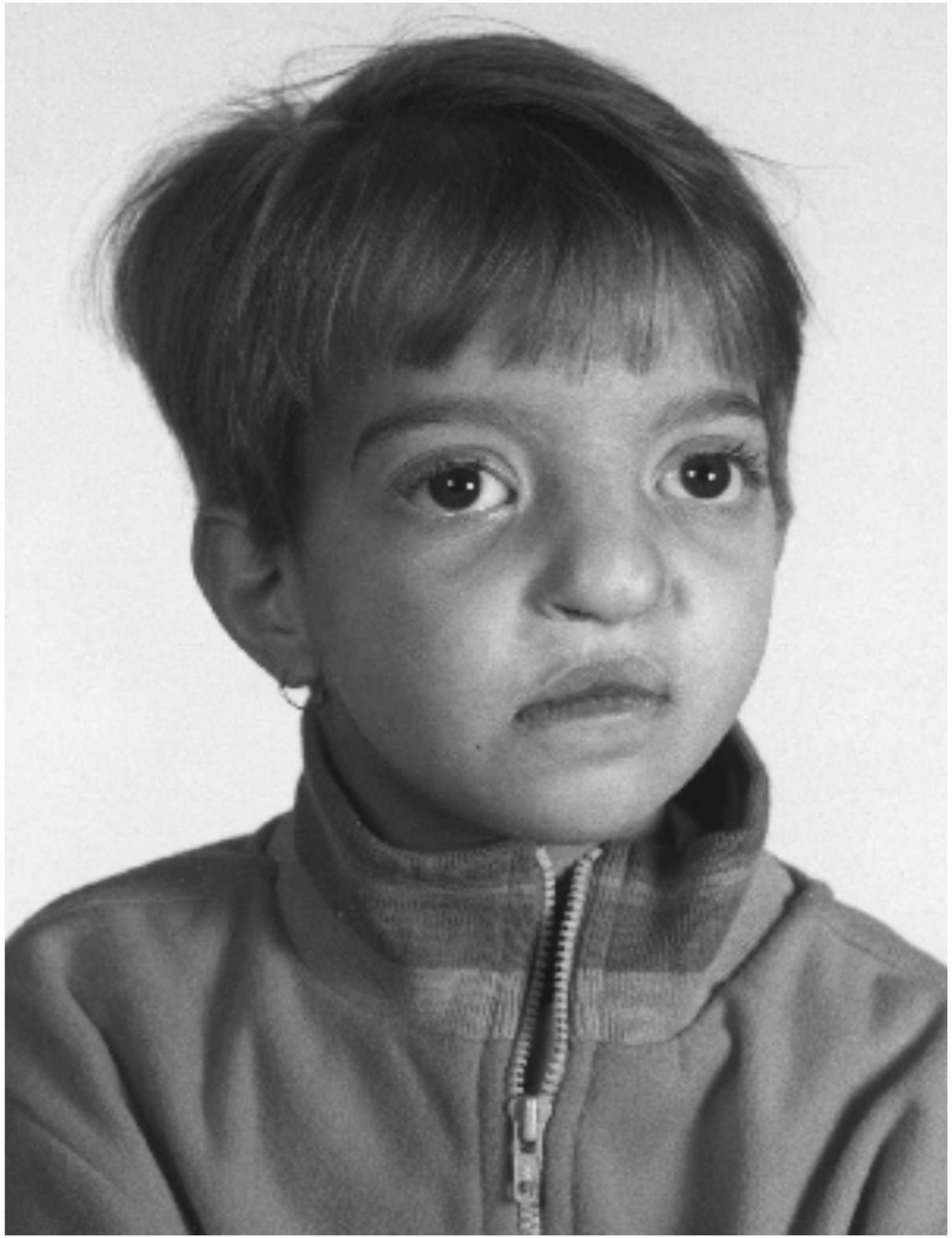
# Cri Du Chat del(5p) 5p deletion

- **Cat-like cry in babies (hypoplastic larynx)** They cry like a meow sound
- **IUGR, microcephaly, hypotonia, ID** Intellectual disability
- **Hypertelorism, round face, epicanthal folds, down slanting palpebral fissures, strabismus**
- **Heart defect**
- **Transverse palmar creases**
- **Most *de novo*, ~15% from balanced carrier parent**

Telling the patient its denovo is important if they consider to have another baby

# Cri du chat (5p minus syndrome)

**Responsible gene(s)**: RPS14?, microRNA 145 and 146a?
**Protein(s):**
**Cytogenetic locus**: 5p15.2
**Inheritance**: 12% due to unequal segregation of a translocation or recombination involving a pericentric inversion in one of the parents, 85% sporadic de novo deletions (80% are on the paternal chromosome)
**Clinical Features and Diagnostic Criteria**: Cat-like cry (abnormal laryngeal development), slow growth, microcephaly, ID, hypotonia, strabismus, characteristic facial features. Cat-like cry only when deletion limited to band 5p15.32
we can do is microarray
**Molecular Tests**: Most are visible, a few are submicroscopic and diagnosed by FISH for the critical region.
**Disease Mechanism**: A study of 50 patients with deletions ranging from 5p15.2 to 5p13 and found no correlation with size of deletion and degree of mental impairment
**Treatment/Prognosis**: Supportive care



medgen.genetics.utah.edu

**Facial Features:**
**'Greek warrior helmet appearance' of the nose (the broad bridge of the nose continuing to the forehead)**
**Microcephaly**
**High forehead with prominent glabella**
**Ocular hypertelorism**
**Epicanthus**
**Highly arched eyebrows**
**Short philtrum**
**Downturned mouth**
**Micrognathia**
**Poorly formed ears with pits/tags**

# Wolf-Hirschhorn syndrome /del(4p)

- **IUGR, microcephaly, hypotonia, severe ID**
- **Dysmorphic facial features** Most imp feature is the Greek warrior helmet appearance
  - **hypertelorism, prominent glabella, arched eyebrows, nose broad or beaked, CL/P, short upper lip**
- **Other**
  - **scalp defect, hypospadias, heart defect, seizures, preauricular pit**
- **Most *de novo*, 10-15% from balanced carrier parent**

So, when we counsel the parents after getting the microarray report, we tell them its mostly denovo don't worry however we need to do karyotyping for both of you to see if you are carriers balanced translocation or not , to give them reassuring results.

Most imp part of the lecture the mendelian disease

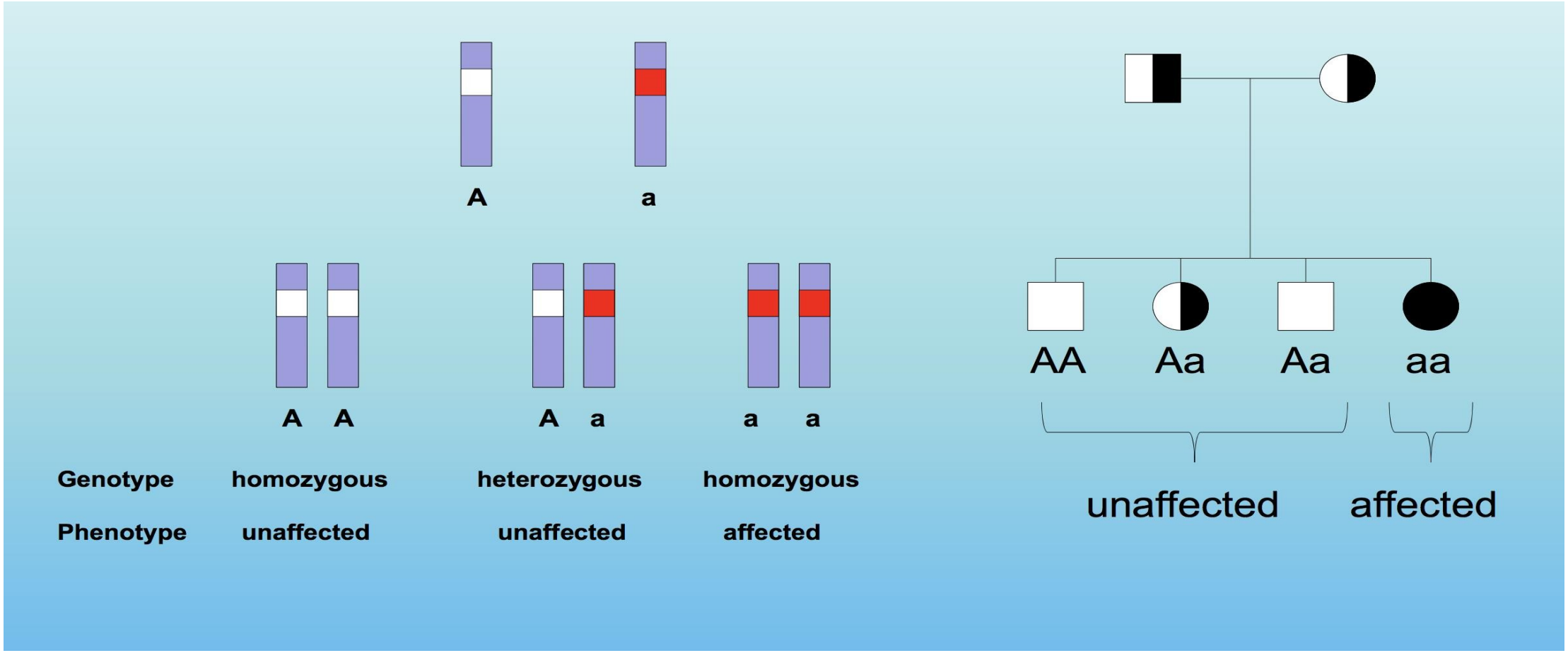
# Single gene disorders

- Recognize patterns of Mendelian transmission
- Describe deviations from classical Mendelian transmission
- Common examples of mendelian disorders
- Genetic counseling

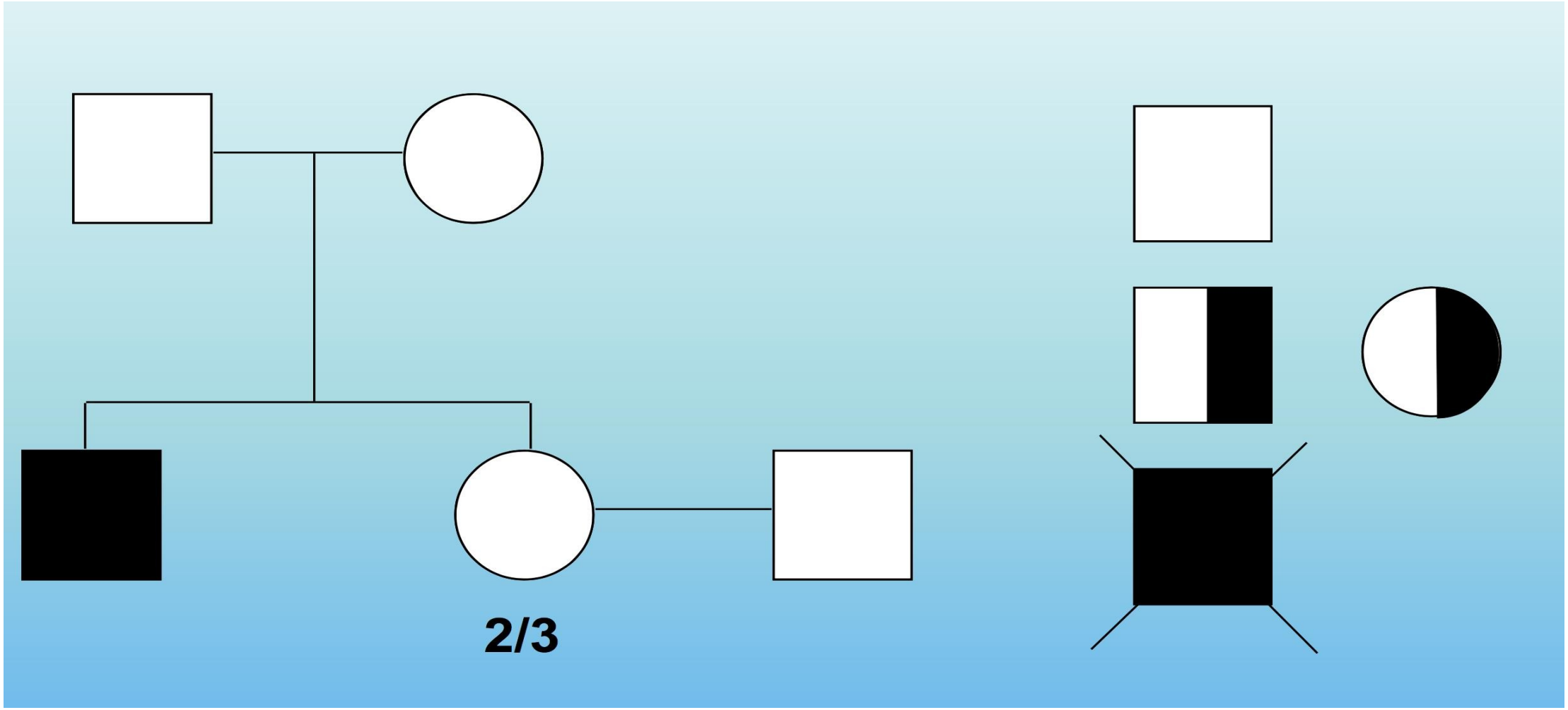
When we counsel, we tell them the chances are 4, 1 chance is homozygous taking both mutant allele (affected) , wild type taking both healthy alleles from parents, and 50% taking a mutant allele either from the mother or father (heterozygous)

# Autosomal recessive

Scenario: a family with one affected offspring with cystic fibrosis a recessive disease both parents are carriers and the mother brought one of her healthy offspring (a sibling) and told you what is the chance of this child to be carrier?
First we exclude the healthy one and we remain with 3 chances, and the chance of being a carrier will be 2/3. and the chance of having a wild type (healthy) not carrier is 1/3

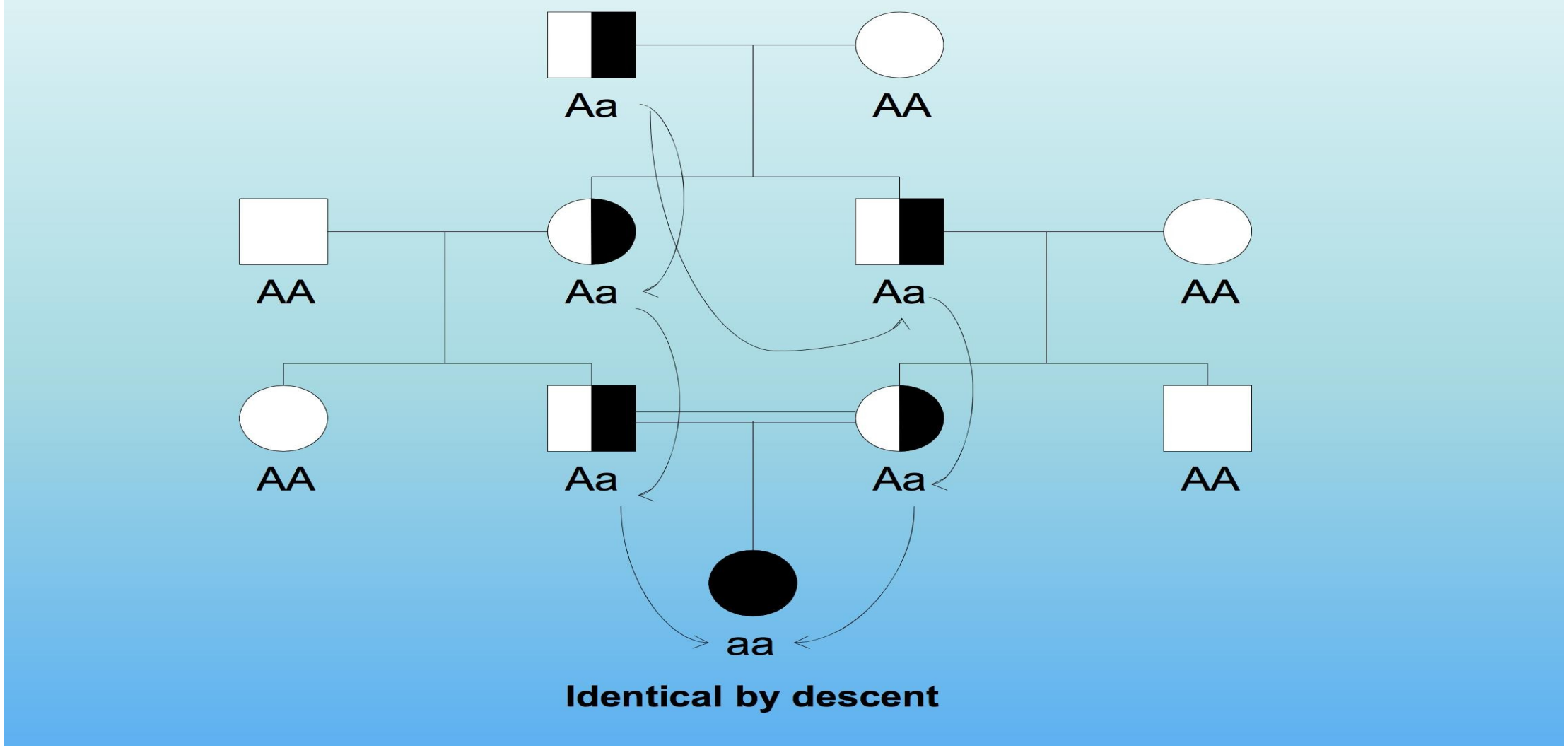


# Genetic counselling



# Consanguinity

It increases the risk of recessive disease because they're identical by descent and carry the same genetic variation

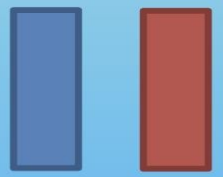


# Recessive mechanism

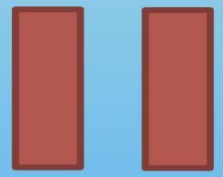

Loss of function mutations: deletion, frameshift, stop, missense

A problem in the gene causes a deficiency in protein (ex. Enzyme)


Complete absence of product or significant reduction of function

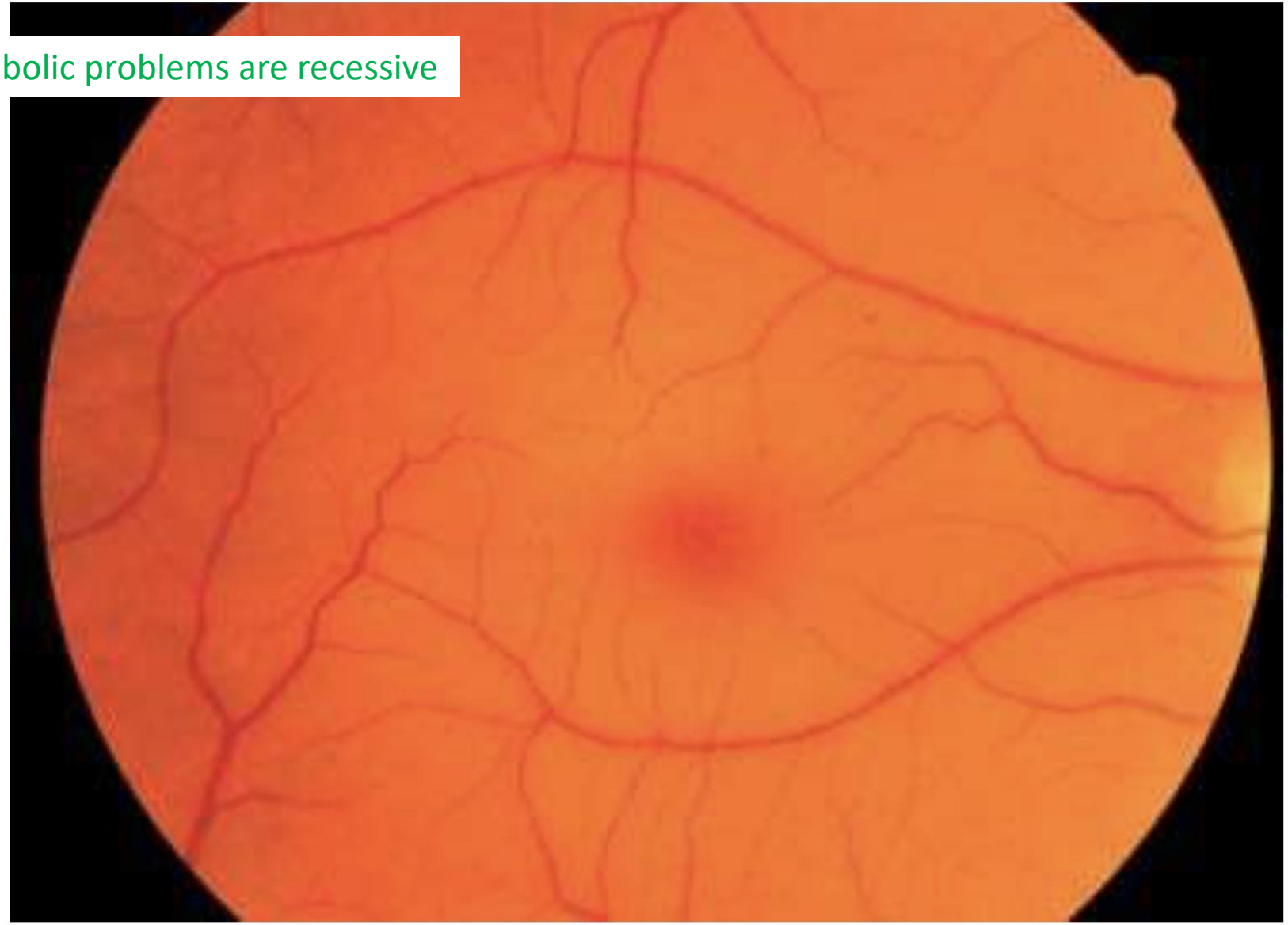


Heterozygote – sufficient activity to avoid phenotype



Homozygote – profound loss of activity results in phenotype

Most metabolic problems are recessive



**Cherry red spot of the macula**

http://themedicalbiochemistrypage.org/images/cherryredspot.jpg

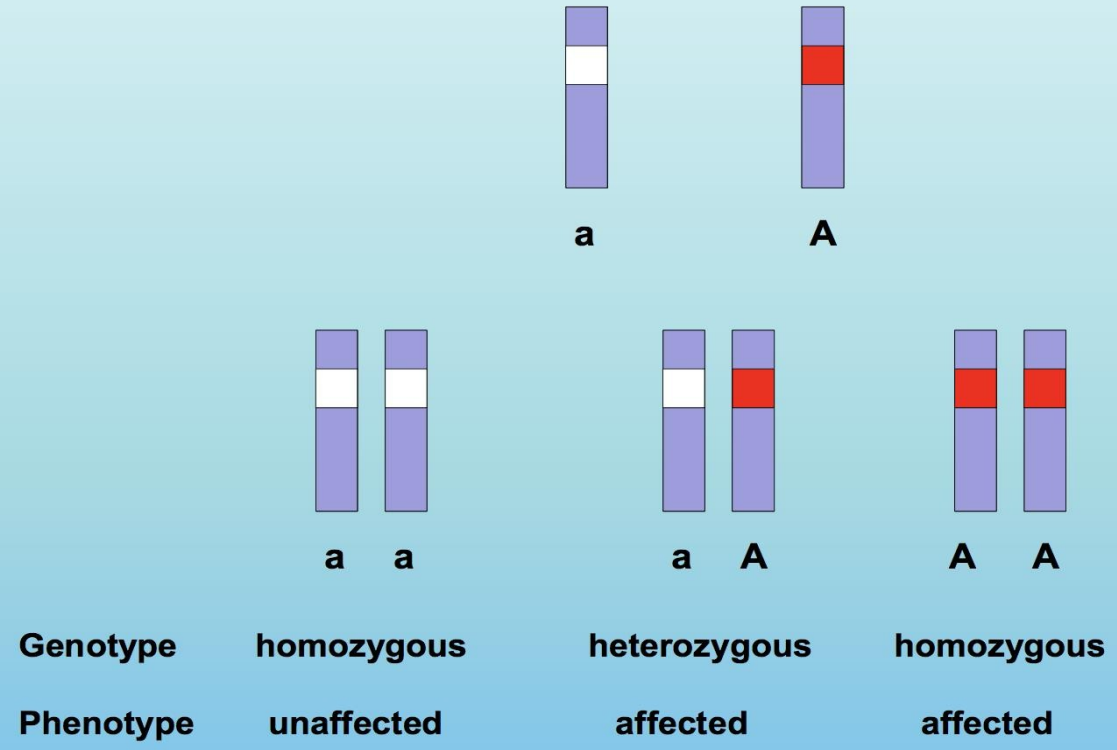
No need to go into details, just know that cystic fibrosis and tay sachs are all example of autosomal recessive

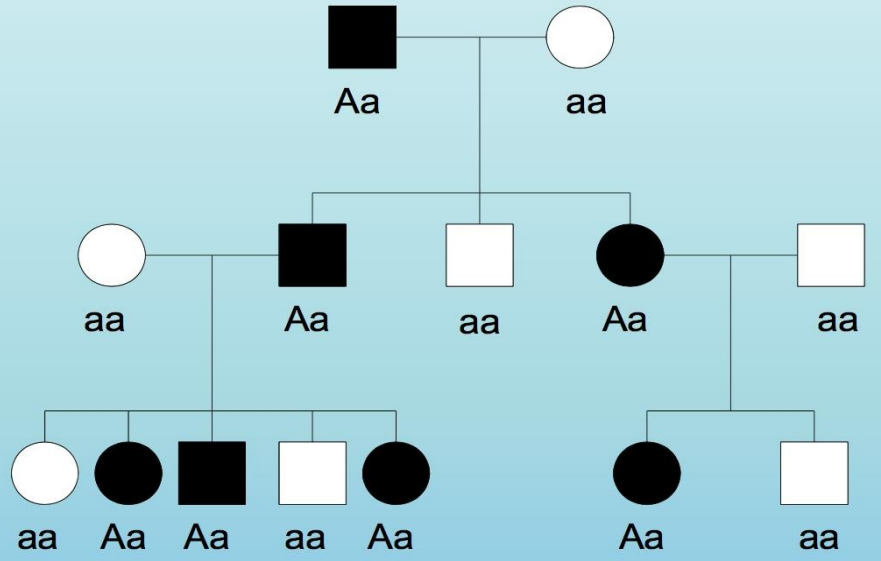
# Tay Sachs disease

**Responsible gene**: *HEXA*
**Protein:** Hexosaminidase A
**Cytogenetic locus**: 15q23-q24
**Inheritance**: AR
**Clinical Features and Diagnostic Criteria**: Infantile weakness starts at 6 mo, exaggerated startle, seizures and vision loss by the end of the first year, neurodegeneration continues- deaf, cannot swallow, weakening of muscles, and eventual paralysis, death in toddler years. Juvenile muscle coordination problems, seizures, and vision problems starting as young children. Chronic and adult onset start later, progress more slowly, more rare.
**Clinical Tests**: HEXA enzyme activity, cherry red spot on eye exam
**Molecular Tests**: Follow enzyme testing with DNA testing (some with a positive enzyme assay have a pseudodeficiency allele that does not cause Tay Sachs). *HEXA* 6 common mutation panel: 92% of Ashkenazi Jewish
**Disease Mechanism**: Accumulation of GM2 gangliosides in the brain
**Treatment/Prognosis**: Supportive only

# Autosomal dominant

Heterozygous is affected in autosomal dominant, one copy of allele is enough with 50% risk

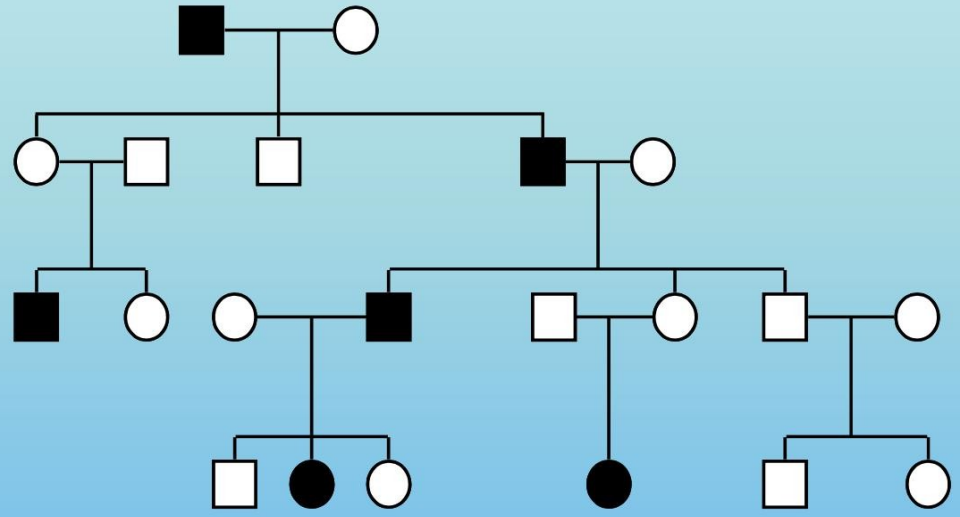


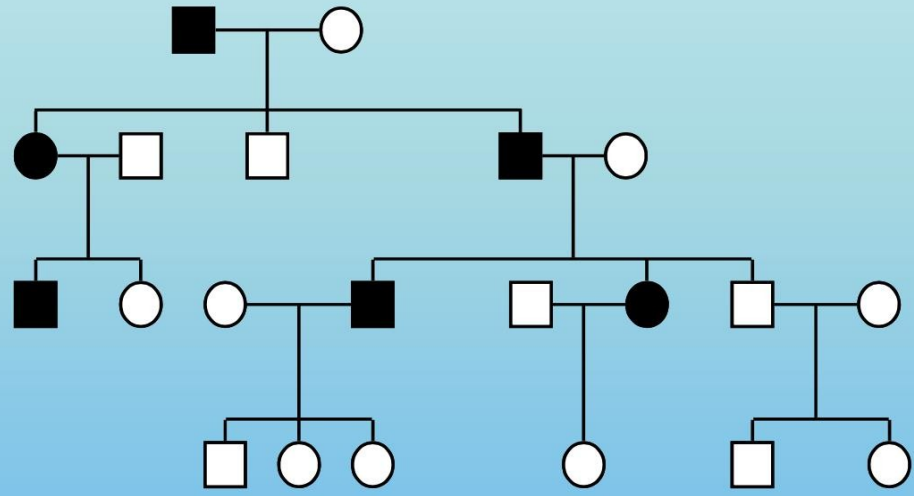



# Penetrance So this is showing or not showing

The presentation of the phenotype if you carry the genotype, penetrance is the chance of showing the phenotype
Reduced penetrance means that its not always if you carry the genotype, you'll show the phenotype (skipping generations)

*Fraction of individuals who carry a gene who manifest a specified phenotype*



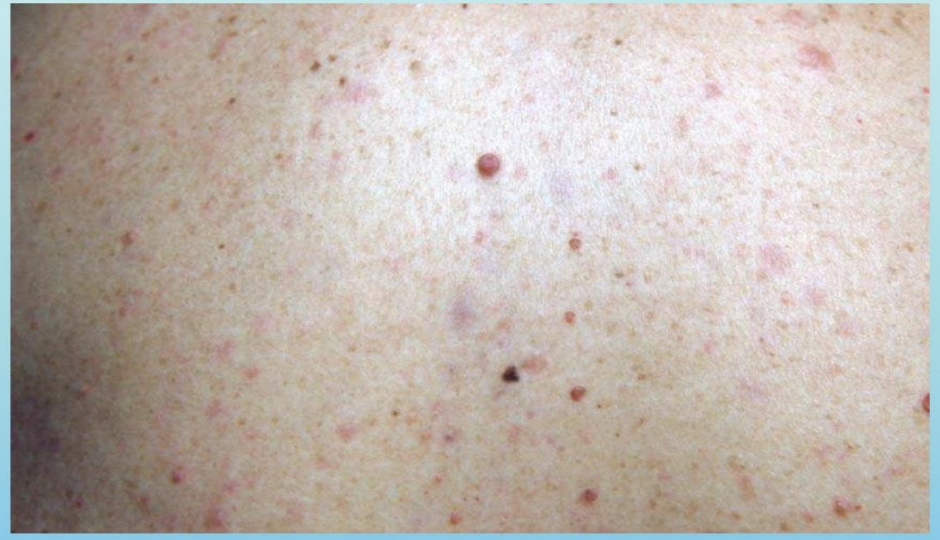


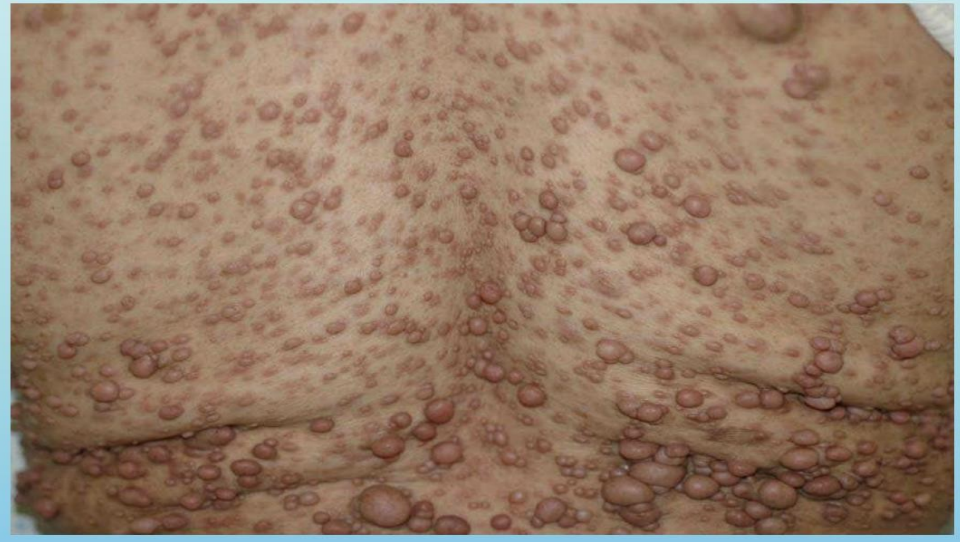
Variable phenotype for ex. Mother has MS with very reduced phenotype and symptoms and her offspring carry the same genotype but show the complete phenotype of MS

# Expressivity

So this is like the severity

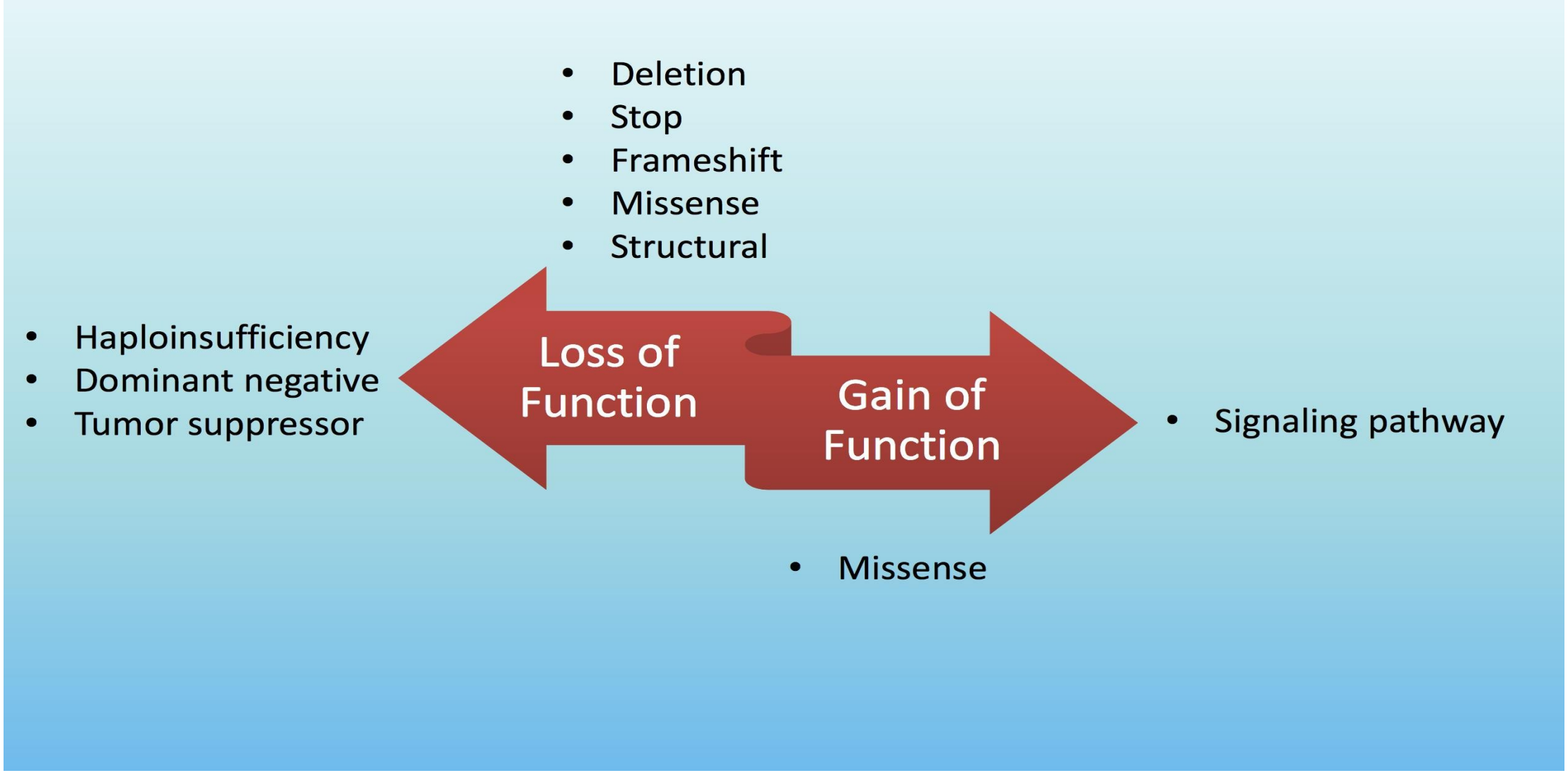
different modes or degrees of expression of trait in population



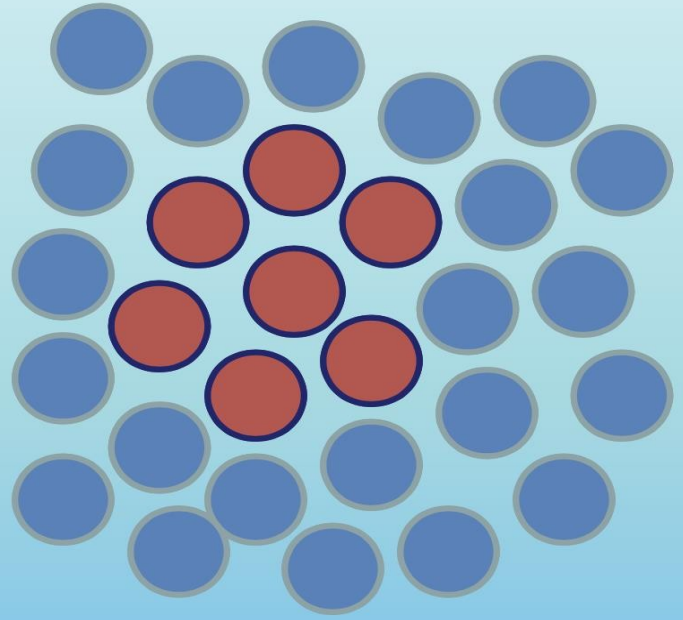


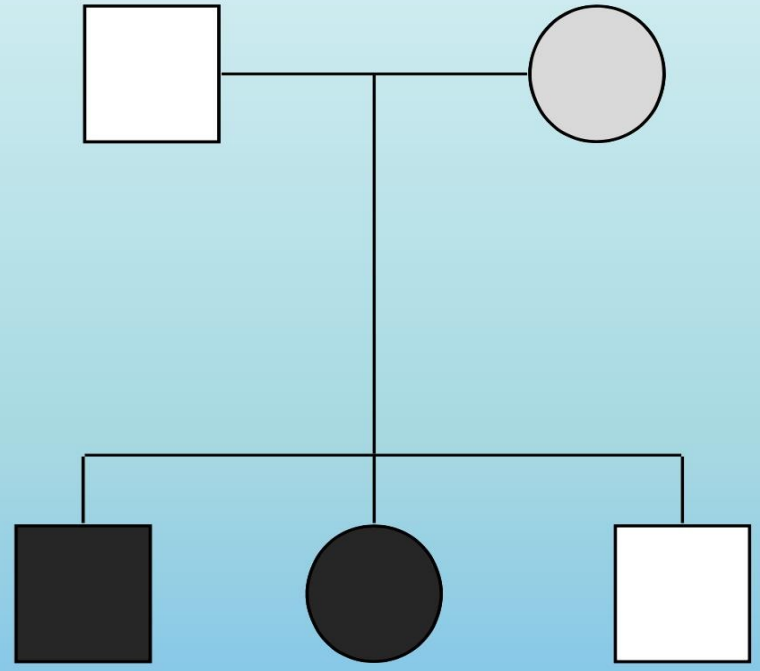
Neurofibromas in NF1

# Dominant mechanism

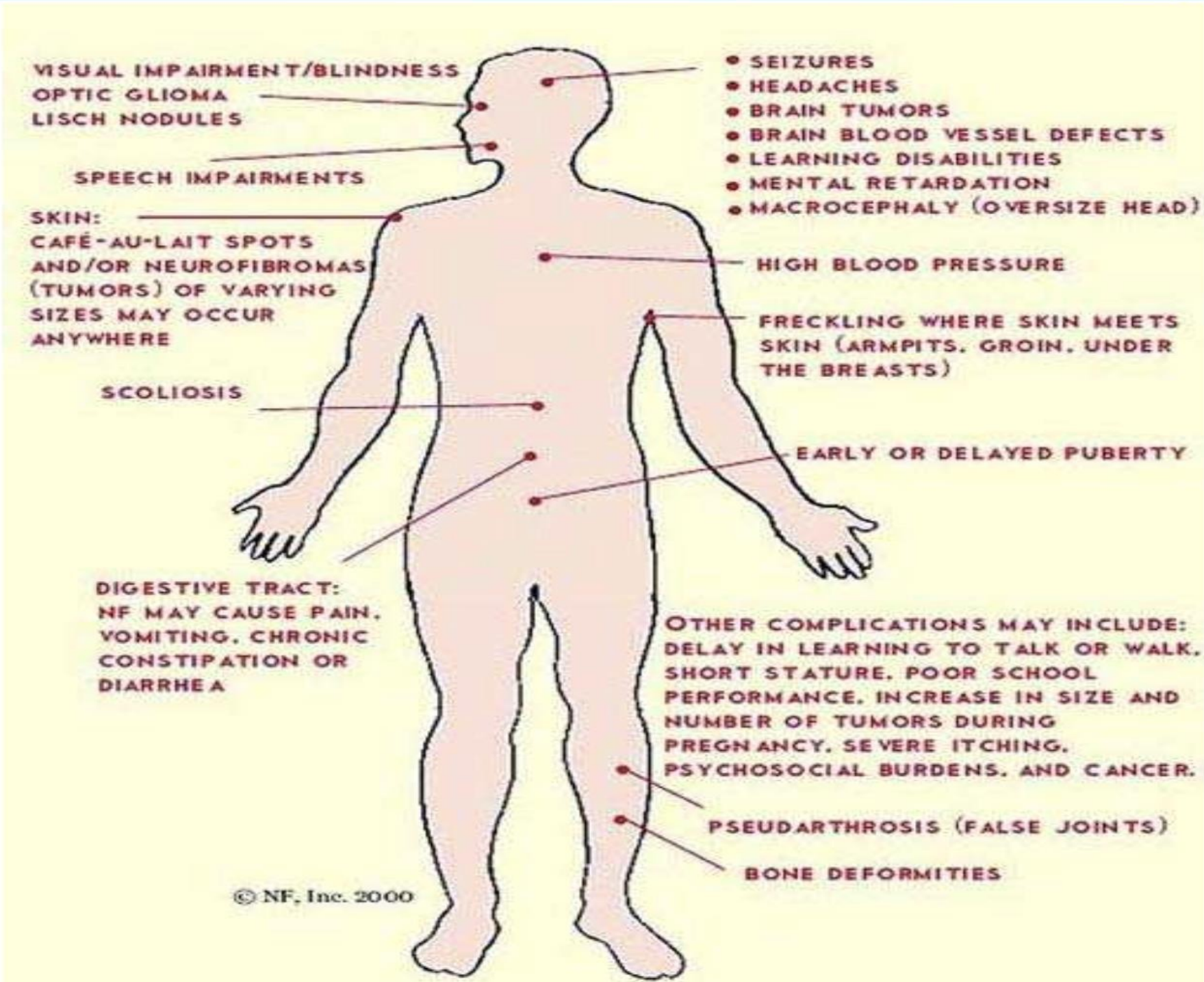


# Mosaicism





- Germ line
- Somatic

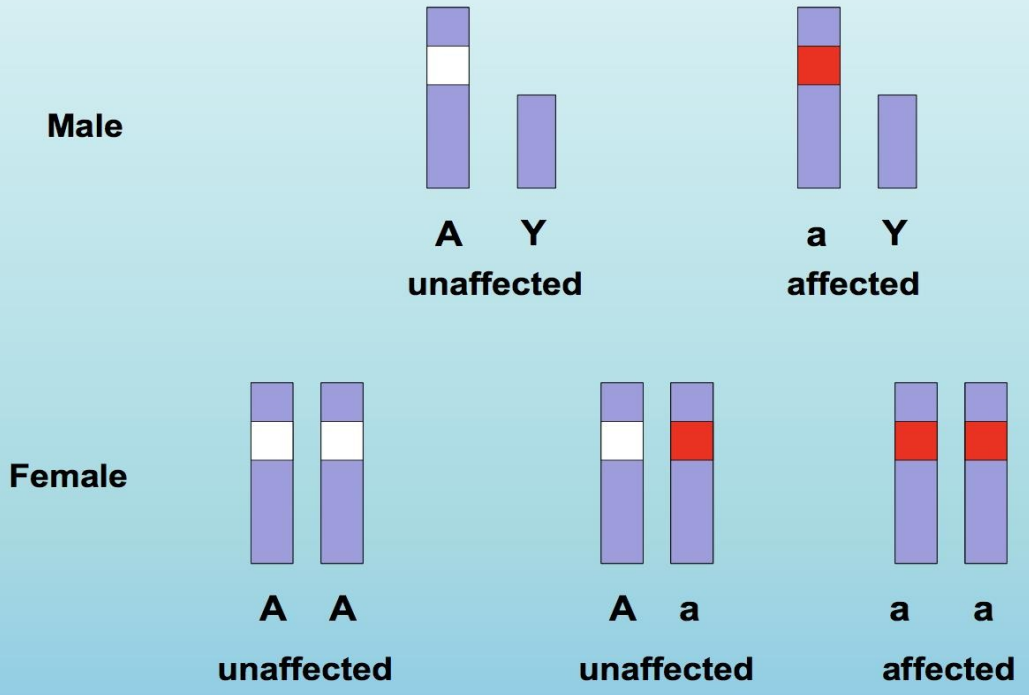

VISUAL IMPAIRMENT/BLINDNESS
OPTIC GLIOMA
LISCH NODULES
SPEECH IMPAIRMENTS
SKIN:
CAFÉ-AU-LAIT SPOTS AND/OR NEUROFIBROMAS (TUMORS) OF VARYING SIZES MAY OCCUR ANYWHERE
SCOLIOSIS
DIGESTIVE TRACT:
NF MAY CAUSE PAIN, VOMITING, CHRONIC CONSTIPATION OR DIARRHEA
SEIZURES
HEADACHES
BRAIN TUMORS
BRAIN BLOOD VESSEL DEFECTS
LEARNING DISABILITIES
MENTAL RETARDATION
MACROCEPHALY (OVERSIZE HEAD)
HIGH BLOOD PRESSURE
FRECKLING WHERE SKIN MEETS SKIN (ARMPITS, GROIN, UNDER THE BREASTS)
EARLY OR DELAYED PUBERTY
OTHER COMPLICATIONS MAY INCLUDE: DELAY IN LEARNING TO TALK OR WALK, SHORT STATURE, POOR SCHOOL PERFORMANCE, INCREASE IN SIZE AND NUMBER OF TUMORS DURING PREGNANCY, SEVERE ITCHING, PSYCHOSOCIAL BURDENS, AND CANCER.
PSEUDARTHROSIS (FALSE JOINTS)
BONE DEFORMITIES
© NF, Inc. 2000

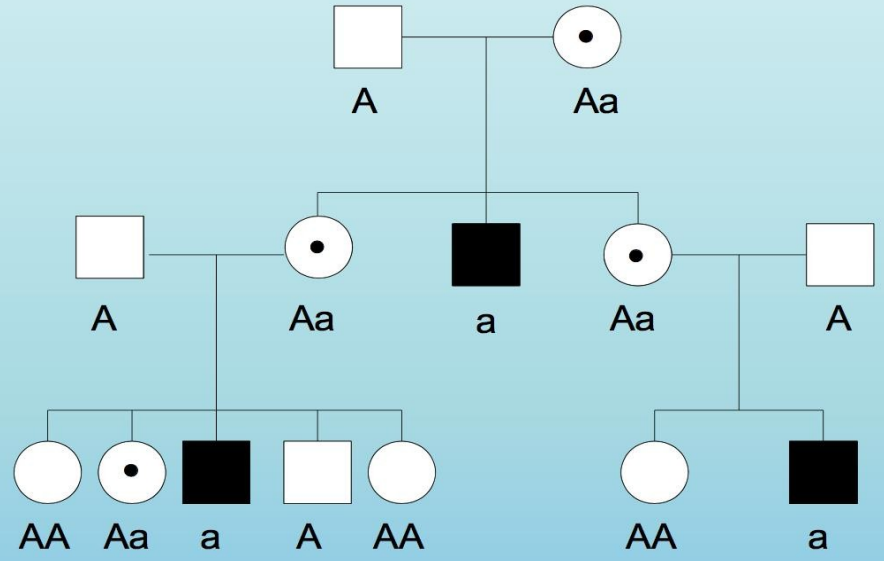
# Neurofibromatosis 1

**Responsible gene**: *NF1*
**Protein: Neurofibromin**
**Cytogenetic locus**: 17q11
**Inheritance**: AD One of the commonest autosomal dominant mutations
**Clinical Features and Diagnostic Criteria**: 2 or more of: 6x5mm (prepubertal) or 6x15mm (postpubertal) café au lait, 2 or more neurofibromas, one plexiform neurofibroma, axillary or inguinal freckling, optic glioma, 2 or more Lisch nodules, sphenoid dysplasia or thinned long bone cortex, 1st degree relative with NF-1
**Clinical Tests**: x-ray, eye exam, brain MRI Clinical criteria is enough for diagnosis
**Molecular Tests**: >500 mutations reported, usually unique to a particular family
**Disease Mechanism**: Loss of function mutations impair ras GTPase mediated cellular proliferation and tumor suppression
**Treatment/Prognosis**: The majority live normal lifespan. Surgery for bone malformations or painful or disfiguring tumors

# X-linked

The phenotype will be expressed in males, females are carrier s
If the mother is a carrier, then the chance of the female offspring is 50% carrier 50% healthy and the male offspring will be 50% affected and 50% healthy

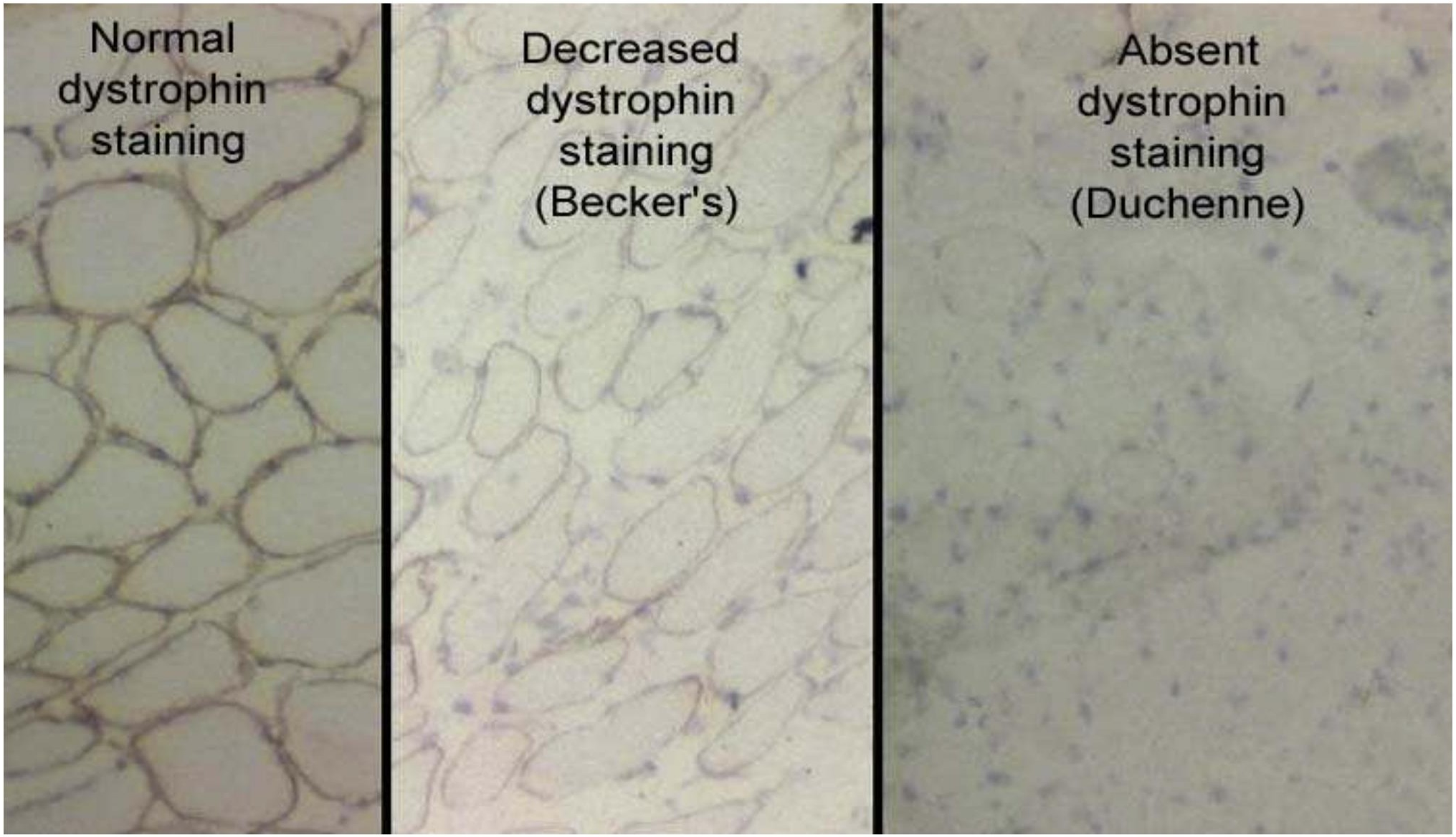



No male to male transmission

# Duchene and Becker muscular dystrophy (DMD/BMD)

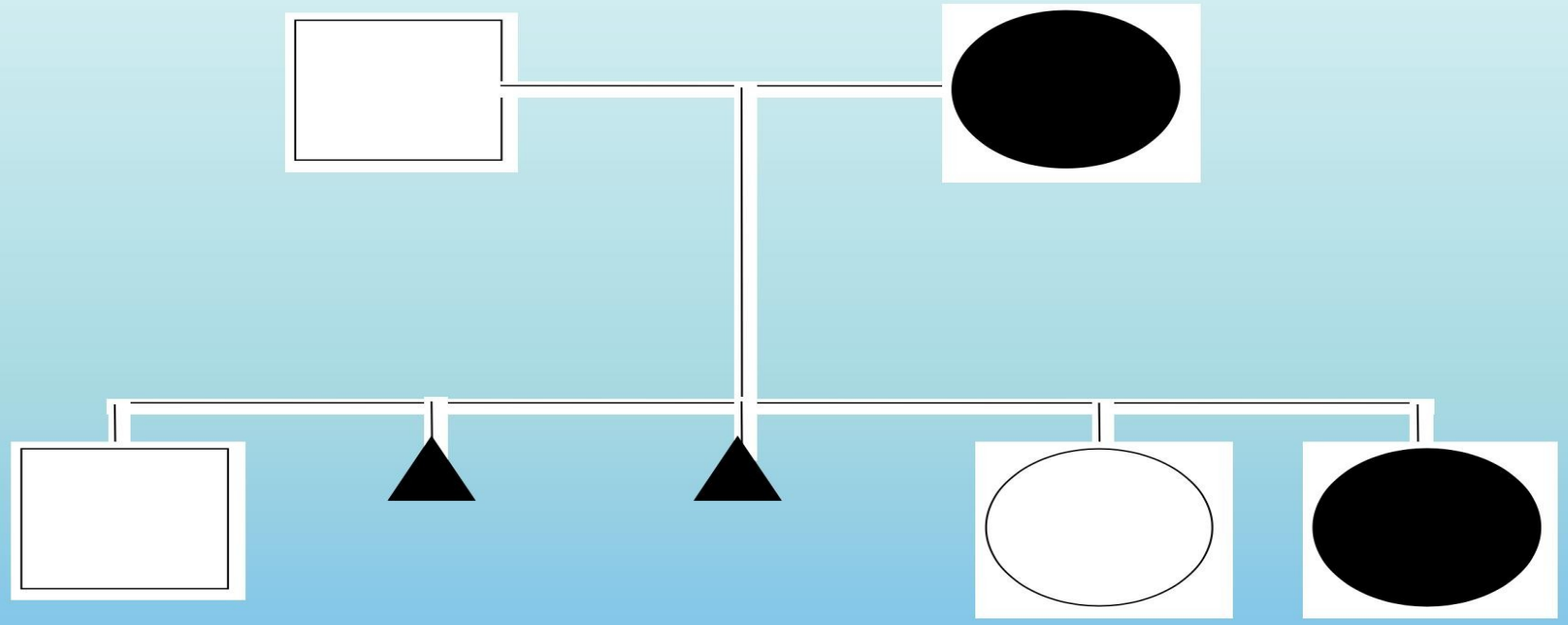
**Responsible gene**: *DMD* A big gene in X chromosome
**Protein:** Dystrophin
**Cytogenetic locus**: Xp21.2
**Inheritance**: XLR
**Clinical Features and Diagnostic Criteria**: DMD: Symptoms present before age 5, progressive symmetrical muscular weakness, proximal>distal, calf hypertrophy, dilated cardiomyopathy (DCM). BMD: Later onset, less severe, weakness of quadriceps may be only sign, activity induced cramping. Preservation of neck flexor muscles (unlike DMD). DCM can occur in isolation
**Clinical Tests**: CK 10x nl in DMD, 5x nl in BMD. Unreliable test for carrier females, tends to decrease with age.
**Molecular Tests**: Multiplex PCR: DMD gene deletion (65% DMD, 85% BMD). Southern or quantitative PCR for gene duplication (6% DMD), *DMD* sequencing for small del/ins or point mutations (30% DMD)
**Disease Mechanism**: Dystrophin binds actin and other membrane proteins. Mutations that lead to lack of dystrophin expression: DMD, those that lead to abnormal quality or quantity of dystrophin: BMD.
**Treatment/Prognosis**: Supportive therapy, steroids may prolong walking 2-3 yrs. DMD: wheelchair dependent by age 13, ventilator by age 20, survival into 20's. BMiDs: Wheelchair after age 16 (if at all), survival 40-50's. Carrier females at risk for DCM.




http://img.orthobullets.com/Pediatrics/Neuromuscular%20problems/Duchenes%20Muscular%20Dystrophy/Images/dystrophin_stains.jpg

# X-linked dominant lethal in male

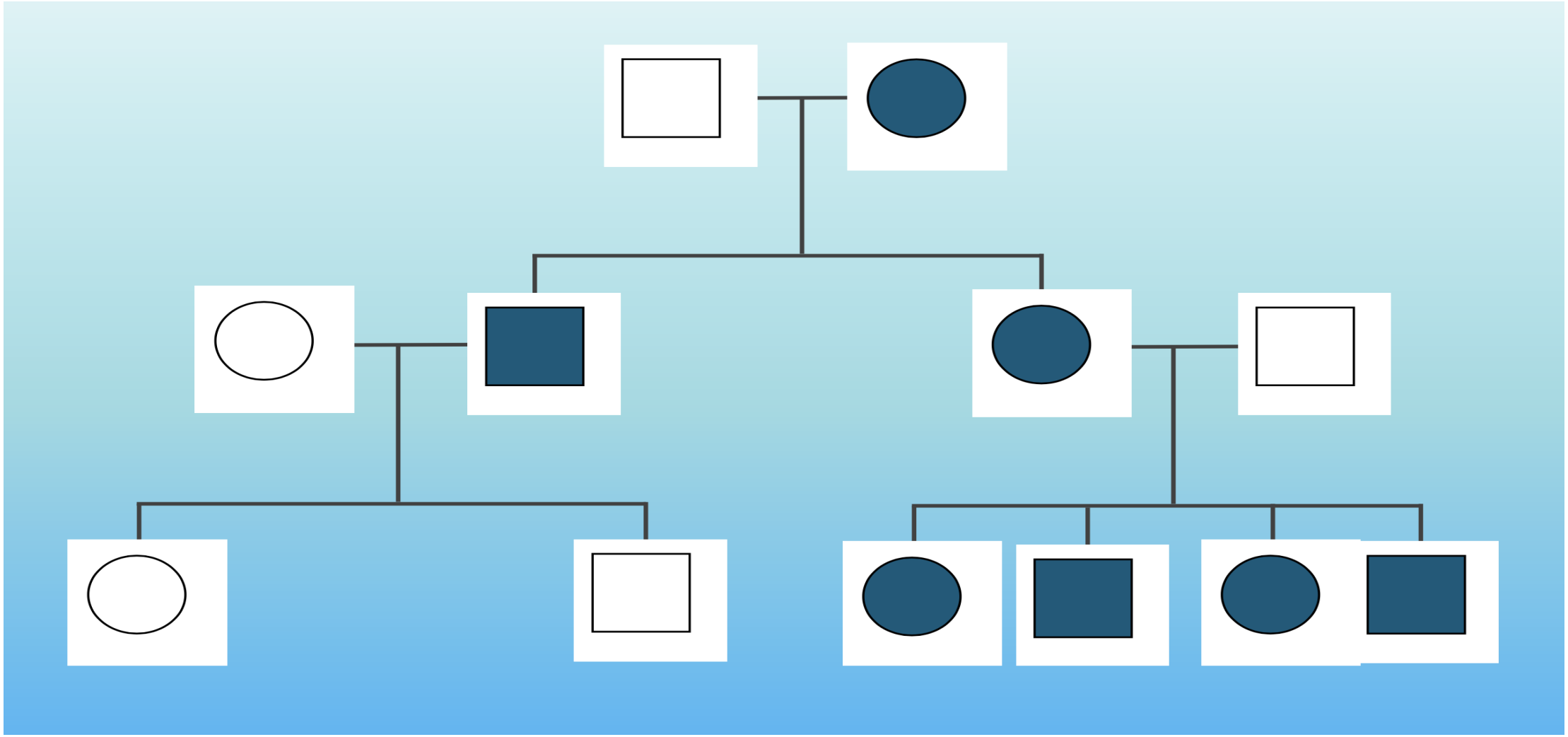
Its very rare and dominant in males, it can show in the female but its lethal in males



Males who inherit mutation die *in utero*
Females who inherit mutation are affected

# Maternal inheritance

Transmitted both to the male and female from the maternal side, ex. Most mitochondrial disorders

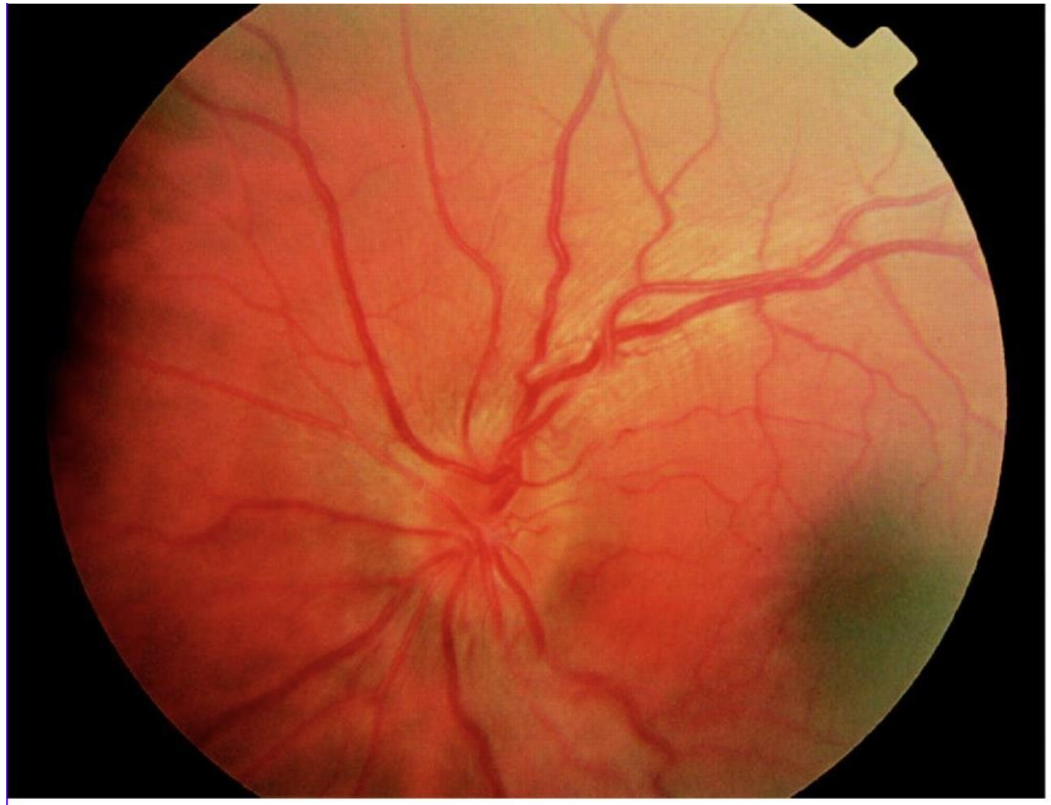


# Leber hereditary optic neuropathy

**Responsible genes**: *MTND1, MTND4, MTND5, MTND6*
**Proteins:** Complex I subunits of the mitochondrial respiratory chain Mitochondrial have maternal inheritance bc its present in the egg and absent in the sperm
**Cytogenetic loci**: Mitochondrial
**Inheritance**: Mitochondrial
**Clinical Features and Diagnostic Criteria**: Blurred or clouded vision progressing to degeneration of the retinal nerve and then optic atrophy. Fundus: vascular tortuosity of central retinal vessels, circumpapillary telangiectatic macroangiopathy, and swelling of the retinal nerve fibers
**Clinical Tests**: Visual field assessments, ERG, VEP
**Molecular Tests**: Targeted mutation analysis: G11778A (70% cases), G3460A, T14484C (15%)
**Disease Mechanism**: Focal degeneration of the retinal ganglion cell layer and optic nerve
**Treatment/Prognosis**: No treatment available, worsened by smoking or EtOH

Example of a mitochondrial disease

# Leber hereditary optic neuropathy



(Yu-Wai-Man P et al. J Med Genet 2009;46:145-158)

**Acute fundal appearance in Leber hereditary optic neuropathy showing disc hyperaemia, swelling of the parapapillary retinal nerve fibre layer and retinal vascular tortuosity.**

Most common is fragile X, you should know the meaning of dynamic mutation

# Dynamic mutation (unstable repeat expansion)

- Dynamic mutation: that change from generation to generation.
- The expansion beyond the normal can alter gene expression and function Might be silenced or overactivated
- Parental transmission bias: anticipation occurs the mutant allele transmitted through the affected father or mother .

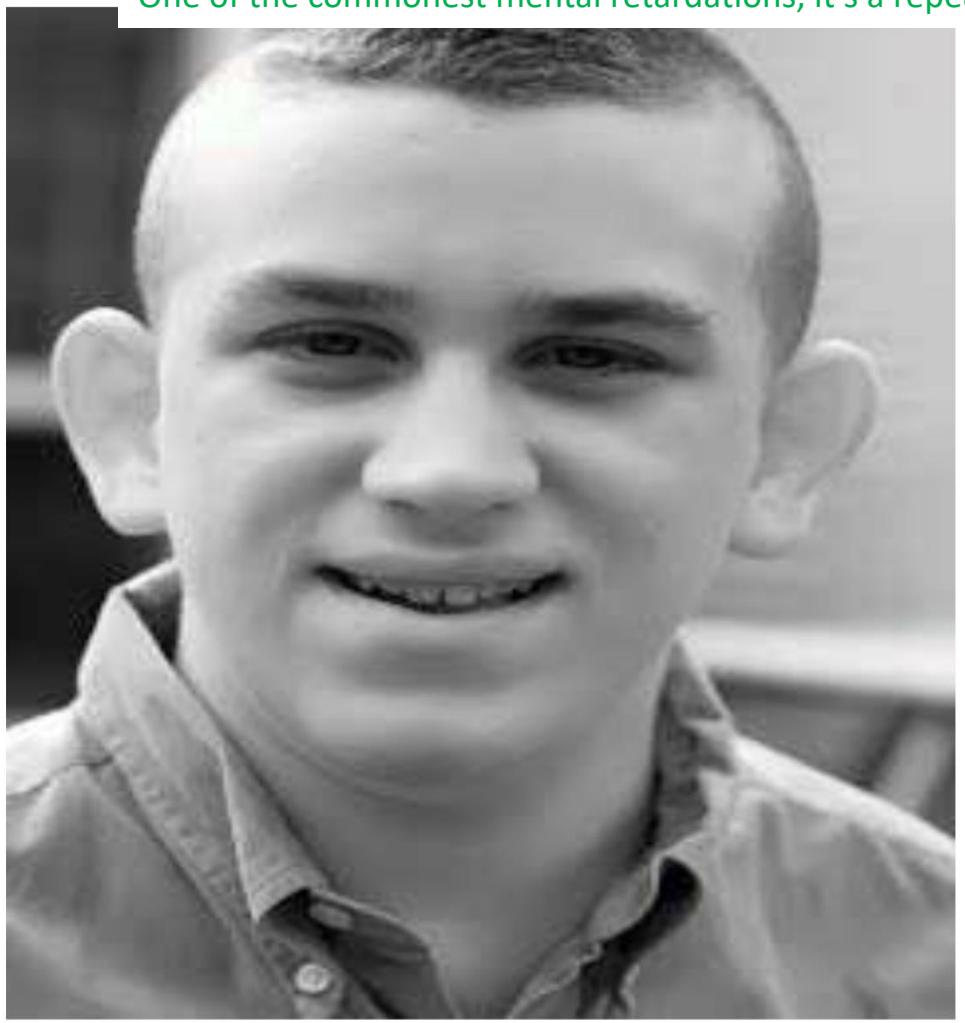
  Sometimes its worse and severe if transmitted through the father and sometimes it gets worse and severe if transmitted through the mother
- The expansion of premutation alleles occurs primarily in the female germline in FGXS but largest expansion causing juvenile onset HD in male germline

  If the father is a carrier of the premutation its more likely, it'll cause severe phenotype in his offspring
  If the mother is a carrier of the premutation allele of FGXS she'll more likely transmit to her male offspring

# FRAGILE X

NEUROLOGIC DISORDERS

One of the commonest mental retardations, it's a repeat expansion mutation



**Facial Features:**
**Long face,**
**Prominent forehead**
**Large ears**
**Prominent jaw**

(suzannebalvanz.blogspot.com/2007_07_01_archive.html)

In the female carriers, they suffer from milder form but with anxiety, ocd , ovarian failure
In the carrier male (<200 repeats) progressive intention tremor, ataxia, parkinsonism its called fraxF

# Fragile X syndrome

NEUROLOGIC DISORDERS

**Responsible gene**: *FMR-1*
**Protein:** FMRP (Fragile X Mental Retardation Protein)
**Cytogenetic locus**: Xq27.3
**Inheritance**: X-linked triplet repeat
**Clinical Features and Diagnostic Criteria**: Delayed motor and verbal development, ID (mod-severe in boys, milder in girls), prominent jaw and forehead, high activity, autistic features. Carrier females: anxiety, OCD, depression, 20% have POF. Carrier Males: (>30% of males >50y), progressive intention tremor, ataxia, parkinsonism, and autonomic dysfunction. Two other loci: FraXE: only ID, FraXF: no phenotype
**Clinical Tests**: None
**Molecular Tests**: CGG triplet repeat detection. Southern Blot: good for small or large expansions, doesn't give repeat #. PCR: Better quantification of repeat number, subject to allele dropout with large expansions. NL (normal): 5-44 repeats, Intermediate: 45-58 repeats (gray zone), Pre-mutation: 59-200 repeats, Mutation (Pathogenic mutation): >200 repeats
**Disease Mechanism**: >200 repeats leads to silencing by methylation. POF and ataxia thought to be due to toxic gain of function.
**Treatment/Prognosis**: No specific treatment.

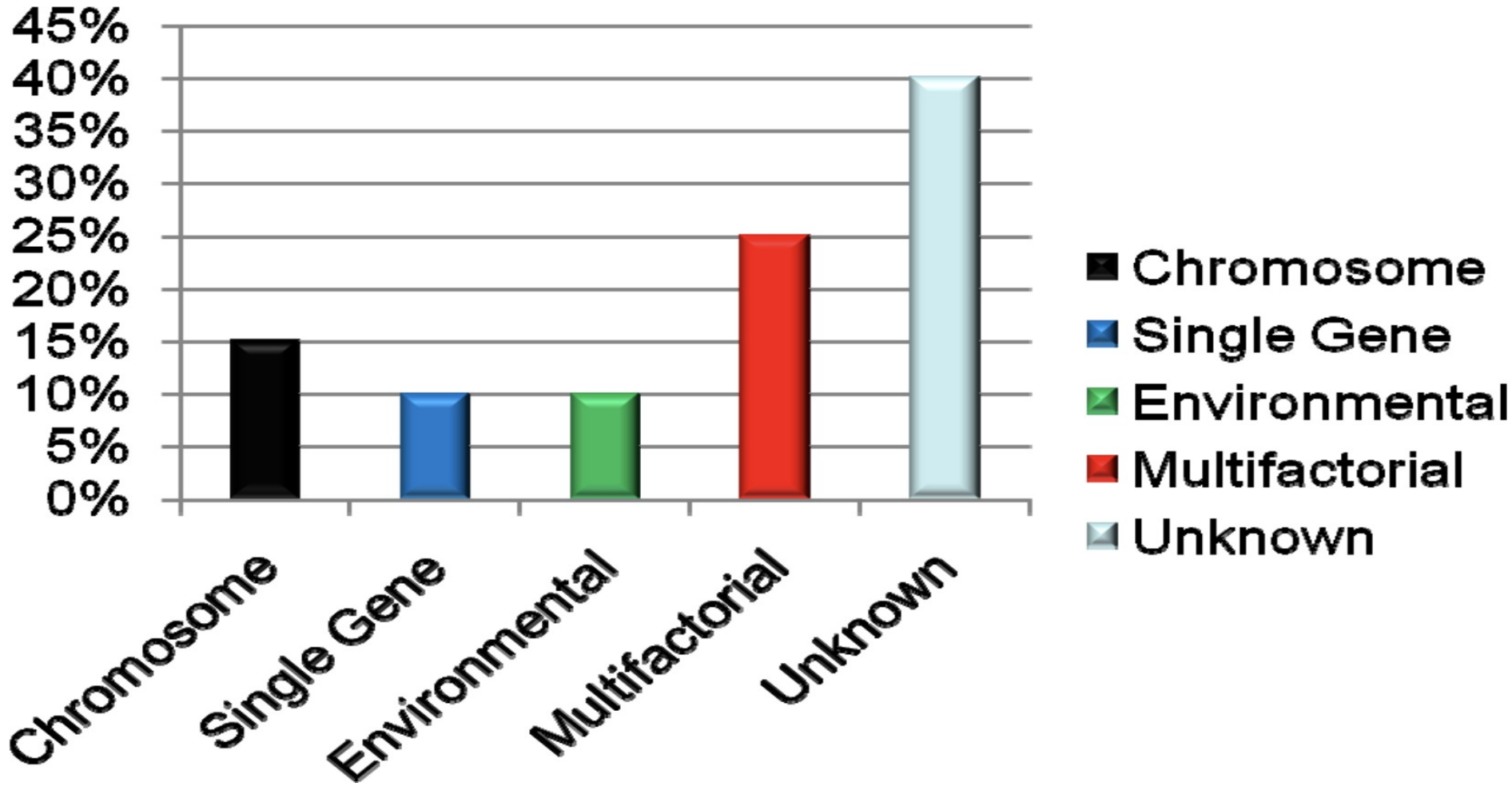
# Developmental genetic

- Dysmorphology
- Pleiotropy
- Congenital anomalies

# CONGENITAL ANOMALIES

- 1 3% of all newborns
  Leading cause of neonatal morbidity and
- mortality
  20% of infant deaths
  10% NICU admissions, 25 35% of deaths
- Pediatrics admissions
  25% to 30% have major birth defect

# Causes of congenital anomalies



# Congenital anomalies

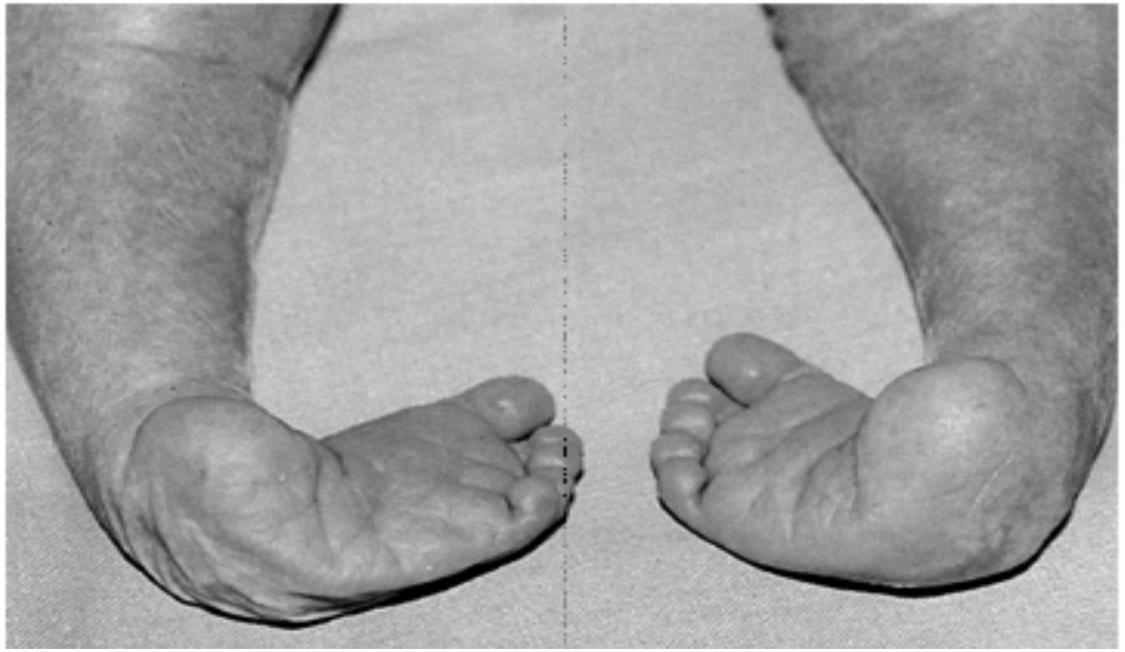
| Isolated Anomaly | Incidence per livebirths |
| --- | --- |
| Undescended testes | 1:30 |
| Heart defect | 1:150 |
| Club foot | 1:300 |
| Neural tube defects | 1:500 |
| Cleft lip ± cleft palate | 1:1000 |
| Hypospadias | 1:1000 |
| Polydactyly | 1:1500 |
| Cleft palate | 1:2000 |
| Craniosynostosis | 1:2000 |
| Syndactyly | 1:2000 |

# Deformation

- Developmental Process is *normal* Formed initially normal
- Mechanical force alters structure , extrinsic factors impinging physical on the fetus during development usually second trimester.
- Most of them are reversible. Causing pressure leading to deformation
- Examples: maternal or fetal force
  - Oligohydramnios
  - Breech presentation
  - Bicornuate uterus

# Deformation

Reversible can be treated with physiotherapy



Clubbed feet

- spina bifida

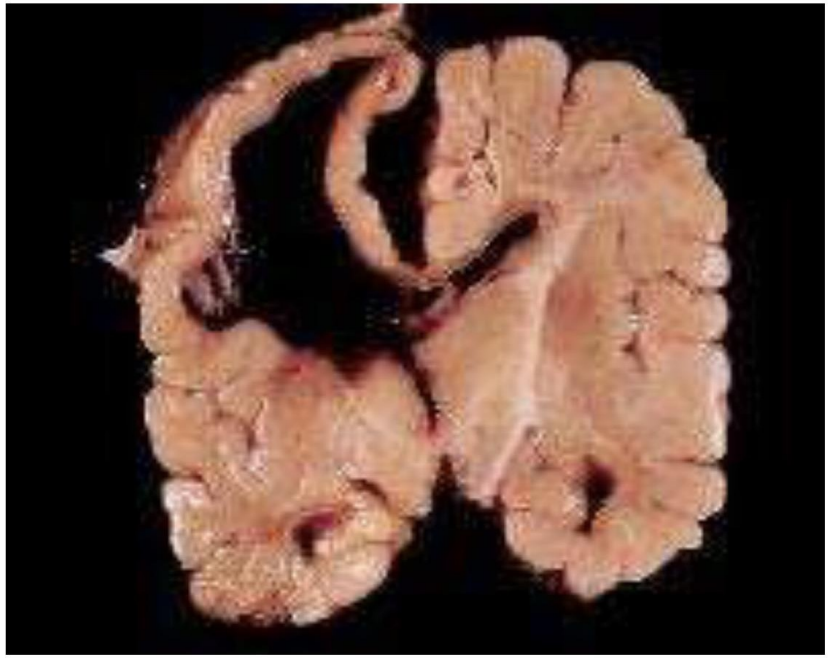
Moore. The Developing Human. Saunders, 1994

# Disruption

Was normal initially then the growth process is interrupted

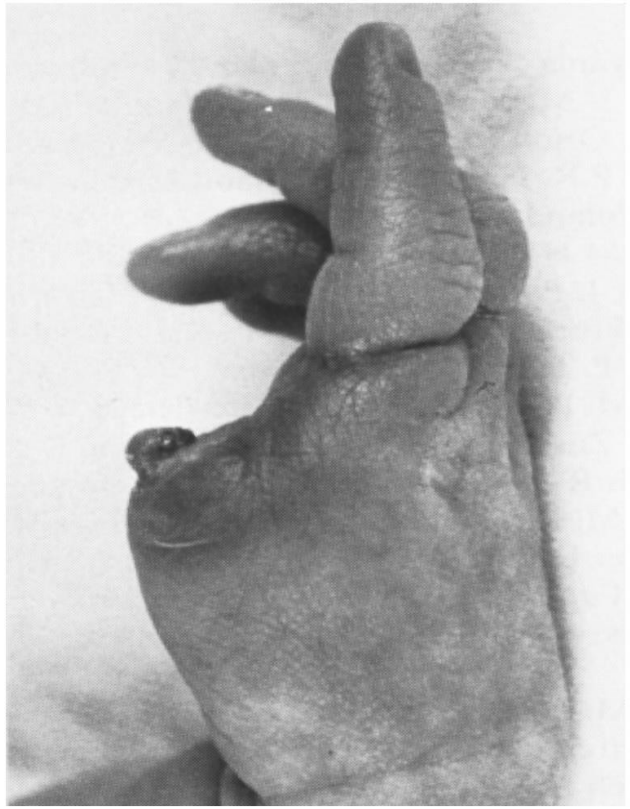
- Developmental process is *normal*, but interrupted.
- Destruction of irreplaceable normal fetal tissue--->actual loss of tissue.
- Vascular insufficiency , trauma, or teratogen.
- Examples:
  - Amniotic band sequence
  - Fetal Cocaine exposure

Here's a vascular insufficiency leading to tissue loss



Porencephaly

http://www.neuropat.dote.hu/develop.htm#Porencephaly

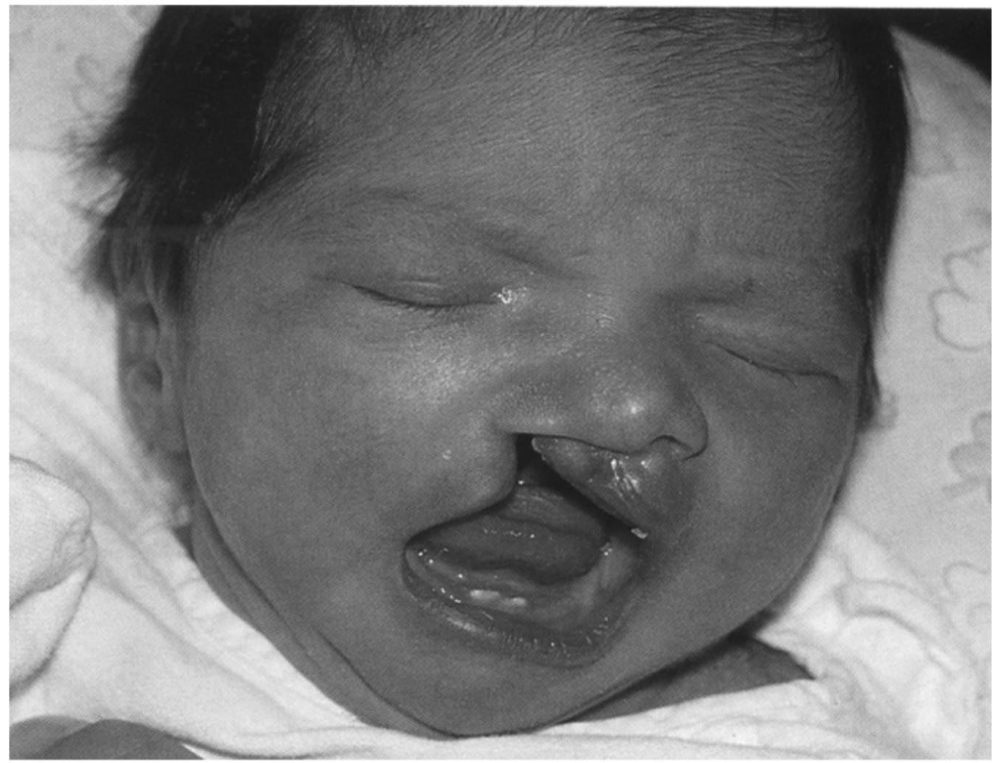


Amniotic Band Tissue loss

ıze. Clinical Syndromes. Mosby-Wolfe, 1997

# Malformation The developmental process is abnormal initially

- Morphological defect from an intrinsically *abnormal* developmental process.
- Malformation in one part is often but not always associated with malformation elsewhere.
- Examples: When you have one anomaly look for others
  - holoprosencephaly,
  - congenital heart disease,
  - neural tube defect
  - polydactyly



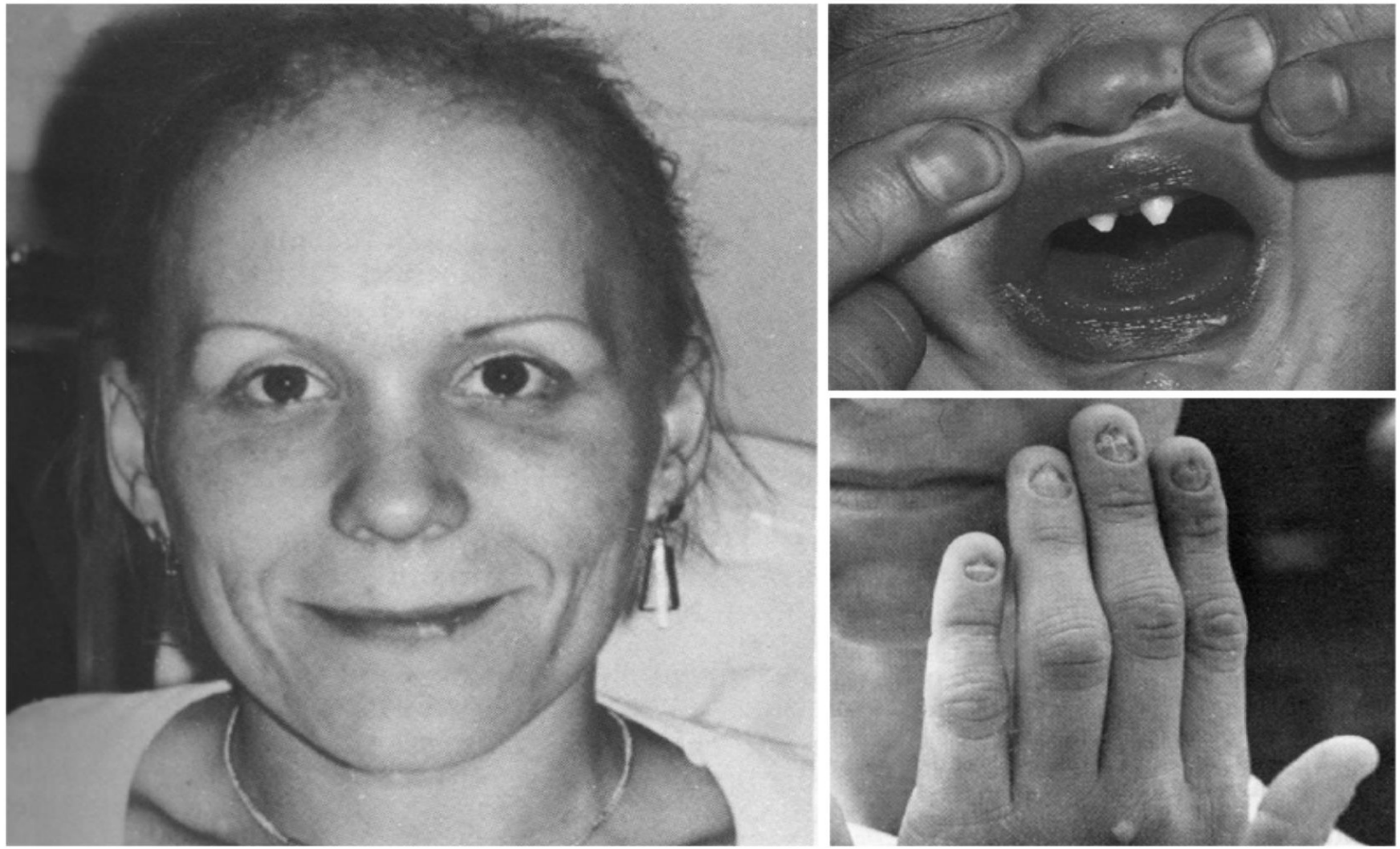
# Unilateral Cleft Lip and Palate

Moore, Persaud, and Shiota. Color Atlas of Clinical Embryology. Saunders, 1994

# Dysplasia

- Abnormal tissue organization, microscopic structure.

- Examples:
  - Skeletal or connective tissue dysplasia
  - Ectodermal dysplasia

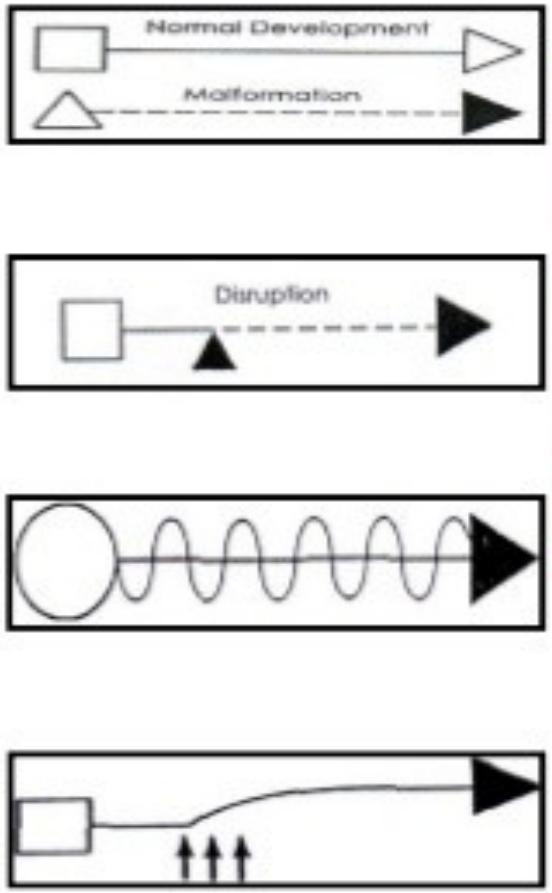


# Ectodermal Dysplasia

Buyse. Birth Defects Encyclopedia. Blackwell Science, 1990;
Baraitser and Winter. Color Atlas of Congenital Malformation Syndromes, Mosby-Wolfe, 1996;
Bergsma. Birth Defects Compendium, Alan R. Liss, 1979.

Summary of the slides and terminology

# Diagramatic Sketch




Production, Intrinsic

From the beginning abnormal and is irreversible

- *Malformation* → Production intrinsic defect → failure of embryonic proliferation and/or differentiation → Abnormal structure.

Started normal then something happened (ex.trauma, teratogen) causing abnormal growth of the organ

- *Disruptions* → Production extrinsic (disruptive) agents → interferes with embryonic development of a structure → destruction or removal of structure.

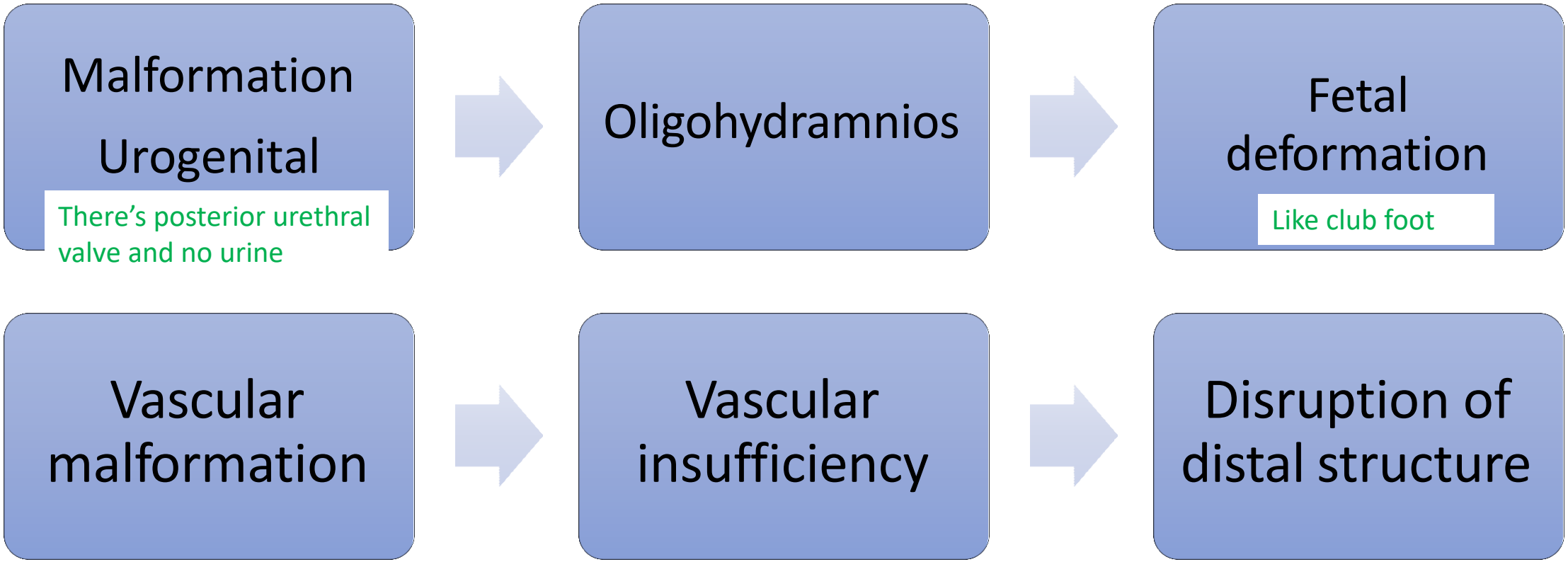
Abnormal organization from the beginning

- *Dysplasias* → Production intrinsic defect → abnormal cellular organization → abnormal model of structure.

Mechanical forces After period of normal development resulting deformation (reversible)

- Deformation → Packaging extrinsic defect → normally formed structure pushed out by mechanical forces.

Extrinsic


Malformation Urogenital
There's posterior urethral valve and no urine
Oligohydramnios
Fetal deformation
Like club foot
Vascular malformation
Vascular insufficiency
Disruption of distal structure

# Pleiotropy :Syndrome and Sequences

- A birth defect resulting from a **single underlying causative agent** may result in abnormalities of more than one organ system in different parts of the embryo or in multiple structure that arise at different times during development.
- Causative agents could be a **gene** or **teratogen**.
- When causative agent causes multiple abnormalities **in parallel**, the collection called ?
- When a causative agent affects **only a single organ** at one point of time which then causes the rest of constellation of pleiotropic defect , secondary effect , this referred as ?

Syndrome: a causative agent will cause multiple and parallel anomalies

Sequence: A causative agent causing a problem and them the sequalae will show multiple problems in the tissue

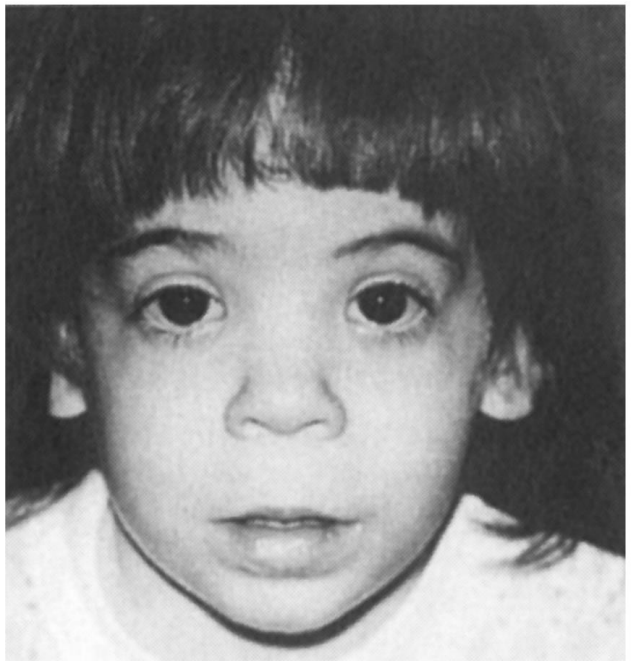
# Syndrome

A constellation of signs and symptoms presumably all related together to one reason like a gene mutation

- A recognizable pattern of anomalies presumed to be causally related
- Genetic: chromosomal, single gene
- Environmental: alcohol, retinoic acid
- Complex: more than one genetic and/or environmental factor

# Fetal alcohol syndrome

Example of a non genetic syndome



Clarren and Smith. NEJM 298:1063, 1978

- Fetal Alcohol
  - Growth retardation
  - Microcephaly
  - Mental retardation
  - Short palpebral fissures
  - Short nose
  - Smooth philtrum
  - Thin upper lip
  - Small distal palanges
  - Hypoplastic finger nails
  - Cardiac defects

One of the commonest examples of sequence

# Pierre – Robin Sequence

**Small Jaw**

1st thing is the micrognathia,

- Primary anomaly

**Displacement of tongue in superior direction**

resulting the tongue to go up bc there's no space,

- Protruding tongue due to inadequate room

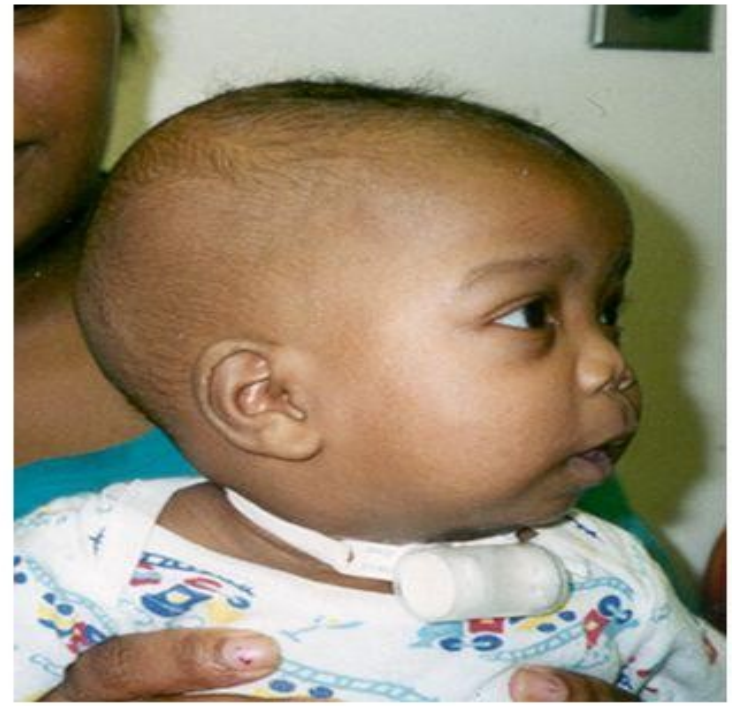

**Cleft Palate**

- Development of Pierre – Robin Syndrome from constellation of the three

because of the superiority of the tongue there's no space for the palate to grow

# Pierre Robin sequence

- Micrognathia, [U-shaped] cleft palate, glossoptosis
- 50% syndromic
  - Stickler (50%),
  - del22q11 (25%)
  - Treacher Collins, Rib gap...



*Micrognathia ---> cleft palate ---> glossoptosis*

Its an epigenetic problem where the genes are expressed from the father or mother

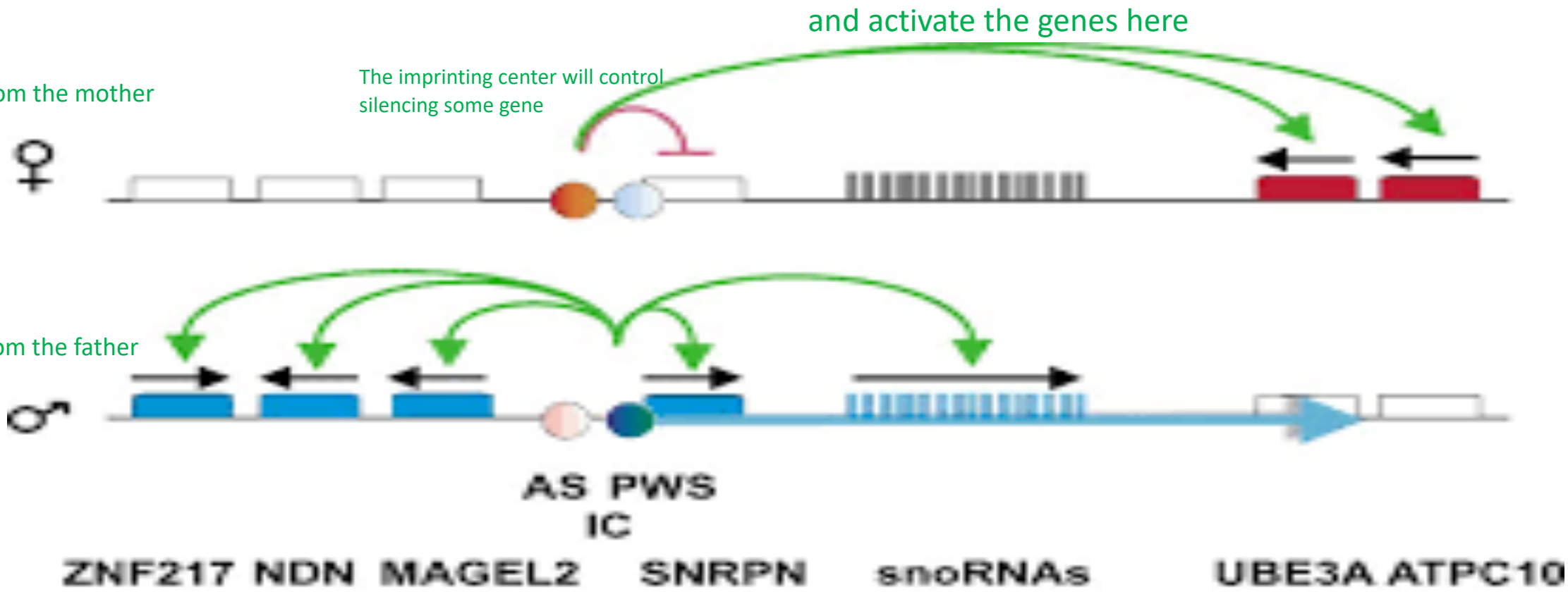
# Imprinting disorders

- The expression of imprinted genes may be **tissue and stage specific** with **one of the parental alleles** being differentially expressed only at a certain developmental stage or in certain cells.
- Imprinted genes show expression from **only one member of the gene pair** (allele) and their expression are determined by the parent during production of the gametes.
- Imprinted genes represent only a small subset of mammalian genes that are present but not imprinted in other vertebrates.
- Genomic imprints are **erased in both germlines and reset accordingly**; thus, reversible depending on the parent of origin and leads to differential expression in the course of development.

| Disorder | Effect | Imprinted genes suspected or known to be affected | Expressed gene copy |
|---|---|---|---|
| **Intra-uterine growth** | | | |
| Beckwith–Wiedemann syndrome | Fetal and postnatal overgrowth; excessively large organs; predisposition to tumours | *IGF2* (encoding a growth factor)<br>*CDKN1C* (encoding a cell-division regulator) | Paternal<br>Maternal |
| Silver–Russell syndrome | Severe intra-uterine growth restriction | Maternal uniparental disomy and duplications of chromosome 7 | |
| Pre-eclampsia | Pregnancy-associated hypertension, often accompanied by intra-uterine growth restriction | Linkage studies suggest involvement of maternally expressed imprinted genes in some families | |
| **Behaviour and brain** | | | |
| Prader–Willi syndrome | Moderate mental retardation; severe obesity; short stature; poor muscle tone | Numerous imprinted genes on chromosome 15 | Paternal |
| Angelman syndrome | Severe motor and mental retardation; paroxysms of laughter; autistic-like behaviour | *UBE3A* (encoding a protein-degradation regulator) | Maternal |
| Turner syndrome (monosomy X) | Affects females only; associated with a characteristic neurocognitive profile, short stature and ovarian failure | Enhanced social cognitive skills in patients inheriting the paternal, rather than maternal, X chromosome may indicate imprinting | |
| Schizophrenia | Perceived distortions of reality; disturbance of thought and language; withdrawal from social contact | Some forms of schizophrenia show lower age of onset after paternal inheritance | |
| Maternal behaviour defects (in mice) | Lack of maternal postnatal care of offspring | *Peg3* (encodes a DNA-binding protein)<br>*Peg1* (encodes an enzyme of the α/β-hydrolase family) | Paternal<br>Paternal |
| **Hormones and metabolism** | | | |
| Albright hereditary osteodystrophy | Short stature; round face; obesity; mental retardation; subcutaneous calcification | *GNAS* (encodes a G-protein subunit) | Maternal (tissue specific) |
| Pseudohypoparathyroidism 1A | As above, accompanied by resistance to parathyroid hormone and other hormones | Occurs only on maternal transmission of inactivating *GNAS* mutations | Maternal (tissue specific) |
| Transient neonatal diabetes mellitus | Pancreatic insufficiency and low secretion of insulin during fetal life; intra-uterine growth restriction | *PLAGL1* (encodes a DNA-binding protein) | Paternal |

The common presentation of imprinting is CNS and hormone and metabolism

Here's an example of prader-willi, this is chromosome 15




Normally we'll have an active copy of this gene, one is active from the mother and one active from the father
And then the imprinting center will control which is active which is not.
the disorder mutation is either:
Deletion in the imprinting center or deletion of the paternal copy (even if the mother's copy is normal we don't care) or maternal unipaternal disomy (he has both copies from the mother)

They don’t have facial characteristics

http://www.bcpwsa.com/images/header.jpg

They usually present initially IUGR, failure to thrive ine 1st year of life, severly hypotonic. After the 1st year they'll have hyperphagia and short stature…

# Prader Willi syndrome

To help you memorize, problem in the paternal gene

**Responsible genes**: Paternally expressed genes within the imprinted locus on 15q11-13 (*SNURF-SNRPN, MKRN3, MAGEL2,* and *NDN* )

**Cytogenetic locus**: 15q11-13

**Inheritance**: autosomal, expressed from paternal Ch 15

**Clinical Features and Diagnostic Criteria**: Hypothalamic insufficiency, neonatal hypotonia, developmental delay, hyperphagia leading to obesity, short stature, small hands and feet, hypogonadism, ID

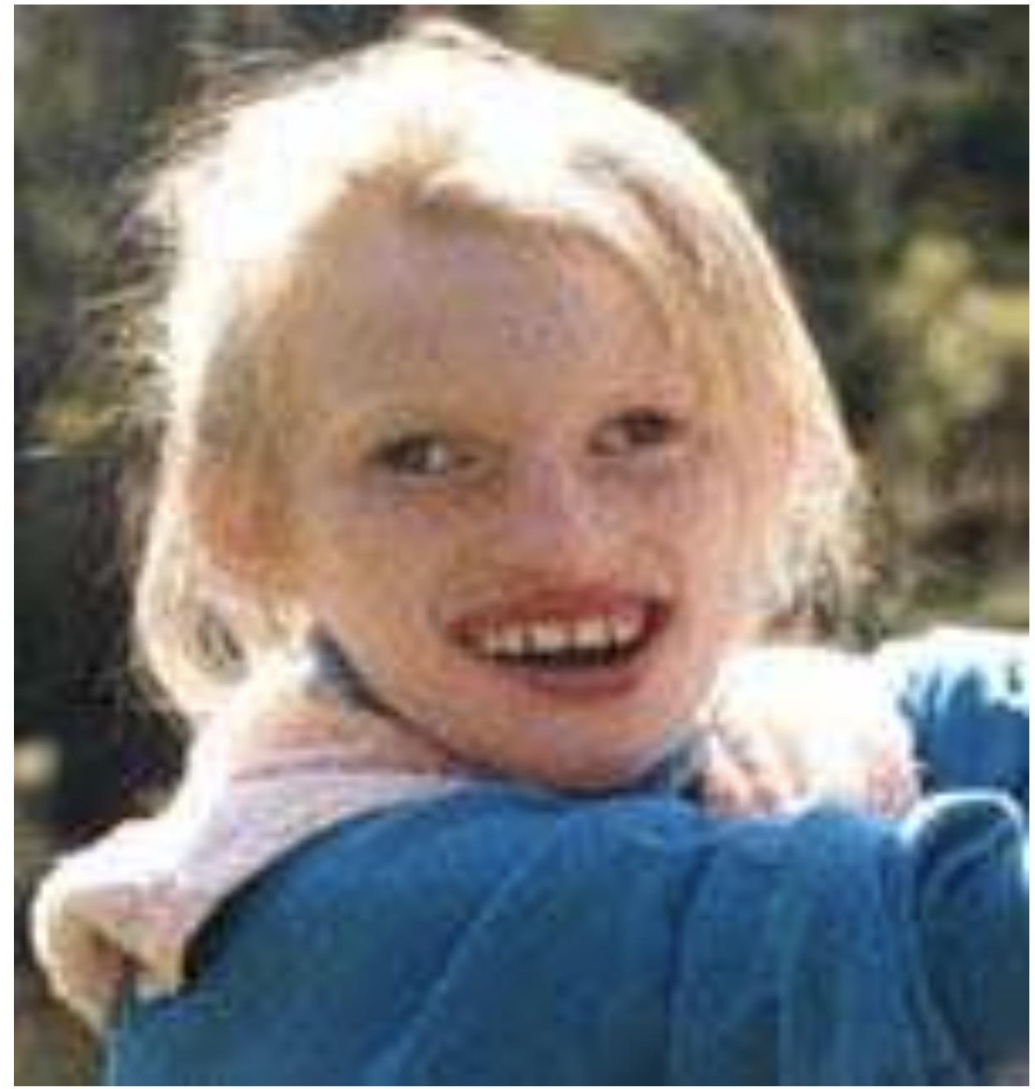
We test it with microarray or methylation study

**Molecular Tests**: 3-5 Mb deletion of 15q11.2-q13 (~70%), matUPD (15%), PWS imprinting center defect (1-2%)

**Disease Mechanism**: unknown

**Treatment/Prognosis**: Monitor for feeding problems in infancy, obesity, OCD, psychosis, scoliosis, obstructive sleep apnea, diabetes, osteopenia

**Facial features:**
**Protruding tongue**
**Prognathia**
**Wide mouth**
**Widely spaced teeth**
**Strabismus**
**Light hair and eye color**



http://www.psychnet-uk.com/dsm_iv/pictures/angel.jpg

Severe mental issues mostly hearing problems, they have a very happy behavior with the ataxia

# Angelman syndrome

**Responsible gene**: *UBE3A*
**Protein:** Ubiquitin protein ligase E3A
**Cytogenetic locus**: 15q11-q13
**Inheritance**: loss of the maternally imprinted contribution in the 15q11.2-q13 (AS/PWS) region Their problem is in the same area as prader-willi but the opposite, its in the maternal copy
**Clinical Features and Diagnostic Criteria**: severe developmental delay or ID, severe speech impairment, gait ataxia and/or tremulousness of the limbs, and an inappropriate happy demeanor that includes frequent laughing, smiling, and excitability, microcephaly and seizures
**Clinical Tests**: acquired microcephaly by age two years, We test with microarray and methylation
Seizures before age three, abnl EEG: large amp. slow-spike waves
**Molecular Tests**: 4-6 Mb del (65-75%), *UBE3A* mutation (11%), imprinting defect (2.5%), unbal chrom transloc (<1%), Pat UPD 15 (<1%), del of imprinting center (0.5%)
**Disease Mechanism**: Disruption of E6AP ultimately causes an abnormality in the ubiquitin protein degradation pathway, but no clear AS-causing target protein yet identified
**Treatment/Prognosis**: Typical care for medical issues, PT, OT, ST, and individualized education and behavior program.

The questions of the exam will be similar to those but not the same

Following are true about Turner's syndrome, EXCEPT

- (1) Adult height < 150 cm
- (2) Coarctation of aorta
- (3) Cubitus varus of elbow
- (4) Horseshoe kidney

- Ans. 3
  Turner’s syndrome is due to functional monosomy of ‘p’arm of X-chromosome.
- Clinical features
  - Short stature (<150cms)
  - Sexual infantilism
  - Bicuspid aortic valve CoA (Coarctation of Aorta)
  - Low hairline, webbed neck, widely placed nipples.
  - Horse shoe kidney, cubitus valgus of the elbow.

- All are true regarding Trisomy 21, EXCEPT
- 1) Chromosomal non-dysjunction during maternal meiosis responsible for 80-90% of cases
- (2) Brush-field spots on iris
- (3) Epicanthal fold
- (4) Hypertonic at birth

- Ans. 4
  92% of Down’s syndrome have trisomy with an extra. 21 chromosome in all body cells. Chromosomal non- dysjunction during maternal meiosis is responsible for 90% of cases. Clinical features ® Mental retardation, Epicanthal fold, upturned nose, brushfield iris, hypotonia at birth.

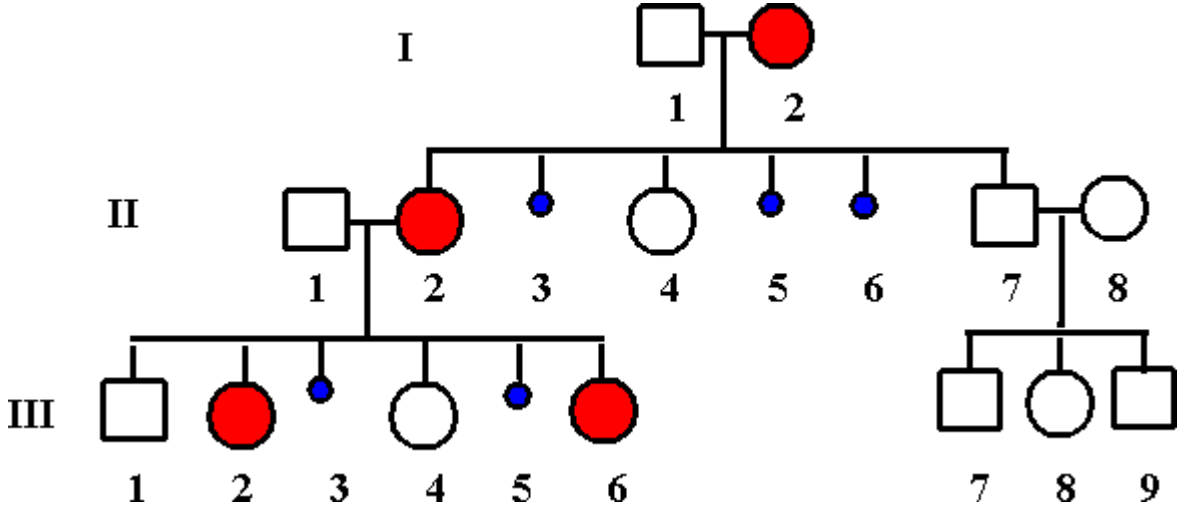
- In 1991, it was discovered that the fragile X syndrome was caused by a mutation in the fragile X mental retardation-1 (FMR-1) gene. An area of CGG trinucleotide repeats just upstream of the coding area was found to be variable in size. All the following statements regarding the FMR1 gene are true, EXCEPT
- 1) “Premutations” may expand to full mutations in future generations
- (2) Offspring of male carriers inherit a premutation
- (3) Offspring of female carriers may inherit a premutation or a full mutation
- (4) Individuals with premutation are likely to have mental retardation

- Ans. 4
  several disorders have recently been found to be the result of expanding series of triplet repeats.
- These include the fragile X syndrome, myotonic dystrophy, and Huntington’s disease.
- Although the length of the region is variable in normal individuals, unaffected female carriers, and non-penetrant, transmitting males have “premutations” which are generally 50 to 230 repeats in length.
- Individuals with premutations are, therefore, phenotypically unaffected. Nonpenetrant males transmit only unstable premutations; female carriers may transmit either premutations or full mutations, which are associated with mental retardation and the other phenotypic features of the syndrome.
-

The pedigree described below is an example of what pattern of inheritance?

- (1) X-linked recessive inheritance
- (2) X-linked dominant inheritance
- (3) Autosomal recessive inheritance
- (4) Autosomal dominant inheritance

Solid figure = Affected individuals
Open figure = Unaffected individuals



The deaths are expected to be male and the female are either healthy or affected, and they are the only one showing the phenotype. And all generations are effected.

- Ans. 2
  The X-linked dominant inheritance pattern is characterized by having affected females in the heterozygote state.
- Affected females are twice as common as affected males, and the affected males are hemizygotes.
- In vitamin D-resistant rickets, both sexes are affected.
- However, the serum phosphate level is less depressed; hence, the rickets is less severe in the heterozygous female than in the hemizygous male.

- Chromosomal imbalance is most frequent during which of the following stages of human development?
- (1) Embryonic
- (2) Fetal
- (3) Childhood
- (4) Adult

- Ans. 1
  Chromosomal aberrations occur in approximately 1 in 200 live born infants.
- Although the exact frequency of chromosomal anomalies in human embryos (i.e., <8 weeks' gestation) is unknown, the numbers above indicate a substantial frequency of at least 7.5 percent.

Match the following:

1) Heterozygote
2) Compound heterozygote
3) Double heterozygote

a) Two locus for different allele
b) One locus, one allele
c) One locus, one normal, one mutant allele
d) One locus, two different, mutant allele

- (1) 1-b, 2-a 3-d
- (2) 1-c, 2-a 3-d
- (3) 1-c, 2-d 3-a
- (4) 1-b, 2-c 3-d

- Ans. 3
  A heterozygote, or in the case of an autosomal recessive disorder, a carrier, has one normal allele and one mutant allele at a given locus.
- A compound heterozygote has two different mutant alleles at same locus.
- a double heterozygote has one mutant allele at each of two different loci.

- On physical examination, the patient is noted to have some facial dysmorphism, including a long face, a prominent nose, and flattening in the malar region. In addition, the patient's speech has an unusual quality. Which description best explains the patient's condition?
- (1) Sequence
- (2) Syndrome
- (3) Disruption
- (4) Deformation

- Ans. 2
  The child described in the question has multiple independent anomalies that are characteristic of a syndrome. Although they are likely to be causally related, they do not appear to be sequential. These problems do not appear to be caused by the breakdown of an originally normal developmental process as in a disruption, nor do they appear to be related to a non-disruptive mechanical force as in a deformation.

- Fluorescent in situ hybridization (FISH) analysis is useful in all the following situations, EXCEPT
- (1) Determination of sex in cases of ambiguous genitalia
- (2) Determination of uniparental disomy
- (3) Rapid diagnosis of trisomies
- (4) Identification of submicroscopic deletions

- Ans. 2

  The availability of specific molecular probes allows the use of fluorescent in situ hybridization (FISH) analysis for the evaluation of specific chromosomal regions known to be associated with specific genetic syndromes.
- Probes specific for the X and Y chromosomes are used in determining sex in cases of ambiguous genitalia.
- The identification of three signals for specific chromosomes allows for the diagnosis of trisomies much more rapidly than standard karyotypic analysis.
- Submicroscopic deletions can be detected using FISH probes.
- Because the parental origin of chromosome cannot be determined with this technique, uniparental disomy cannot be detected.

- A male child presents to your clinic with a history of multiple pulmonary infections. The child's birth was complicated by meconium ileus. The child has had a recurrent cough with thick, difficult to mobilize, viscous sputum. There have been multiple episodes of recurrent pulmonary infections and abnormal chest X-rays. The child is also thin for his stated age and seems to be failing to thrive. Which of the following statements is correct concerning the mode of inheritance of this patient's disease? We could mention the diagnosis (CF).
- (1) Most patients will have an affected parent
- (2) Males are more commonly affected than females
- (3) The recurrent risk is 1 in 4 for each subsequent sibling
- (4) The trait is never transmitted directly from father to son

- Ans. 3
  The patient’s clinical syndrome is consistent with cystic fibrosis inherited as an autosomal recessive disorder.
- Characteristically the trait appears only in siblings and not in their parents, offspring, or other relatives.
- On average, one-fourth of the siblings are affected.
- In other words, the recurrence rate for each subsequent child is 1 in 4. The parents of the affected child may be consanguineous. Males and females are equally affected.

- Indications for genetic counselling include all of the following, EXCEPT
- (1) Consanguinity
- (2) Family history of cystic fibrosis
- (3) Family history of congenital infection
- (4) Advanced maternal age

- Ans. 3
  There are many indications for genetic counselling. These include advanced maternal age, family history of birth defects or other known or suspected genetic disease, unexplained mental retardation, and consanguinity. Although not technically a genetic problem, teratogen exposure is also generally accepted as an indication for genetic counseling. Although a history of congenital infection requires that medical information be given to the family, this is not a heritable disorder and, therefore, is not an indication for genetic counselling. However, should a pregnant woman herself contract an infection, such as rubella, which may be teratogenic, genetic counselling should be offered.

- A couple is referred to a physician because the first three pregnancies have ended in spontaneous abortion. Chromosomal analysis reveals that the wife has two cell lines in her blood, one with a missing X chromosome (45, X) and the other normal (46, XX). Her chromosomal constitution can be described as
- (1) Chimeric
- (2) Monoploid
- (3) Trisomic
- (4) Mosaic

- Ans. 4
  The case described in the question represents one of the commoner chromosomal causes of reproductive failure, Turner's mosaicism.
- Turner's syndrome represents a pattern of anomalies, including short stature, heart defects, and infertility. Turner's syndrome is often associated with a 45,X karyotype (monosomy X) in females, but mosaicism (i.e., two or more cell lines in the same individual with different karyotypes) is common.
- However, chimerism (i.e., two cell lines in an individual arising from different zygotes, such as fraternal twins who do not separate) is extremely rare.
- Trisomy refers to three copies of one chromosome; euploidy, to a normal chromosome number; and monoploidy, to one set of chromosomes (haploid in humans).

- Which of the following are due to micro deletion, EXCEPT
- (1) Beckwith-Wiedemann syndrome OR TRISOMY 13
- (2) Retinoblastoma
- (3) Prader-Willi syndrome
- (4) Angelman syndrome

- Ans. 1
  Beckwith-Wiedemann syndrome is due to microduplication on ‘p’ arm of chromosome 11.
- Microdeletion is seen in:
  - (a) WAGR complex (11p13)
  - (b) Retinoblastoma (13q14)
  - (c) Prader-Willi syndrome (15q11)
  - (d) Angelman syndrome (15q11)
  - (e) DiGeorge syndrome (22q11)