Chromosomal and genetic disorders

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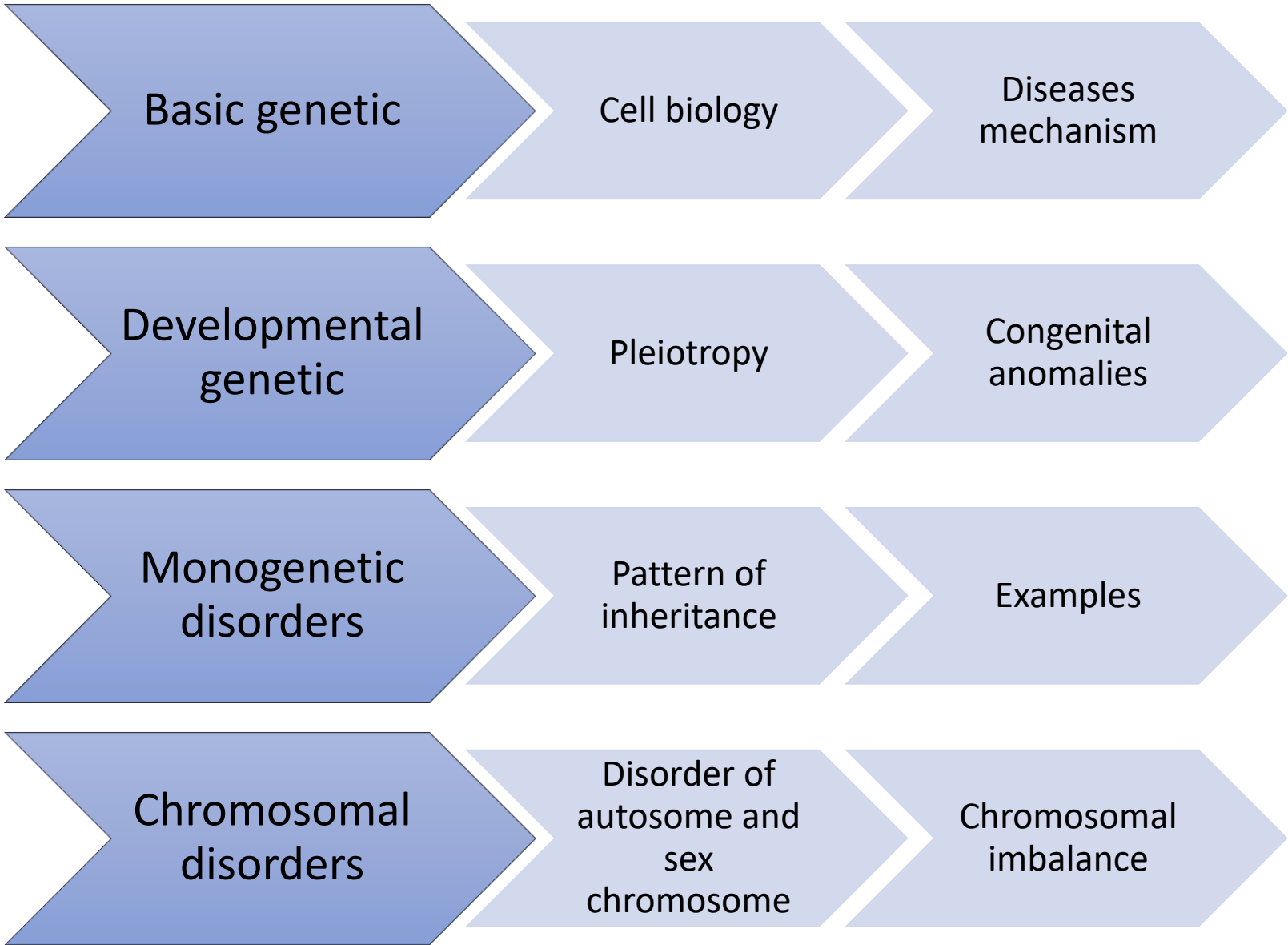
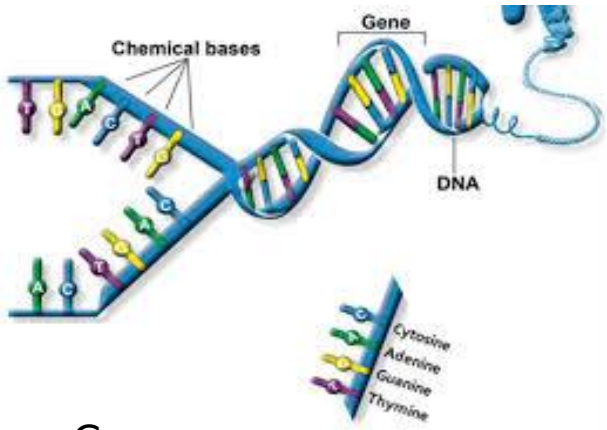
Outlines


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

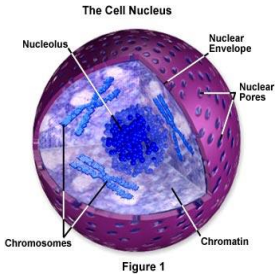
Basic genetic

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



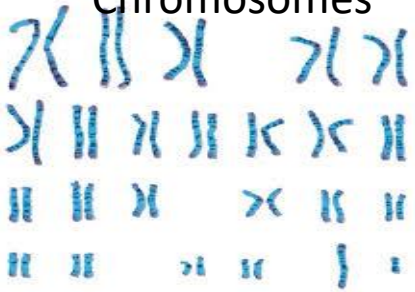
Gene

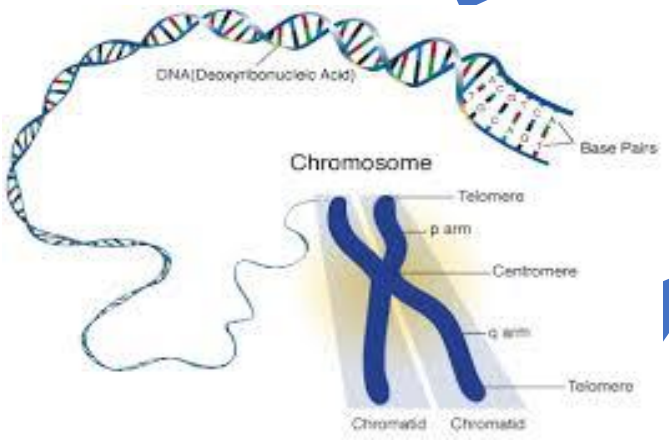
cell

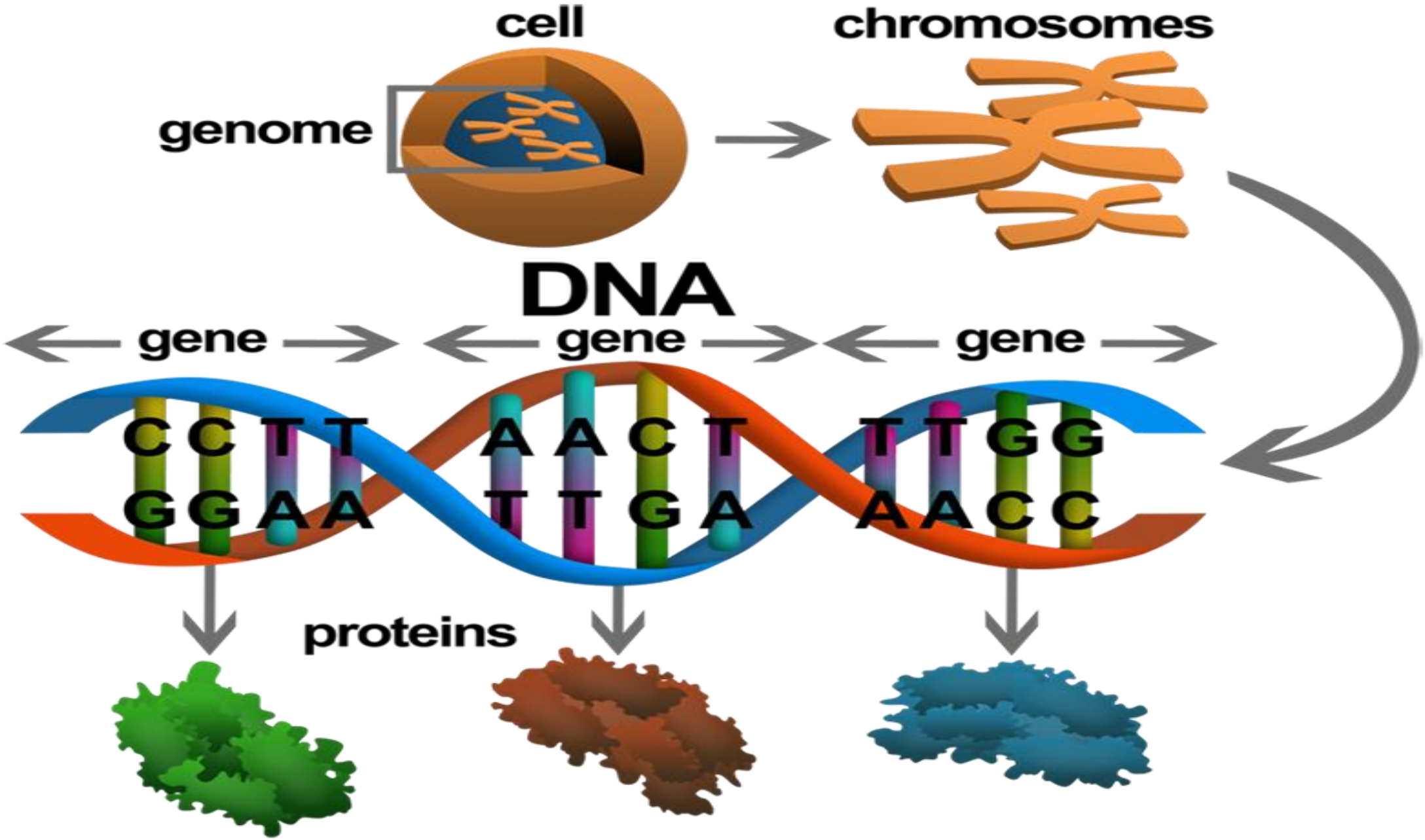


Nucleus

Chromosomes

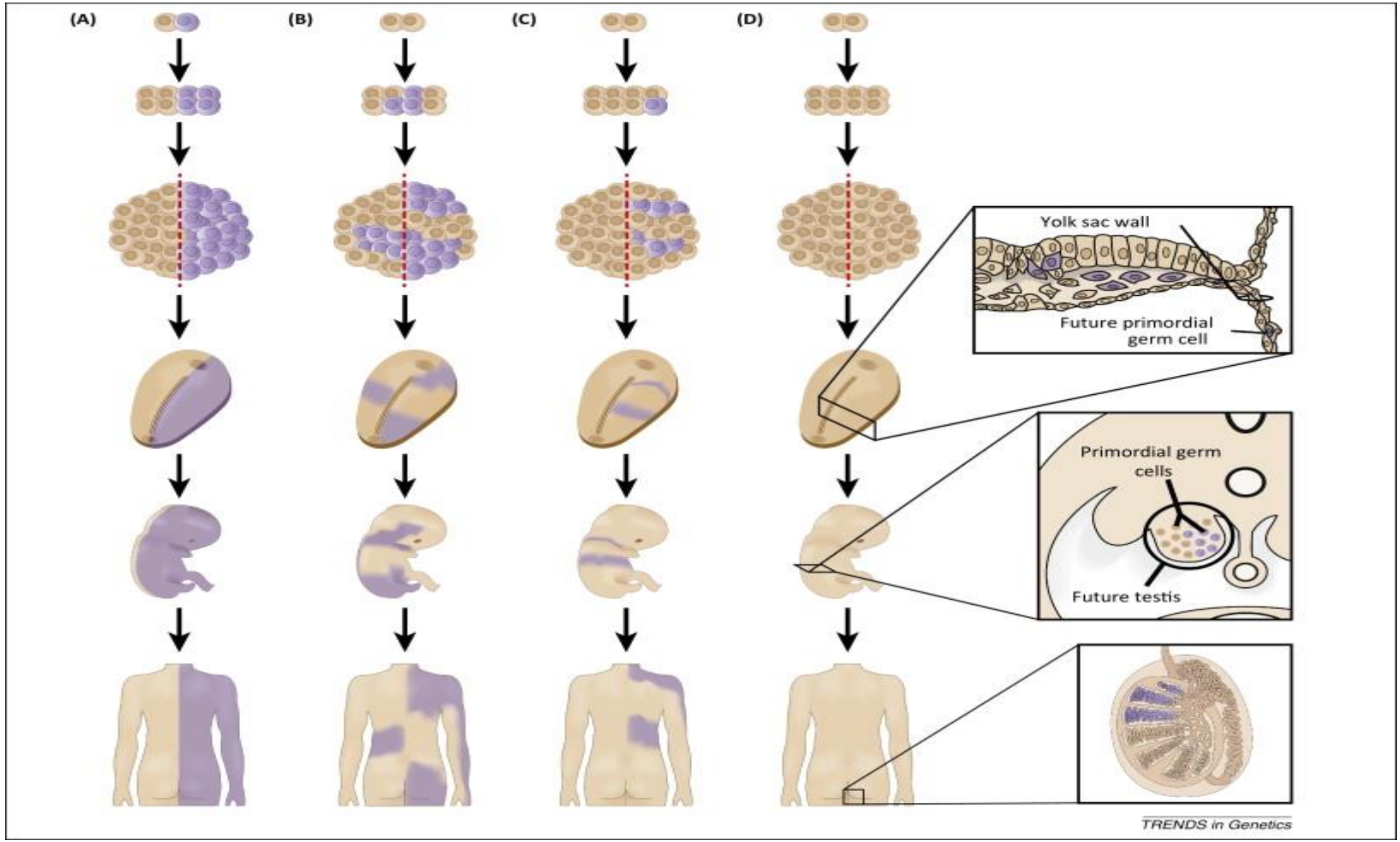


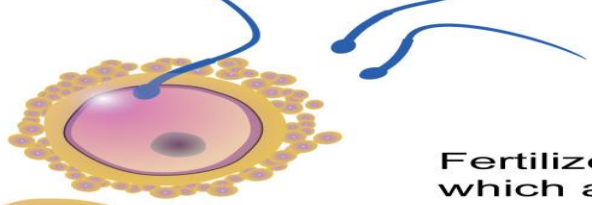



cell
chromosomes
genome
DNA
gene
gene
gene
C C T T
G G A A
A A C T
T T G A
T T G G
A A C C
proteins

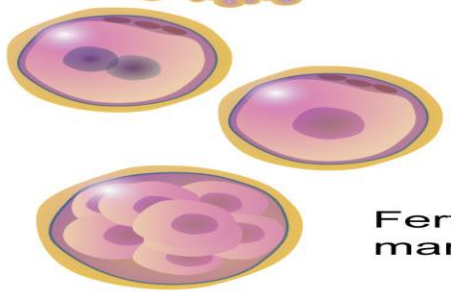
Mosaicism

- 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.
- **Types** :
- Pure Confined placental mosaicism.
- Pure Somatic mosaicism –segmental mosaicism.
- Pure Germline mosaicism.
- Gonosomal mosaicism.


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

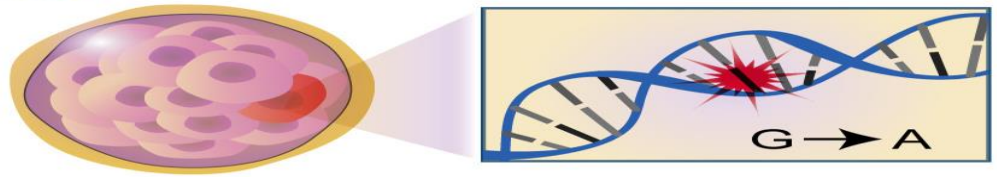


Fertilized egg from
which all body cells arise

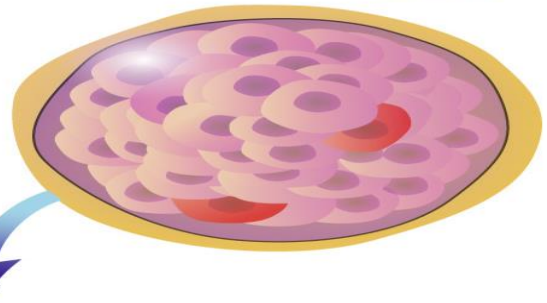


Fertilized egg divides into
many cells to form an embryo

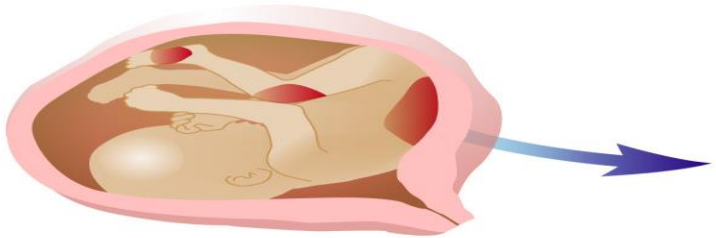
As the cells continue to
divide, the DNA in one of
the cells becomes altered



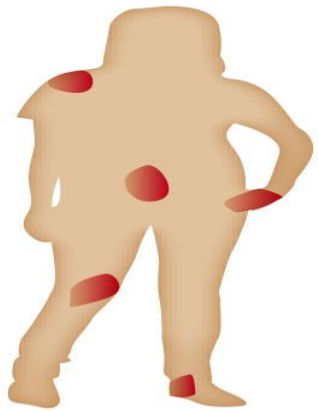
The AKT1 gene in one of
the cells changes - where
the DNA code should have
a "G," it has an "A" instead



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

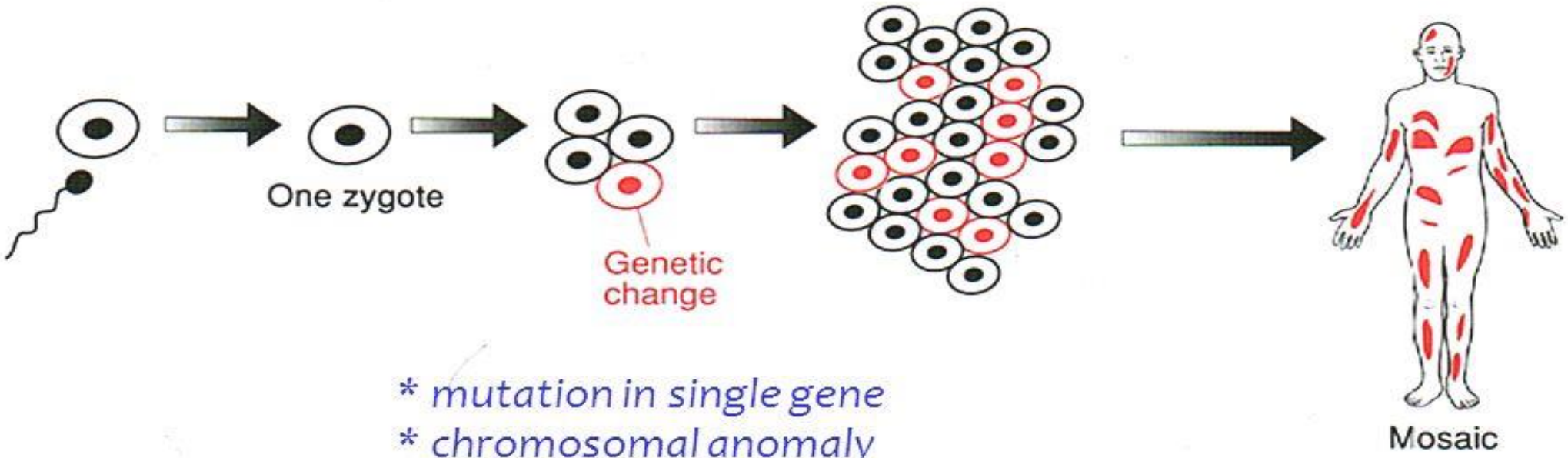


The developing baby has
two types of cells. Some
have the normal AKT1 gene
and somehave the altered
AKT1 gene



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



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

Mosaicism can be:

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

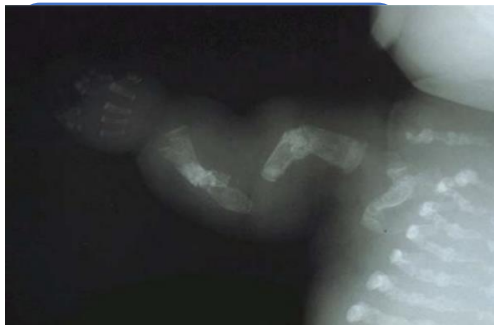
Mosaicism

Germ cell mosaicism

OI II

Turner syndrome

DMD

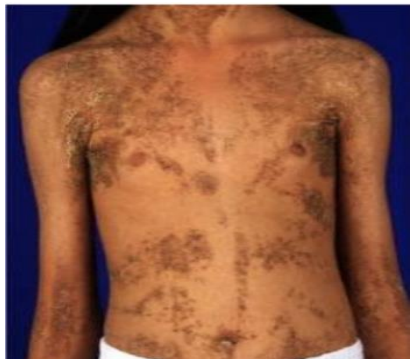


Somatic

Cancer

Line of blaschko

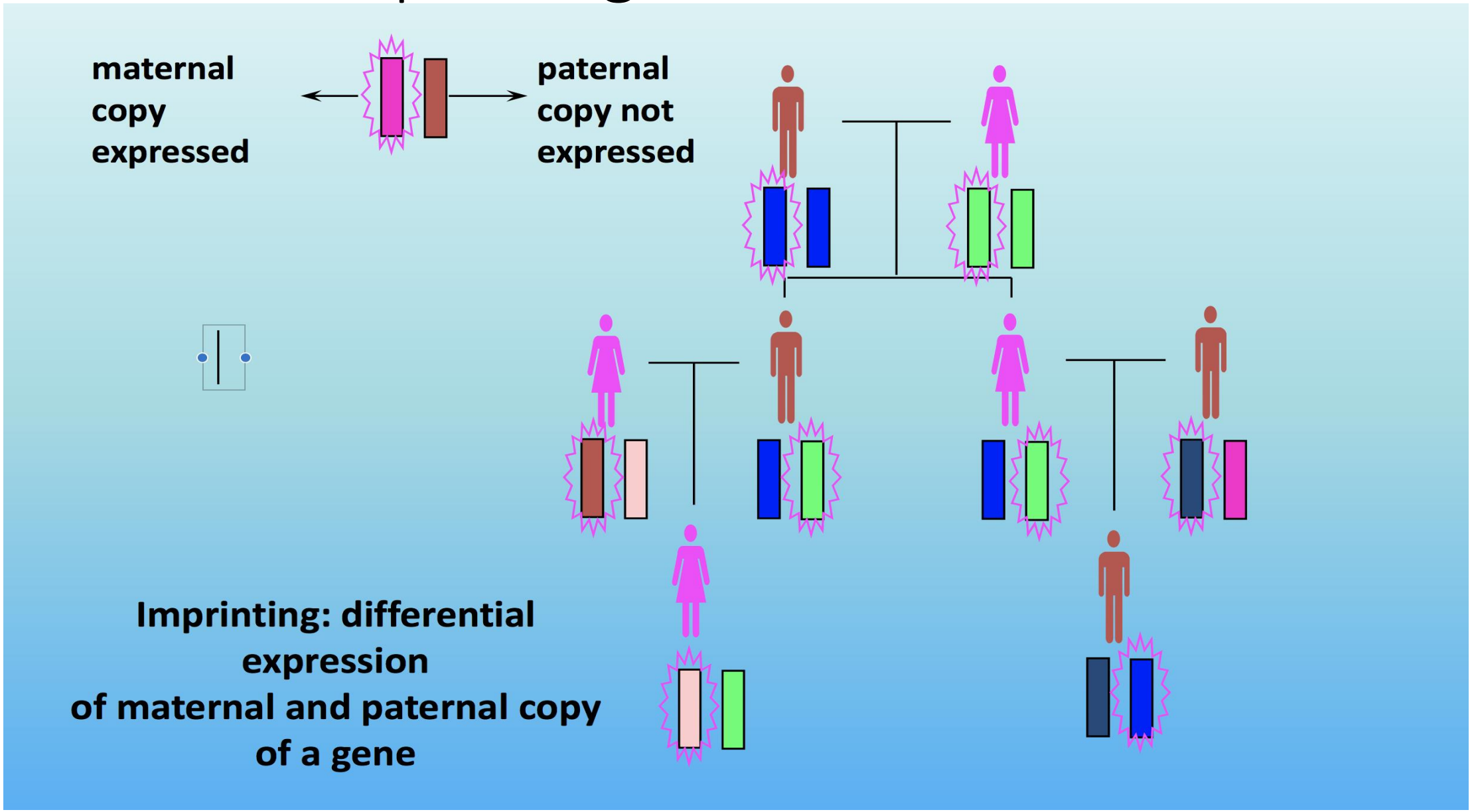
Down syndrome



Gonosomal mosaicism

NF 2

Genomic imprinting



X- inactivation

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???

Explained by X-inactivation resulting in dosage compensation.

Lyon hypothesis

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

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

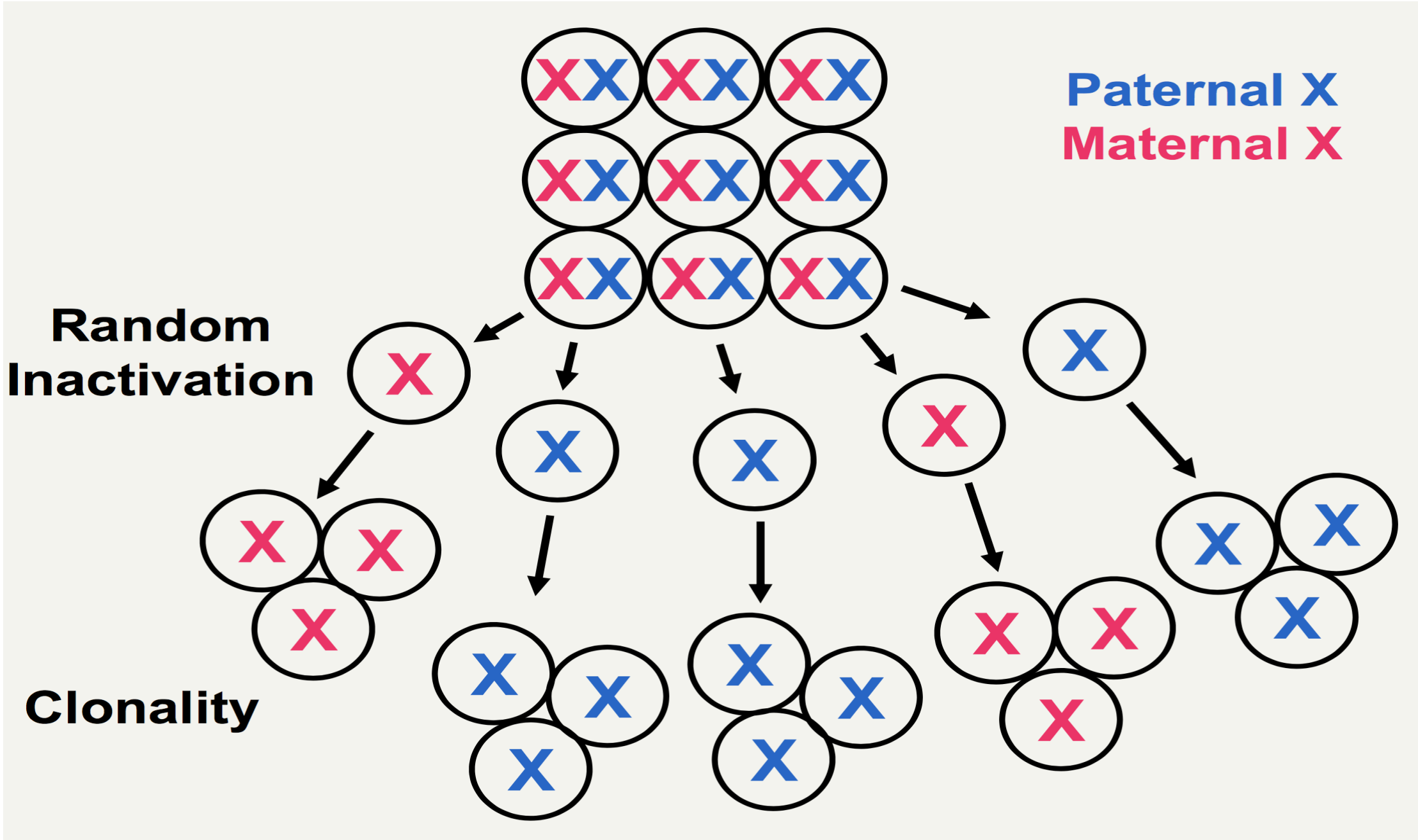
Note: The inactive X must become re-activated in the female's germ line so that each egg can receive an active X chromosome.

- **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.

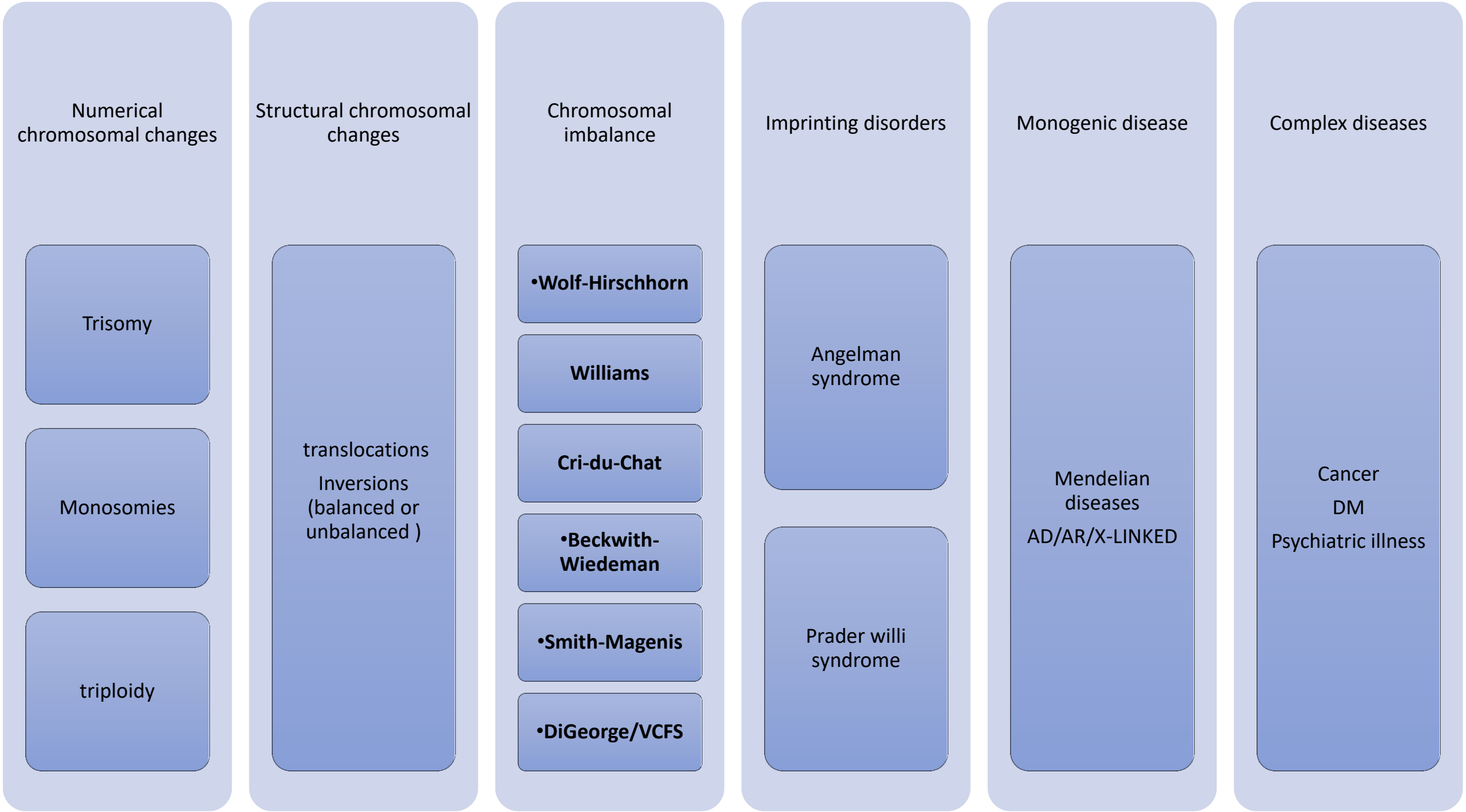
- **X-inactivation is *clonal*.**

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

Basis of diseases

- Chromosomal mutation ; structural or numerical
- Sub-chromosomal mutation ; segmental deletion, duplications.
- Single gene including dynamic mutation
- Imprinting disorders
- Complex genetic

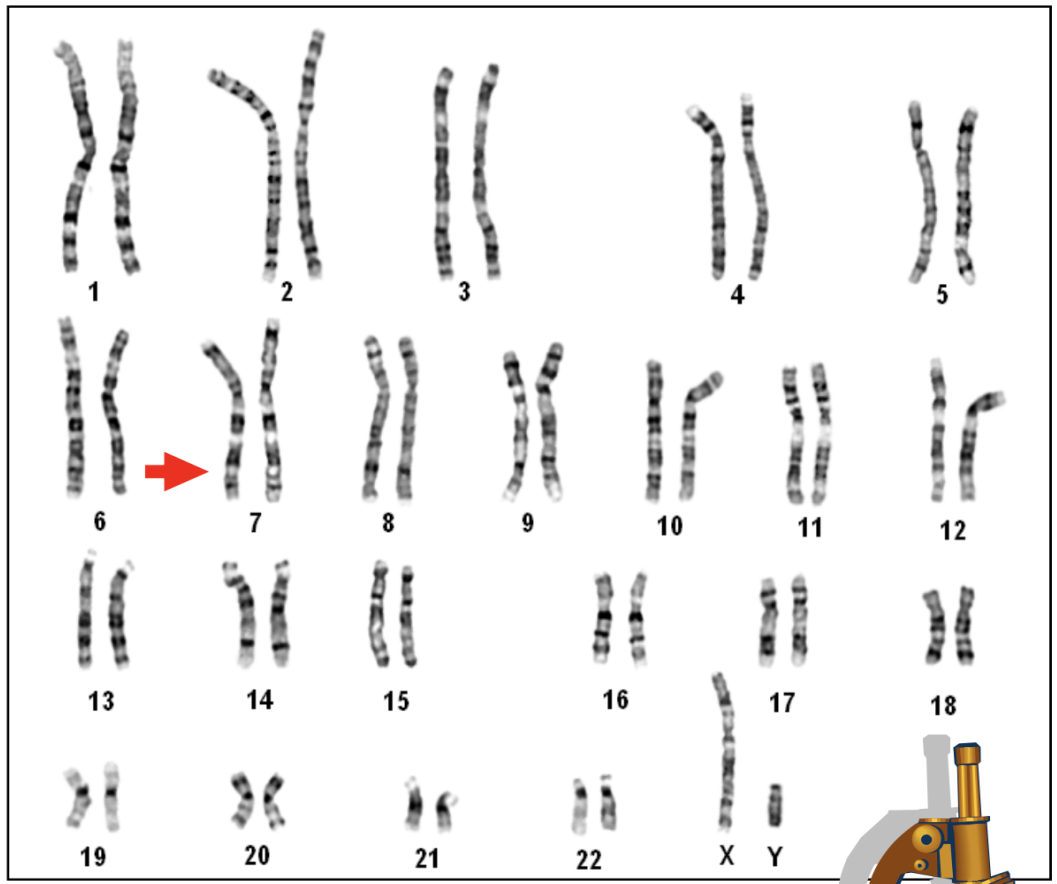

Numerical chromosomal changes
Trisomy
Monosomies
triploidy
Structural chromosomal changes
translocations
Inversions (balanced or unbalanced)
Chromosomal imbalance
•Wolf-Hirschhorn
Williams
Cri-du-Chat
•Beckwith-Wiedeman
•Smith-Magenis
•DiGeorge/VCFS
Imprinting disorders
Angelman syndrome
Prader willi syndrome
Monogenic disease
Mendelian diseases
AD/AR/X-LINKED
Complex diseases
Cancer
DM
Psychiatric illness

Chromosomal disorders

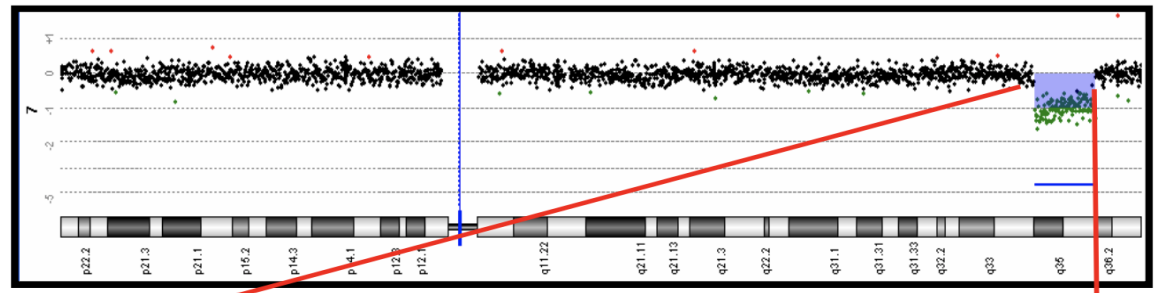
- **Molecular Cytogenetics Techniques**
- **Microdeletions/Microduplications**
- **Syndromes Recurrent Genomic Disorders**
- **X-Chromosome Abnormalities**

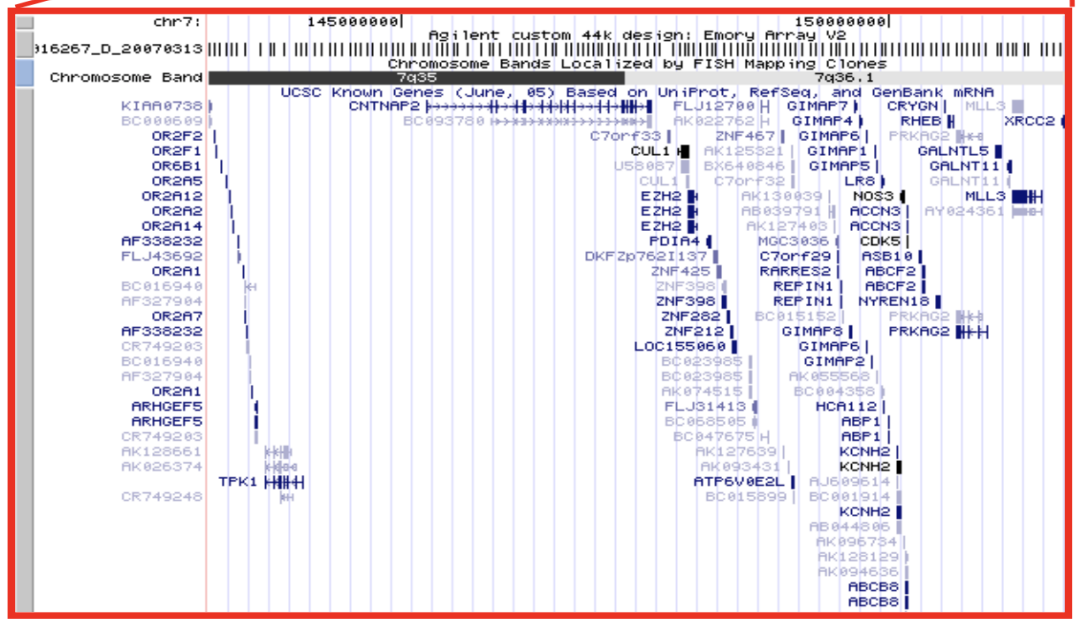
G-band designation (subjective) vs. Array mapping (objective)

7q34 (+/- a band) → 7q35 – q36.1

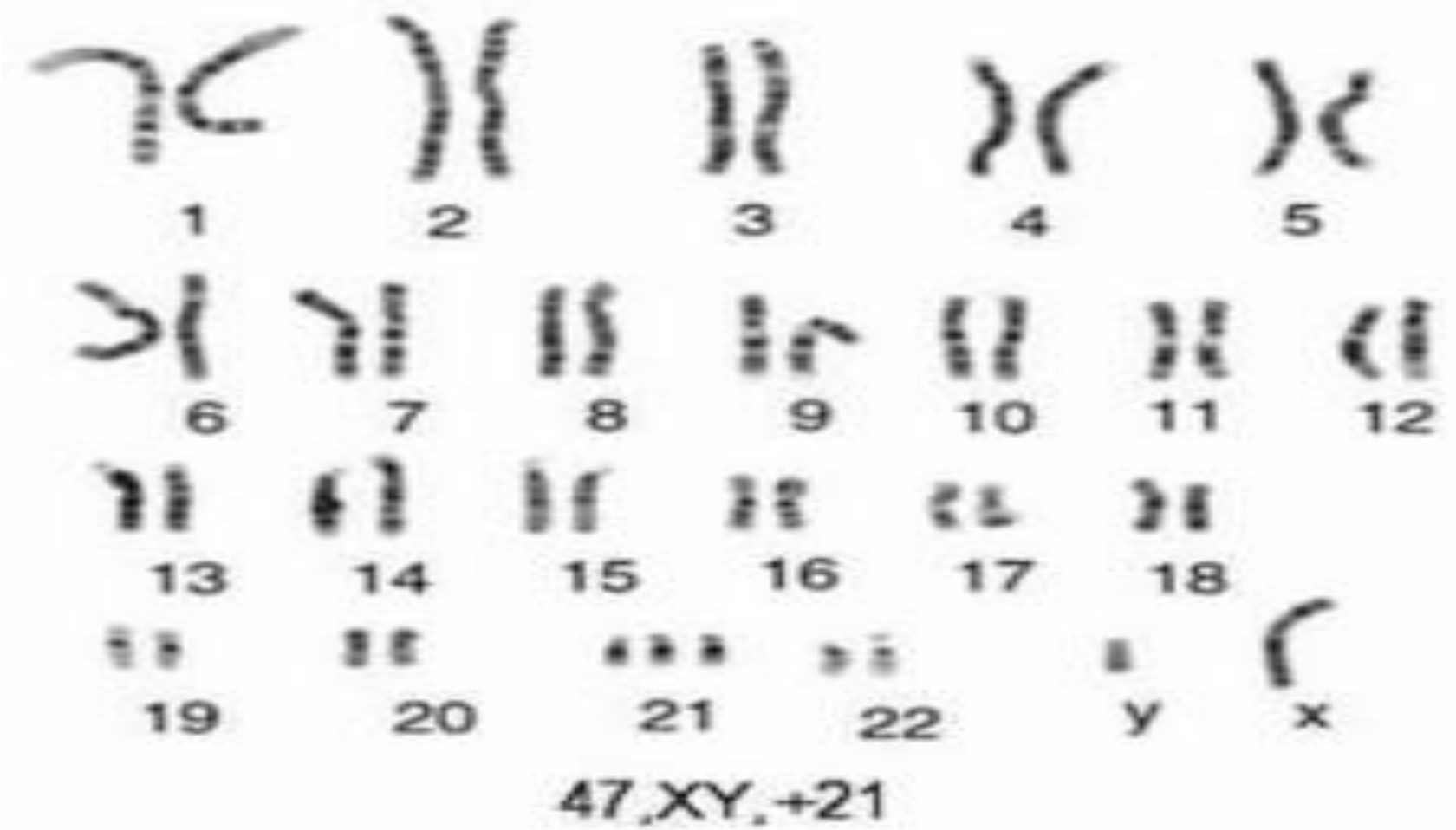


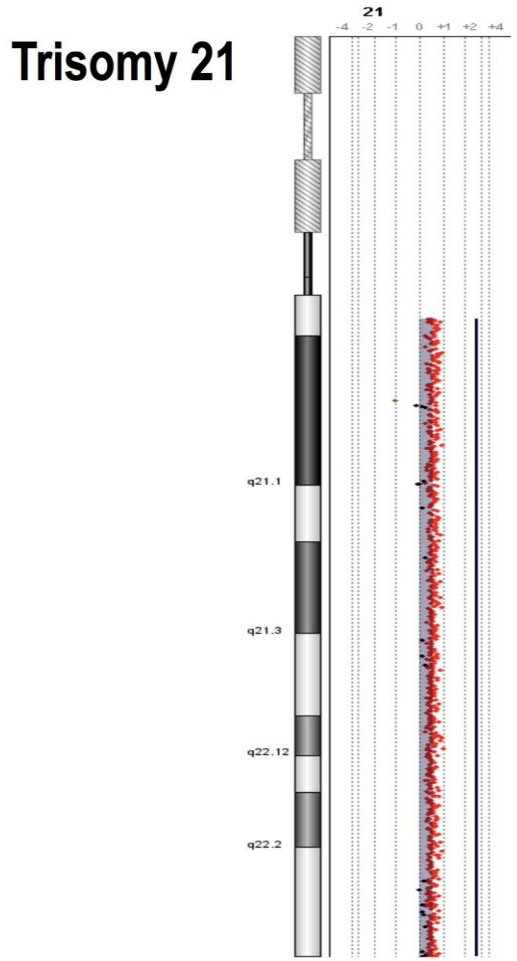
Karyotype courtesy of N.L. Chia
ISCN2009

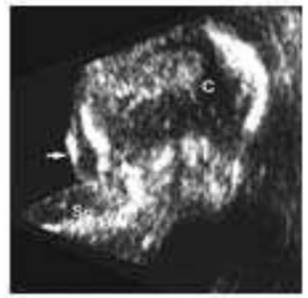




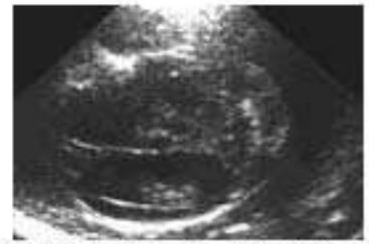
Trisomy 21 karyotyping vs CMA



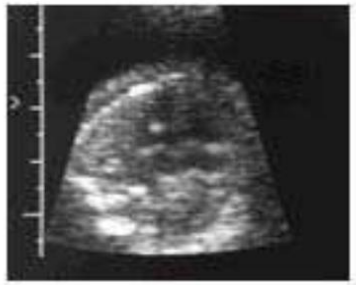




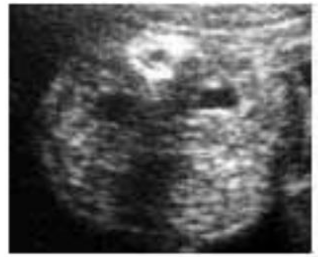
Nuchal Thickening



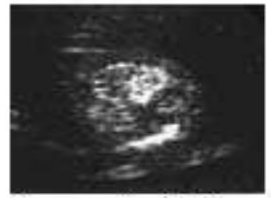
Mild Ventricular Dilatation



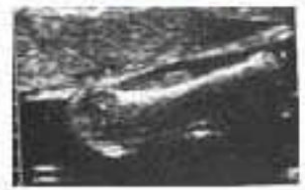
Echogenic Intracardiac Focus



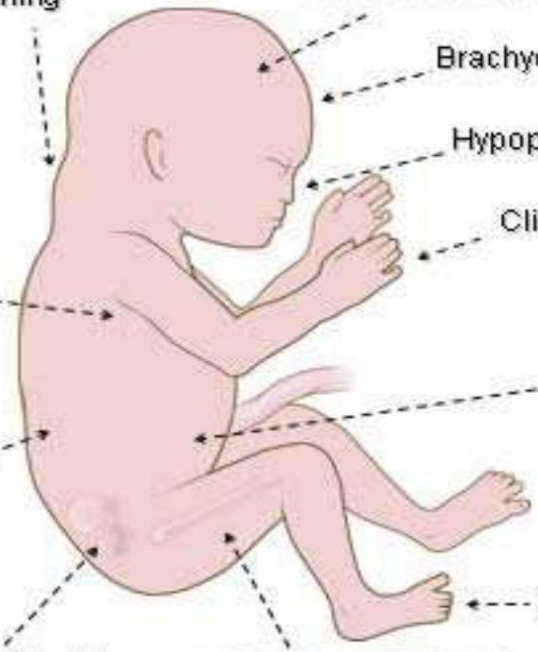
Pyelectasis



Hyperechoic Bowel



Shortened Limbs



Brachycephaly

Hypoplastic Nose

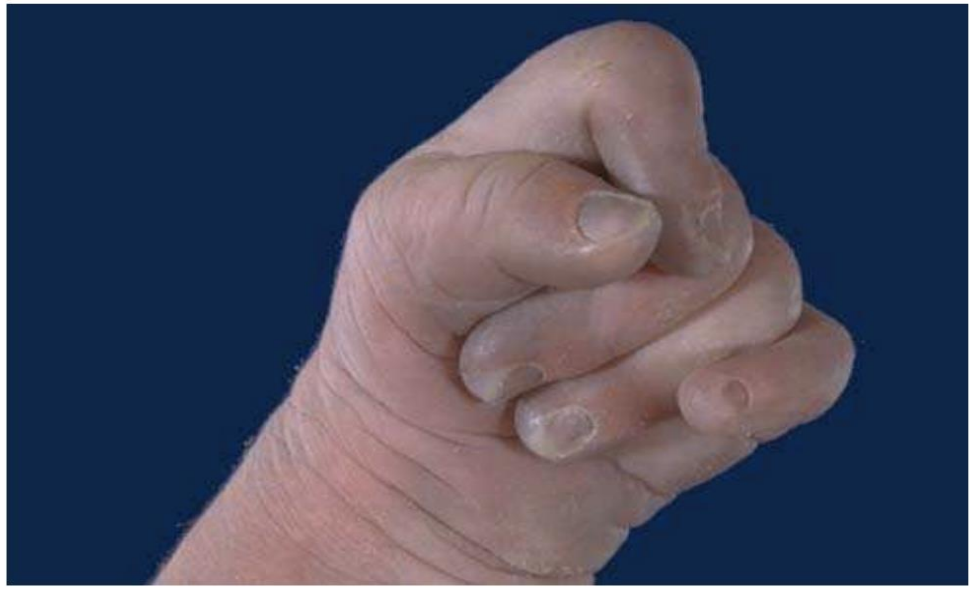
Clinodactyly

Sandal Gap

Widened Pelvis

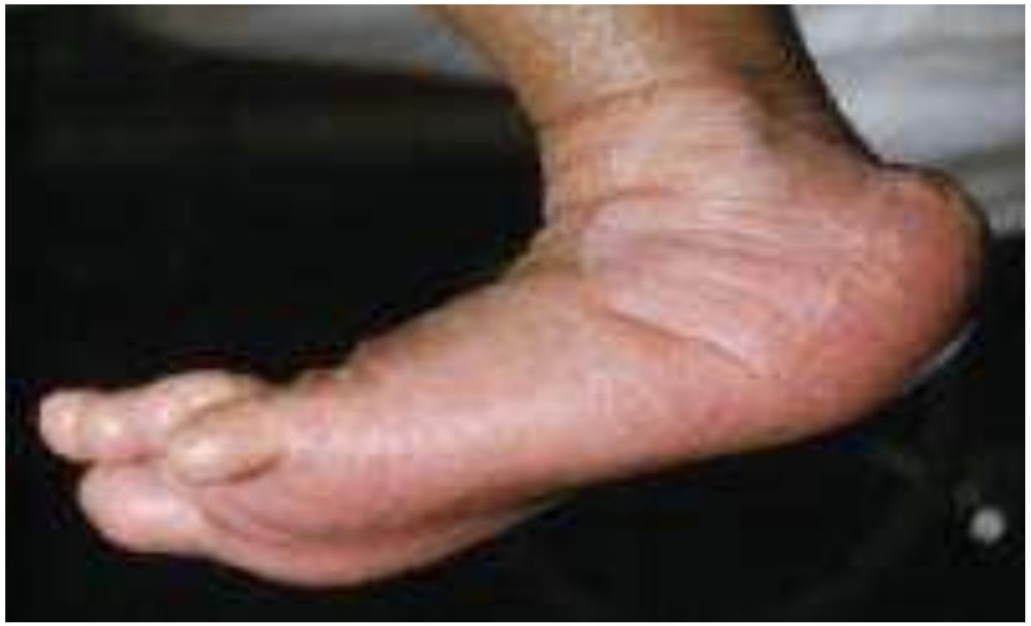
Trisomy 21

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
Inheritance: 95% de novo, 5% due to Robertsonian translocation or isochromosome 21
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
Clinical Tests: prenatal US abnormalities detected in 50%, maternal serum screen: high free beta HCG, low PAPP-A,
Molecular Tests: maternal fetal free DNA testing, karyotype is diagnostic
Disease Mechanism: 90% due to maternal meiosis nondisjunction (¾ MI error, ¼ MII error)
Treatment/Prognosis: Supportive care, overall life expectancy is reduced



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

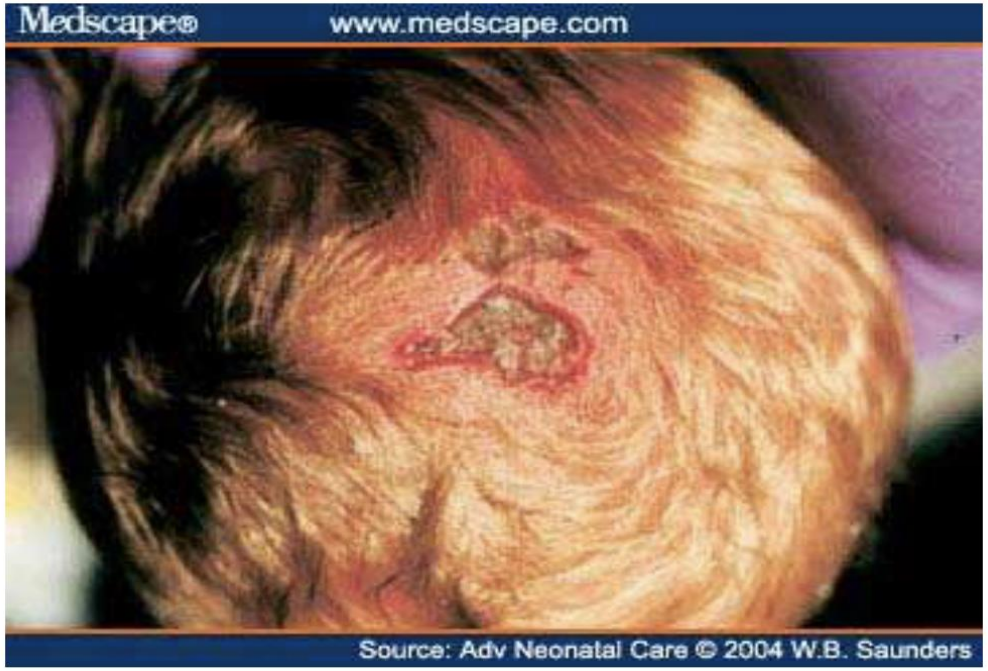
Typical rocker bottom foot of Trisomy 18



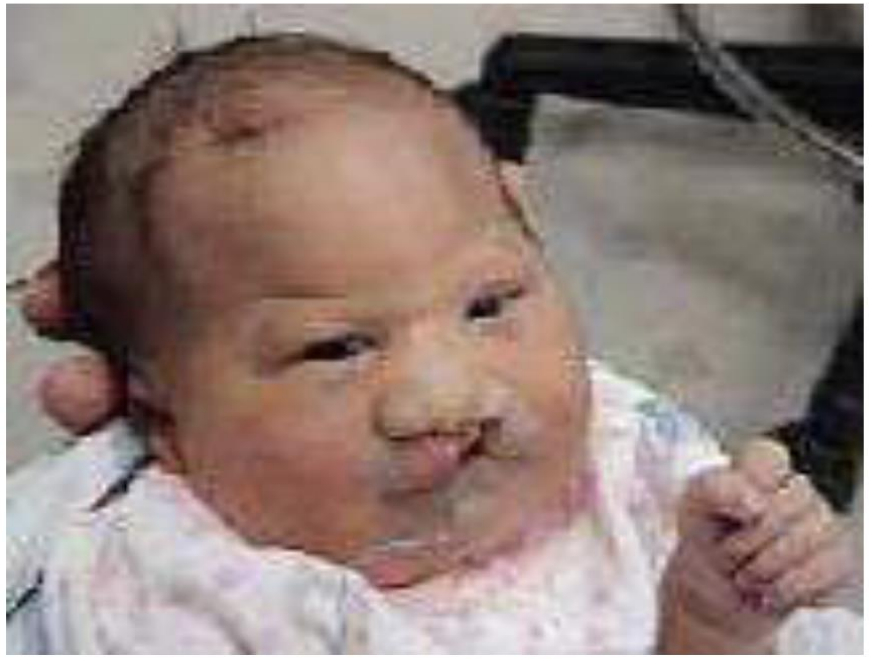
www.gfmer.ch/.../gendis

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.
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%)
Treatment/Prognosis: 50% die in first week, 90% die by one year



Cutis Aplasia



www.prenatalpartnersforlife.org

Trisomy 13

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
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.

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

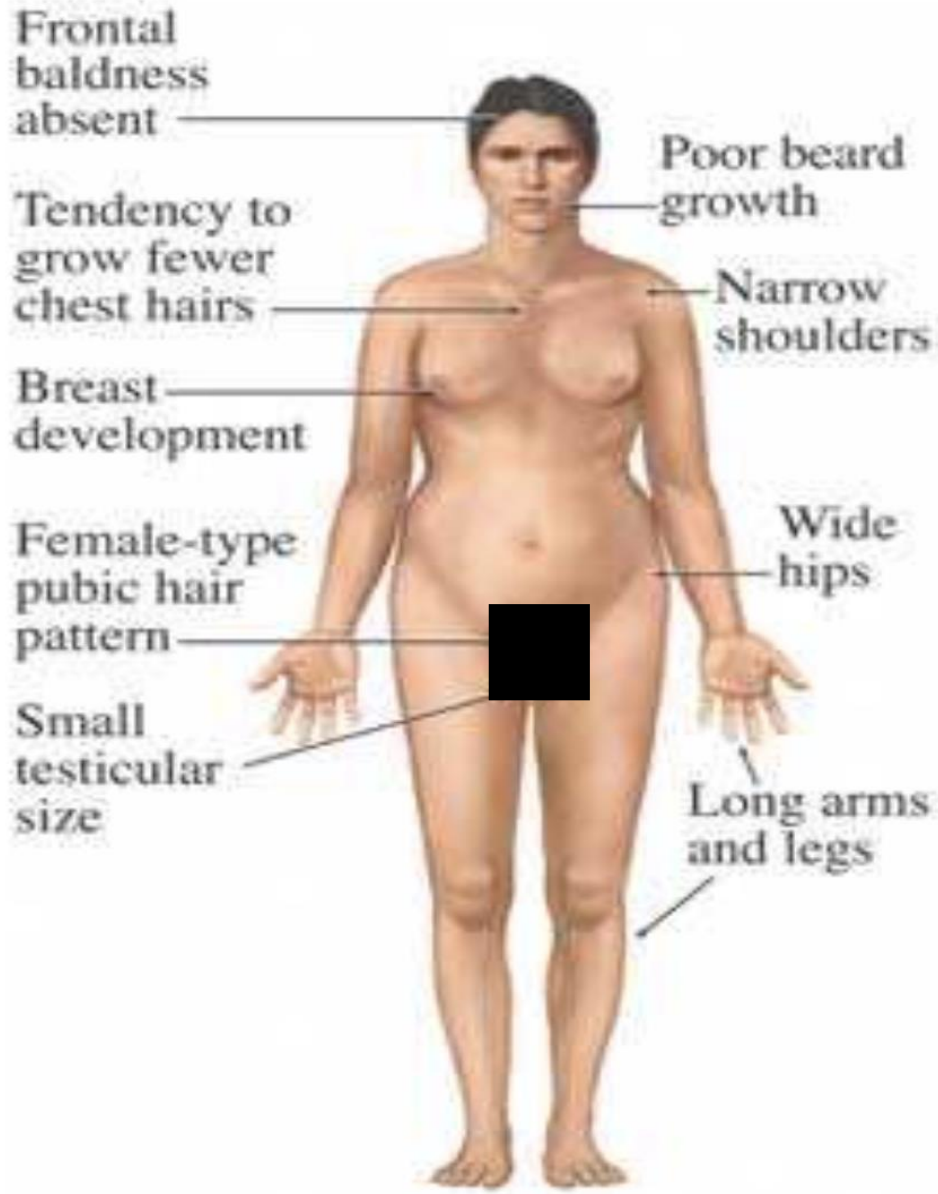
Low posterior hairline and neck webbing

www.healthofchildren.com

Hypertelorism and low set ears

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
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
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.
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)

Clinical Tests:

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

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

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

Microdeletion/microduplication syndromes

- **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**
- **Segmental aneusomy syndromes**
- **Genomic Disorders (subset mediated by segmental duplications – seg dup)**
- **Mechanisms include deletion, duplication, and UPD = any deviation from normal, biparental inheritance**

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:**
  - **Micrognathia, ear anomalies, cleft palate, short palpebral fissures, short upper lip**

del(22)(q11.2)

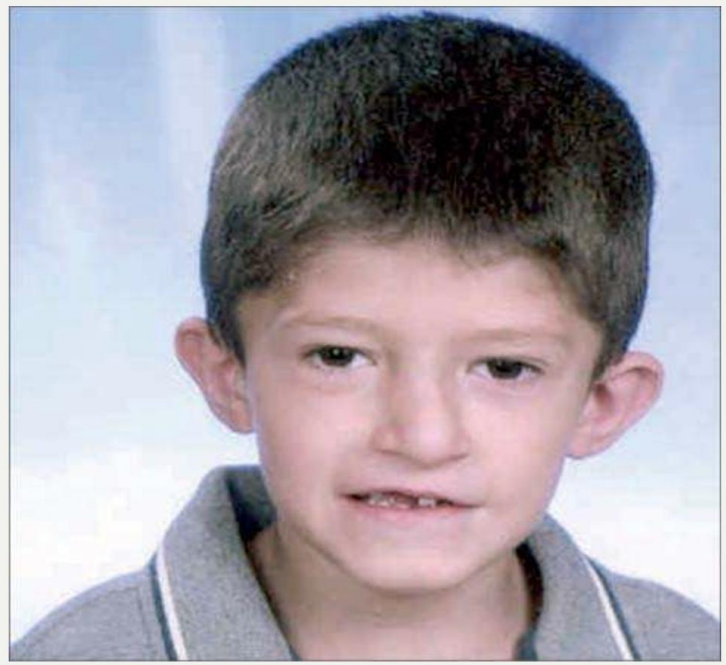
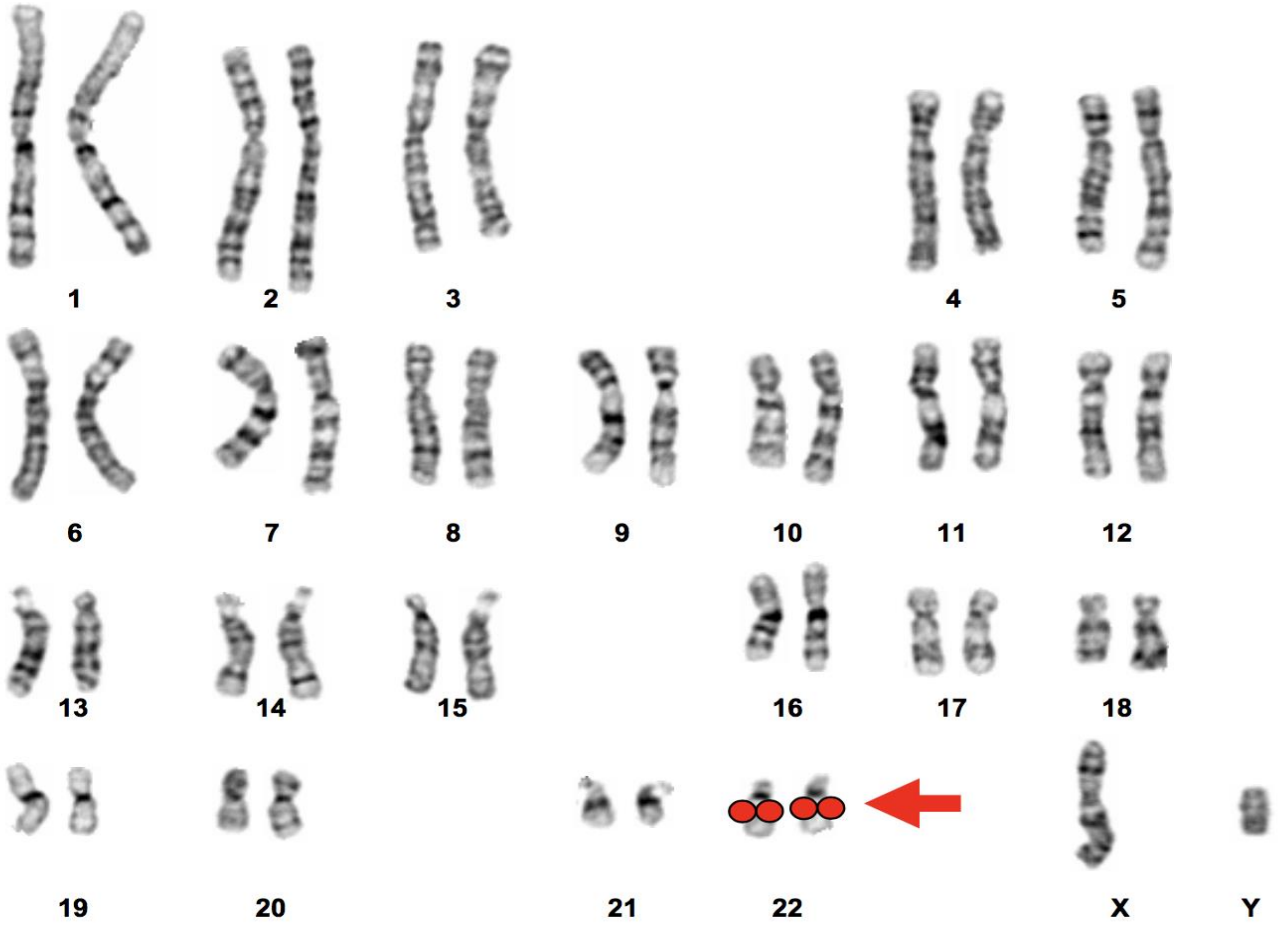


Image from www.thelancet.com

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!!!

Facial Features

Microcephaly
Round face
Hypertelorism
Micrognathia
Epicanthal folds
Low-set ears

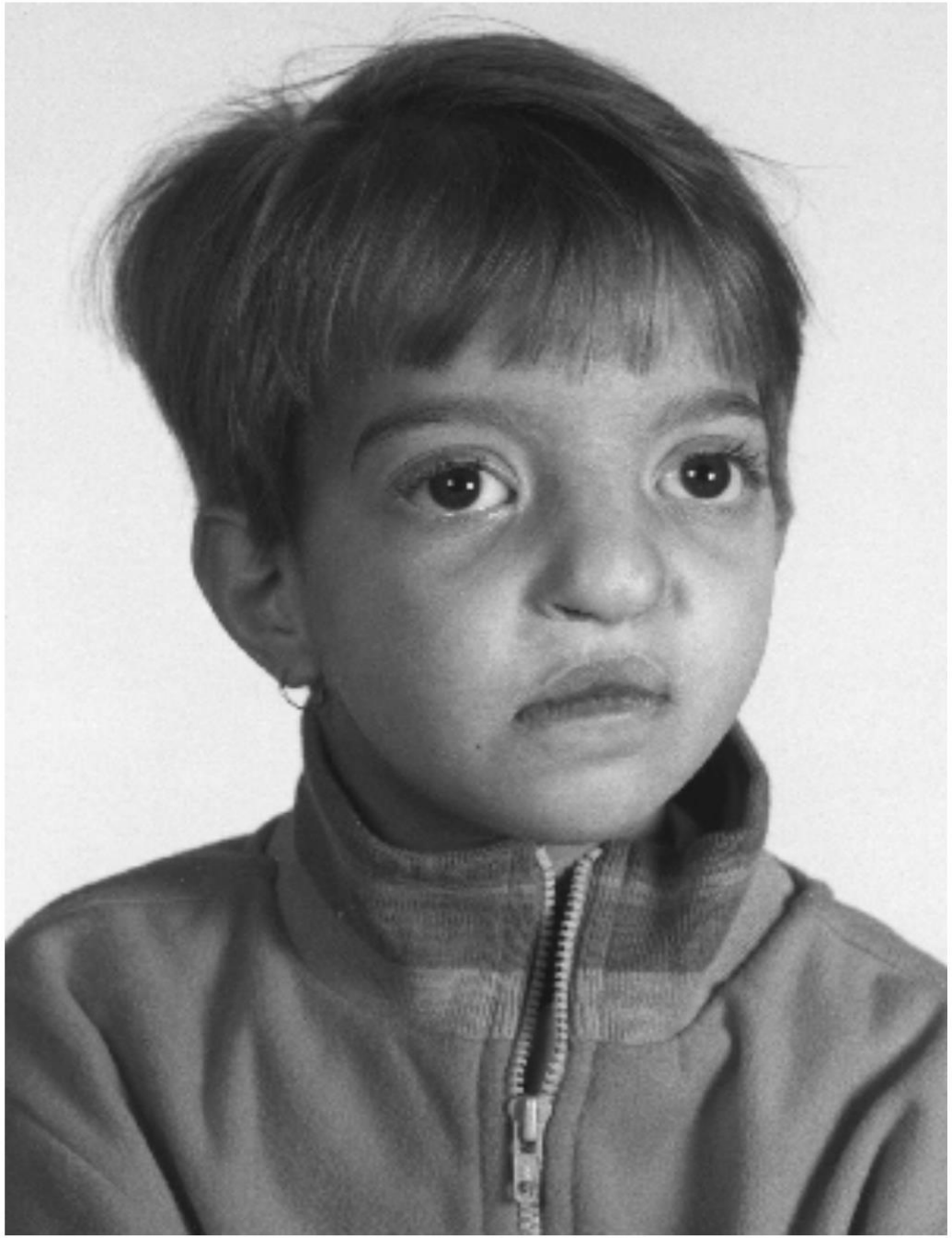
www.specialchild.com/archives/poster-child023

Cri Du Chat del(5p)

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

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
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

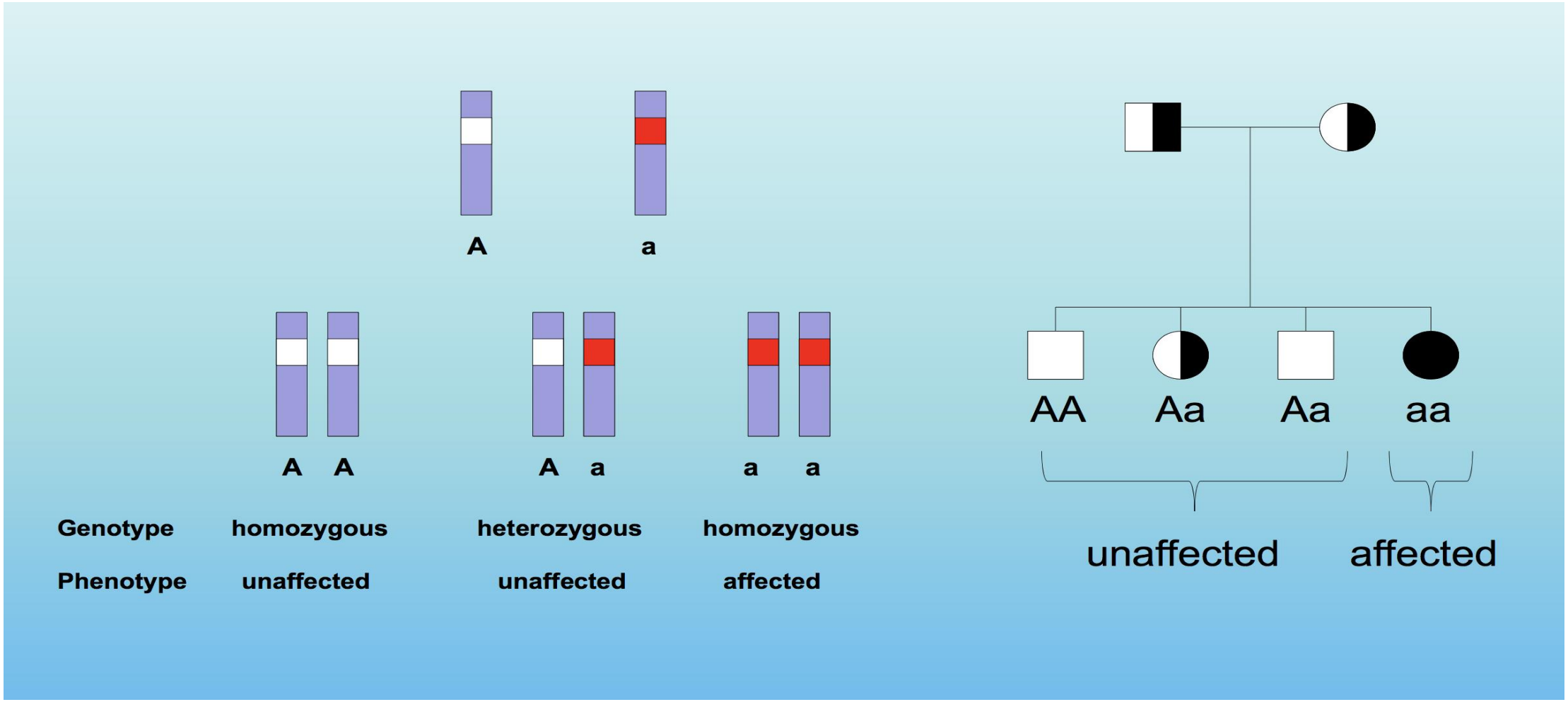
Wolf-Hirschhorn syndrome /del(4p)

- **IUGR, microcephaly, hypotonia, severe ID**
- **Dysmorphic facial features**
  - **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**

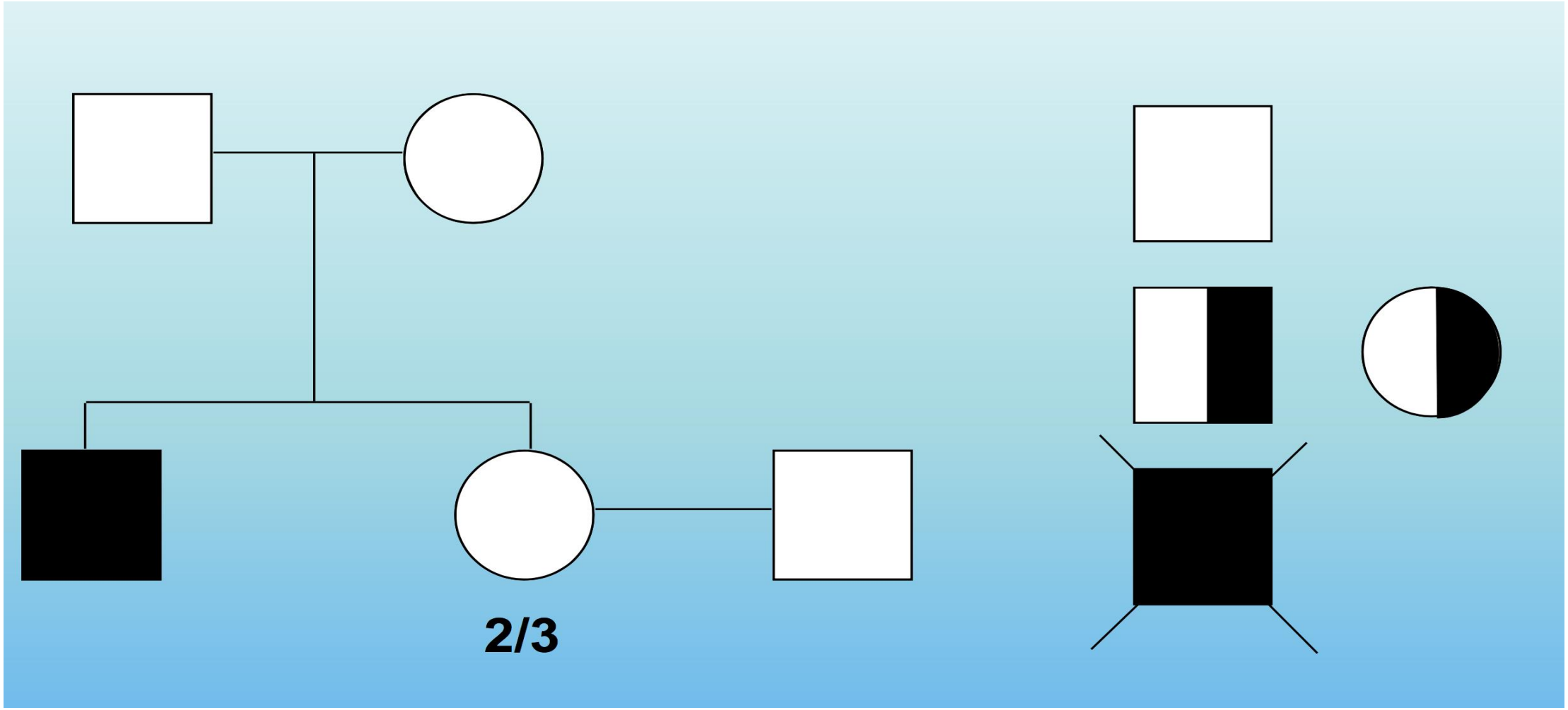
Single gene disorders

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

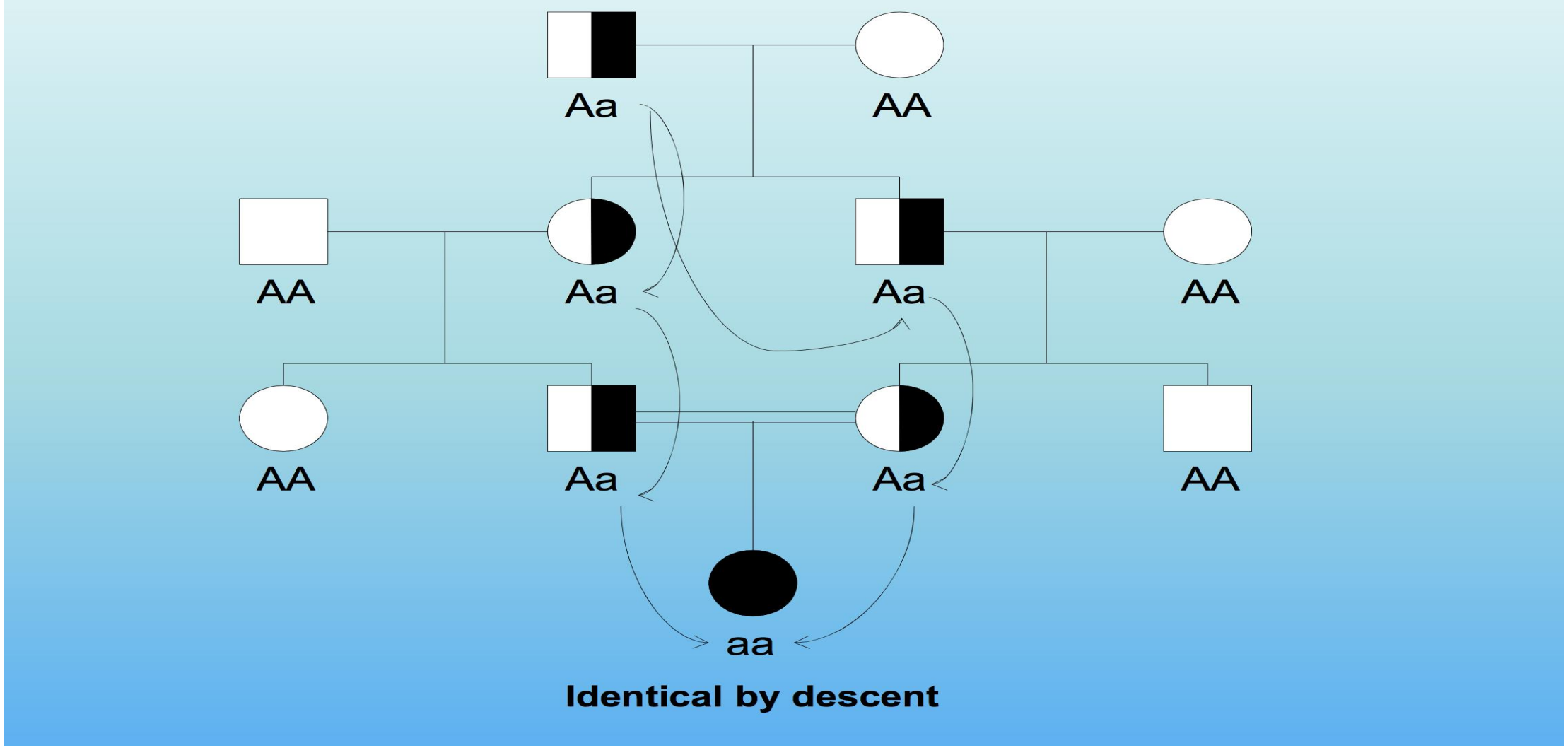
Autosomal recessive



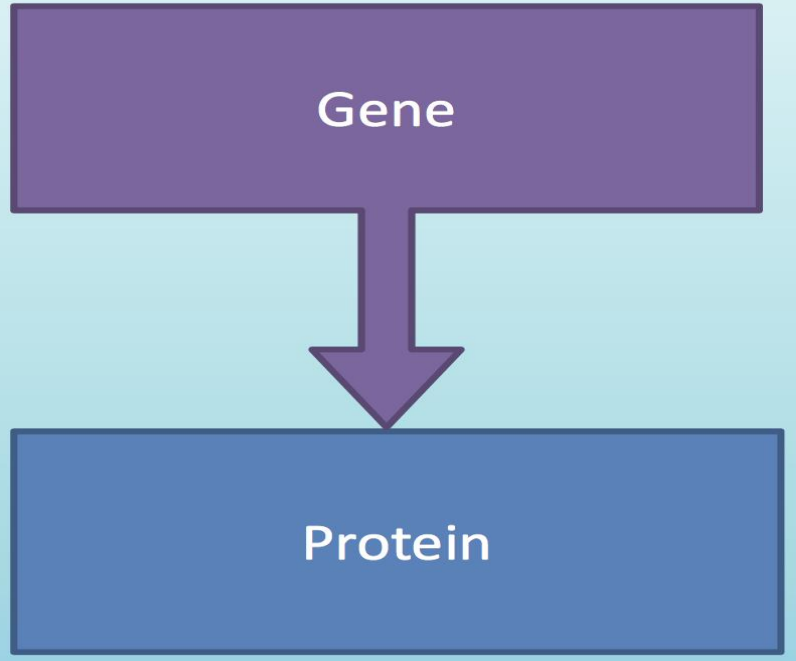
Genetic counselling



Consanguinity

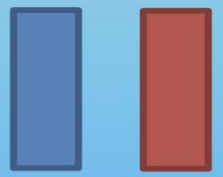


Recessive mechanism

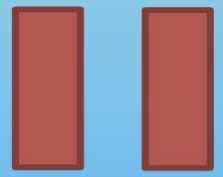


Loss of function mutations: deletion, frameshift, stop, missense

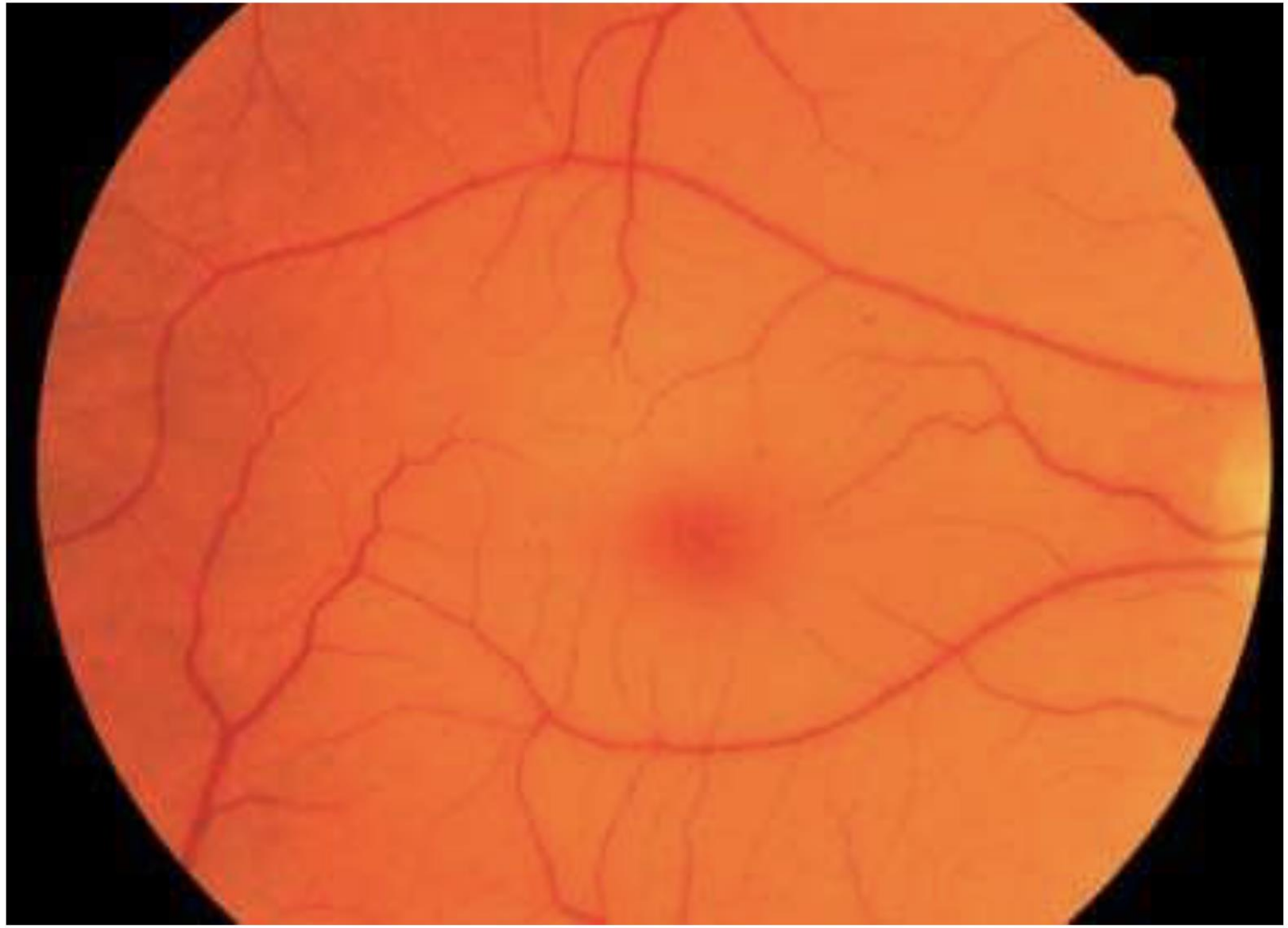
Complete absence of product or significant reduction of function



Heterozygote – sufficient activity to avoid phenotype



Homozygote – profound loss of activity results in phenotype



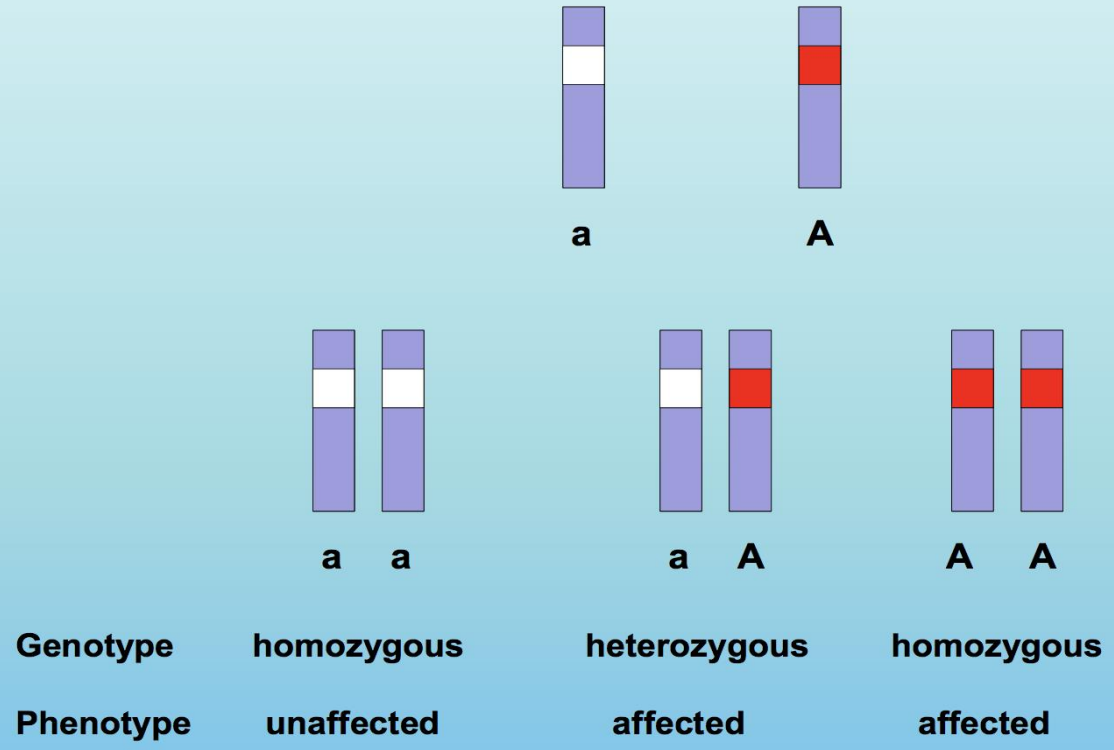
Cherry red spot of the macula

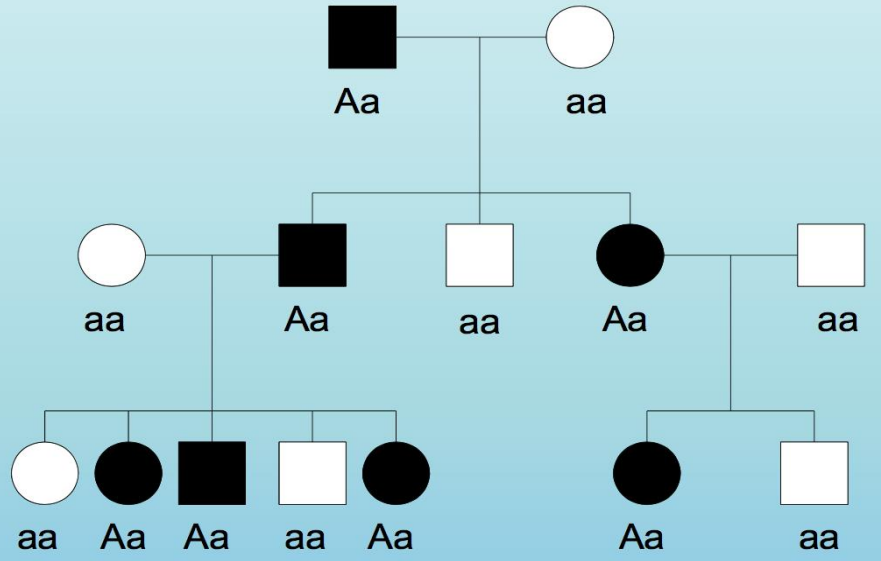
http://themedicalbiochemistrypage.org/images/cherryredspot.jpg

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

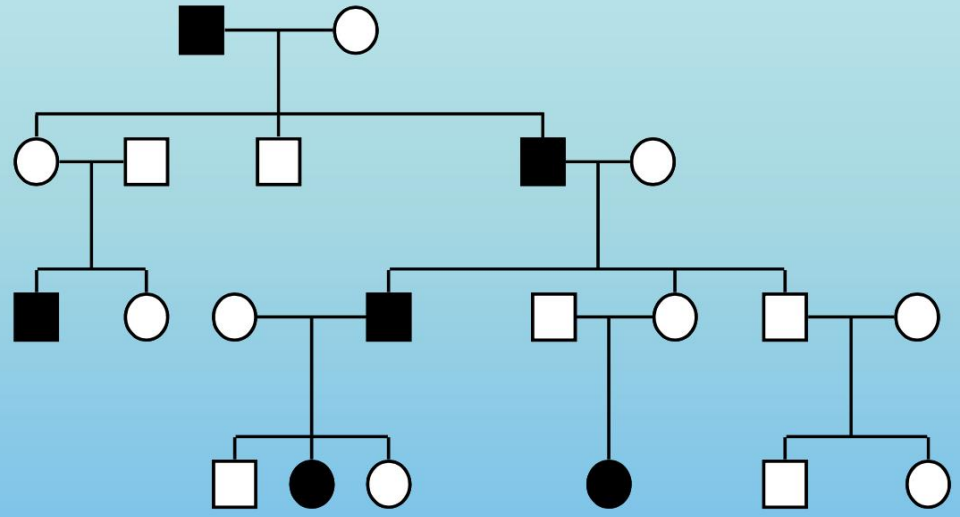
Autosomal dominant

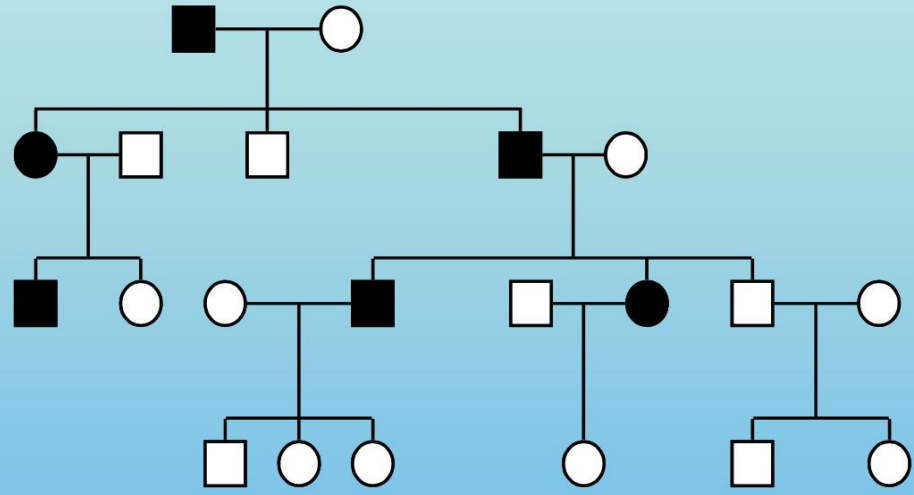




Penetrance

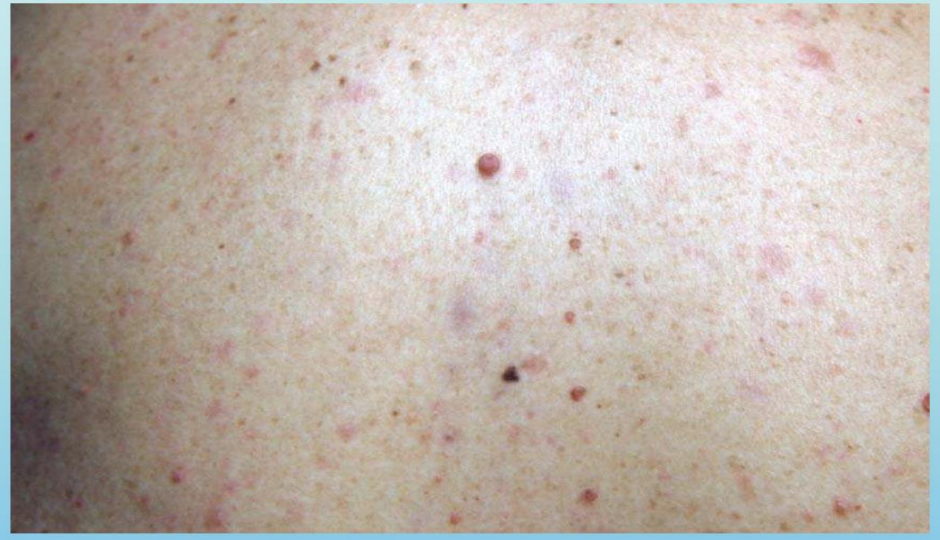
Fraction of individuals who carry a gene who manifest a specified phenotype

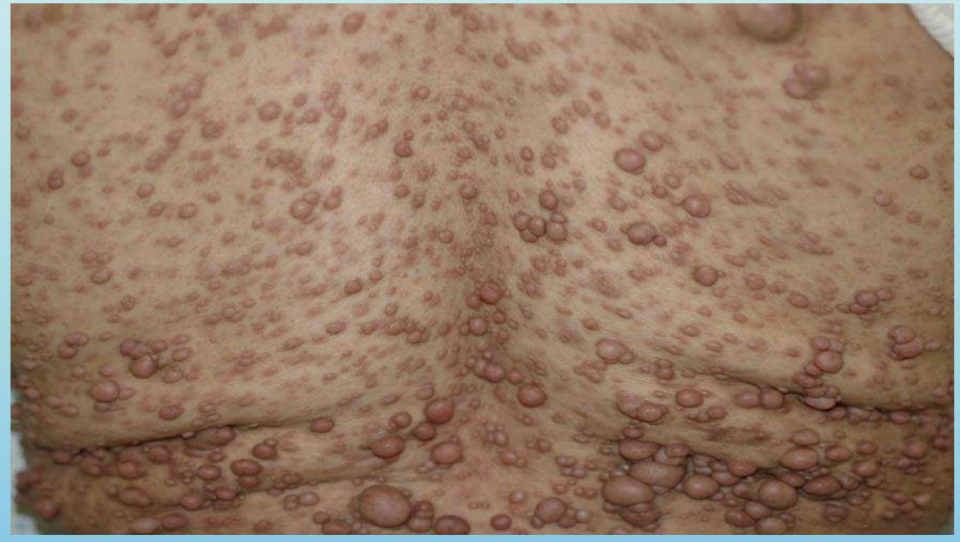




Expressivity

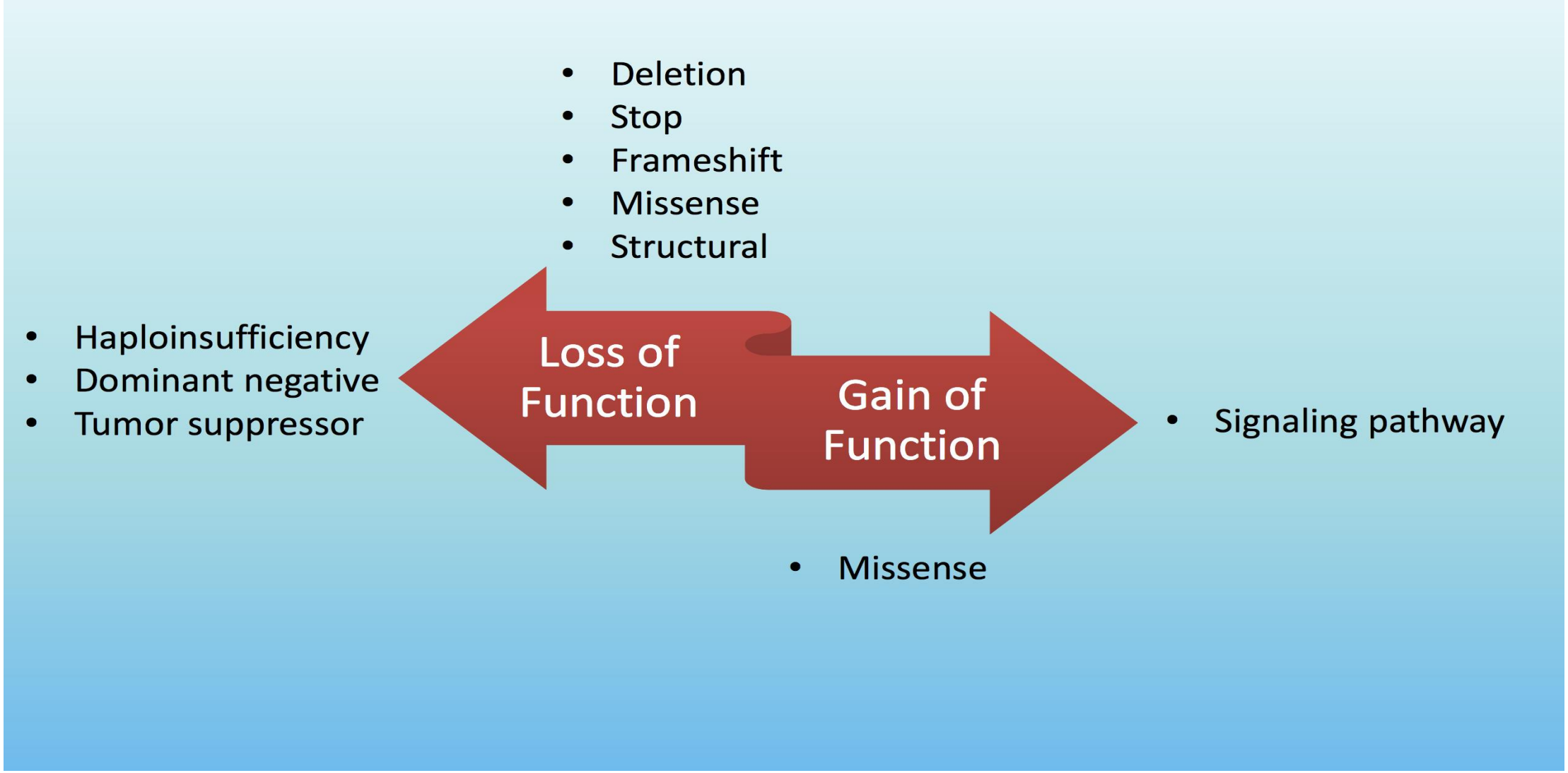
different modes or degrees of expression of trait in population



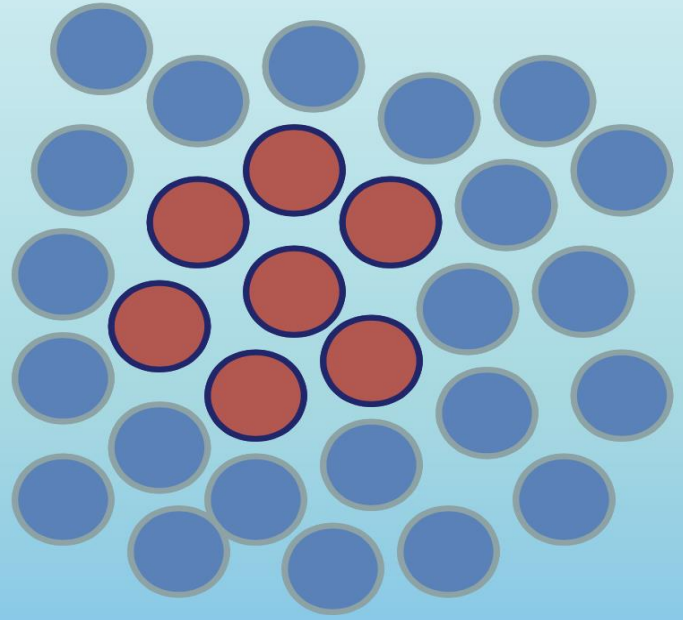


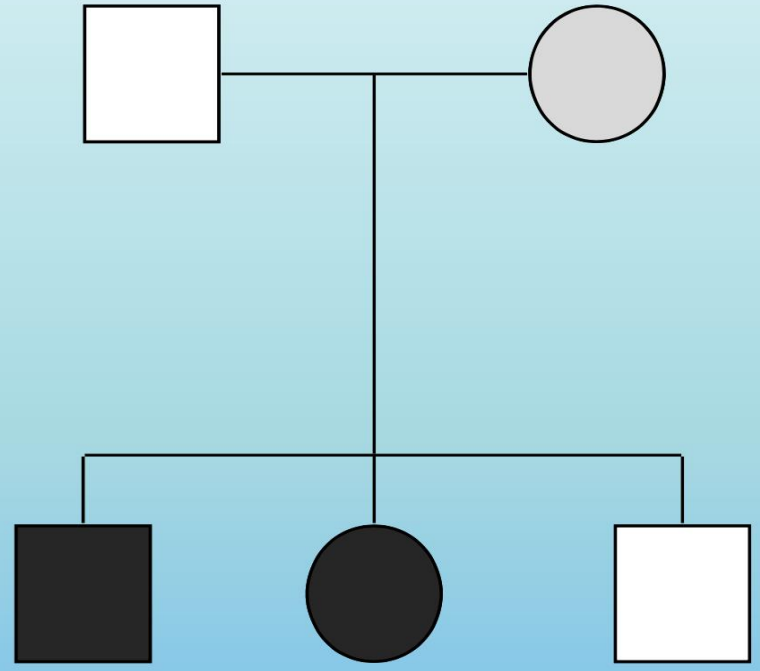
Neurofibromas in NF1

Dominant mechanism

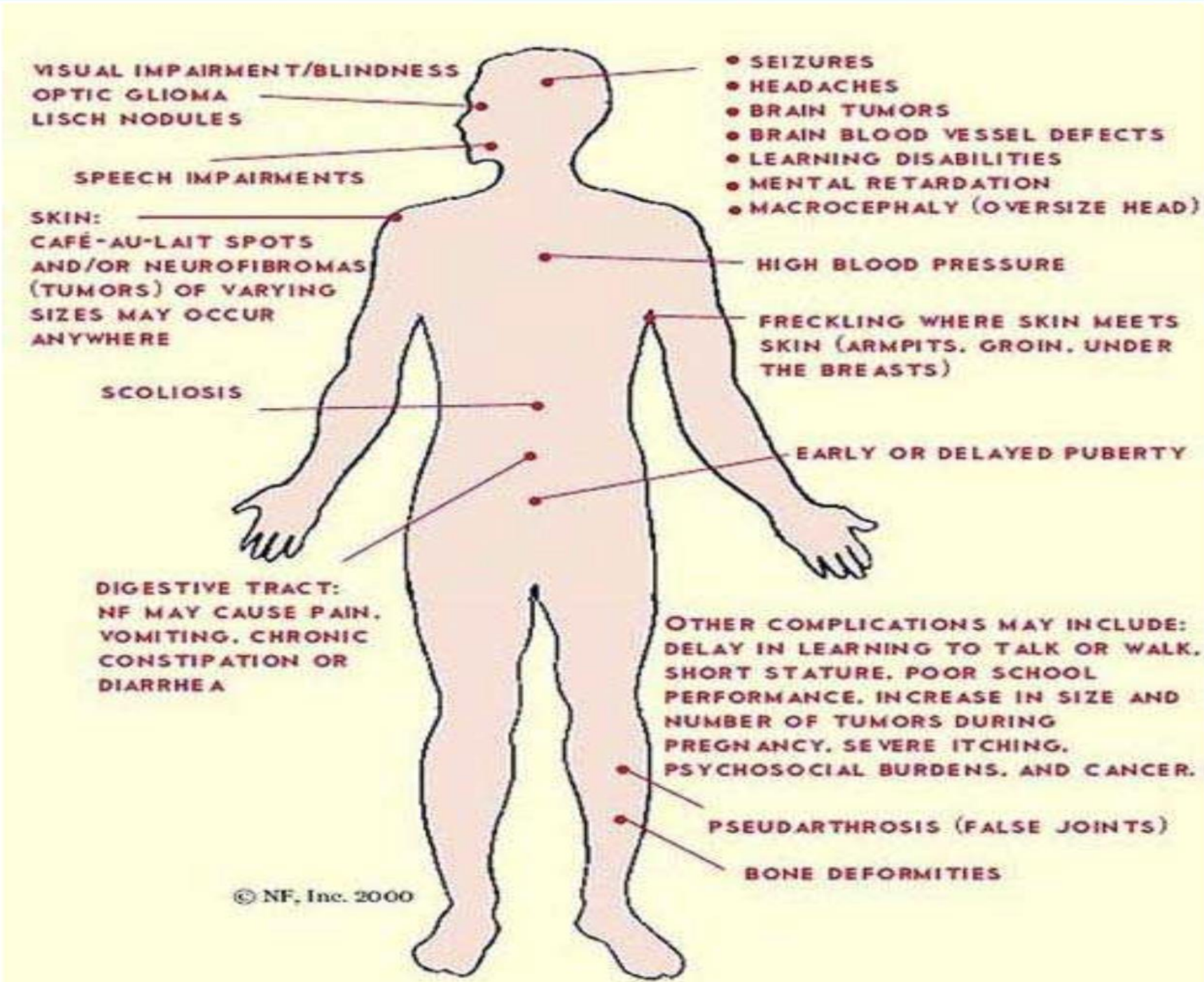


Mosaicism





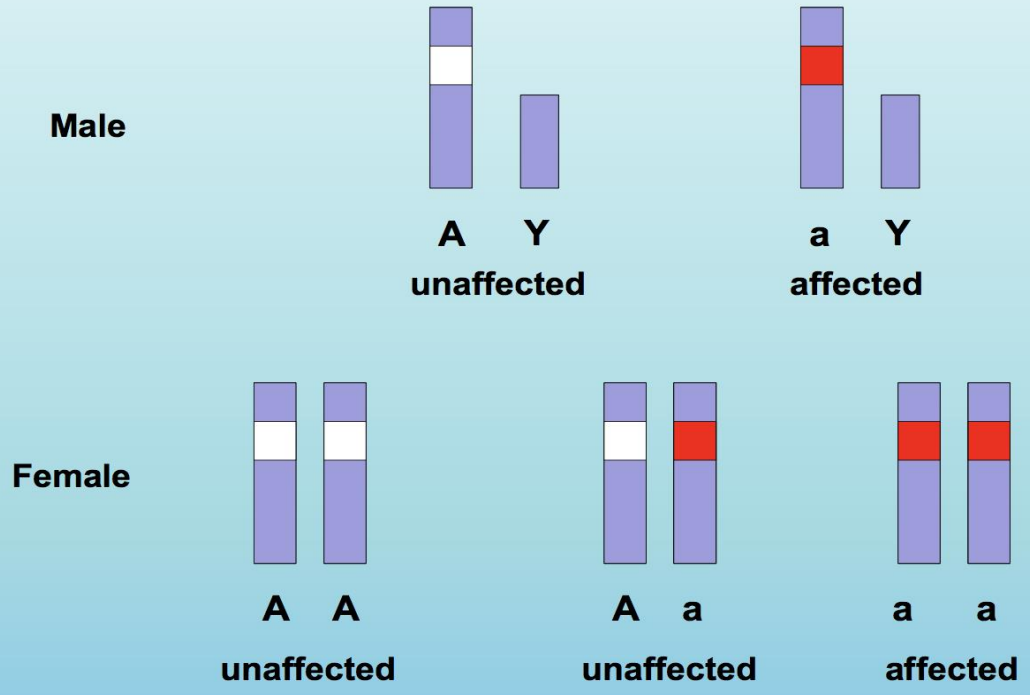
- Germ line
- Somatic

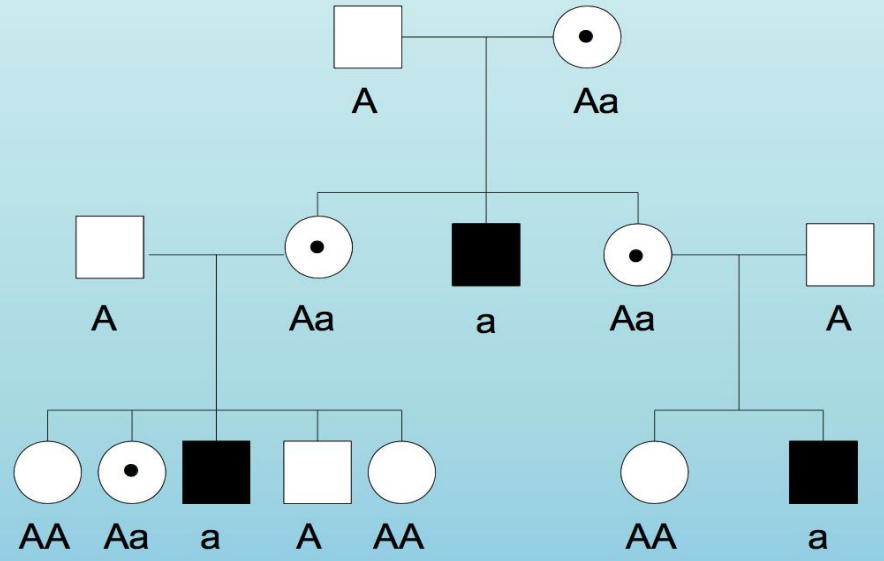

VISUAL IMPAIRMENT/BLINDNESS
OPTIC GLIOMA
LISCH NODULES
SPEECH IMPAIRMENTS
SKIN:
CAFÉ-AU-LAIT SPOTS AND/OR NEUROFIBROMAS (TUMORS) OF VARYING SIZES MAY OCCUR ANYWHERE
SCOLIOSIS
DIGESTIVE TRACT:
NF MAY CAUSE PAIN, VOMITING, CHRONIC CONSTIPATION OR DIARRHEA
SEIZURES
HEADACHES
BRAIN TUMORS
BRAIN BLOOD VESSEL 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
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
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

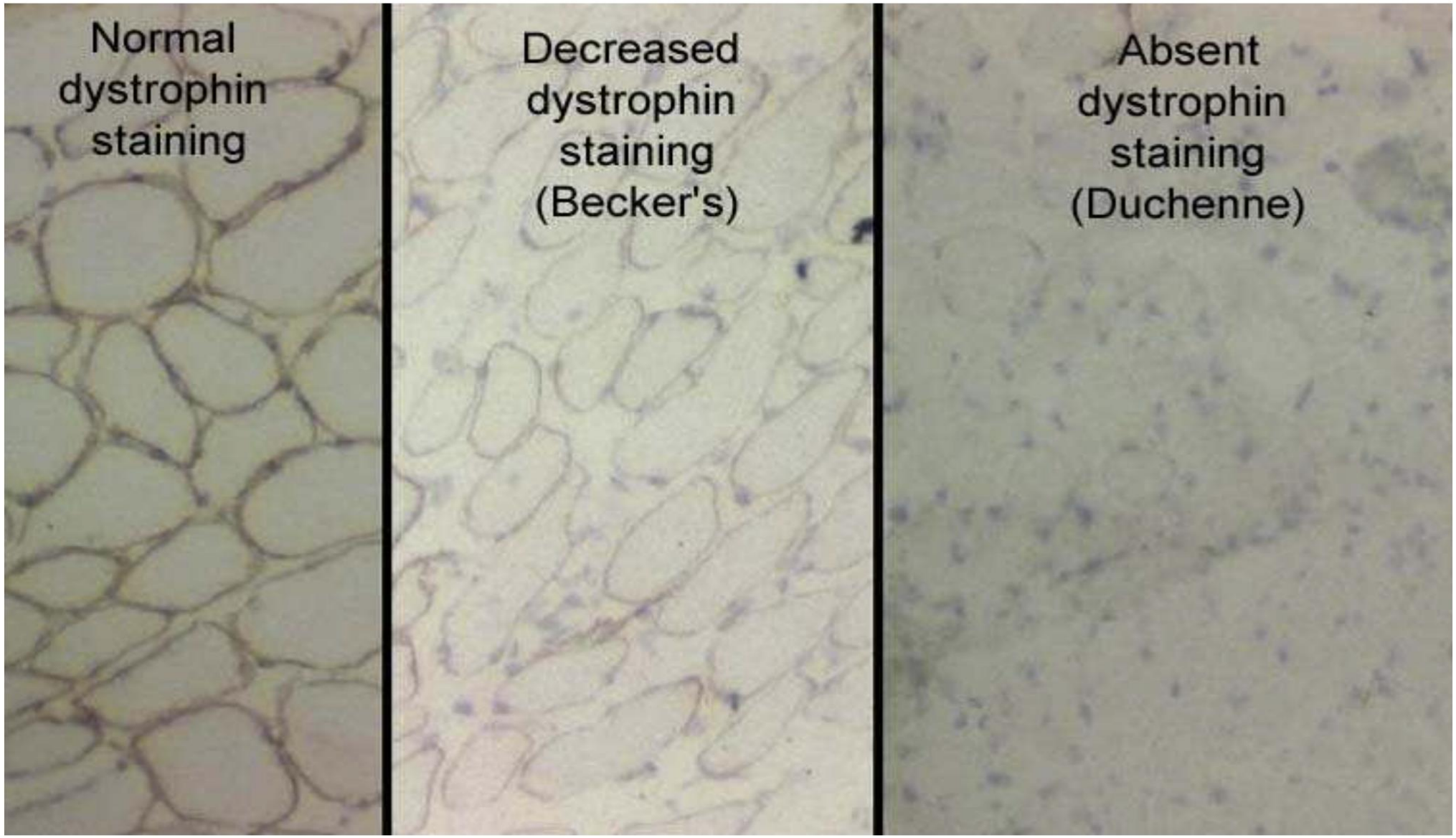




No male to male transmission

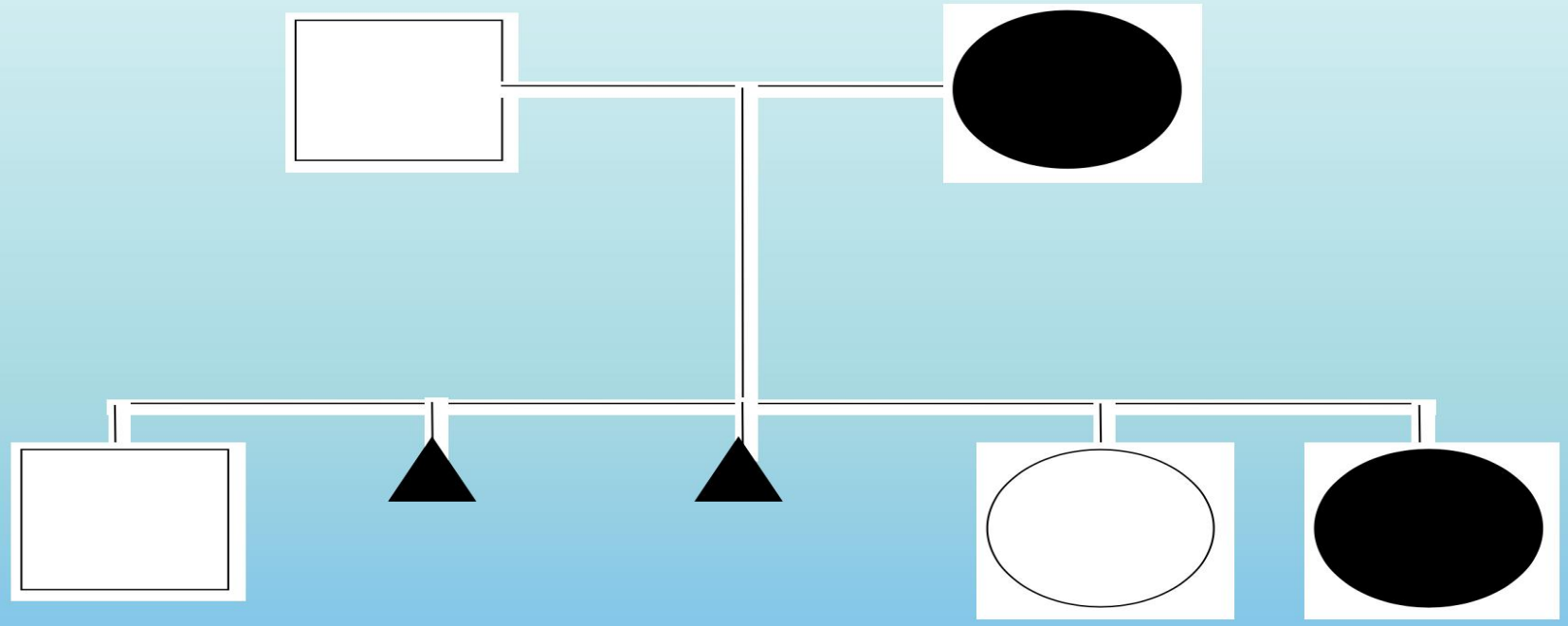
Duchene and Becker muscular dystrophy (DMD/BMD)

Responsible gene: *DMD* **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.



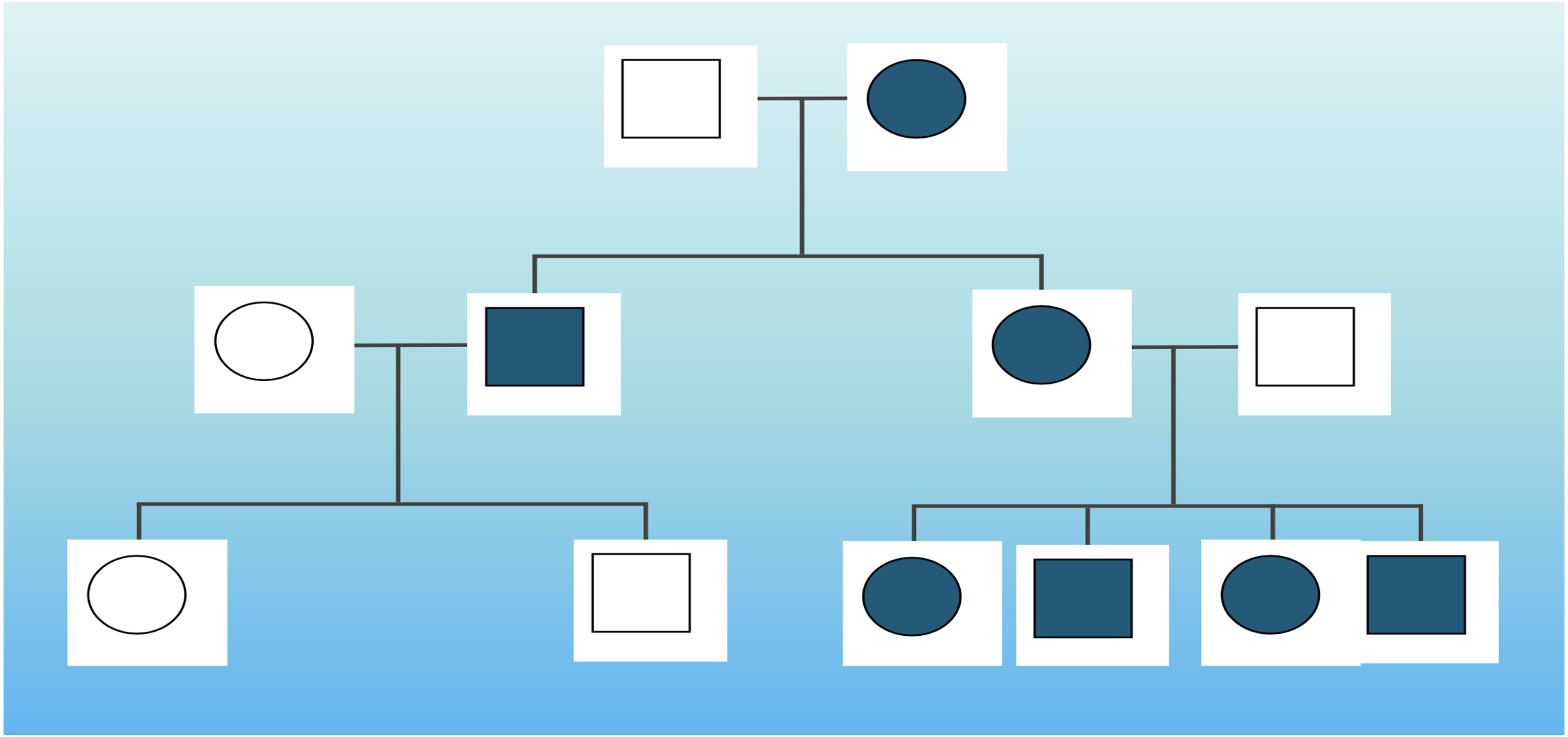
http://img.orthobullets.com/Pediatrics/Neuromuscular%20problems/Duchenes%20Muscular%20Dystrophy/Images/dystrophin_stains.jpg

X-linked dominant lethal in male



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

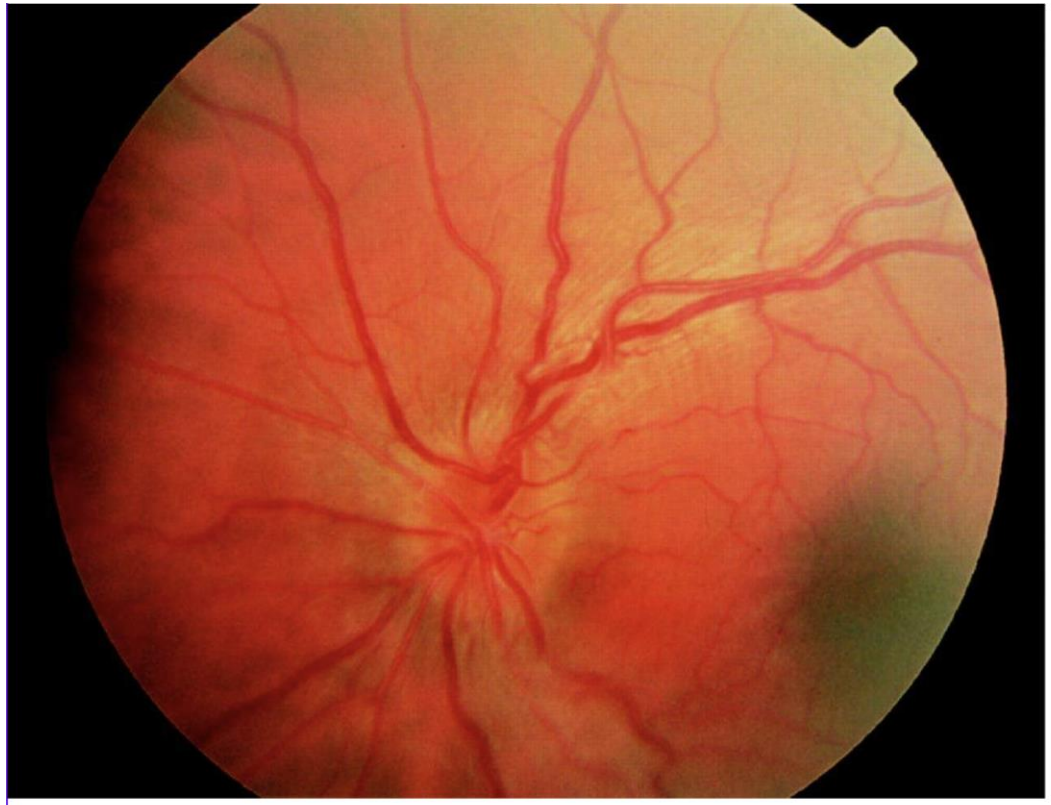
Maternal inheritance



Leber hereditary optic neuropathy

Responsible genes: *MTND1, MTND4, MTND5, MTND6*
Proteins: Complex I subunits of the mitochondrial respiratory chain
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

Leber hereditary optic neuropathy



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

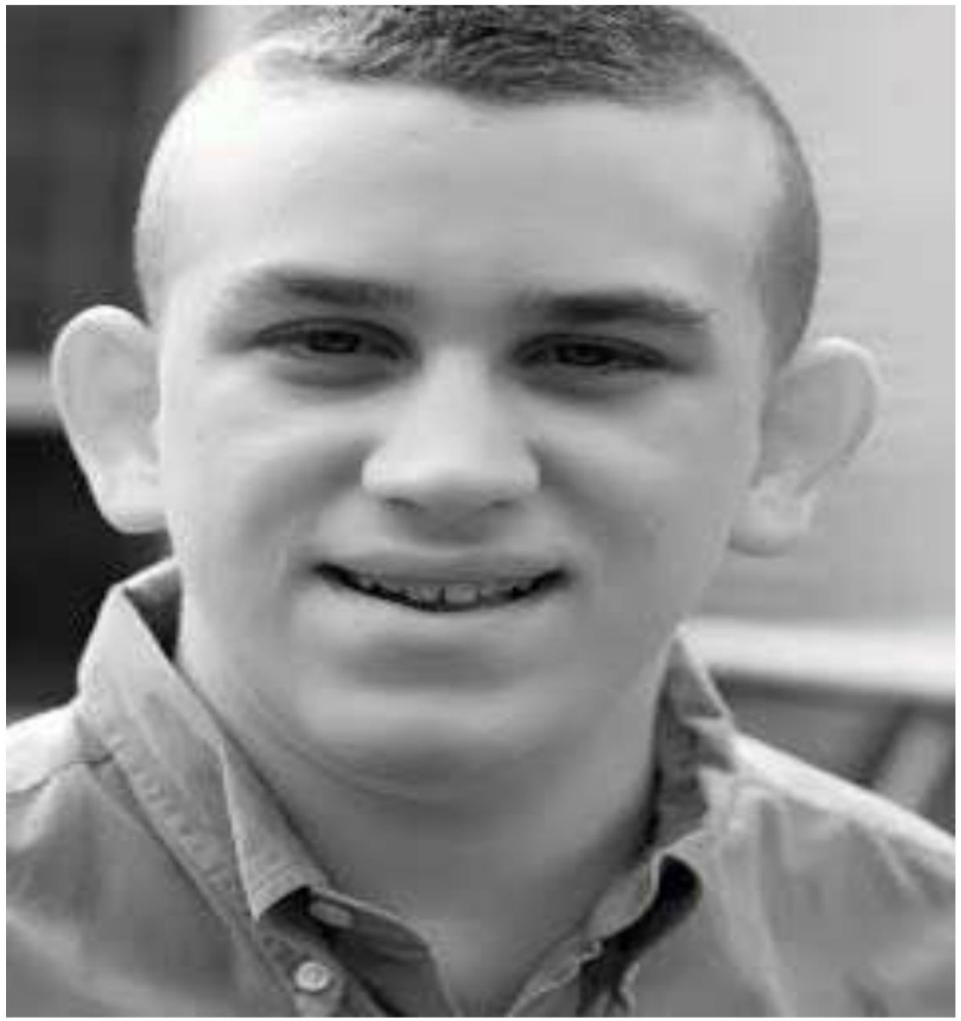
(Yu-Wai-Man P et al. J Med Genet 2009;46:145-158)

Dynamic mutation (unstable repeat expansion)

- Dynamic mutation: that change from generation to generation.
- The expansion beyond the normal can alter gene expression and function
- Parental transmission bias: anticipation occurs the mutant allele transmitted through the affected father or mother .
- The expansion of premutation alleles occurs primarily in the female germline in FGXS but largest expansion causing juvenile onset HD in male germline

FRAGILE X

NEUROLOGIC DISORDERS



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

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

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: 5-44 repeats, Intermediate: 45-58 repeats (gray zone), Pre-mutation: 59-200 repeats, 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.

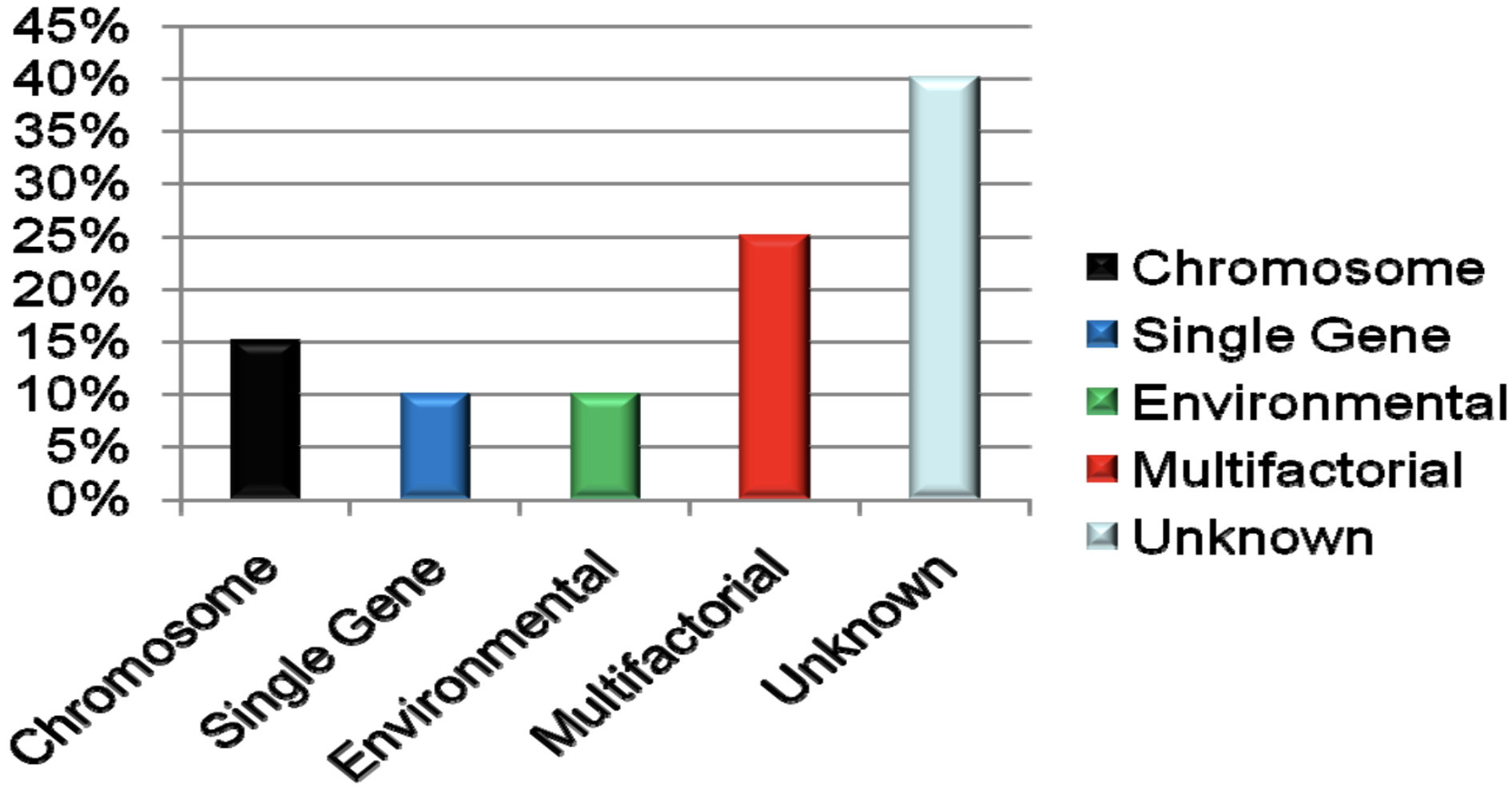
Developmental genetic

- 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



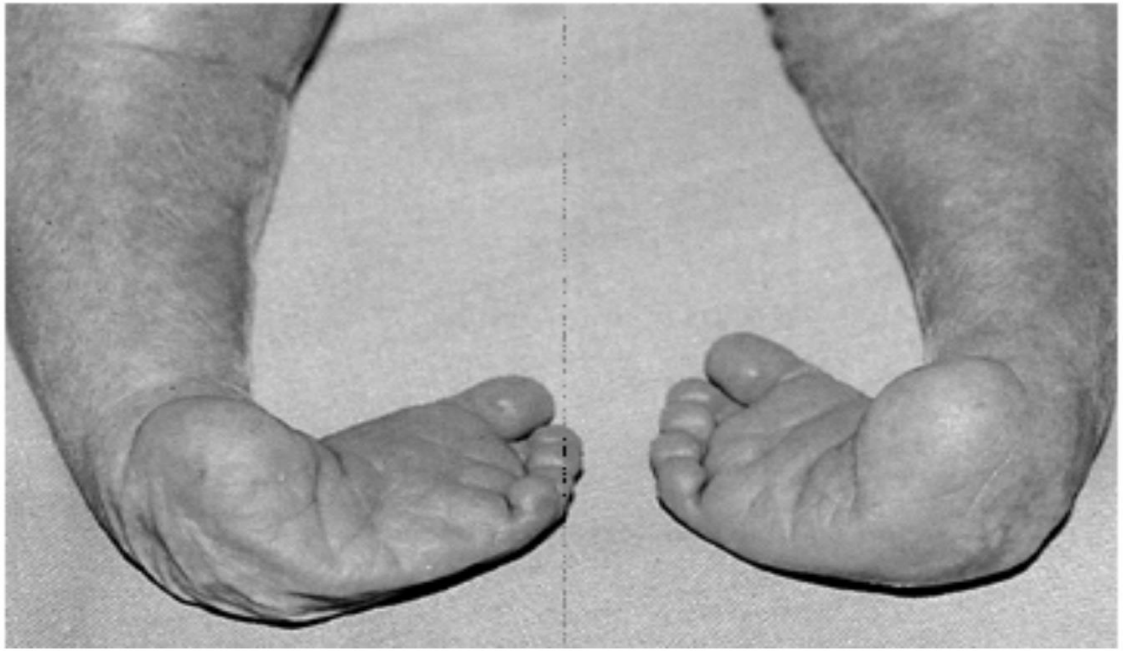
Congenital anomalies

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*
- Mechanical force alters structure , extrinsic factors impinging physical on the fetus during development usually second trimester.
- Most of them are reversible.
- Examples: maternal or fetal force
  - Oligohydramnios
  - Breech presentation
  - Bicornuate uterus

Deformation



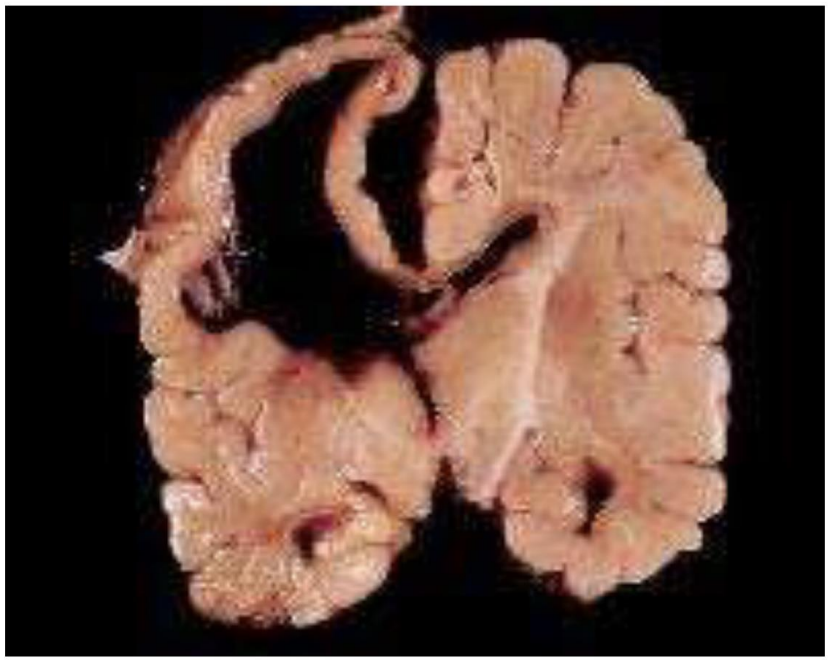
Clubbed feet

- spina bifida

Moore. The Developing Human. Saunders, 1994

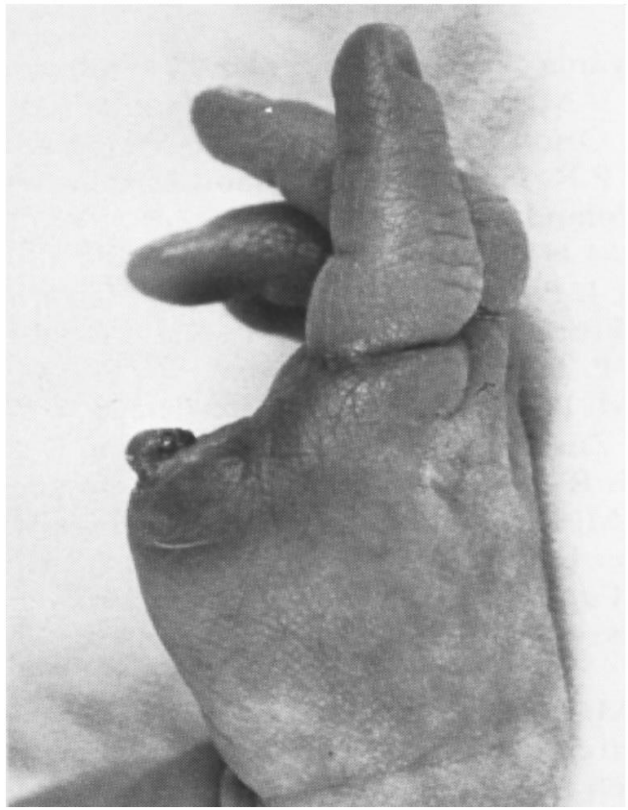
Disruption

- 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



Porencephaly

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

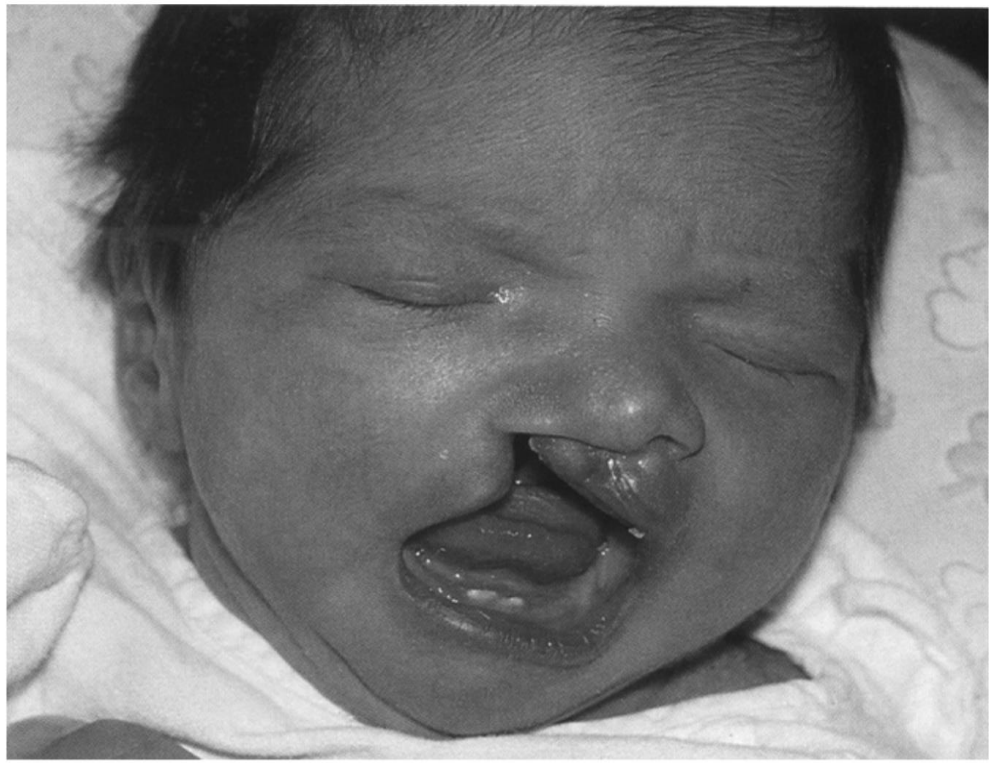


Amniotic Band

ıze. Clinical Syndromes. Mosby-Wolfe, 1997

Malformation

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



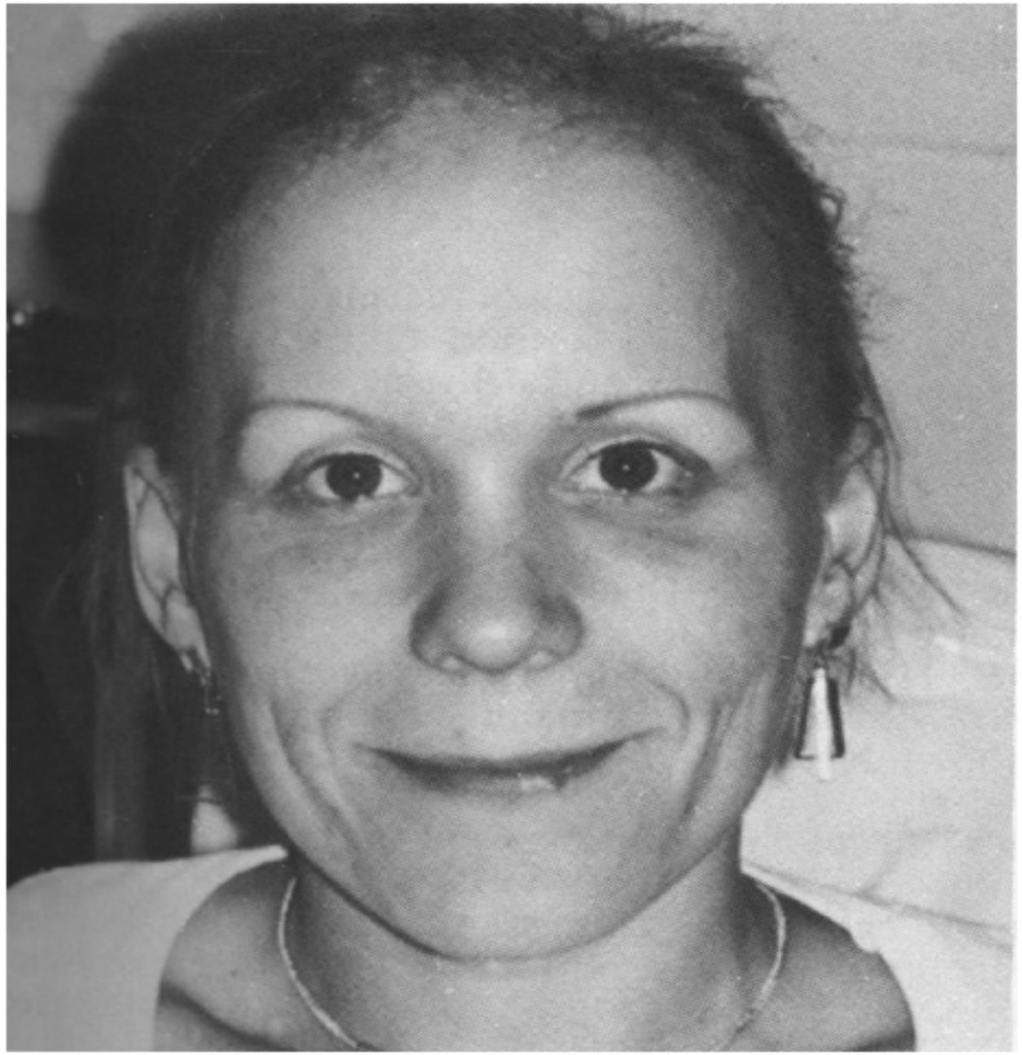
Unilateral Cleft Lip and Palate

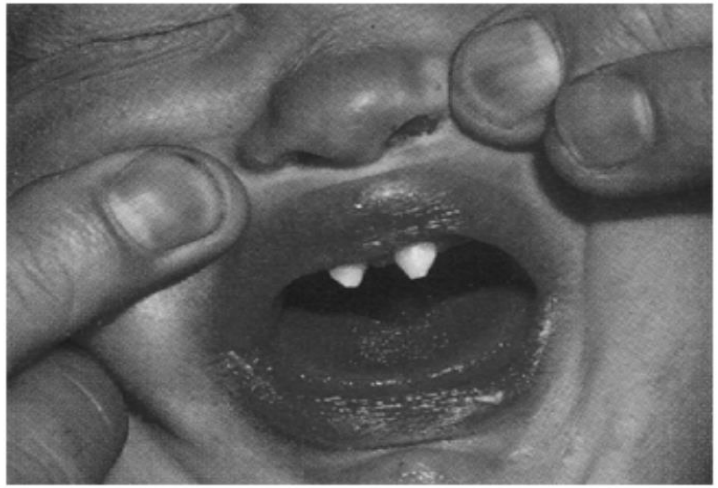
Moore, Persaud, and Shiota. Color Atlas of Clinical Embryology. Saunders, 1994

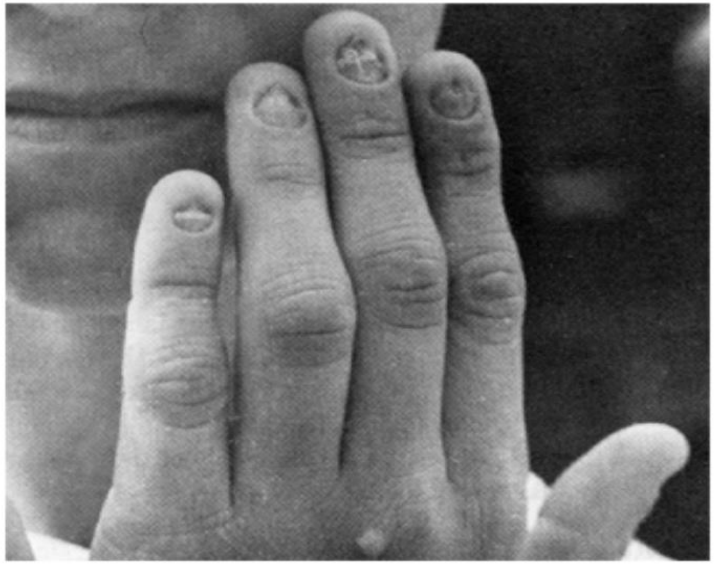
Dysplasia

- Abnormal tissue organization, microscopic structure.

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



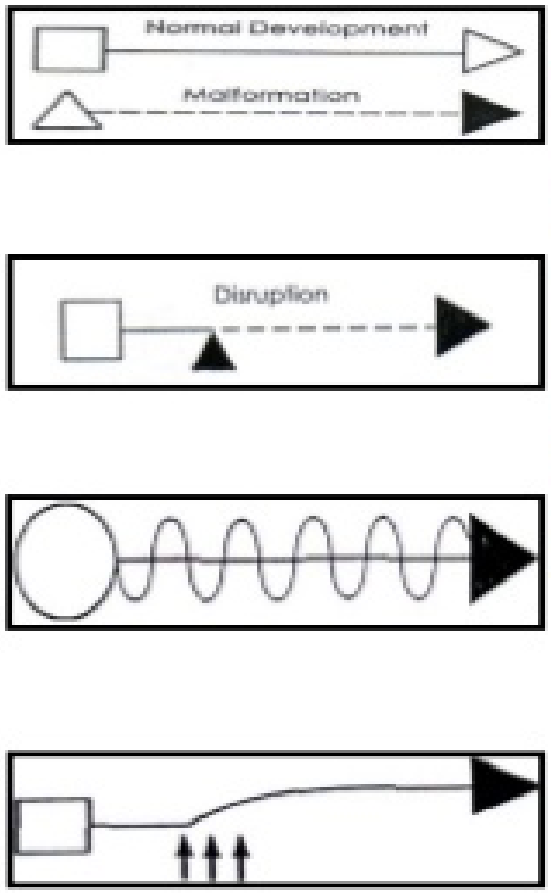




Ectodermal Dysplasia

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.

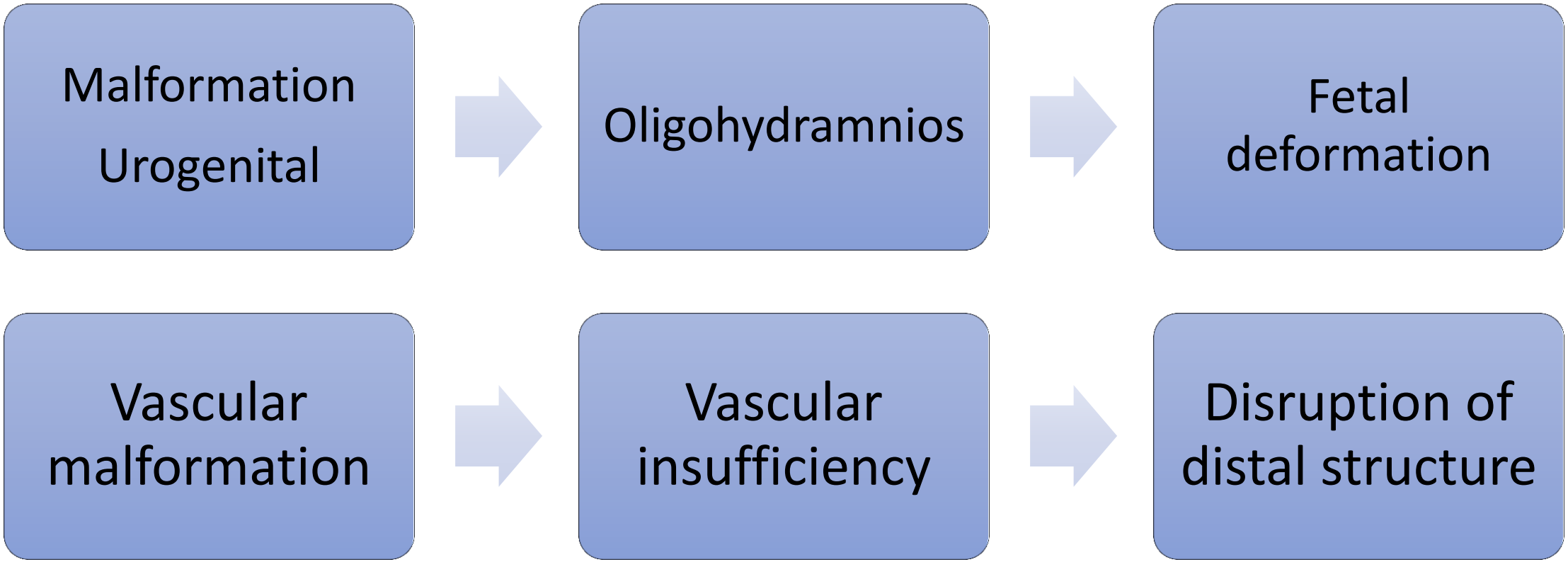
Diagramatic Sketch



Production, Intrinsic

- *Malformation* → Production intrinsic defect → failure of embryonic proliferation and/or differentiation → Abnormal structure.
- *Disruptions* → Production extrinsic (disruptive) agents → interferes with embryonic development of a structure → destruction or removal of structure.
- *Dysplasias* → Production intrinsic defect → abnormal cellular organization → abnormal model of structure.
- Deformation → Packaging extrinsic defect → normally formed structure pushed out by mechanical forces.

Extrinsic


Malformation
Urogenital
Oligohydramnios
Fetal deformation
Vascular malformation
Vascular insufficiency
Disruption of distal structure

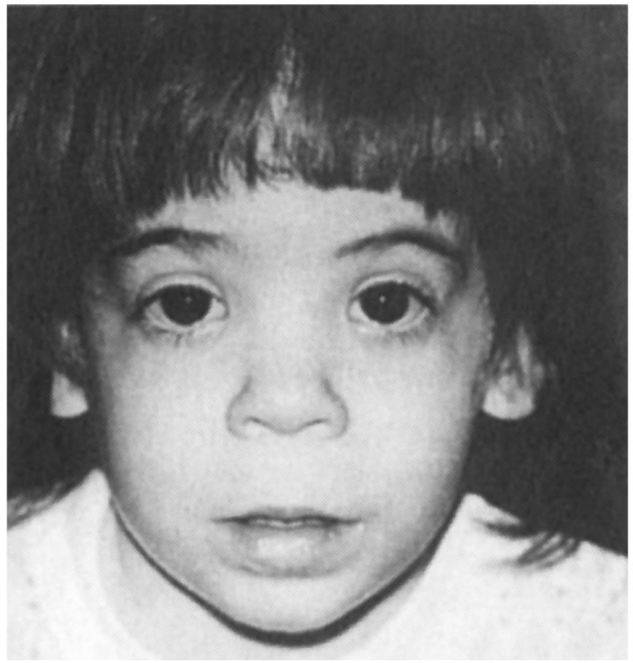
Pleiotropy :Syndrome and Sequences

- 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 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



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

Pierre – Robin Sequence

Small Jaw

- Primary anomaly

Displacement of tongue in superior direction

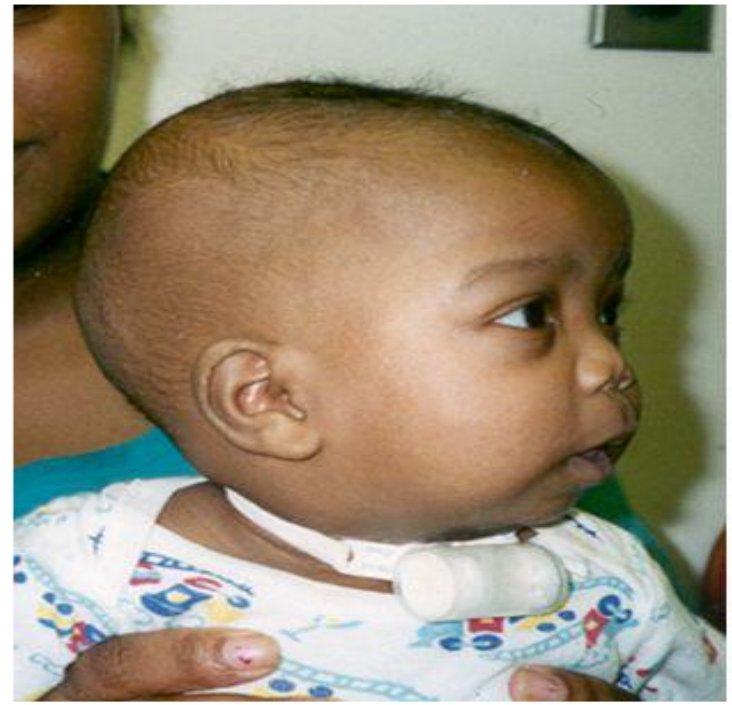
- Protruding tongue due to inadequate room

Cleft Palate

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

Pierre Robin sequence

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

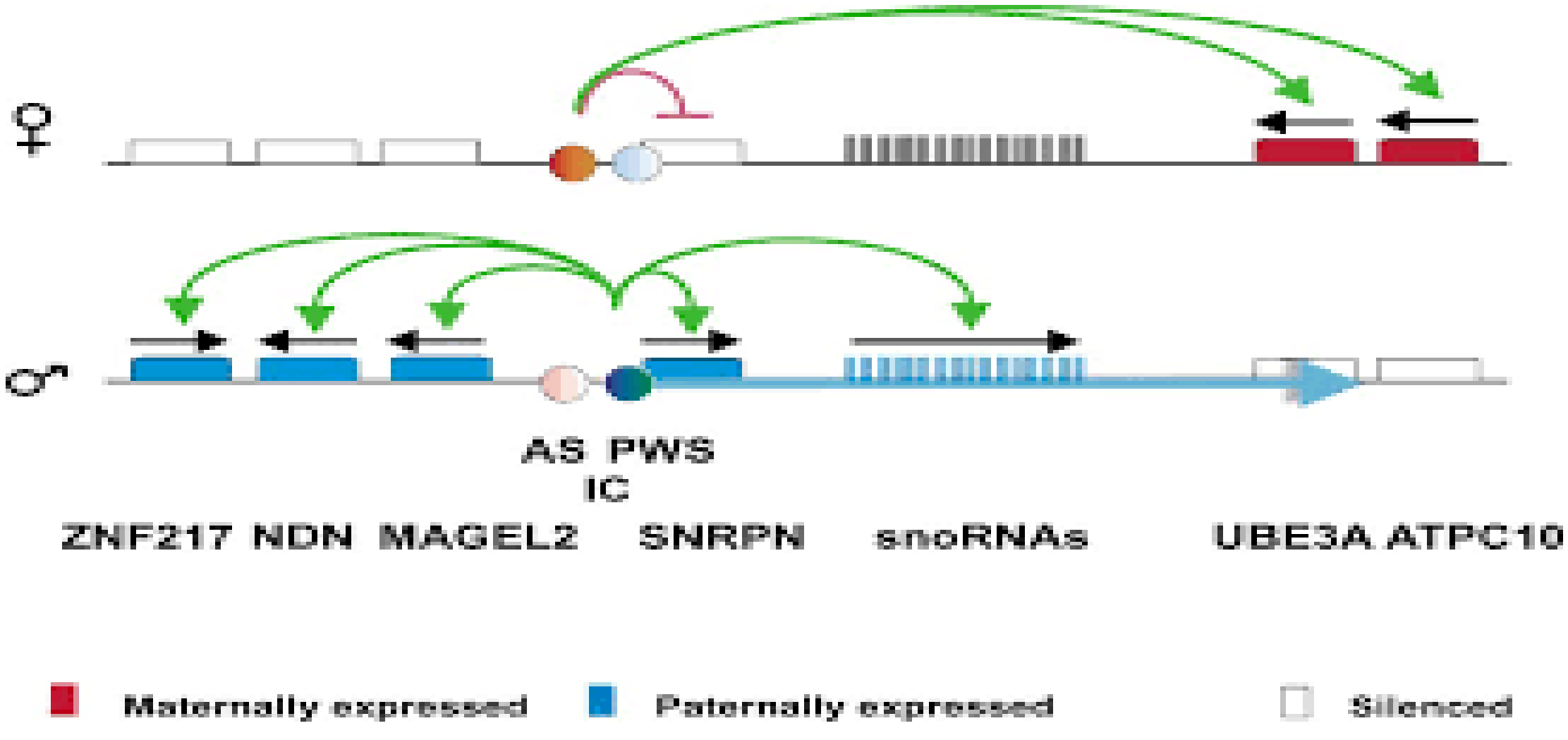


Micrognathia ---> cleft palate ---> glossoptosis

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) *CDKN1C* (encoding a cell-division regulator)	Paternal 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) *Peg1* (encodes an enzyme of the α/β-hydrolase family)	Paternal 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

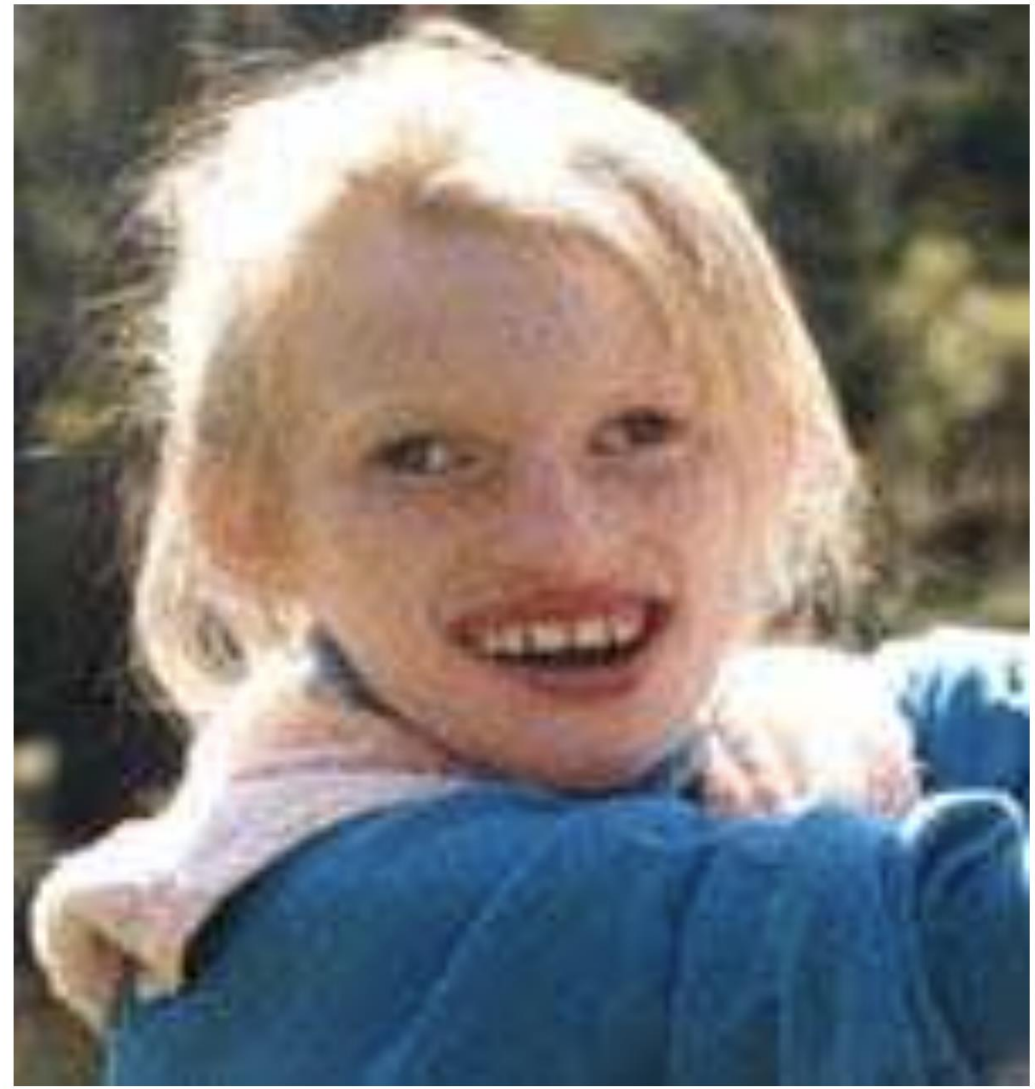

♀
♂
AS PWS
IC
ZNF217 NDN MAGEL2 SNRPN snoRNAs UBE3A ATPC10
Maternally expressed
Paternally expressed
Silenced

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

Prader Willi syndrome

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
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

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
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,
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.

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.

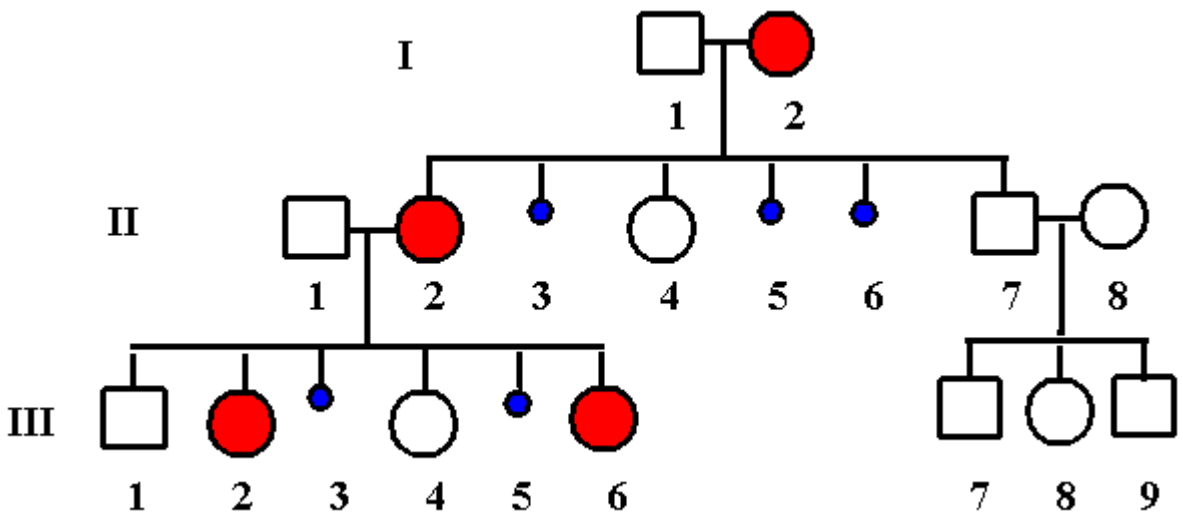
- In 1991, it was discovered that the fragile X syndrome was caused by a mutation in the fragile X mental retardation-1 (FMR-1) gene. An area of CGG trinucleotide repeats just upstream of the coding area was found to be variable in size. All the following statements regarding the FMR1 gene are true,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



- 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	a) Two locus for different allele
2) Compound heterozygote	b) One locus, one allele
3) Double heterozygote	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)