



University of  
Lancashire

# BIRTH DEFECTS

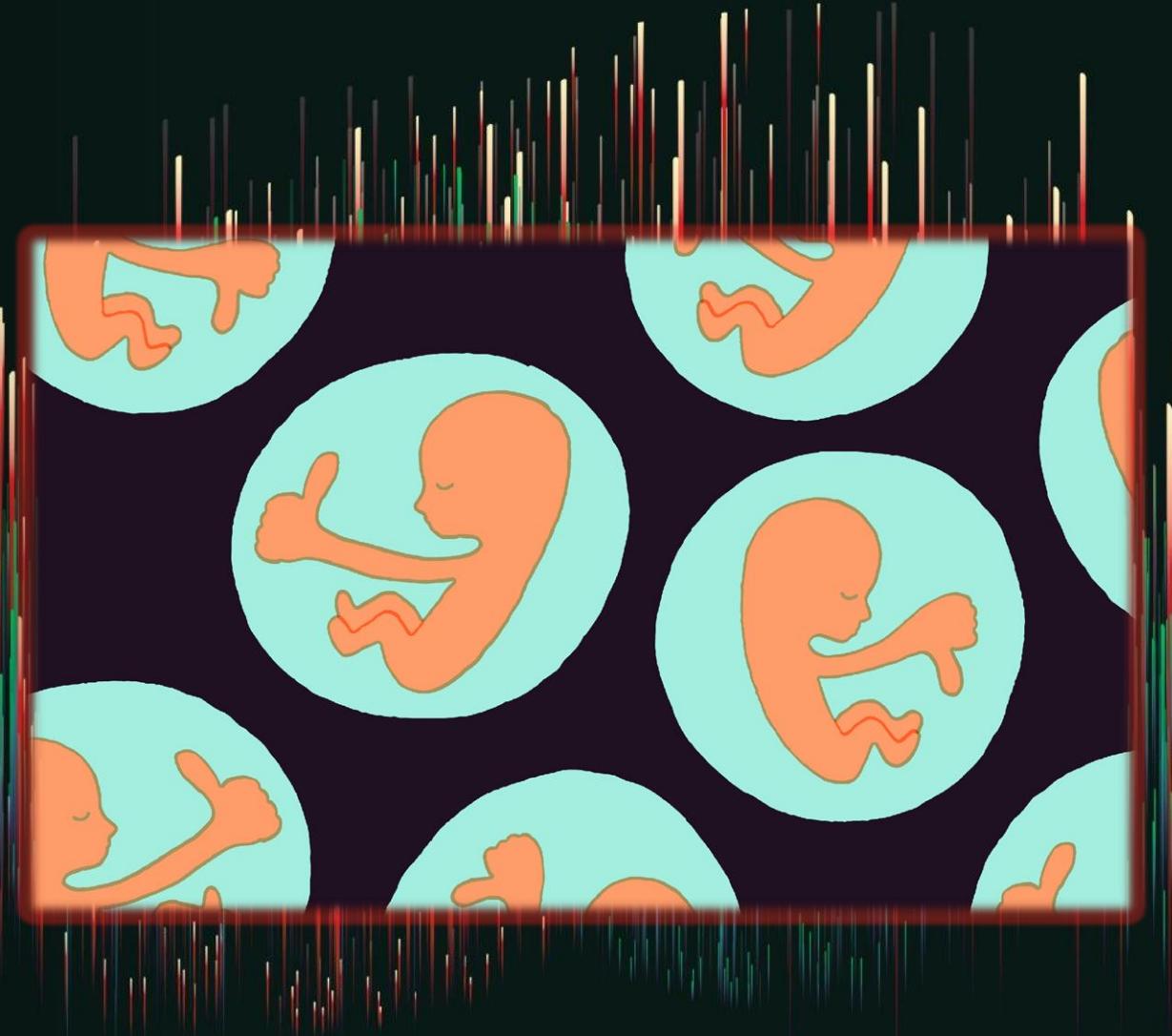
UM2010: DEVELOPMENT

AY 25-26

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# LECTURE OUTLINE



## PART 1:

- I. Definitions and terms
- II. Causes of Birth Defects & Principles of teratogenesis

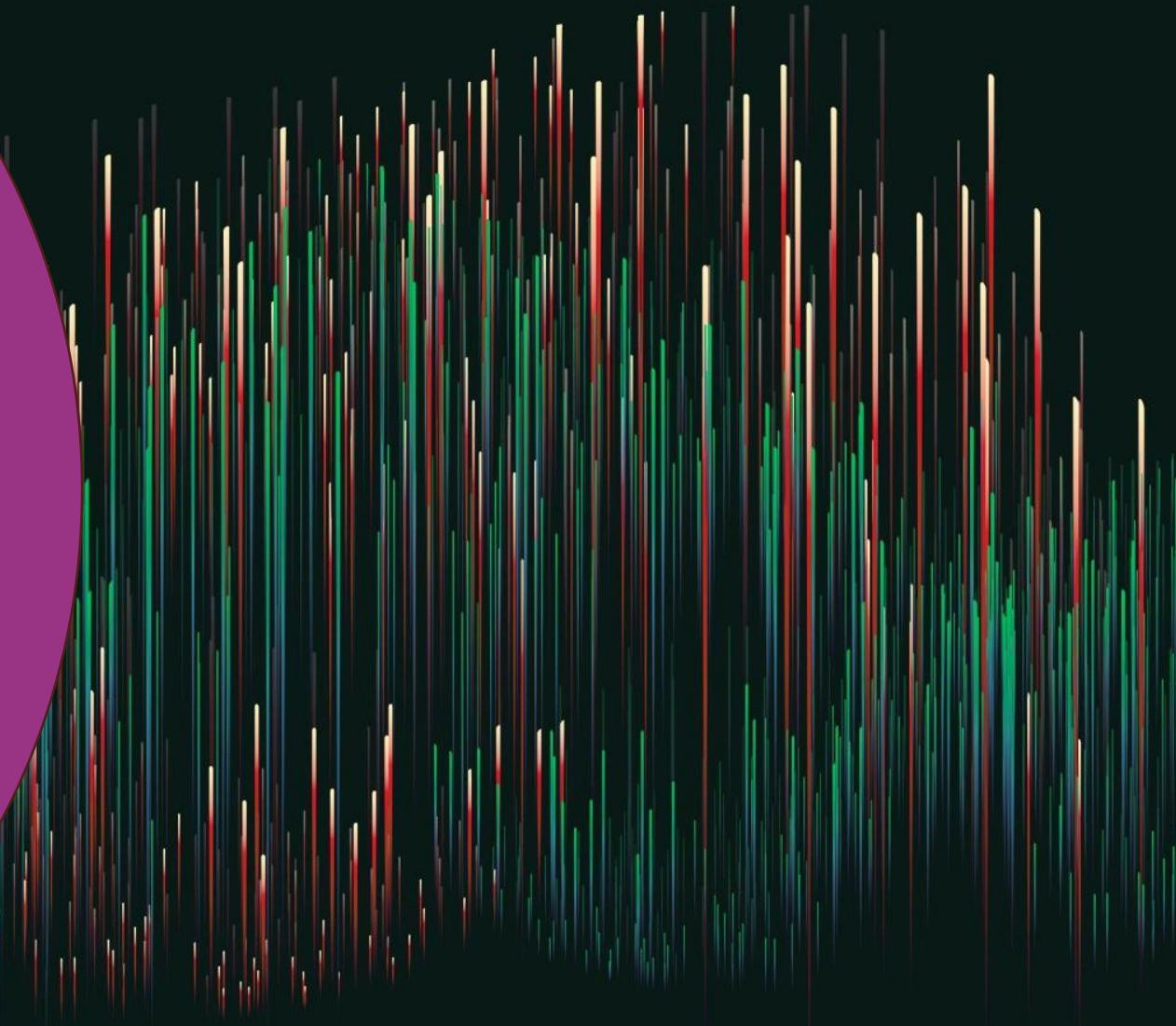
## PART 2:

- III. Types/Classification of birth defects
- IV. Prenatal testing & Prevention of birth defects

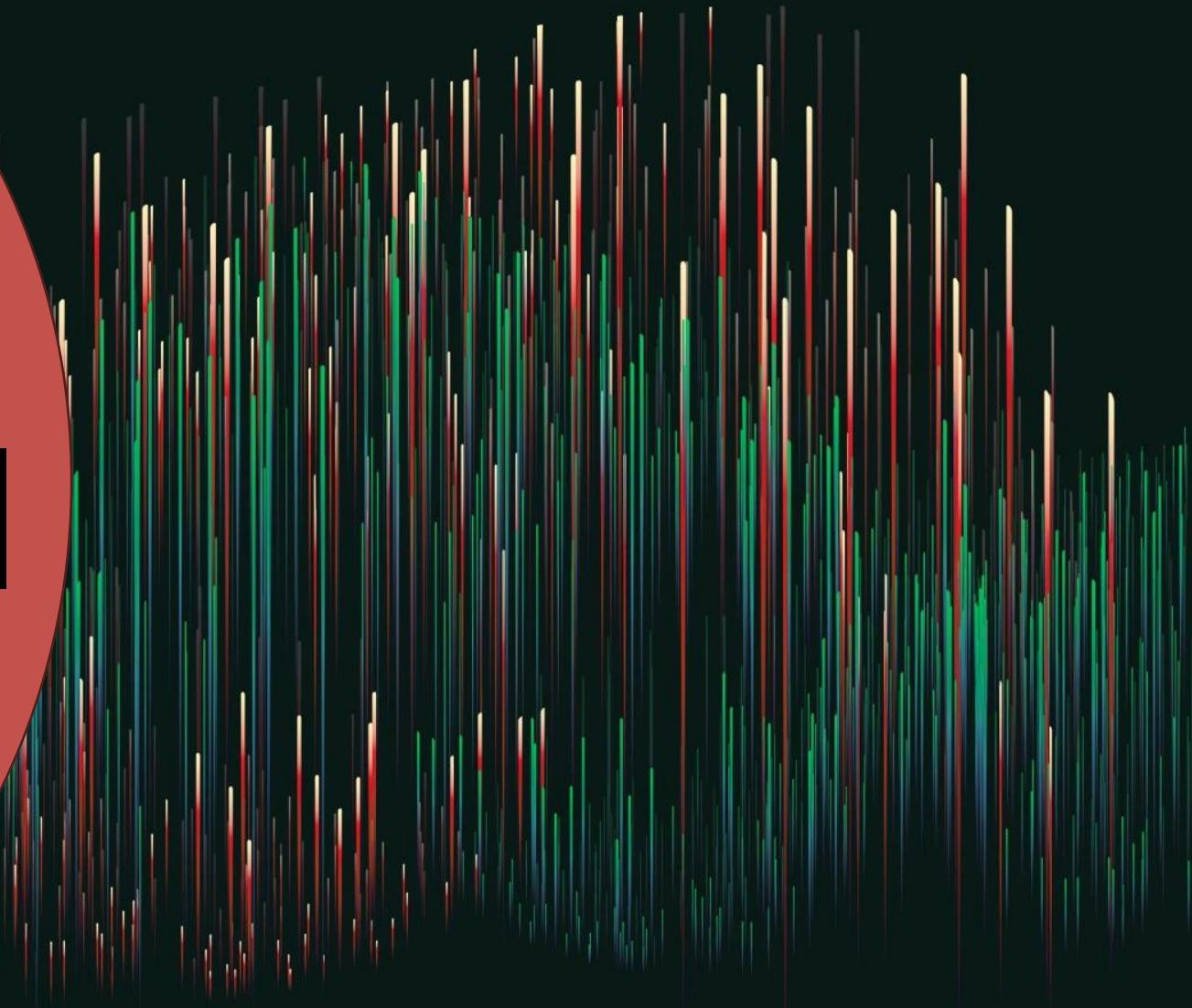
# **MACRO LEARNING OUTCOME**

- Demonstrate an understanding of the **general principles of teratogenesis, classifications of congenital malformations and differences between genetic versus environmental (multifactorial) causes of congenital malformations.**

# PART 1



# INTRODUCTION, DEFINITIONS AND TERMS



**More than 8 million  
babies worldwide are  
born with a serious  
birth defect  
each year.**



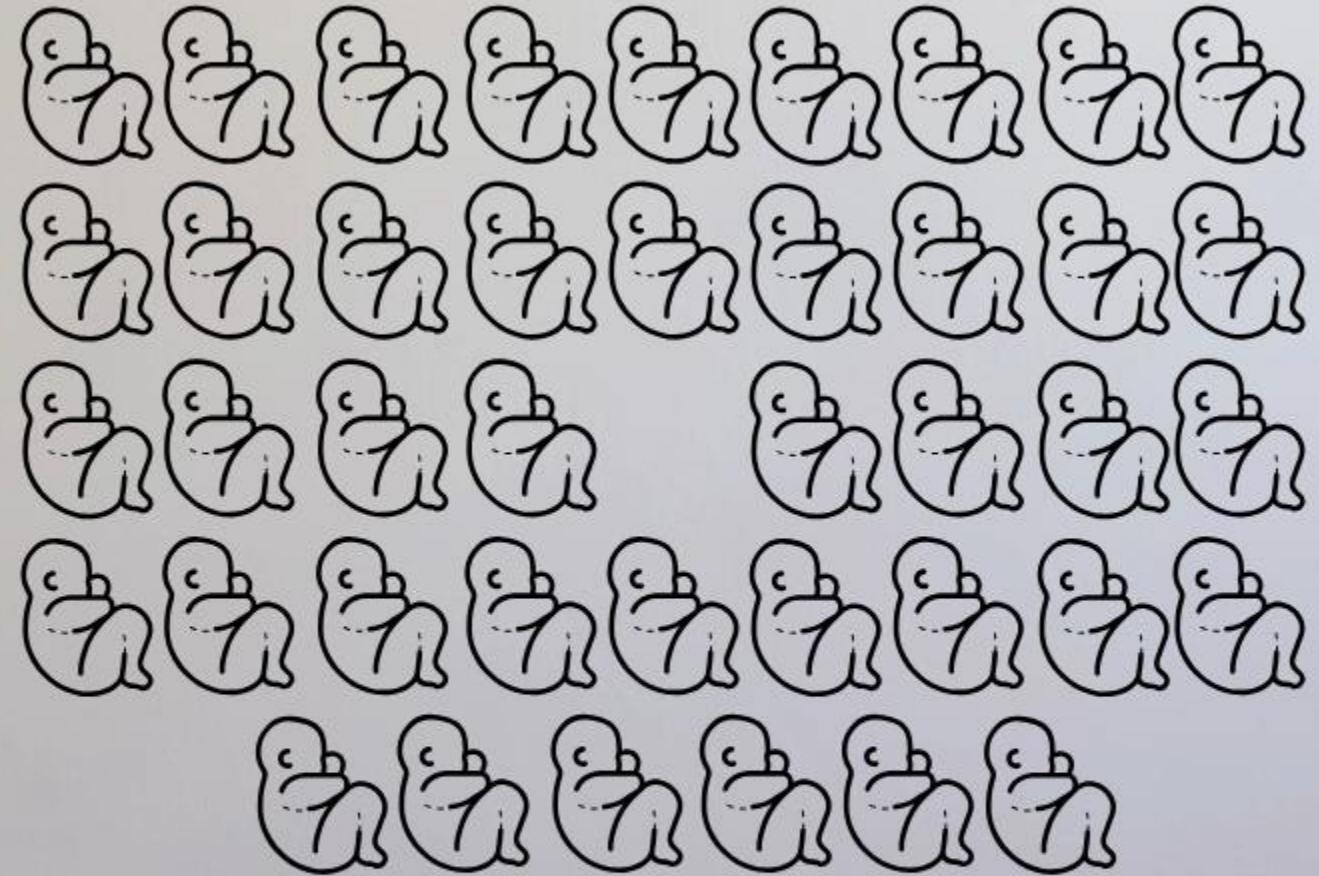
## INTRODUCTION

- Birth defects are the leading cause of infant mortality rates.
- Approximately, 3-6% of total births worldwide or 1 in 17 babies.
- In 2021, overall prevalence of babies born with congenital anomalies in England was 235 per 10,000 total births (includes both live and stillbirth) or 2.3% of babies.

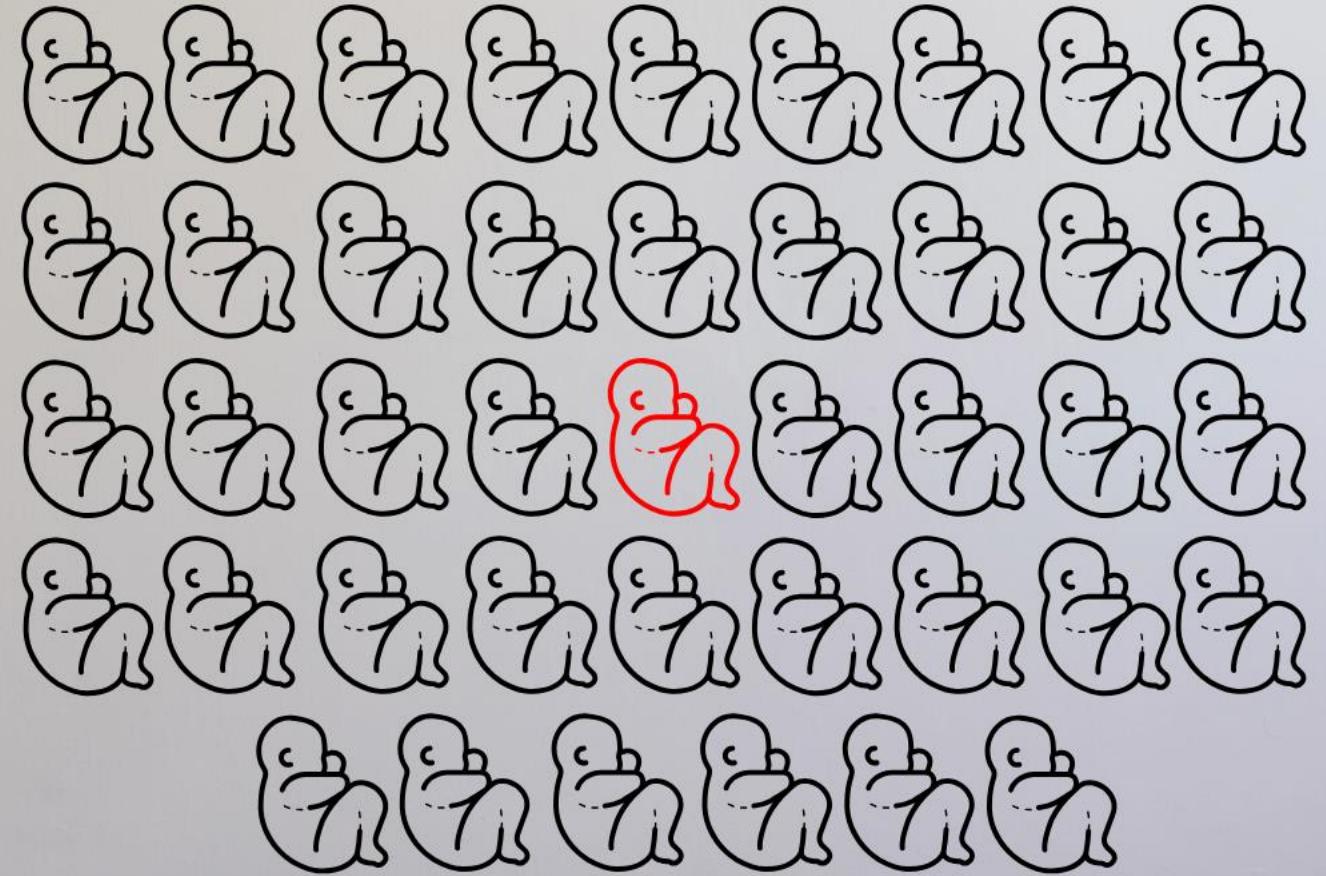
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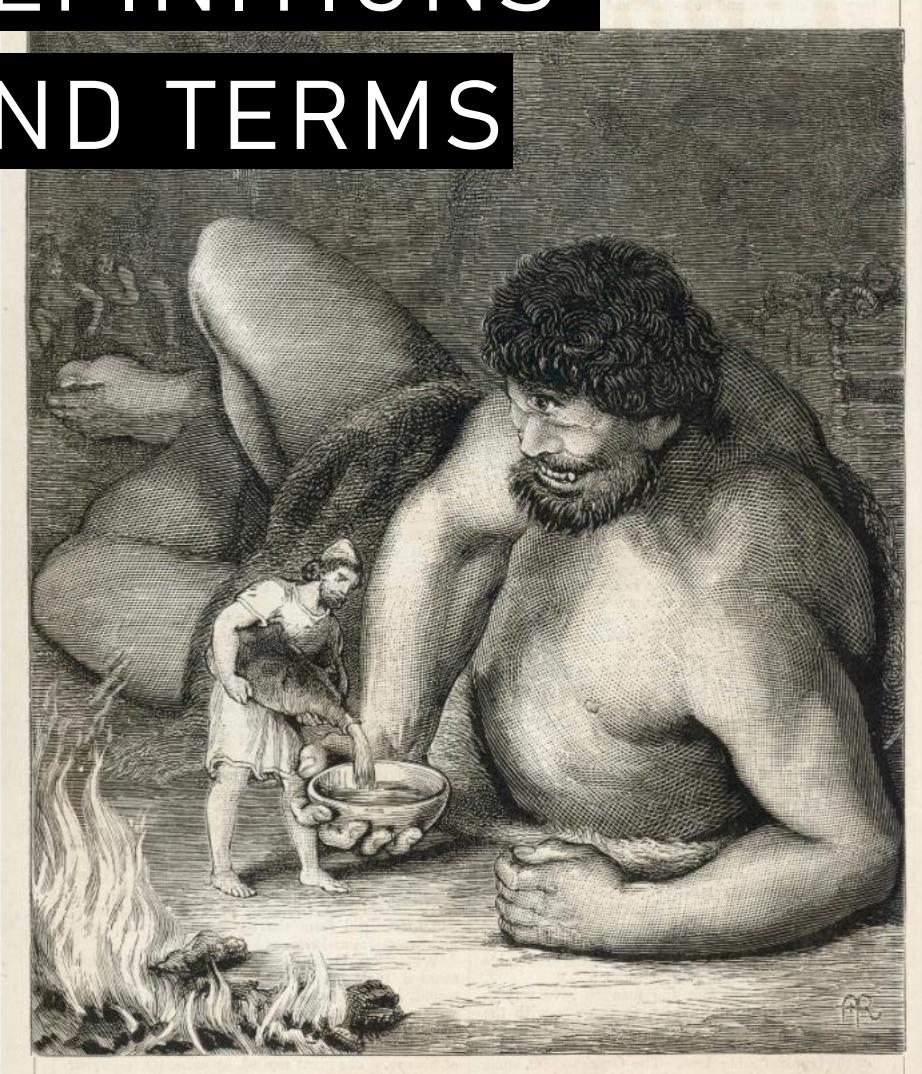
...one baby diagnosed with a congenital anomaly for every 43 births (both live and stillbirth)



...one baby diagnosed with a  
congenital anomaly for every 43  
births (both live and stillbirth)



# DEFINITIONS AND TERMS



- **Birth defect, congenital defects/congenital anomalies** are synonymous terms used to describe structural (morphological), functional, metabolic (biochemical) or behavioural abnormalities produced before or at birth i.e during intrauterine..
- **Teratology** is the branch of science that studies the causes and mechanisms of abnormal development. (*Gr: Teratos; monster*). Includes fields of embryology, pathology and dysmorphology to study and classify malformed embryos and fetuses.

# CONGENITAL ANOMALIES

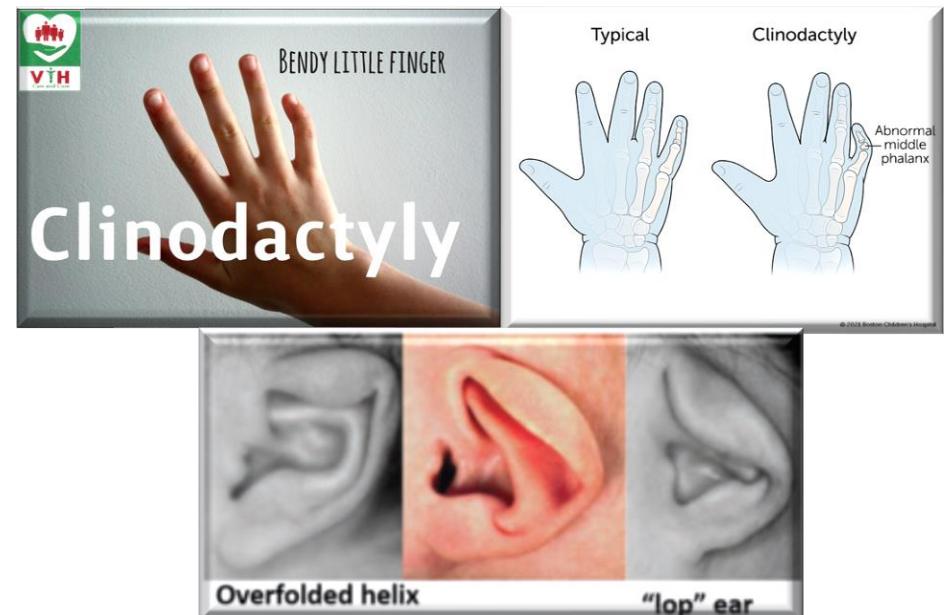
- **Major** structural anomalies

- Account for most of the deaths, morbidity and disability.
- E.g. Cleft lip and spina bifida

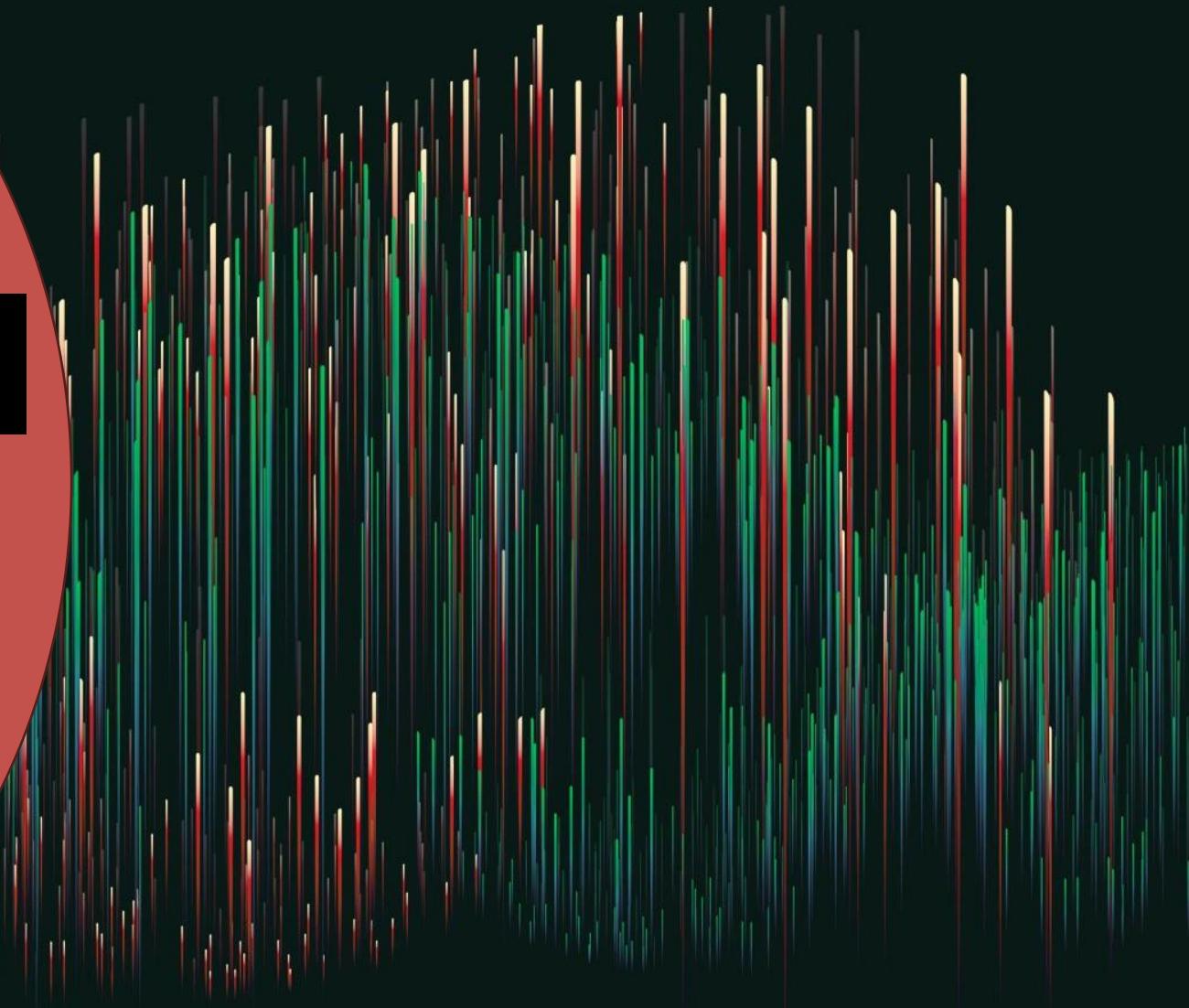


- **Minor** structural anomalies

- More prevalent, are structural changes that pose no significant health problems. May be cosmetic issues but ultimately minimal impact to quality of life (QoL).
- E.g: Overfolded pinna, and clinodactyly



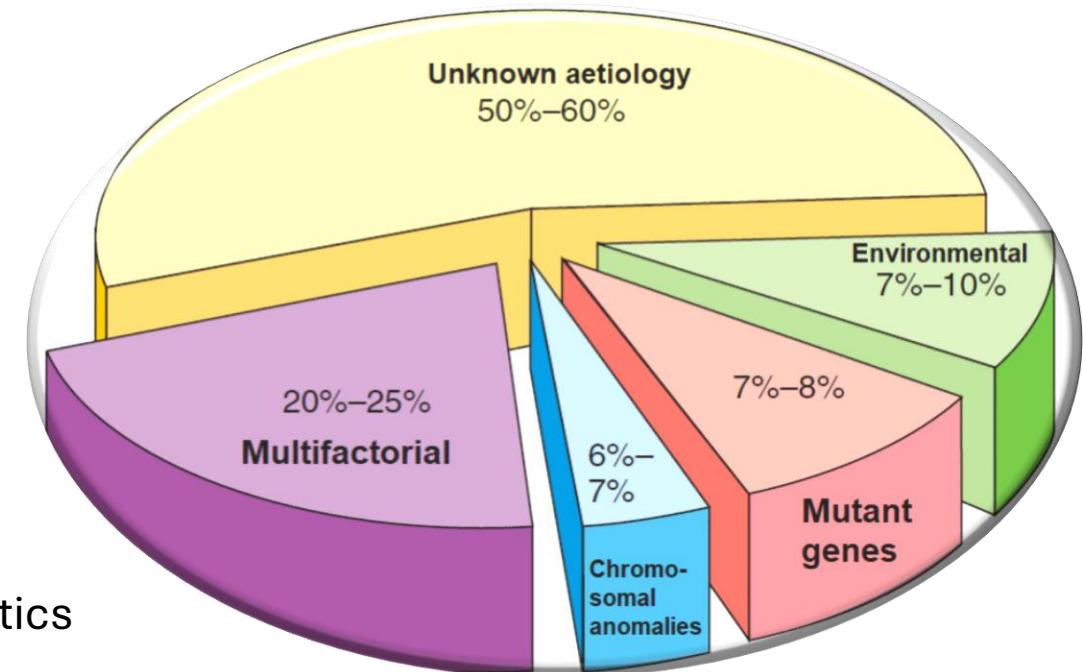
# CAUSES OF BIRTH DEFECTS



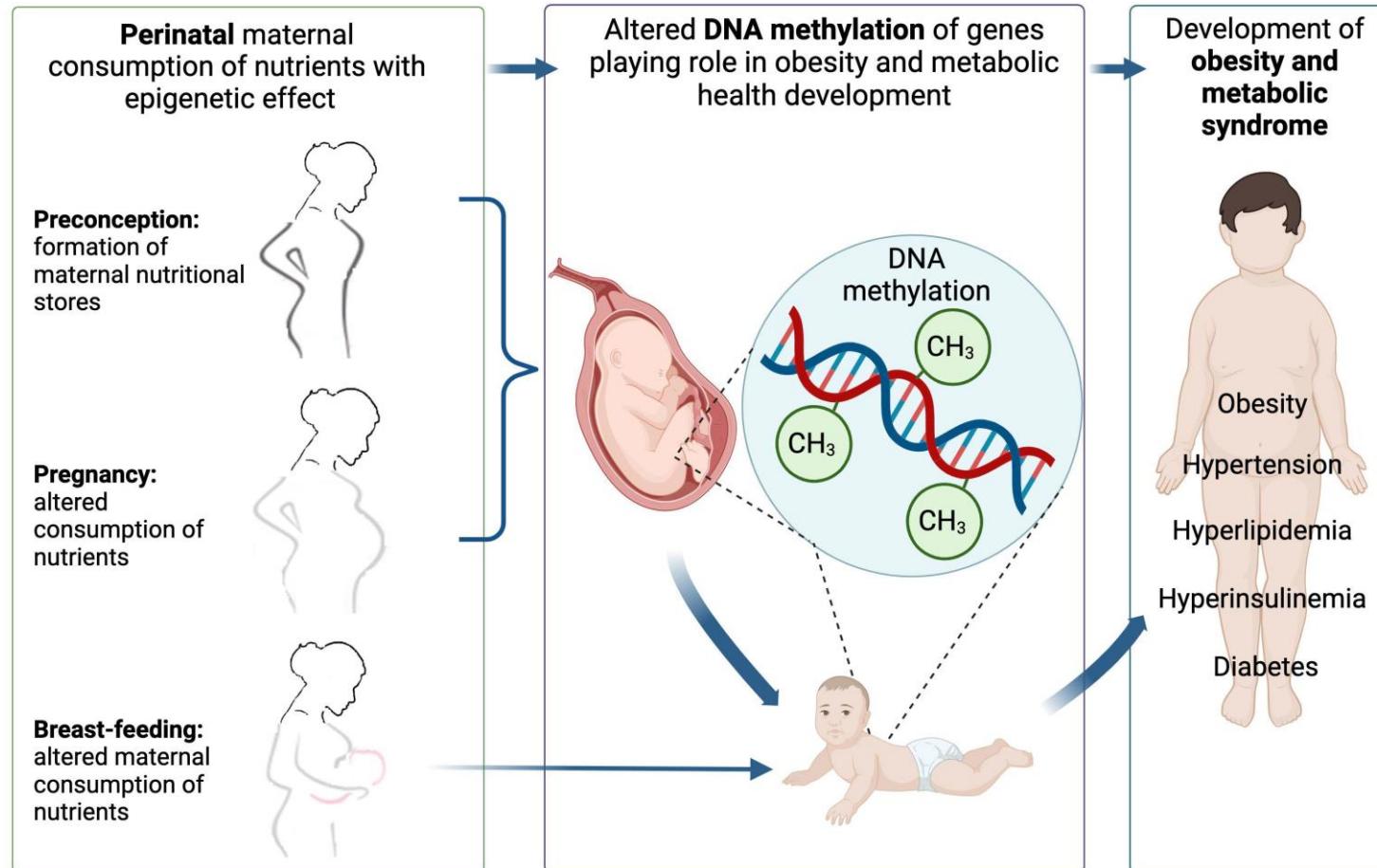
# AETIOLOGY OF BIRTH DEFECTS

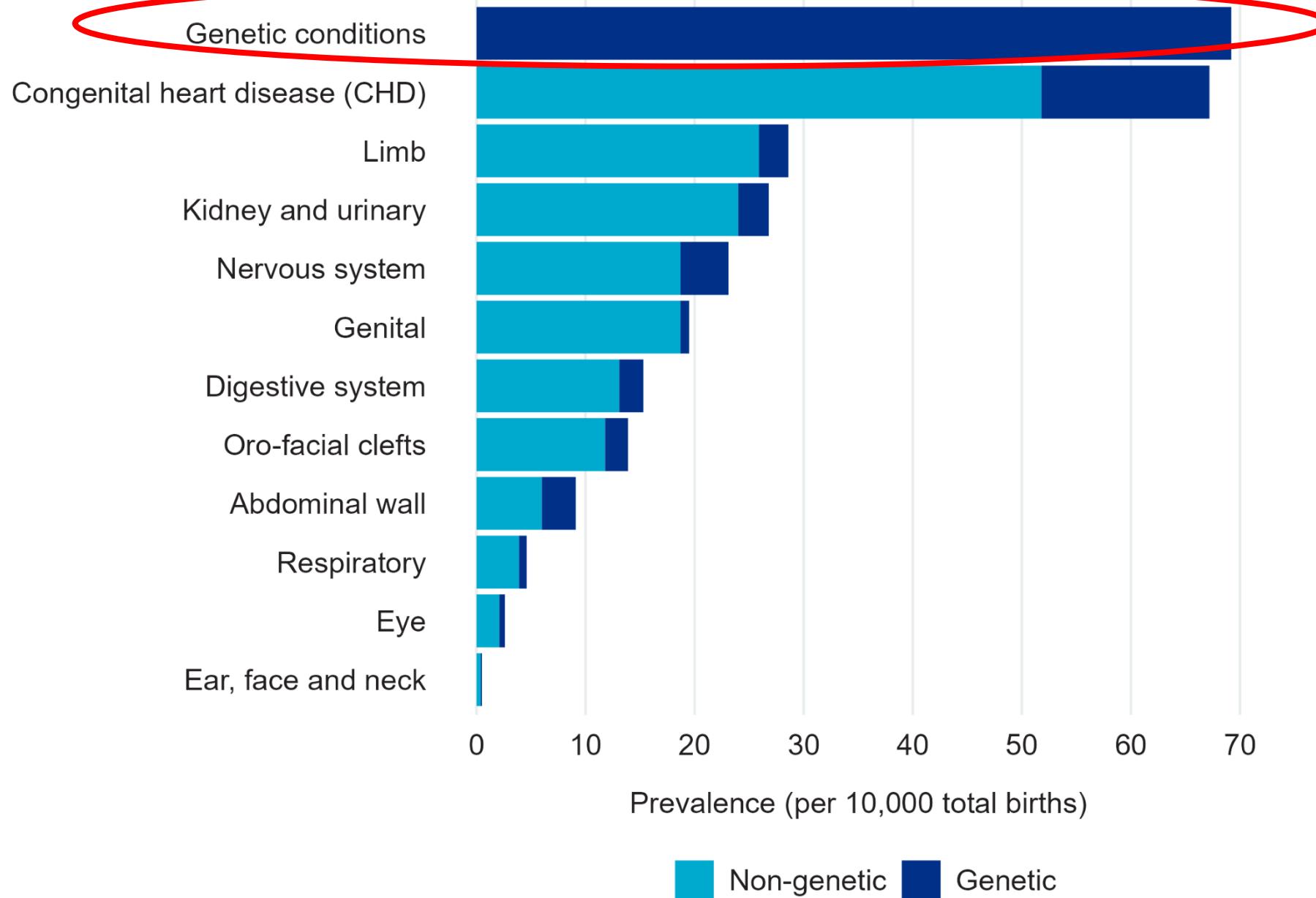
The causes of birth defects are categorised into two main categories:

- **IDIOPATHIC (Unknown)**
- Known
  - Genetic factors
  - Environmental factors
  - Multifactorial factors
    - Genetic and environment acting together; epigenetics



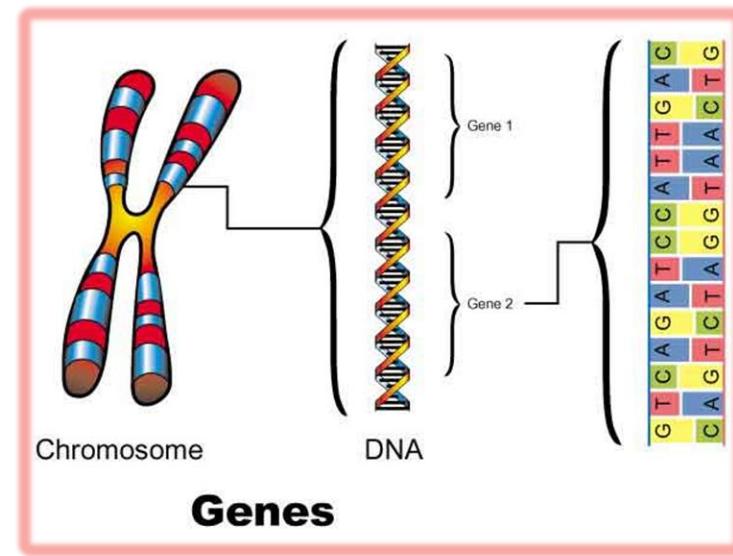
# AETIOLOGY OF BIRTH DEFECTS





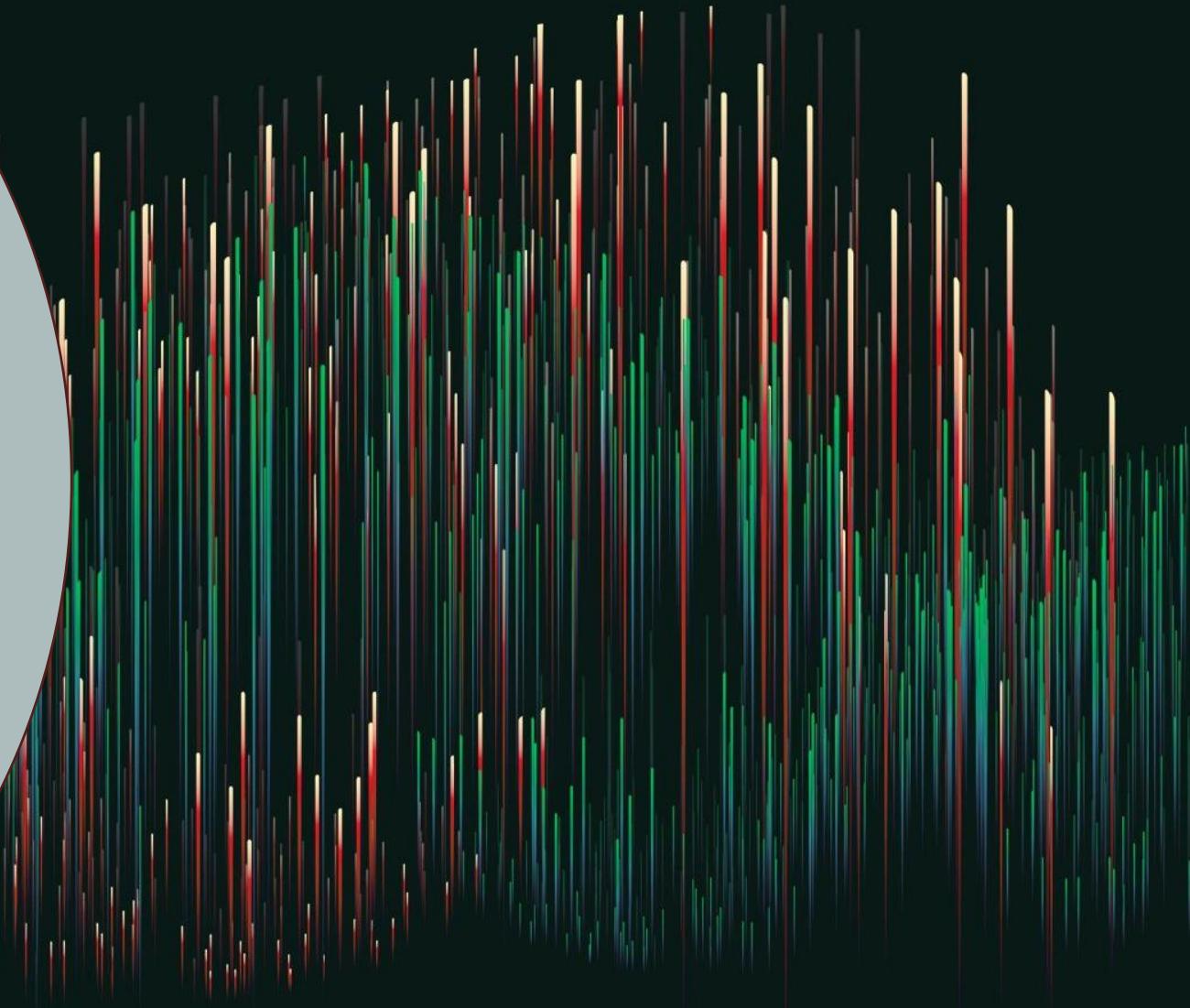
# WHAT DO WE MEAN BY GENETIC FACTORS?

- **Genetic factors** causing malformations can be simply classified into:
    - **Chromosomal abnormalities**
    - **Mutant genes**



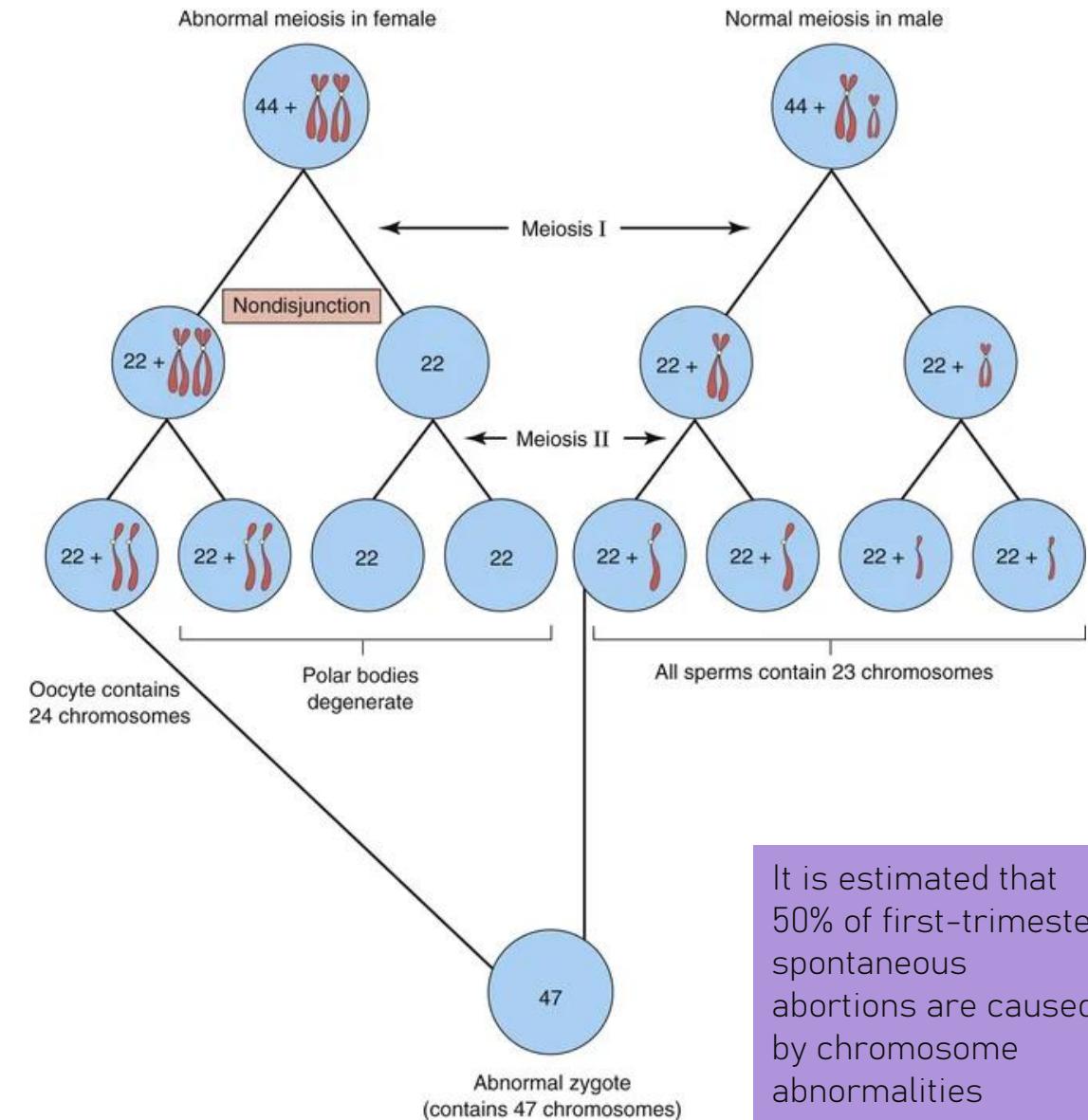
# CHROMOSOME ABNORMALITIES

Usually classified as structural  
or numerical errors.

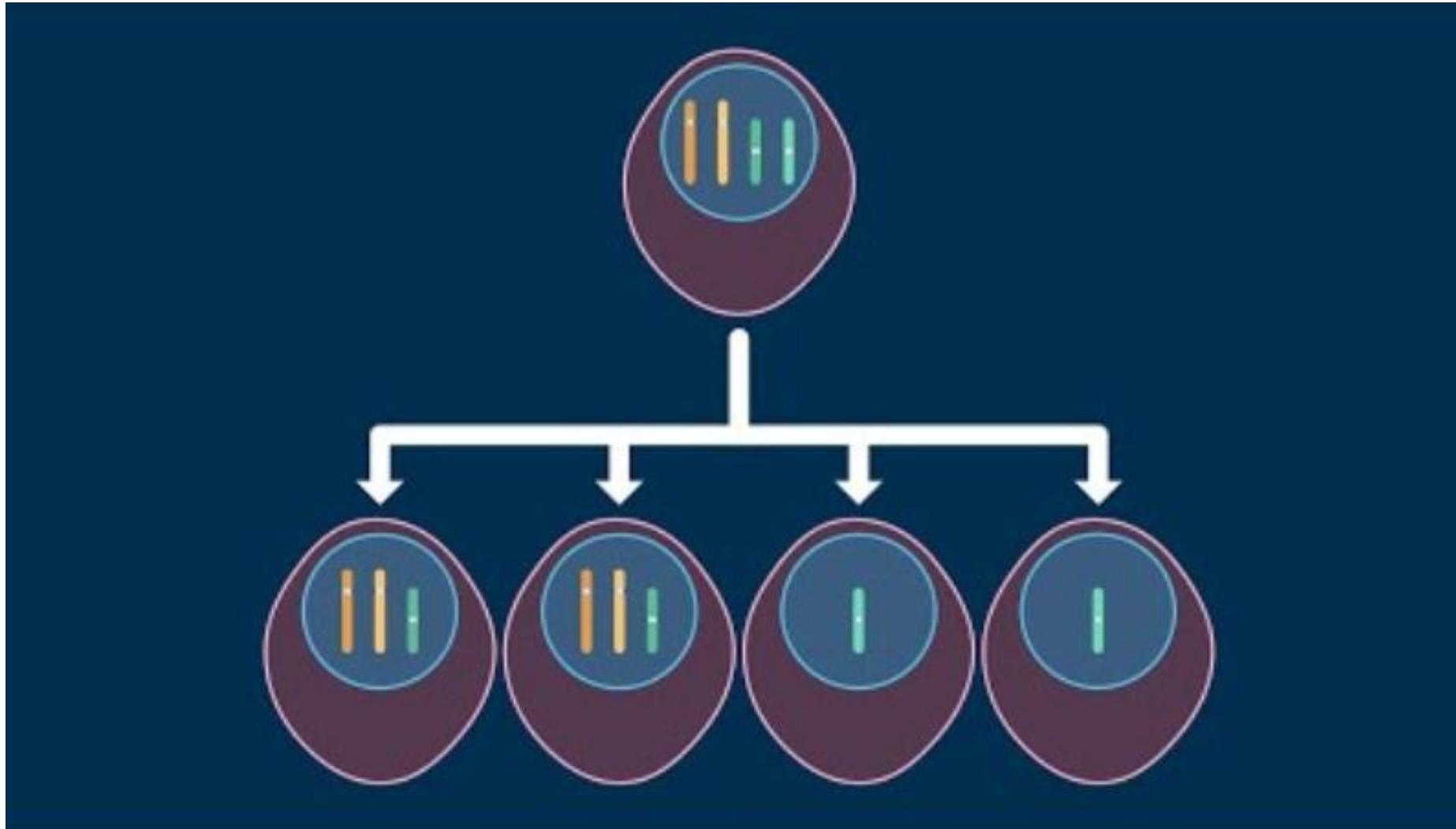


# CHROMOSOMAL ABNORMALITIES

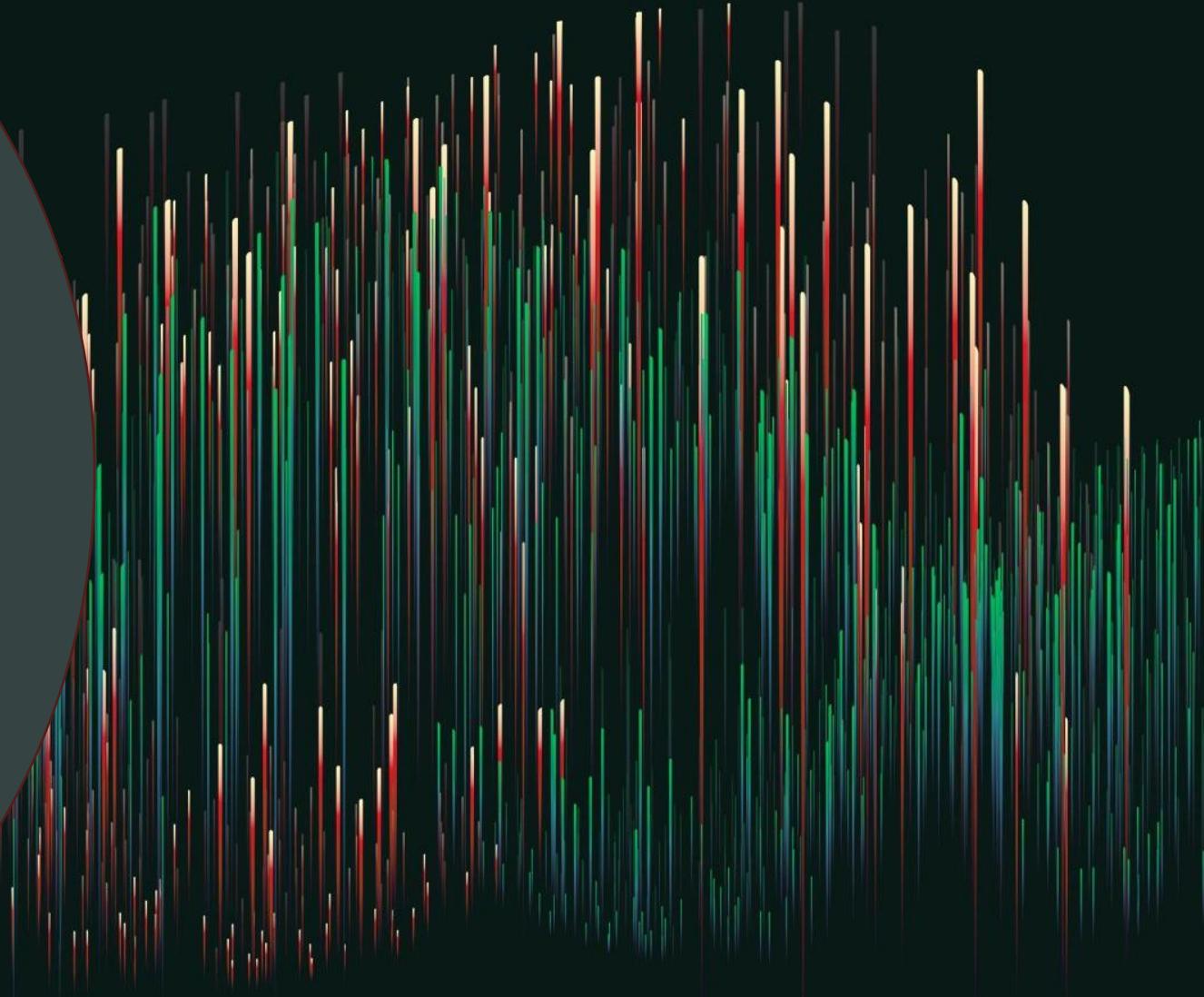
- Numerical abnormalities:
  - Normal gametes are haploid ( $n=23$ )
  - Normal human somatic cell contains 46 chromosomes; Diploid ( $2n=46$ )
  - Euploid-Exact multiple of  $n$
  - Aneuploid**-Any chromosome number that is non-euploid i.e not the normal 46 for somatic cell or 23 for gametes.
    - Additional chromosome
    - Missing chromosome
- Most common cause is **nondisjunction** during either **meiosis or mitosis**.



# NONDISJUNCTION



# NUMERICAL CHROMOSOME ABNORMALITIES



# NUMERICAL ABNORMALITIES

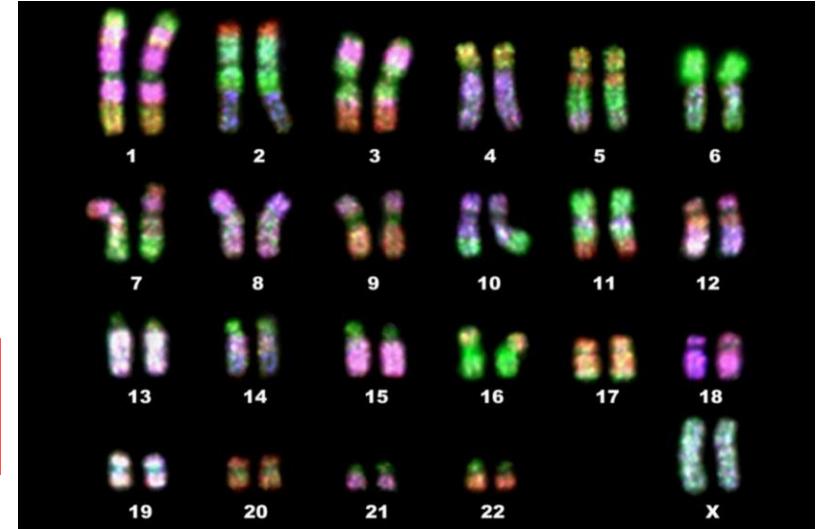
- Examples of most common:

- Trisomy 21 (Down syndrome)
- Trisomy 18 (Edwards syndrome)
- Trisomy 13 (Patau syndrome)

Autosomal chromosomes

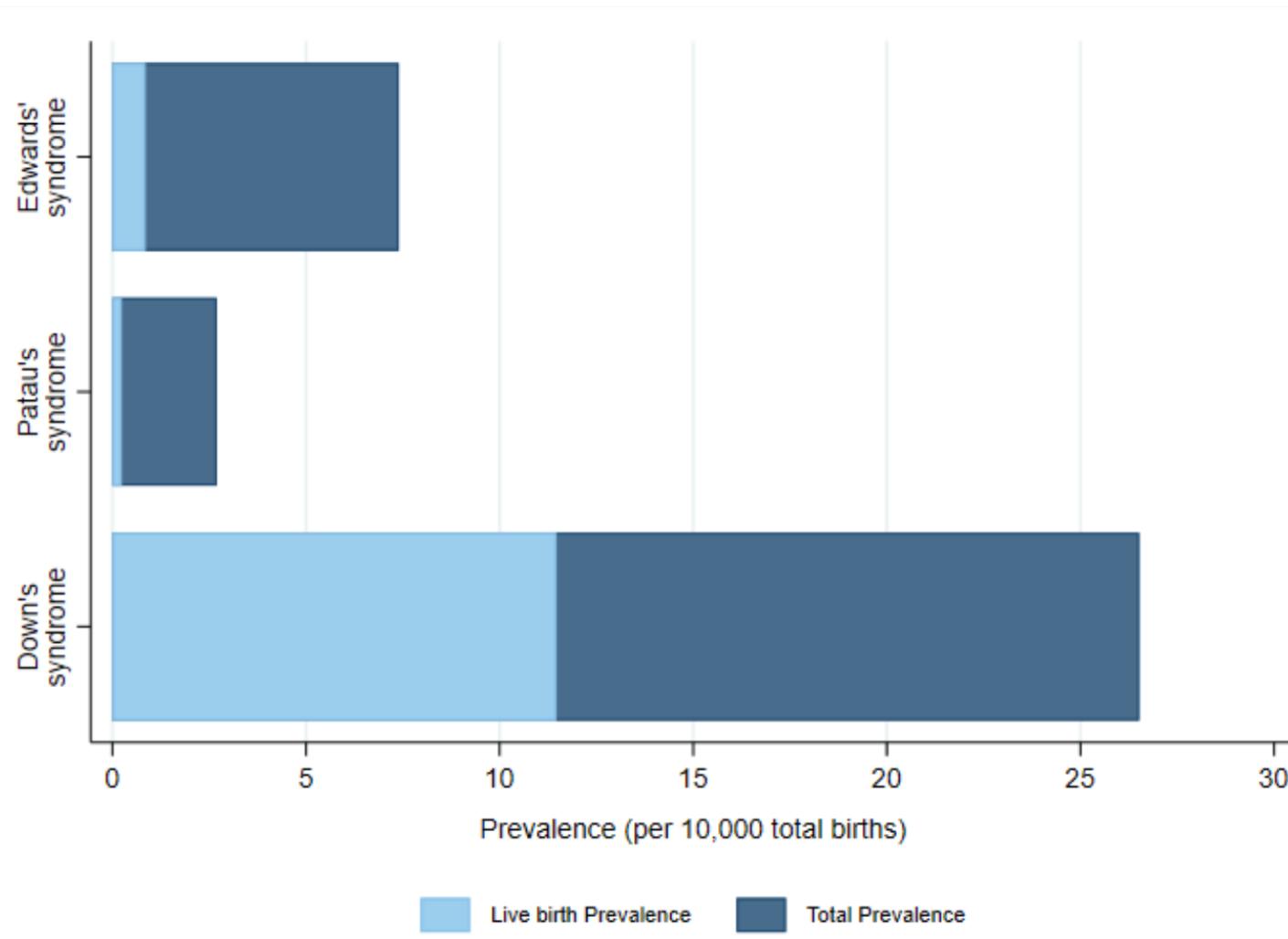
- Klinefelter syndrome
- Turner syndrome

Sex chromosomes



A karyotype characterizes chromosomes based on their size, shape, and number to identify both numerical and structural defects.

# TRISOMY 21, 18, 13

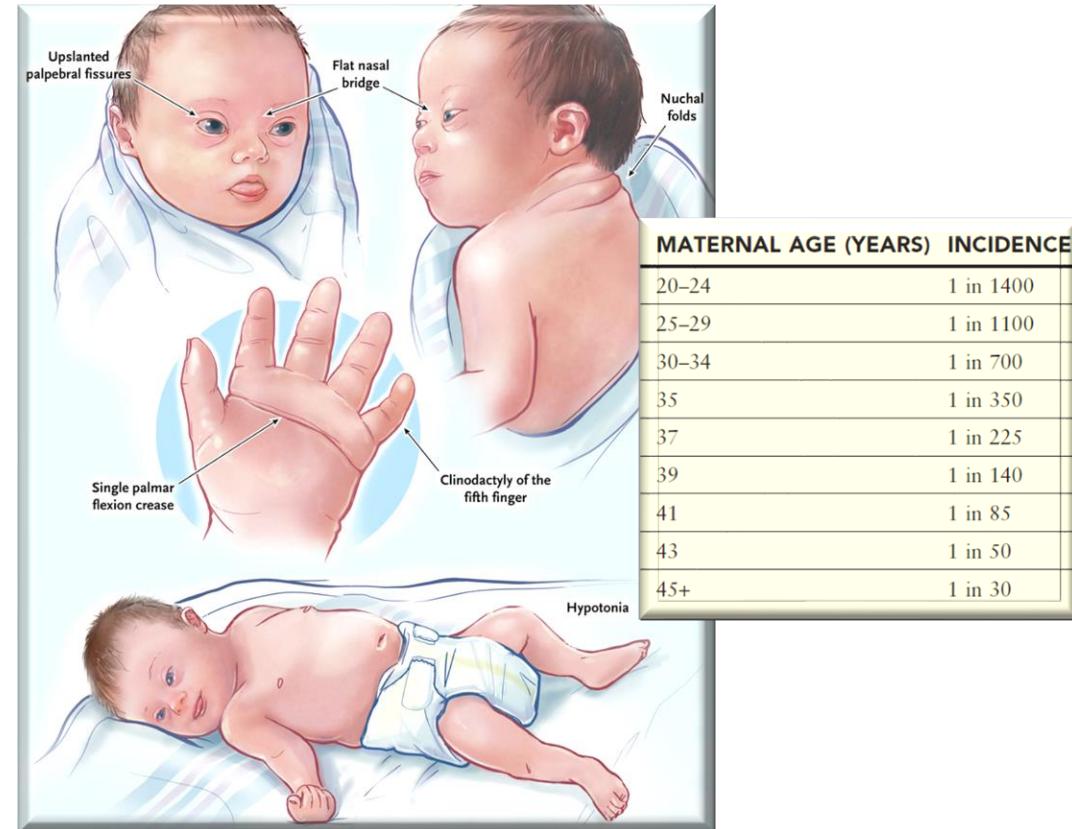


- Trisomy 21, 18 and 13 are the most common forms of autosomal trisomy associated with pregnancies that can progress to full term.
- Trisomy 21 being the most common among them.

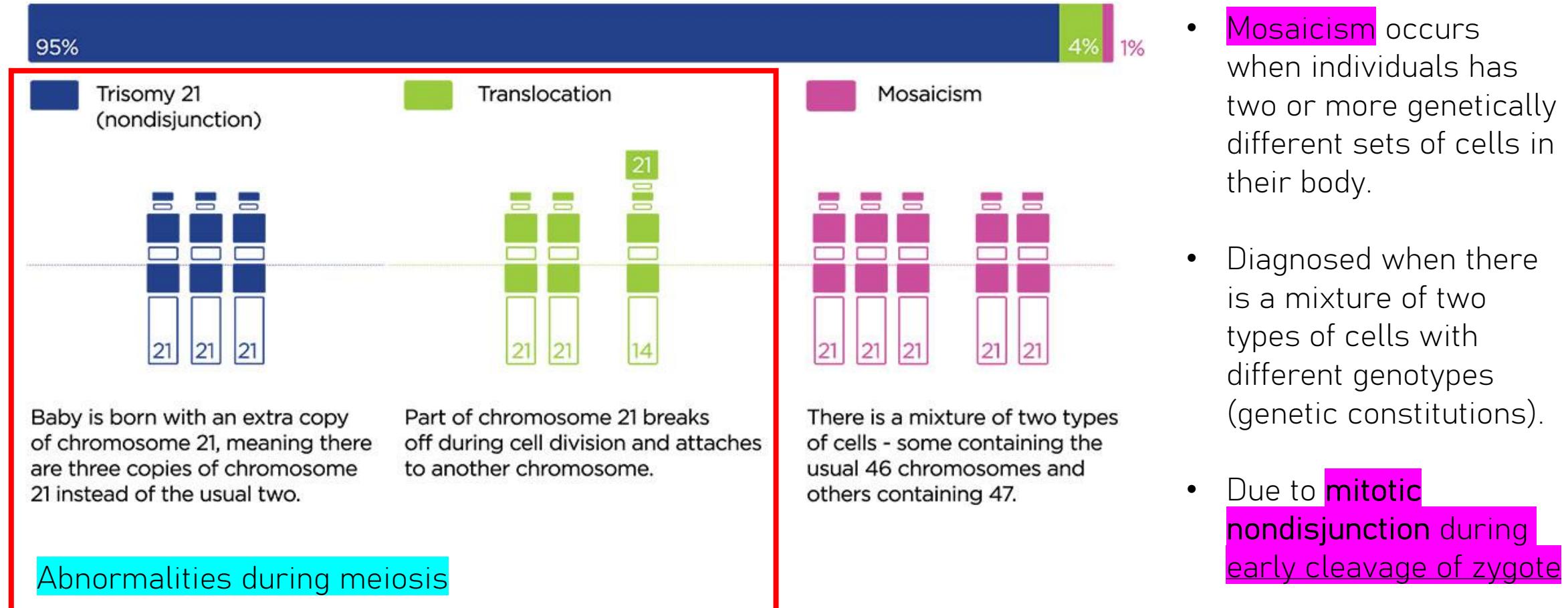
Prevalence of Down's syndrome, Edward's syndrome and Patau's syndrome per 10,000 births in 2020 (NHS England)

# TRISOMY 21:DOWN SYNDROME

- Extra copy of chromosome 21 (95%, common type)
  - Incidence rate 1 : 800
  - Growth retardation
  - Some form of mental retardation (usually severe)
  - Craniofacial abnormalities – examples
    - Upward slanting eyes
    - Epicanthal folds
    - Flattened facies
    - Small ears
  - Cardiac defects (Tetralogy of Falot, Atrial Septal Defects)
  - Hypotonia
  - Premature senescence leading to early cataracts and Alzheimer disease
- Caused by meiotic nondisjunction.
  - Correlation with children born to women of increased maternal age (>35 years).



# TRISOMY 21:DOWN SYNDROME-TYPES



# TRISOMY 21:DOWN SYNDROME-TYPES

- Mosaics for trisomy 21 have a **milder phenotype** and may have normal or near-normal intelligence.

## Mar Galcerán makes history as Spain's first parliamentarian with Down's syndrome

After being elected to Valencia's regional assembly, Galcerán says she wants to be seen as a person, not for her disability



START // Global // Pablo Pineda //



SPAIN, CORDOBA

## Pablo Pineda

Pablo Pineda is the first person in Europe with Down syndrome who has completed a university degree. He works as a teacher.



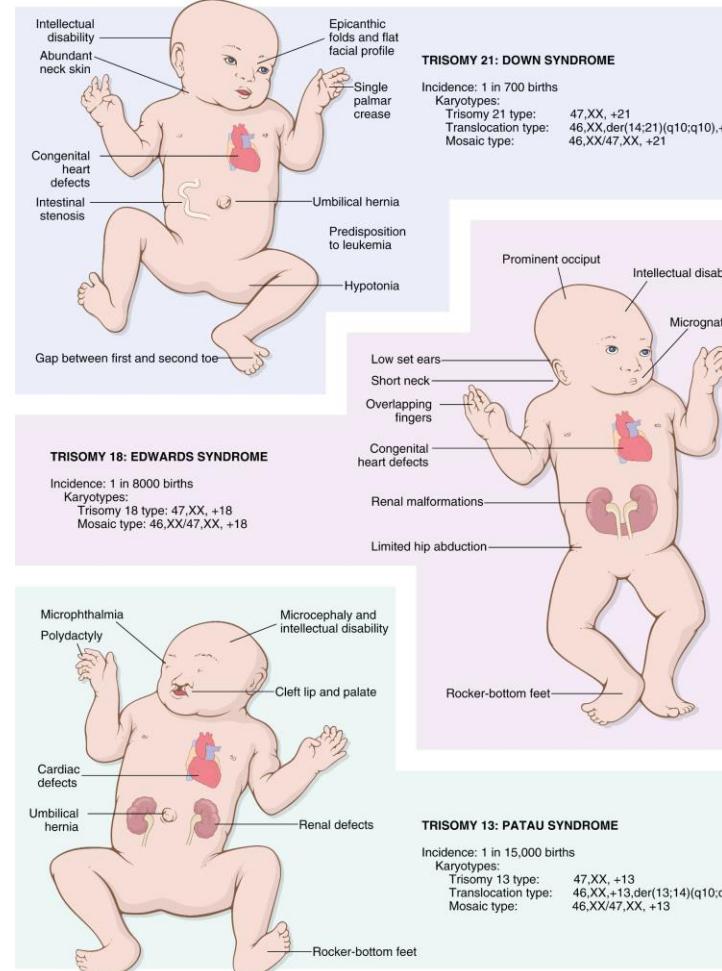
Ana Victoria Espino De Santiago has made history as the world's first lawyer with Down syndrome.

Her goal is to become a legislator to advocate for people with disabilities.

@femalequotient

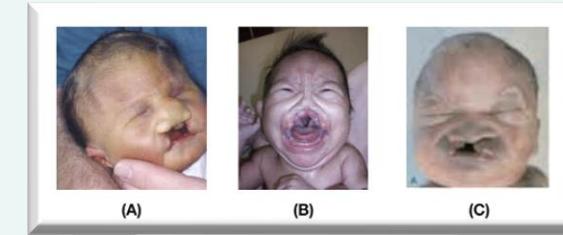
# TRISOMY 18 (EDWARD'S SYNDROME)

- Incidence varies between 1 in 3,600 to 1 in 10,000 live births (worldwide).
- 95% die in utero with <10% survive first year, therefore overall prevalence may be higher.
- High mortality and morbidity rate



# TRISOMY 13 (PATAU'S SYNDROME)

- Incidence varies between 1 in 10,000 to 20,000 (worldwide)
- Least common and most severe mental and physical disabilities.

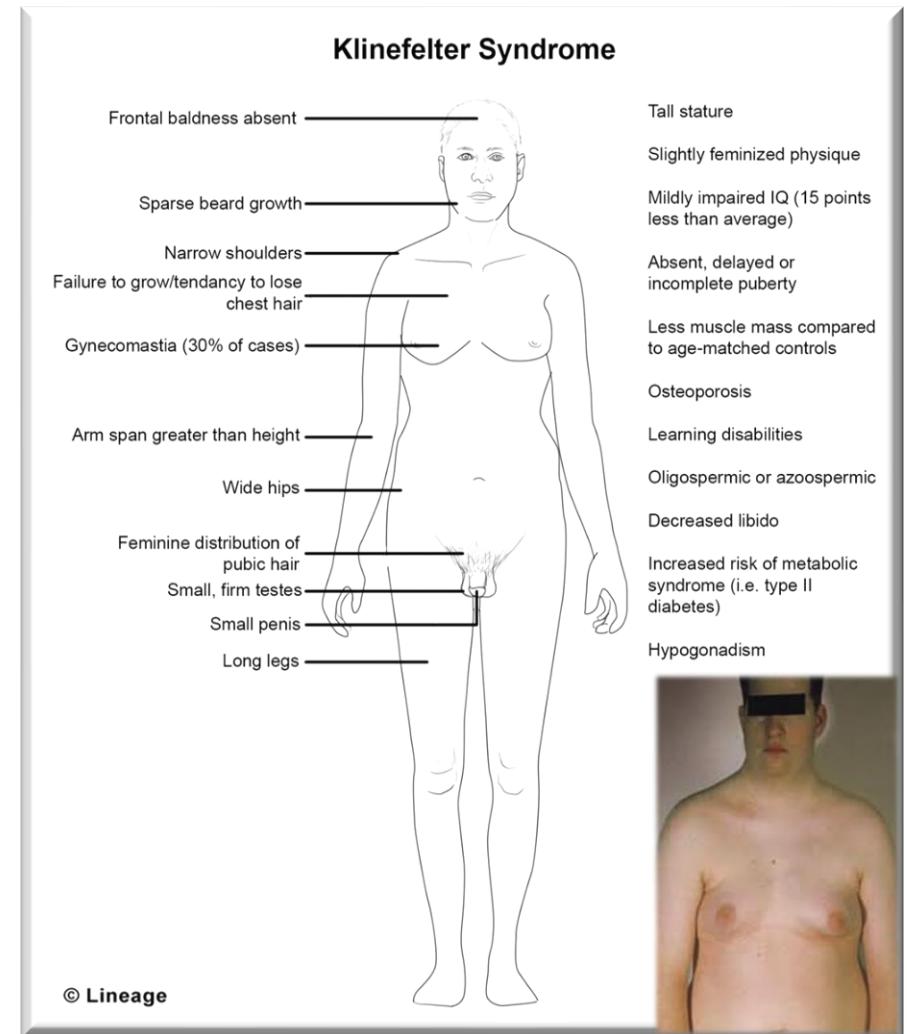


- Median survival 2.5 days

**Trisomy 18 and 13 is associated with a wide range of severe complications that affect multiple organ systems, including severe mental retardations.**

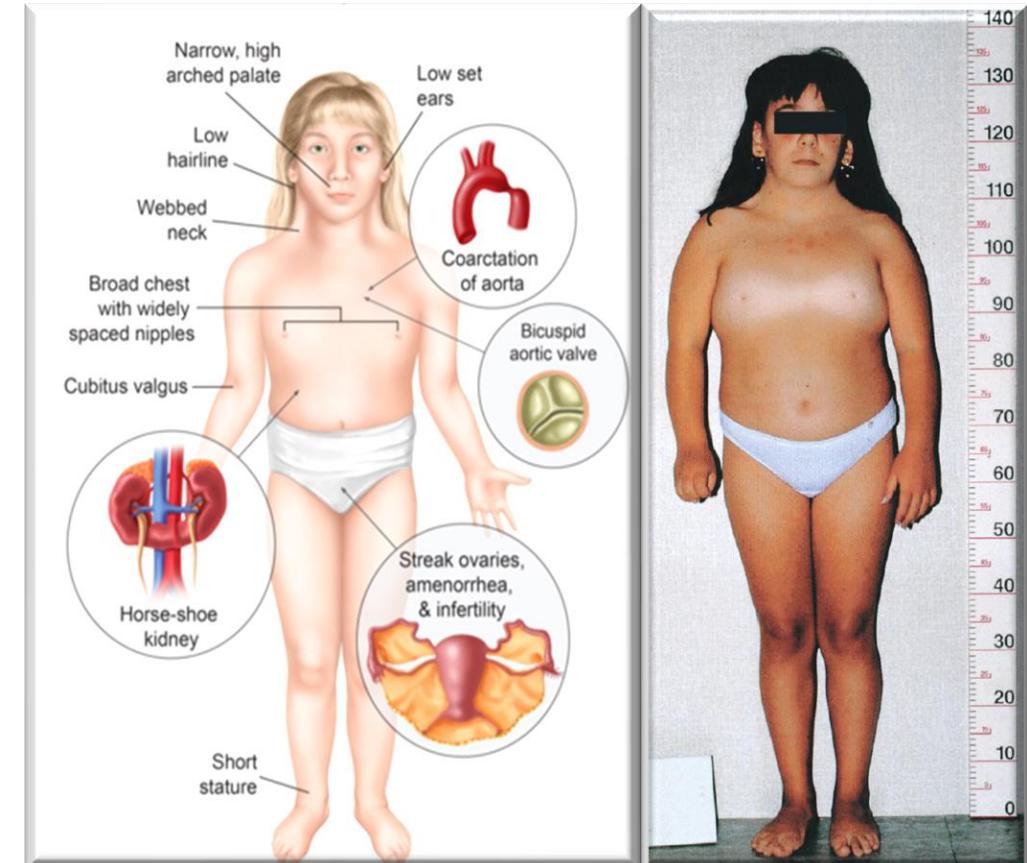
# KLINEFELTER SYNDROME (47, XXY)

- Extra copy of X chromosome (47, XXY, most common).
- 1 in 660 males
- Caused by **nondisjunction during maternal/paternal meiotic division**
- **Male hypogonadism**
- Usually detected at puberty
- **Extra X chromosome → Less ↓ Testosterone:**
  - Decreased virilization
  - Testicular atrophy
  - Hyalinization of seminiferous tubules → Firm testes impaired '↓' sperm production
  - Gynaecomastia
  - Tall stature; decrease upper to lower body ratio (Excess copies of SHOX gene)
  - May have impaired cognitive development
- Greater number X chromosome → Greater phenotypic abnormalities
- **Mosaicism karyotype, 46XY/47XXY – caused by mitotic error (non-disjunction) post-zygotic stage.**

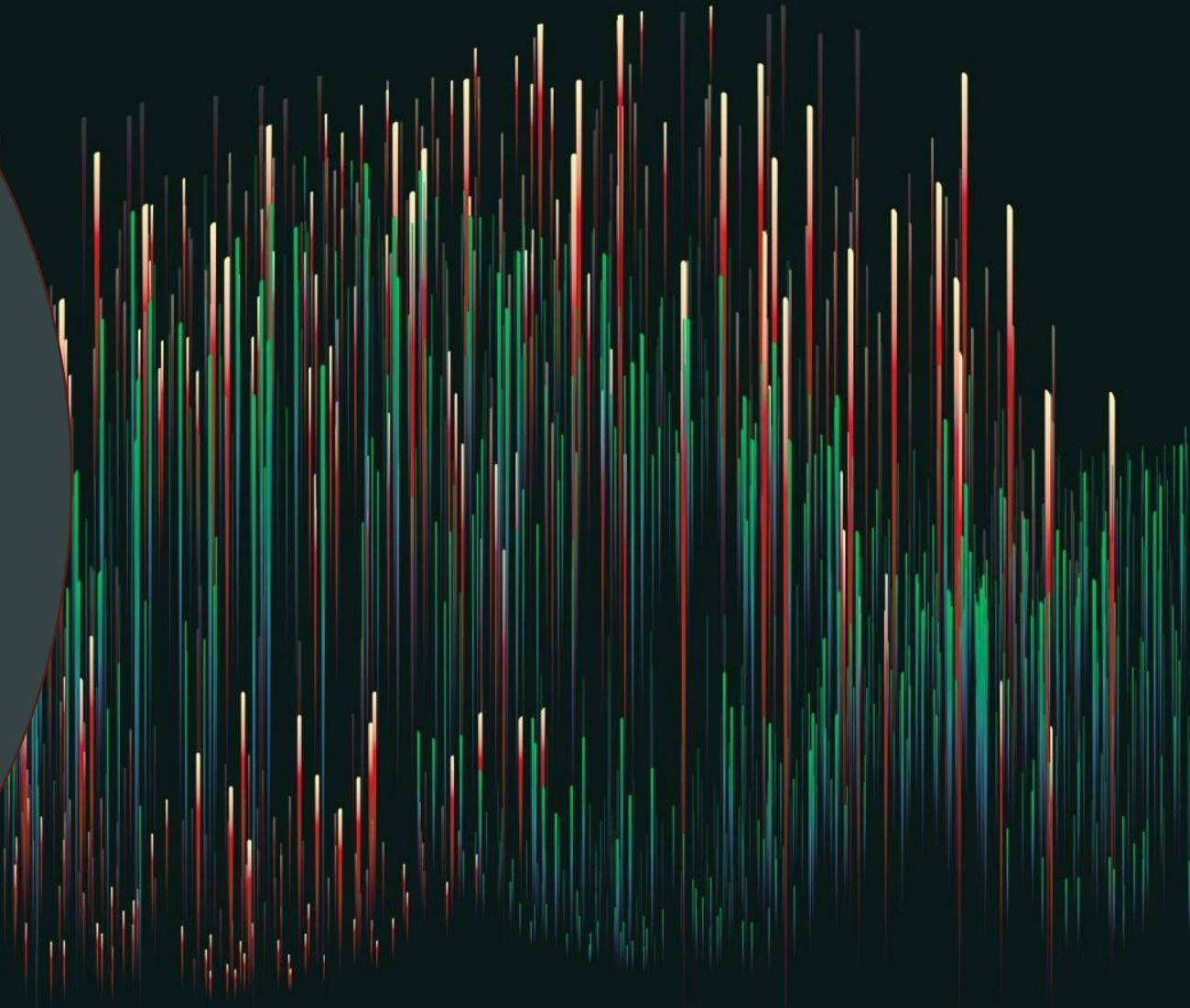


# TURNER SYNDROME (45,XO)

- Entire or partial X-chromosome is missing; Monosomy (XO); 1 in 25,000
- Caused by nondisjunction during maternal/paternal meiotic division.  
(More frequent in sperm)
- Female hypogonadism
- Female phenotype, with female reproductive organs and genitalia but with sterile gonads.
- Missing X chromosome → Accelerated rate of egg lost; menopause occurs by age of 2.
  - Leads to gonadal dysgenesis= streak ovaries-fibrotic non-functional ovaries → Reduced oestrogen
  - Primary amenorrhea and failure to develop secondary sexual characteristics at puberty
  - Short stature, increased upper-to-lower body segment ratio (SHOX gene haploinsufficiency)
  - Webbed neck (Frequently)
  - Peripheral lymphedema
  - Congenital heart defects-coarctation of aorta; bicuspid aortic valve
  - Horseshoe kidney – increased risk of UTI
  - Metabolic disorders: Increase risk for type 2 diabetes and hypothyroidism
- Mosaic karyotype, 45X/46XX – Will undergo puberty and have secondary amenorrhea.

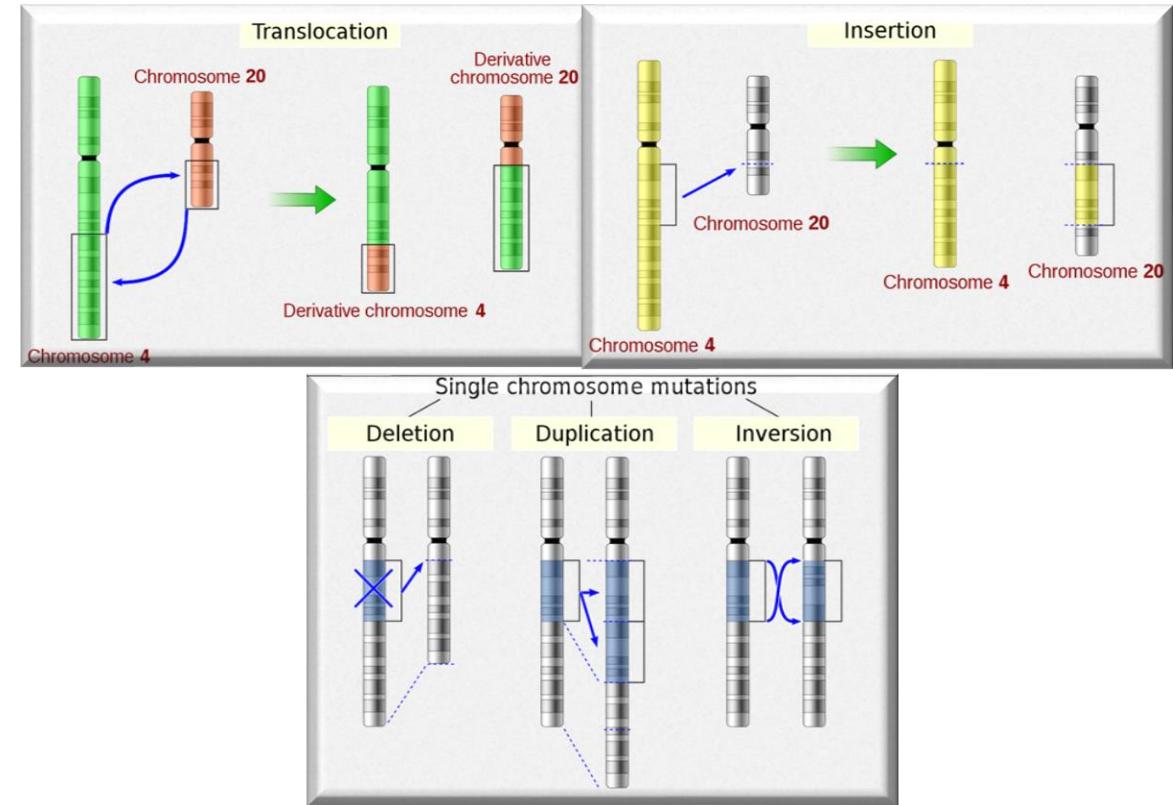


# STRUCTURAL CHROMOSOME ABNORMALITIES



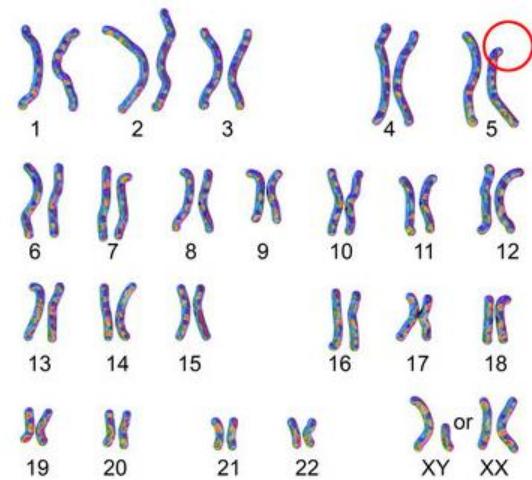
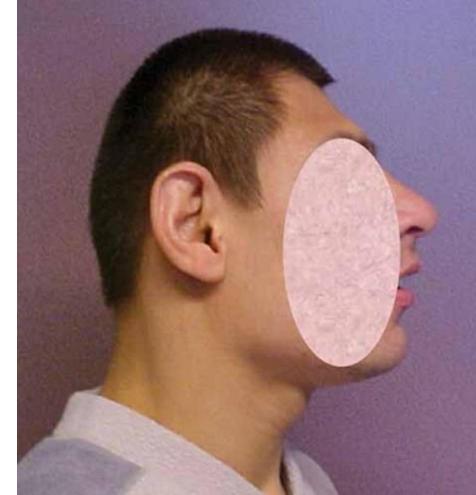
# CHROMOSOMAL ABNORMALITIES

- All **structural abnormalities** result from some form of chromosomal breakage.
- The resulting abnormalities depends on what happens to the broken pieces.
- **Common types:**
  - 1) Translocation
  - 2) Insertion
  - 3) Inversion
  - 4) Duplication
  - 5) Deletion



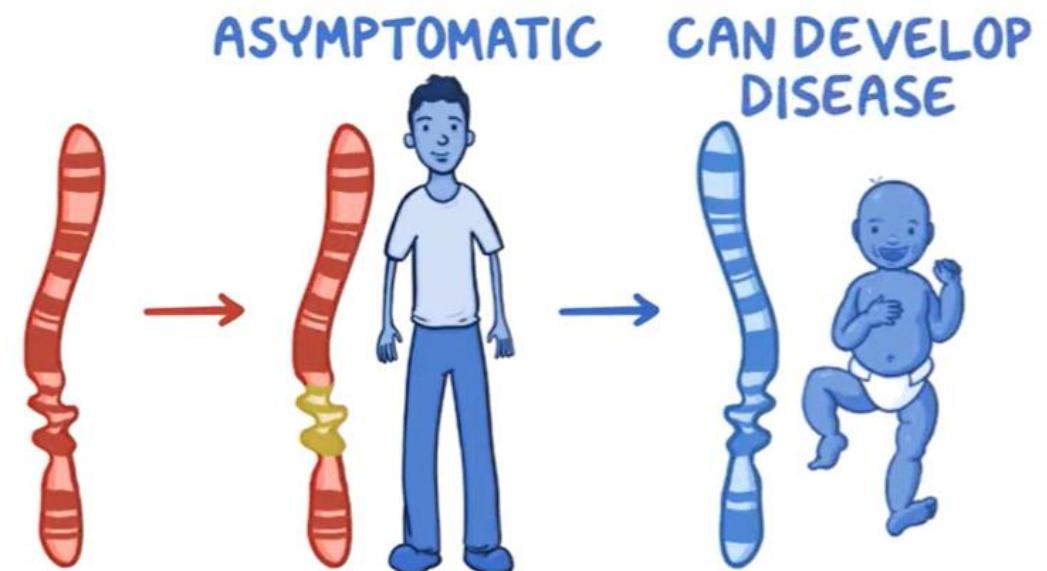
# PARTIAL DELETION: CRI-DU-CAT SYNDROME

- **Microdeletion** – short arm of C5, **occurs spontaneously** during formation of reproductive cells or during early embryonic development.
  - Microcephaly
  - Mental retardation
  - Congenital heart disease
  - **Makes a cry that sounds like a cat**
- Many other relatively rare syndromes result from partial chromosome loss.



# IMPRINTING DISORDERS

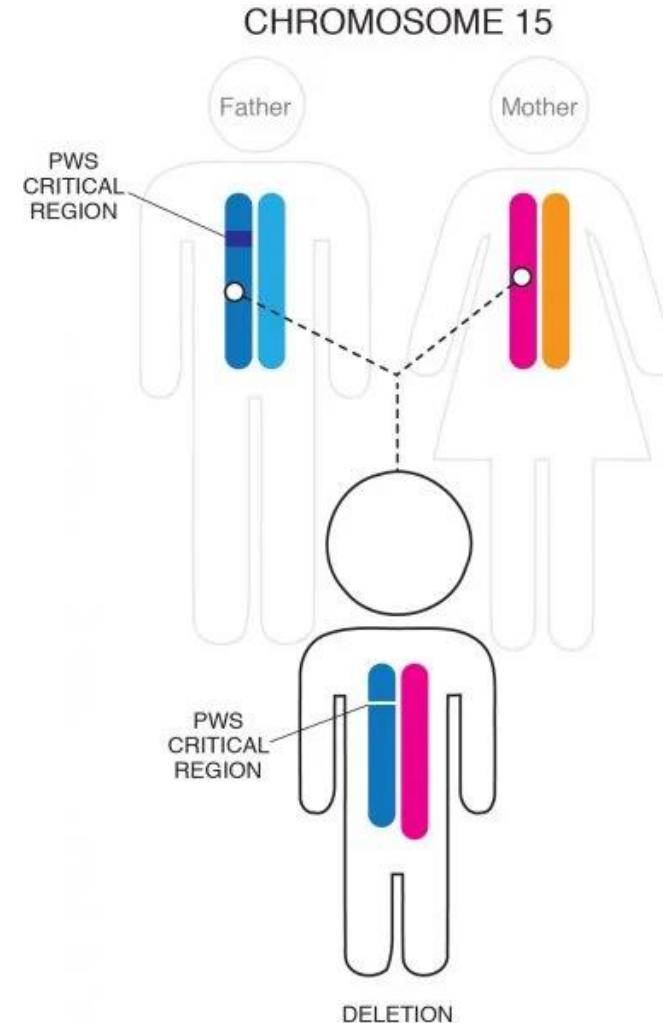
- **Genomic imprinting:** epigenetic phenomenon that causes genes to be expressed or not, depending on whether they are inherited from the female or male parent —meaning only the allele from the mother or the father is active, while the other is silenced.
- Imprinting disorders can occur sporadically or passed down from an asymptomatic parent.
- Prominent example **Prader-Willi syndrome** and **Angelman syndrome**
  - Both involve defects in C15 – microdeletion - spans a few contiguous genes.



# MICRODELETIONS: ANGELMAN VS. PRADER-WILLI SYNDROME

- **Prader-Willi syndrome**

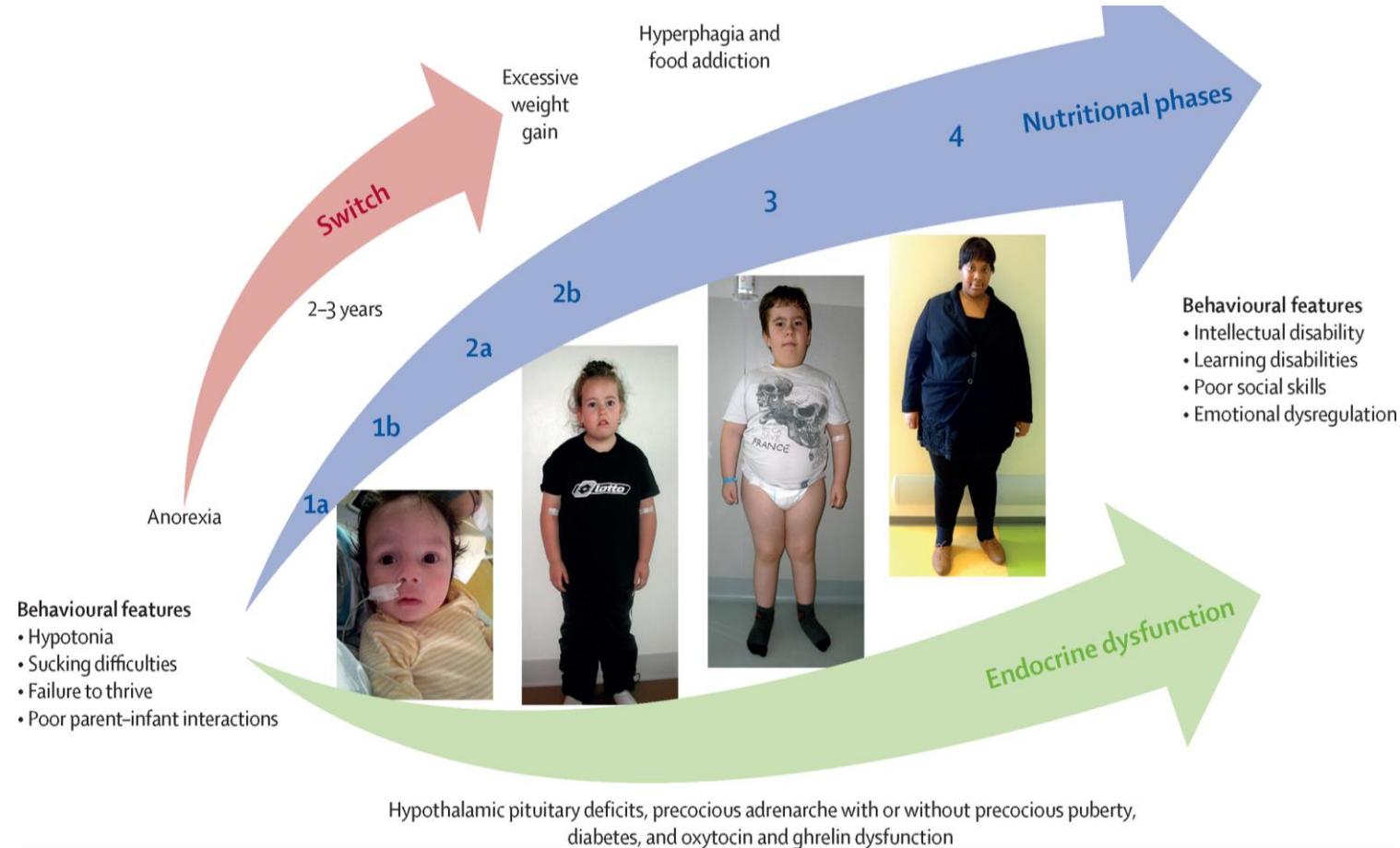
- **Paternal chromosome – microdeletions causes specific gene (SNRPN) to defective.**
- The maternal copy of the same gene is silenced, therefore no active copy of the SNRPN gene.



# MICRODELETIONS: ANGELMAN VS. PRADER-WILLI SYNDROME

- **Prader-Willi syndrome**

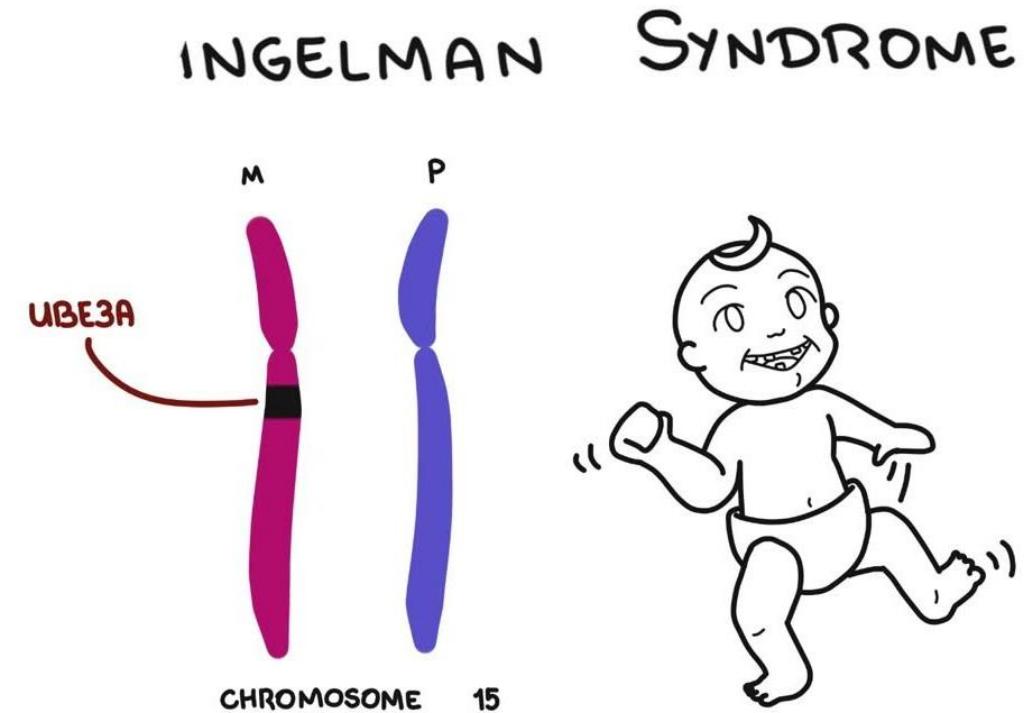
- Hypotonia – floppy baby syndrome
- Obesity
- Short stature
- Prominent forehead, almond-shaped eyes and triangular lips
- Mental retardation
- Hypogonadism
- Cryptorchidism



# MICRODELETIONS: ANGELMAN VS. PRADER-WILLI SYNDROME

- **Angelman syndrome**

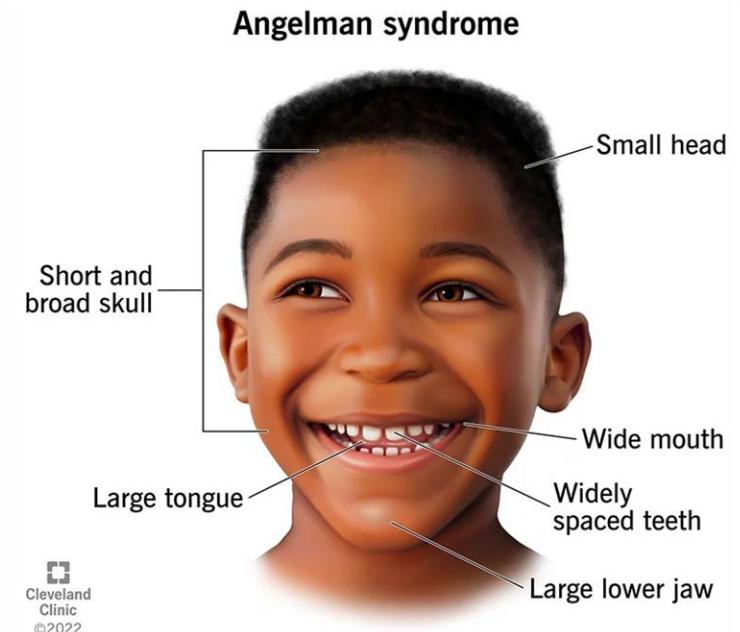
- Maternal chromosome – microdeletions causes specific gene (UBE3A) to defective.
- The paternal copy of the same gene is silenced, therefore no active copy of the UBE3A gene.



# MICRODELETIONS: ANGELMAN VS. PRADER-WILLI SYNDROME

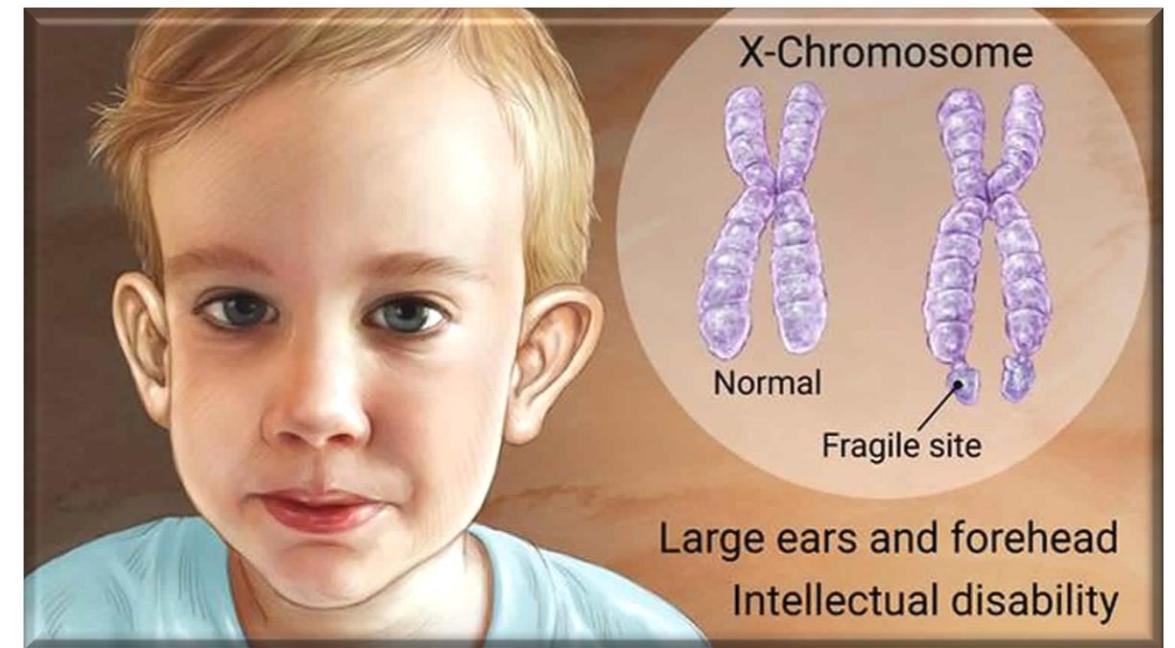
- **Angelman syndrome**

- Mental retardation-absence speech, learning difficulties
- ‘Happy puppet syndrome’-happy disposition, prone to unprovoked and prolong periods of laughter
- Exhibit poor motor development

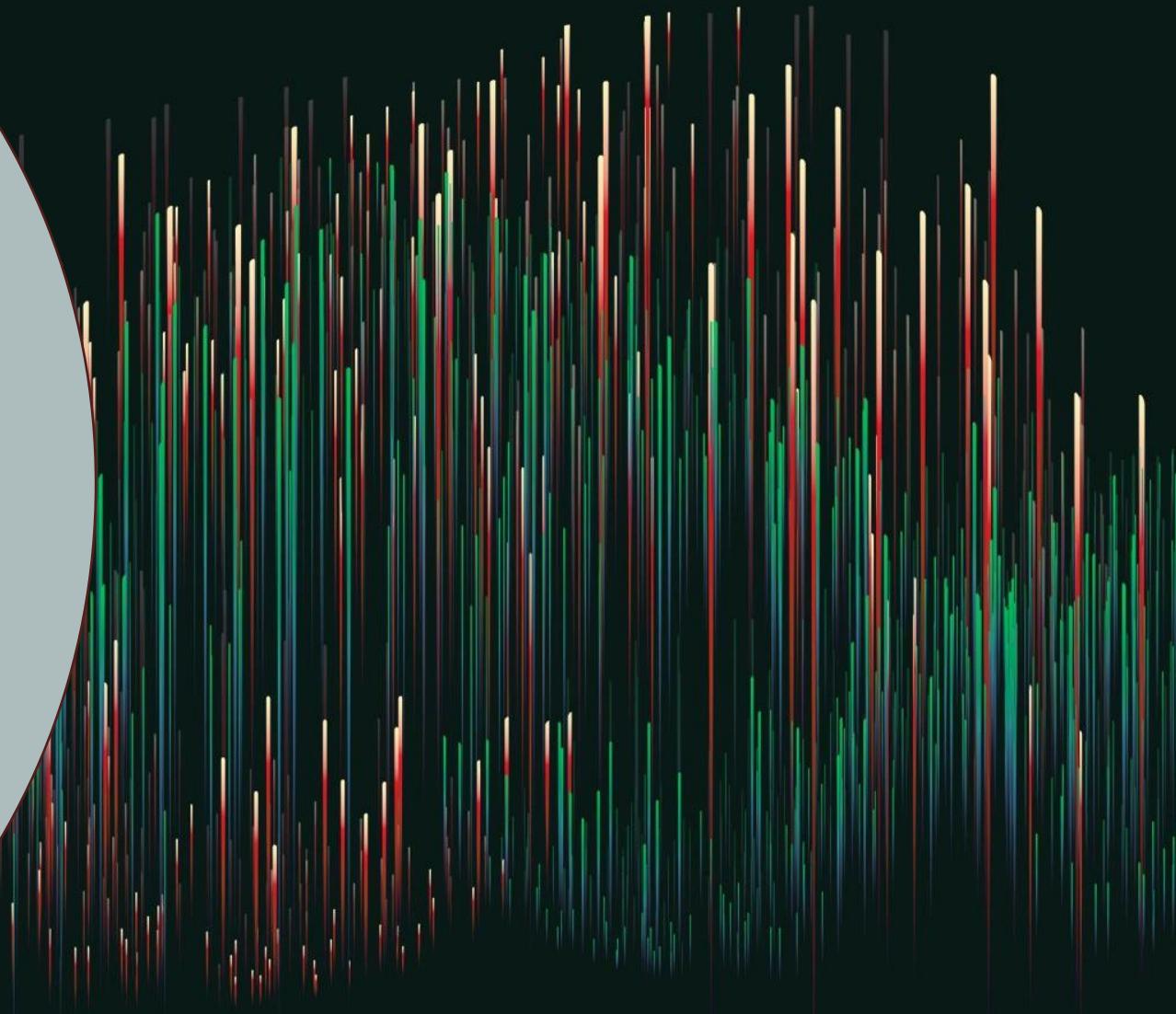


# FRAGILE SITES: FRAGILE X SYNDROME

- Fragile sites: Regions of chromosomes that demonstrate a propensity to separate or break.
- Fragile X syndrome:
  - Commonly known inherited cause of cognitive development
  - Second most common genetic cause of cognitive impairment after Down syndrome
  - Male, 4:2,000 Vs. Female, 1:4,000
  - Large ears
  - Prominent jaw
  - Pale blue irides

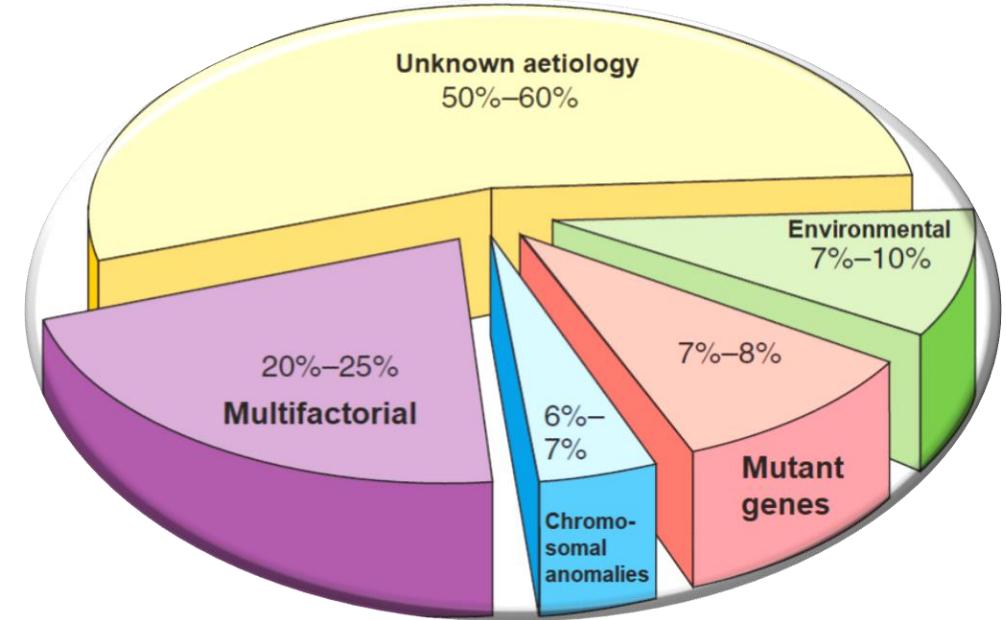


# MUTANT GENES



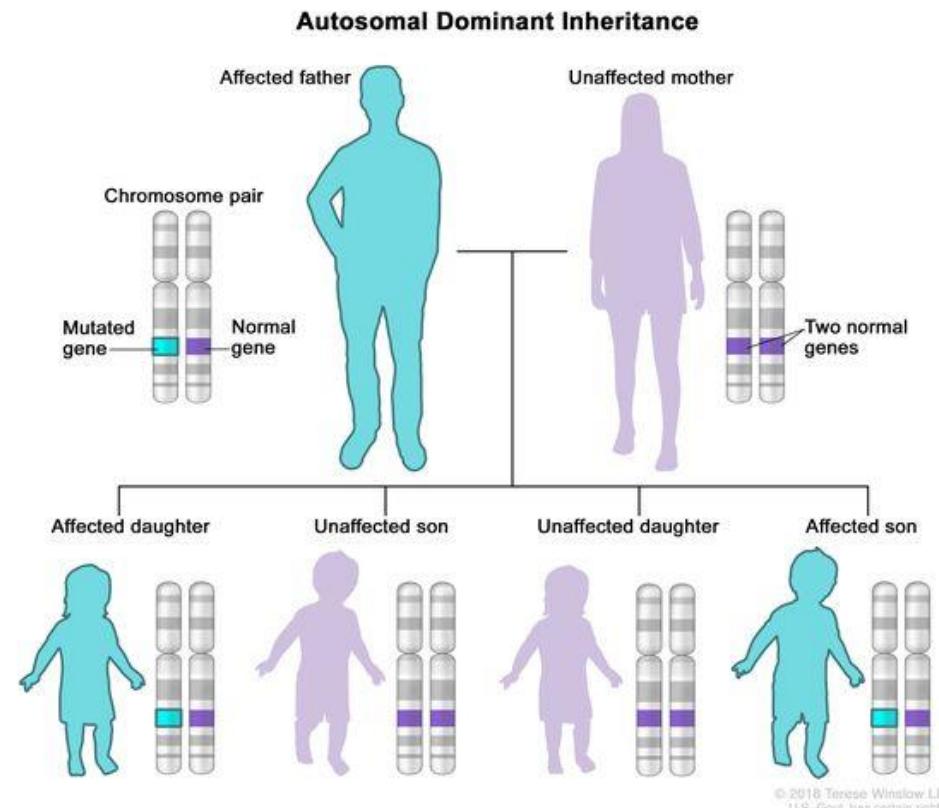
# MUTANT GENES

- Many genetic mutations are expressed as morphological abnormalities
- May be of dominant or recessive genes of either autosomes or sex chromosomes
- Some show a clear mendelian pattern of inheritance
- In many cases abnormality is attributed to a loss or change in the structure or function of a single gene — **single gene mutation.**
  - Estimated to be the cause of 8% of all human malformations



# COMMON AUTOSOMAL DOMINANT

- Only one copy of a mutated gene from a parent is sufficient to cause the condition.



# COMMON AUTOSOMAL DOMINANT

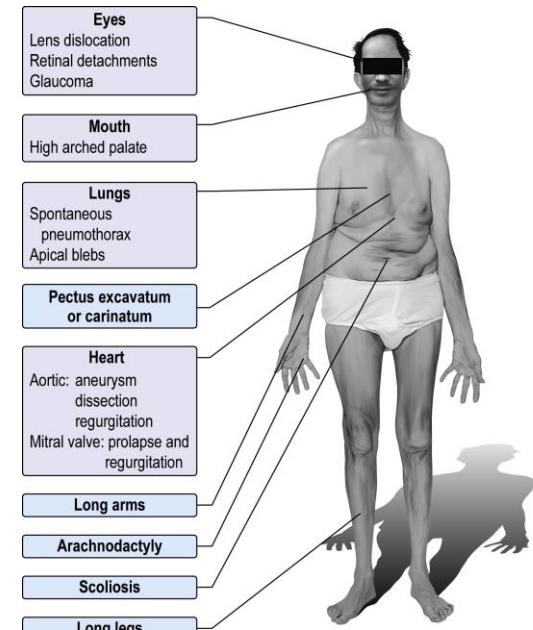
- **Neurofibromatosis** –mutant gene (NF1) causing benign tumours to grow in nerve tissues, impacting brain, spinal cord and nerves.
- **Marfan syndrome** – Mutation in fibrillin-1 (FBN1) encodes fibrillin and elastic fibres, a major component of connective tissue.
- **Achondroplasia** –Mutation in fibroblast growth factor 3 gene (FGF3) on chromosome 4-cartilage does not develop properly, limits bone growth.
- Other e.g. **Huntington's disease; Ehlers-Danlos syndrome, Polycystic kidney disease**



Cutaneous Neurofibromatosis



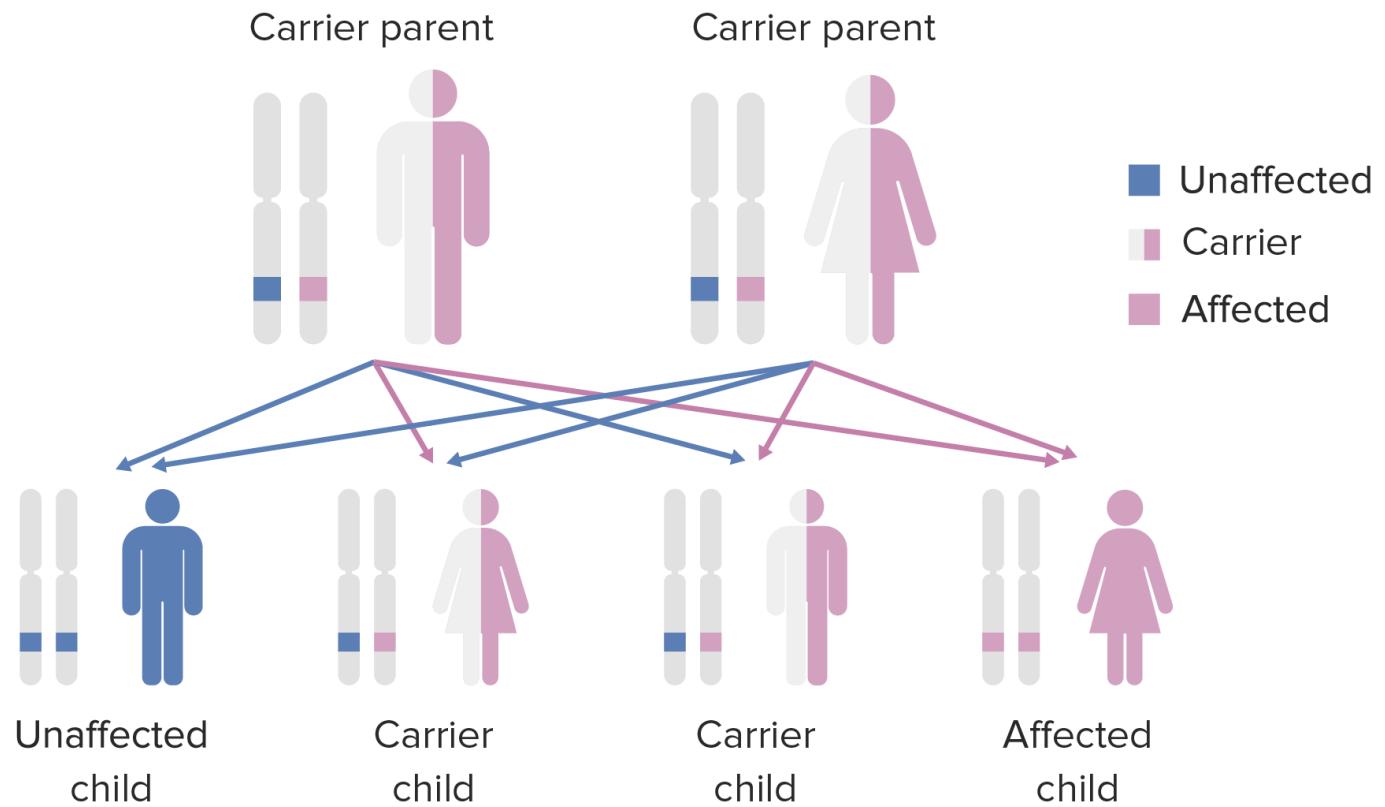
Achondroplasia or dwarfism



Marfan syndrome

# COMMON AUTOSOMAL RECESSIVE

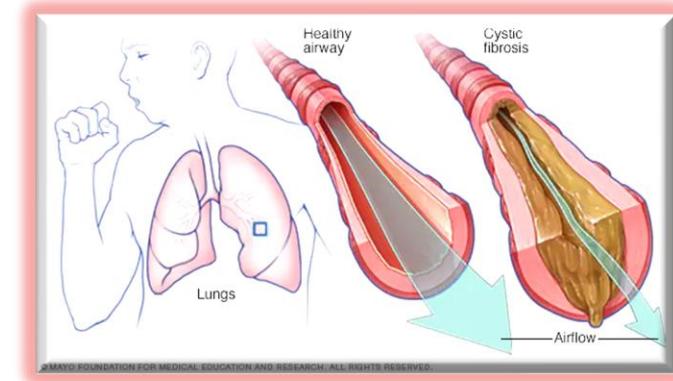
- Requires inheritance of **two copies of the mutant gene** from both parents.



# COMMON AUTOSOMAL RECESSIVE

- **Cystic fibrosis**

- Cystic fibrosis transmembrane conductance regulator (CFTR) gene on chromosome 7
- Affects respiratory and digestive system through thick mucus production
- 1 in 2500 (UK).

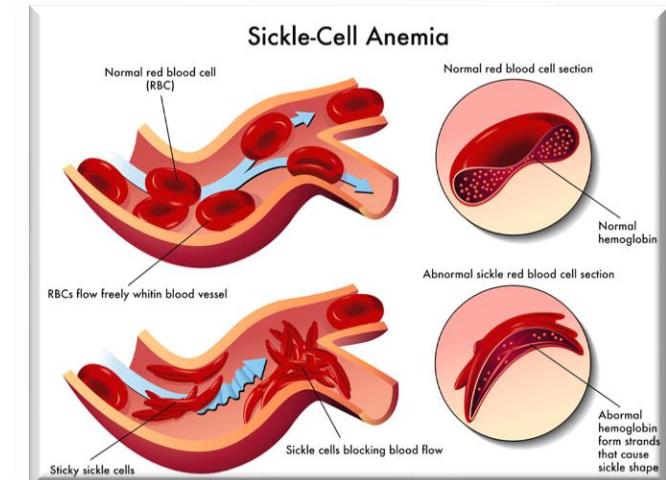


- **Sickle cell anaemia**

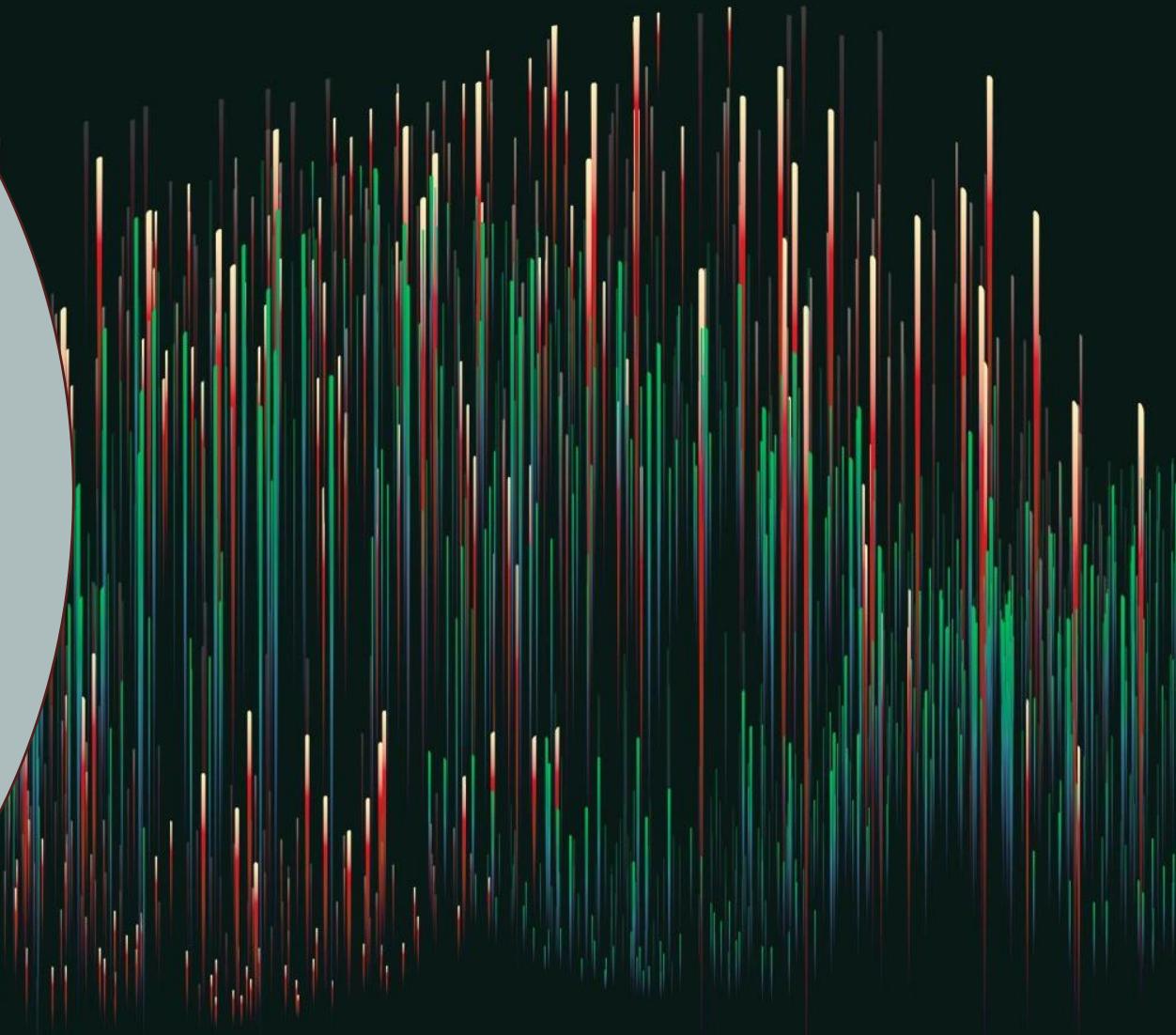
- Haemoglobin subunit beta (HBB) gene
- RBCs usually live for about 120 days, sickle rbc die sooner in 10 to 20 days → anemia

- **Phenylketonuria (PKU)**

- Deficiency or lack of enzyme phenylalanine hydroxylase required to break down protein in foods specifically phenylalanine.
- Phenylalanine build up in blood and brain can lead to brain damage.

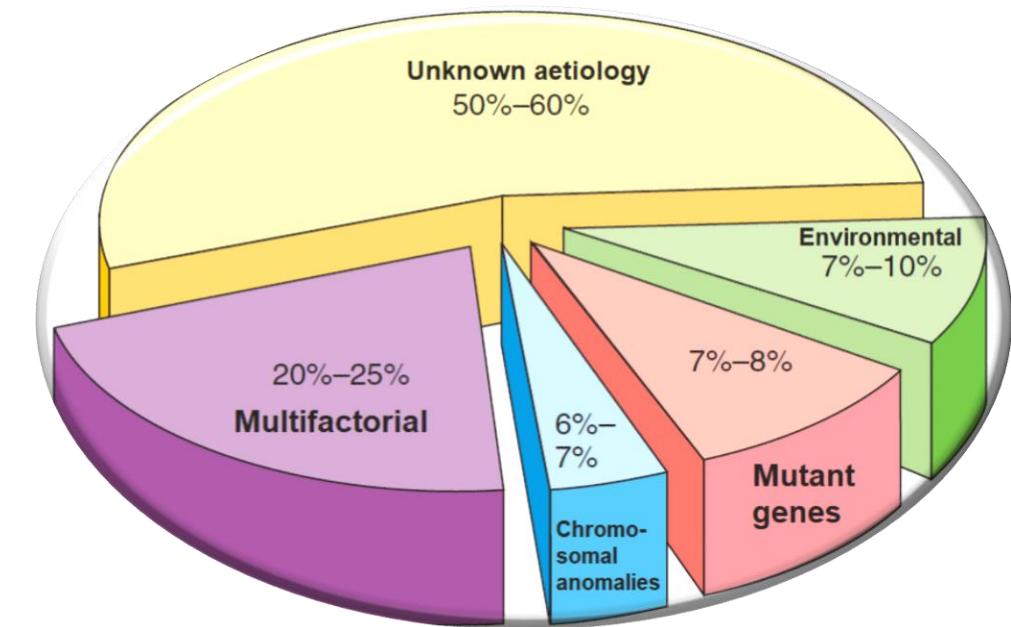


# ENVIRONMENTAL FACTORS

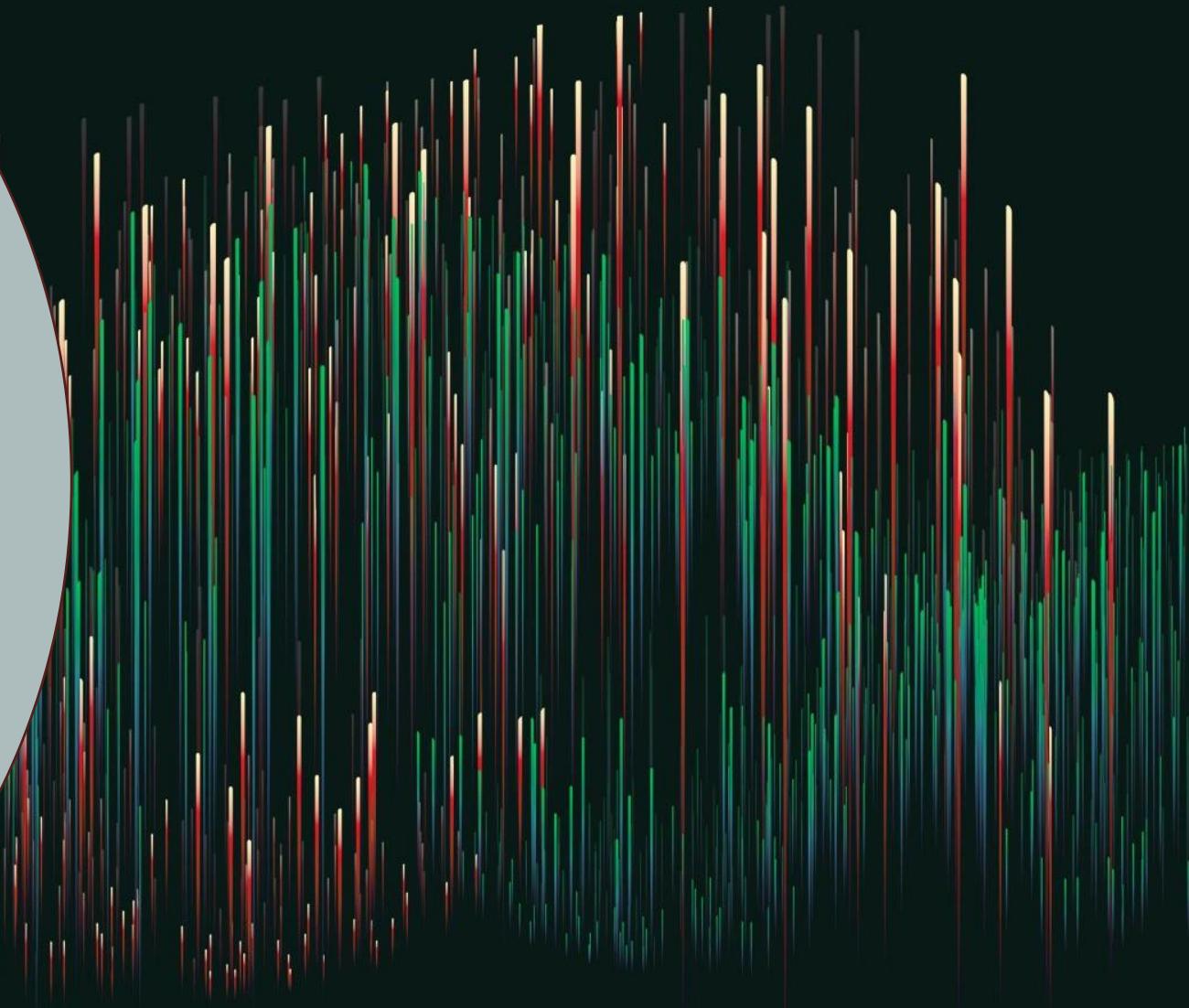


# ENVIRONMENTAL FACTORS

- Maternal exposure to environmental agents-teratogen can affect the embryo development in utero.
- **Teratogens:** Any agent (substance, organism or physical agent) that can cause birth defects in a developing embryo or fetus. List of suspected teratogenic factors is long, some **important ones**:
  1. Infectious agents (viral)
  2. Radiation
  3. Chemical agents including drugs
  4. Hormones
  5. Maternal Disease
  6. Nutritional Deficiencies
  7. Hypoxia

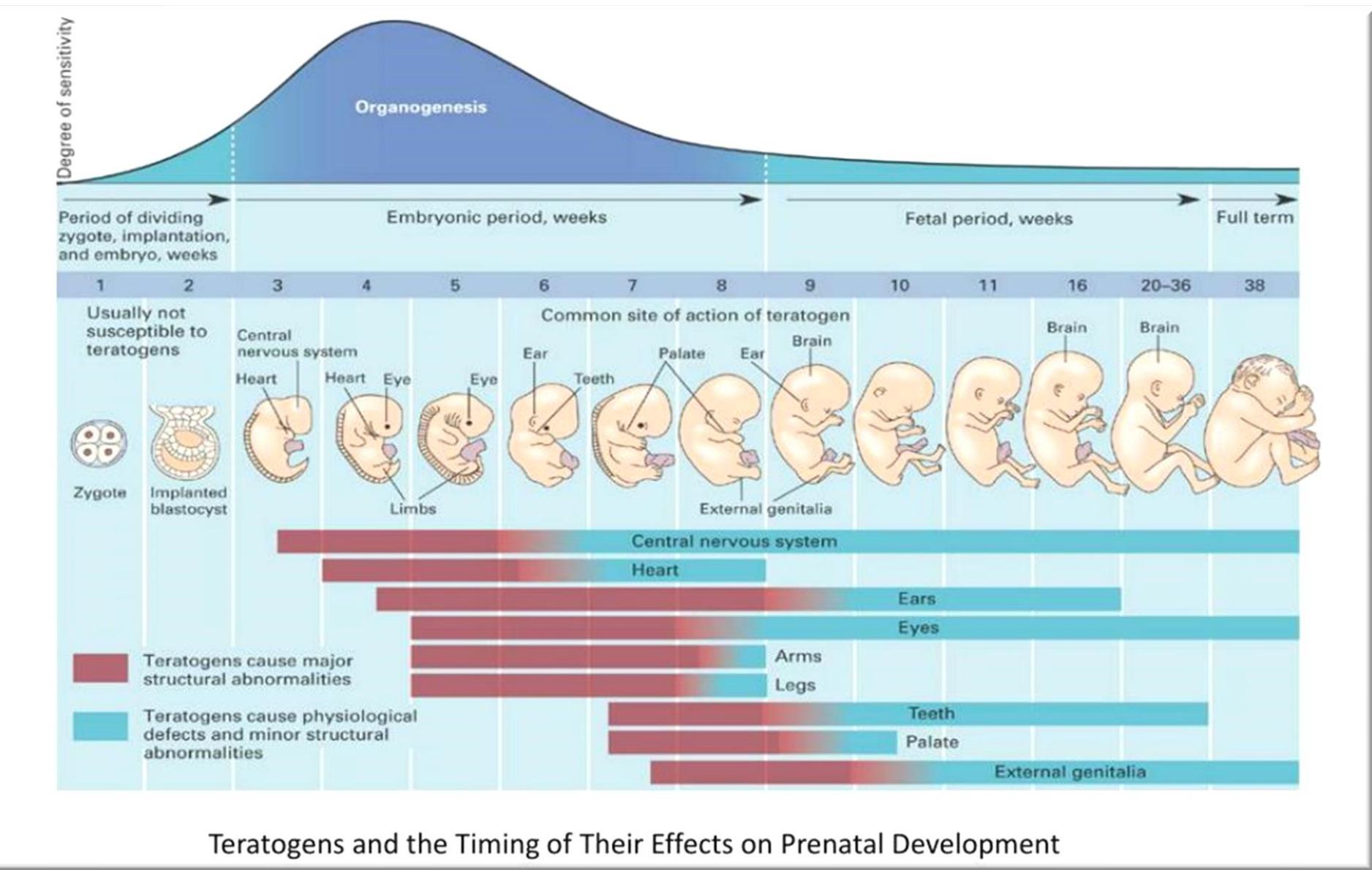


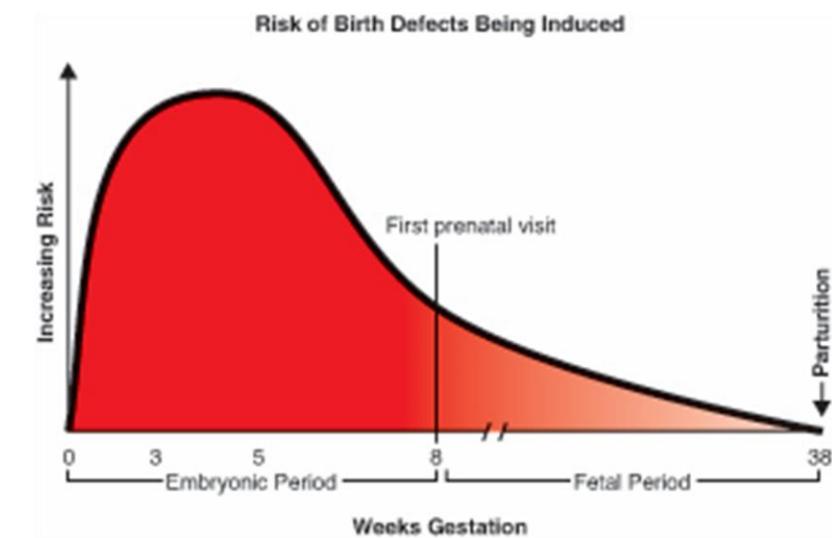
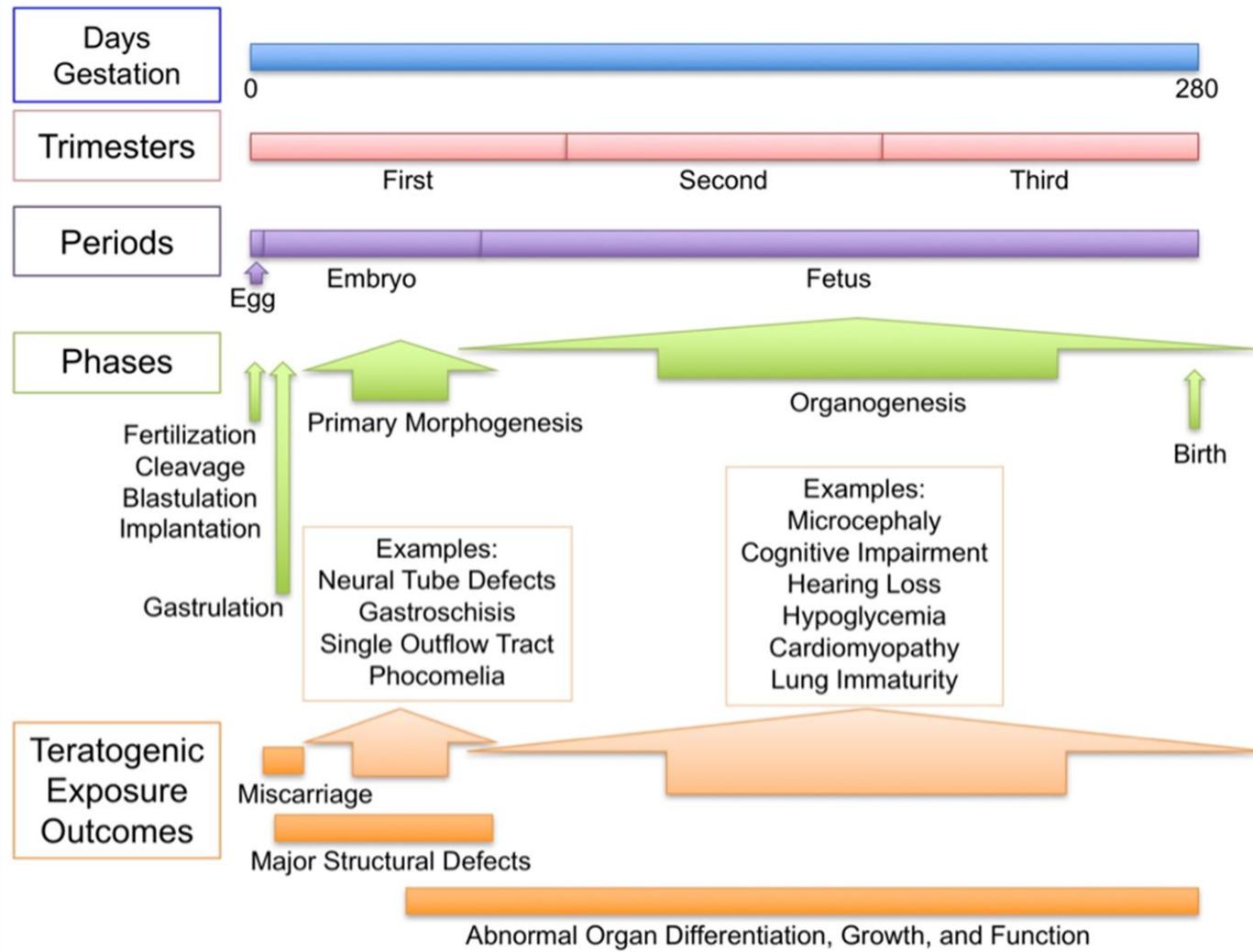
# PRINCIPLES OF TERATOLOGY



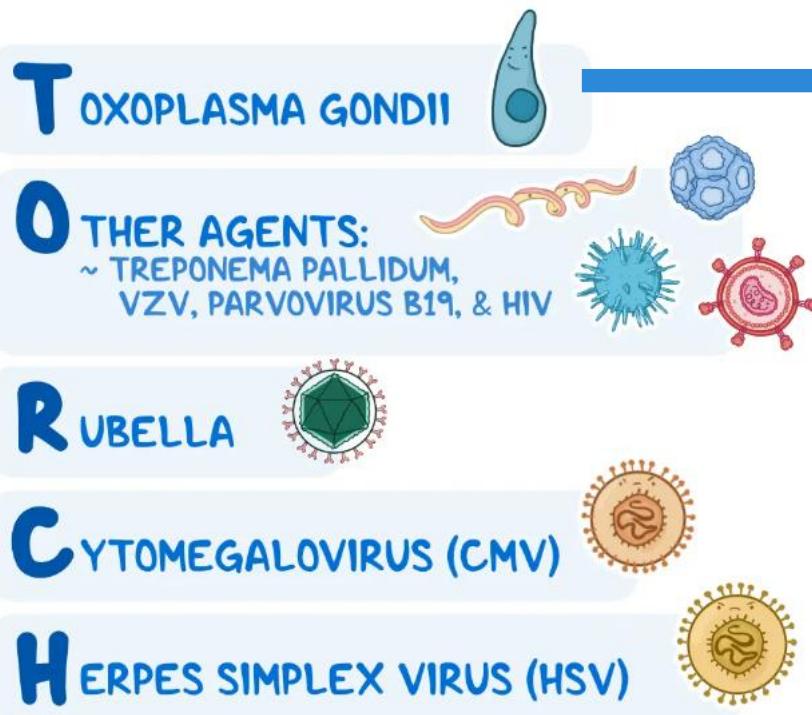
# PRINCIPLES OF TERATOLOGY

- **Main principles of teratology** state that the probability of a malformation being produced depends on the following factors:
  - Genotype of embryo and mother
  - Dose and duration of the agent
  - Stage of embryo being exposed
- These factors interact with each other to influence the developmental outcome, which may range from minor anomaly to major anomaly, to death.
- The mechanisms of action of teratogen includes cell death, altered migration and proliferation. This happens via the inhibition of a specific biochemical or molecular processes.
- Susceptibility varies with developmental stage at the time of exposure – Most sensitive period for inducing birth defects is during embryonic period week 3-8.

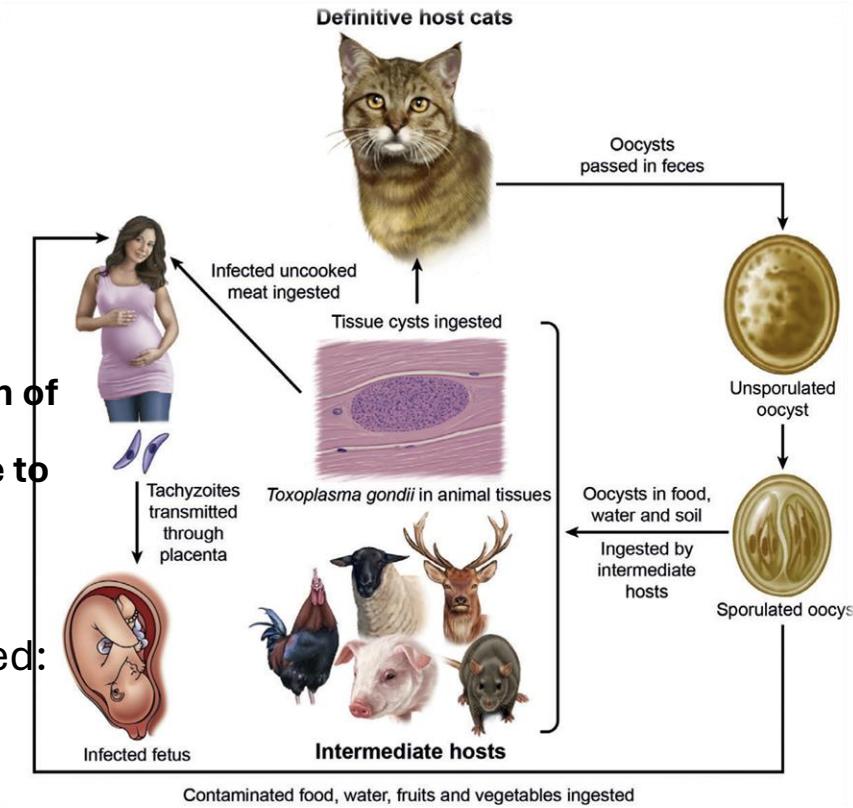




# INFECTIOUS AGENTS



- Protozoan parasite
  - Transmitted via consumption of undercooked meat or exposure to cat feces
  - Congenital abnormalities caused:
    - CNS (Cerebral calcifications, microcephaly, Hydrocephalus)
    - Enlarged liver and spleen
    - Cognitive impairment
    - Dental anomalies
    - Eye and ear

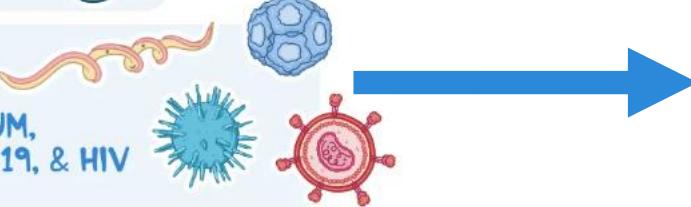


# INFECTIOUS AGENTS

T OXOPLASMA GONDII



O THER AGENTS:  
~ TREPONEMA PALLIDUM,  
VZV, PARVOVIRUS B19, & HIV



R UBELLA



C YTOMEGALOVIRUS (CMV)



H ERPES SIMPLEX VIRUS (HSV)



Others:

- **Zika virus**

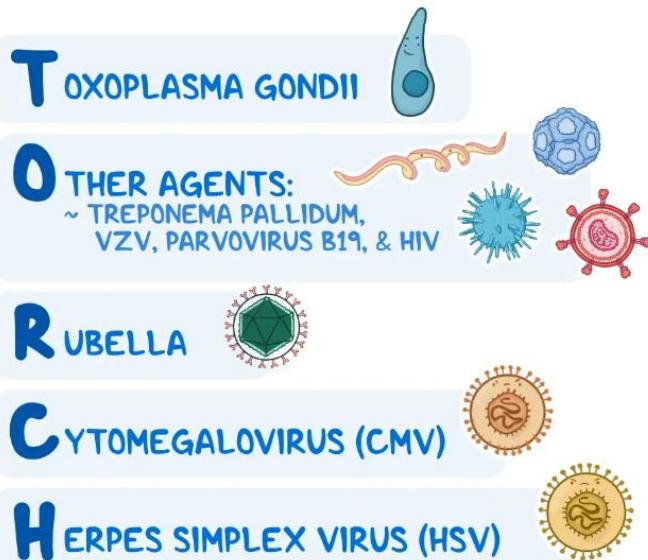
- Mosquito born virus
- Affects function of neural progenitor cells and causes cell death of newly formed brain tissue.

- **Hepatitis B virus**

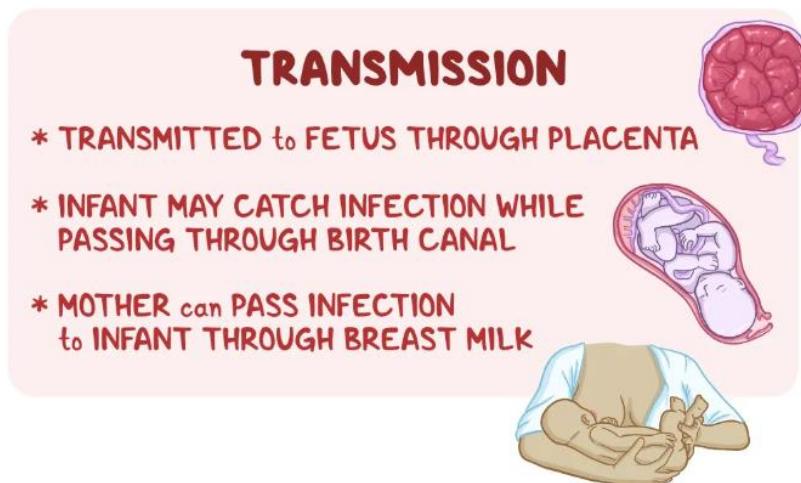


Infants showing the effects of Zika virus infection early in gestation.

# INFECTIOUS AGENTS

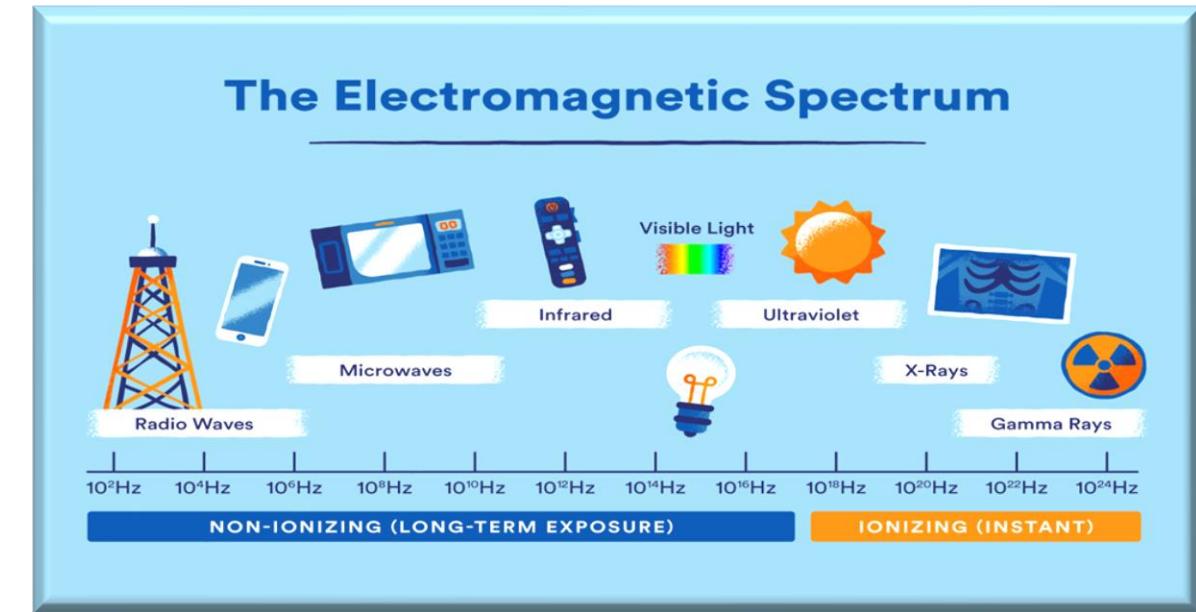


- **Signs and symptoms varies depending on underlying infection.**
- **Non-specific signs:**
  - **Early signs** – fever, microcephaly, IUGR, lethargy or sleepiness, cataracts, hearing loss and congenital heart defects, hepatosplenomegaly, reddish-brown skin rash, jaundice, bluish or purplish skin rash.
  - **Late signs (after age of 2)** – Vision impairment or loss, developmental delays, deafness and seizures.



# RADIATION

- **Teratogenic effect of ionizing radiation** (at high doses) can **produce breaks in DNA and mutations**, possible effects:
  - **Miscarriage** – 1-2 weeks after conception will not survive
  - **Birth defects** – Microcephaly, skull defects, spina bifida, blindness, cleft palate and other extremity defects including genital defects, IUGR.
  - **Dose in diagnostic X-ray is minimal**, however **X-ray of the maternal belly, pelvis and back should be avoided.**



The *risk of radiation-induced malformation is highest during the period of organogenesis (Embryonic period).*

# CHEMICAL AGENTS

- **Mercury or methylmercury**
  - Fish, seed cord sprayed with mercury-containing fungicide
  - Multiple neurological symptoms resembling cerebral palsy
- **Lead**
  - Contaminated water (e.g. Flint, Michigan water crisis), lead-based paint
  - Increased miscarriage and still births
  - Growth retardation
  - Neurological disorders

Flint water crisis led to lower fertility rates, higher fetal death rates, researchers find



**Lead was poisoning the water in Flint, Mich. Dr. Mona Hanna-Attisha put her reputation on the line to prove it.**

Nicole Carroll USA TODAY  
Published 10:00 AM BST Aug. 11, 2020 | Updated 5:26 PM BST Aug. 27, 2020

Lessons Learned From the Crisis in Flint, Michigan Regarding the Effects of Contaminated Water on Maternal and Child Health

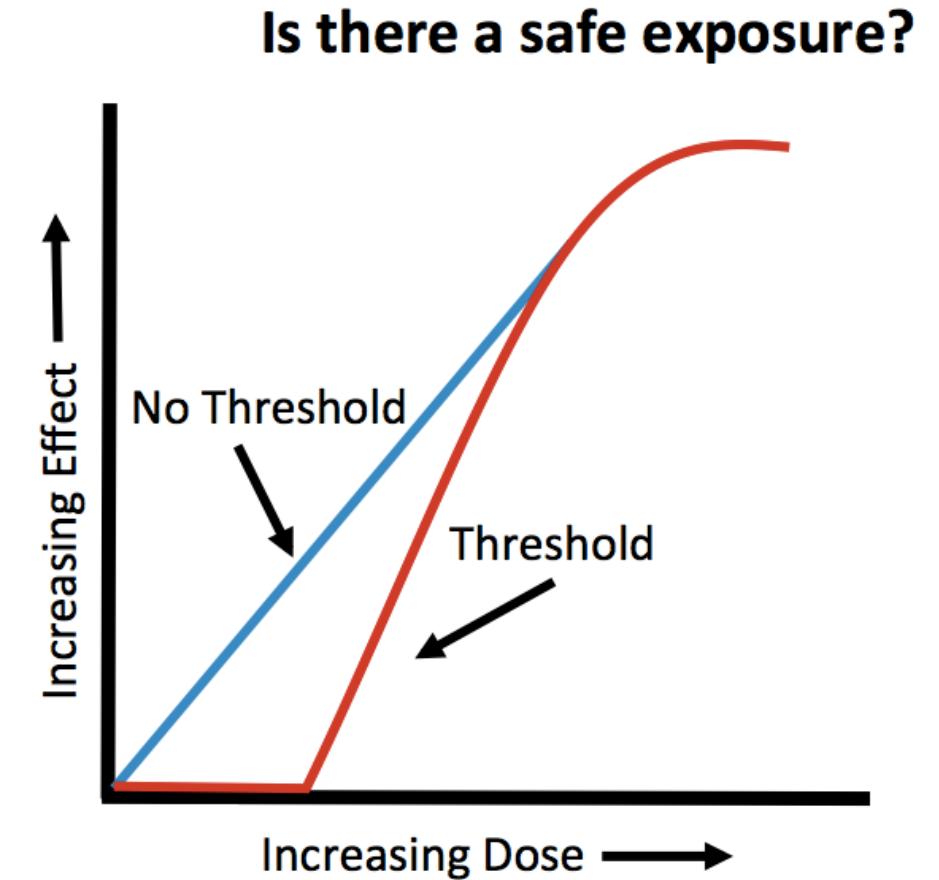
Melva Gale Craft-Blacksheare

# DRUGS

- Thalidomide
- Antibiotics (Teracyclines, Streptomycin)
- Quinine
- Asprins/Paracetamol
- Anticonvulsants
- Antipsychotic
- Antianxiety
- Anticoagulants
- Antihypertensives
- Isotretinoin (Analogue of vitamin A, Retinoic acids)

# KEY CONCEPT: IS THERE A SAFE DOSE OF A MEDICATION ASSOCIATED WITH BIRTH DEFECTS?

- Threshold dose model: The lowest dose of a drug or environmental agent that induces birth defects.

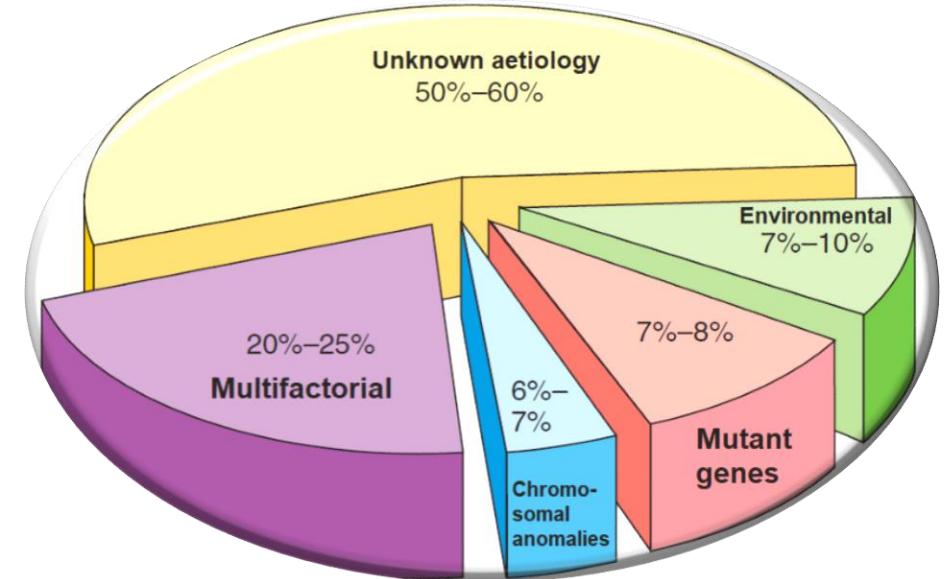


# KEY CONCEPT: IS THERE A SAFE DOSE OF A MEDICATION ASSOCIATED WITH BIRTH DEFECTS?

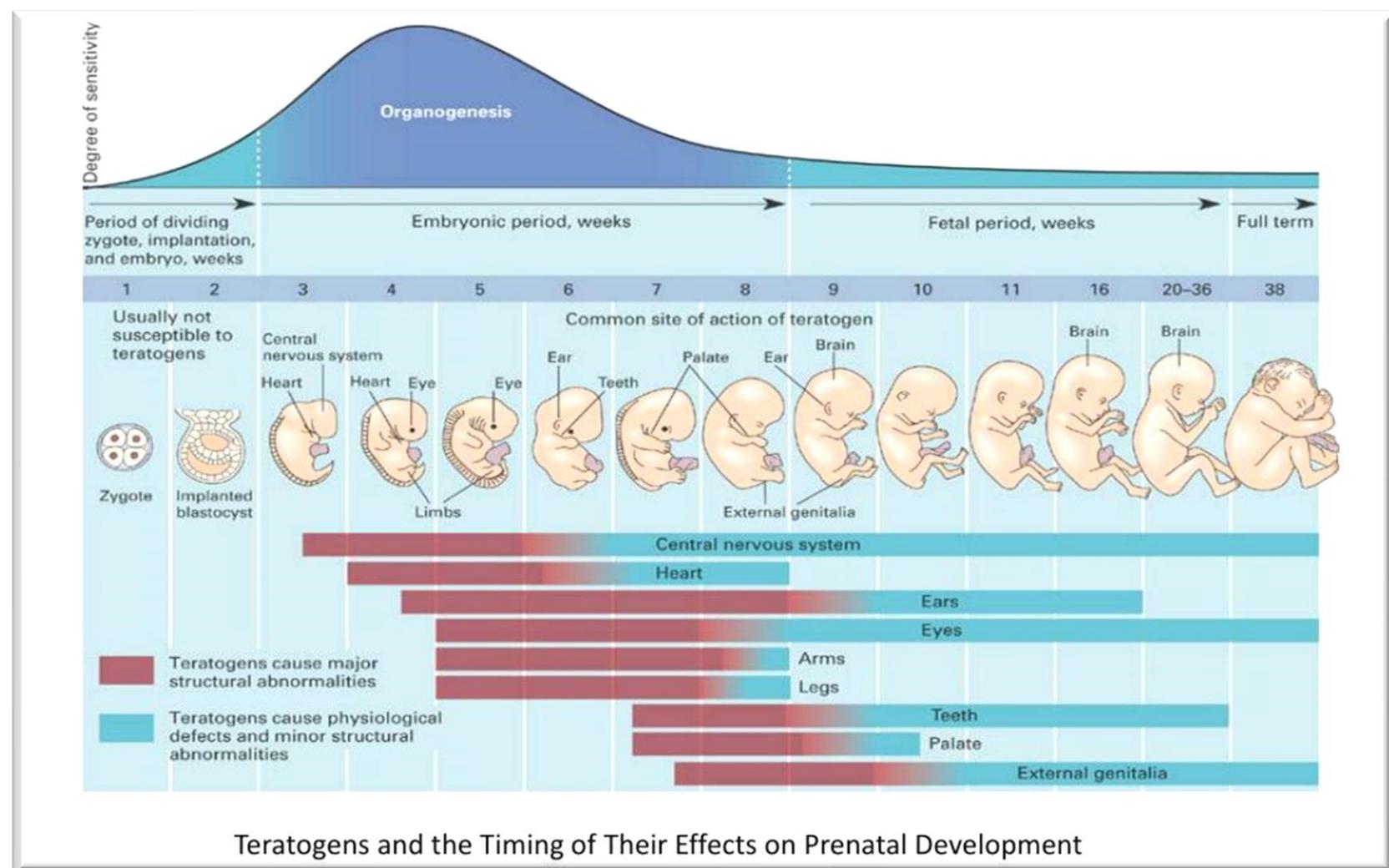
- Continuum model of probability: No safe level of exposure.**

Since most birth defects are of unknown aetiology or 'spontaneous' malformations. These birth defects may be because of tipping the balance of an internal development factors that is sensitive to environmental factors (i.e drugs with unknown prenatal effects).

- e.g. Vitamin A has function in developing embryo for cell differentiation and morphogenesis (Retinoic acid is crucial in limb and GI tube patterning). Some drugs can alter vitamin A concentration levels in embryo e.g Isotretinoin-Too little or too much vitamin A can cause birth defects.

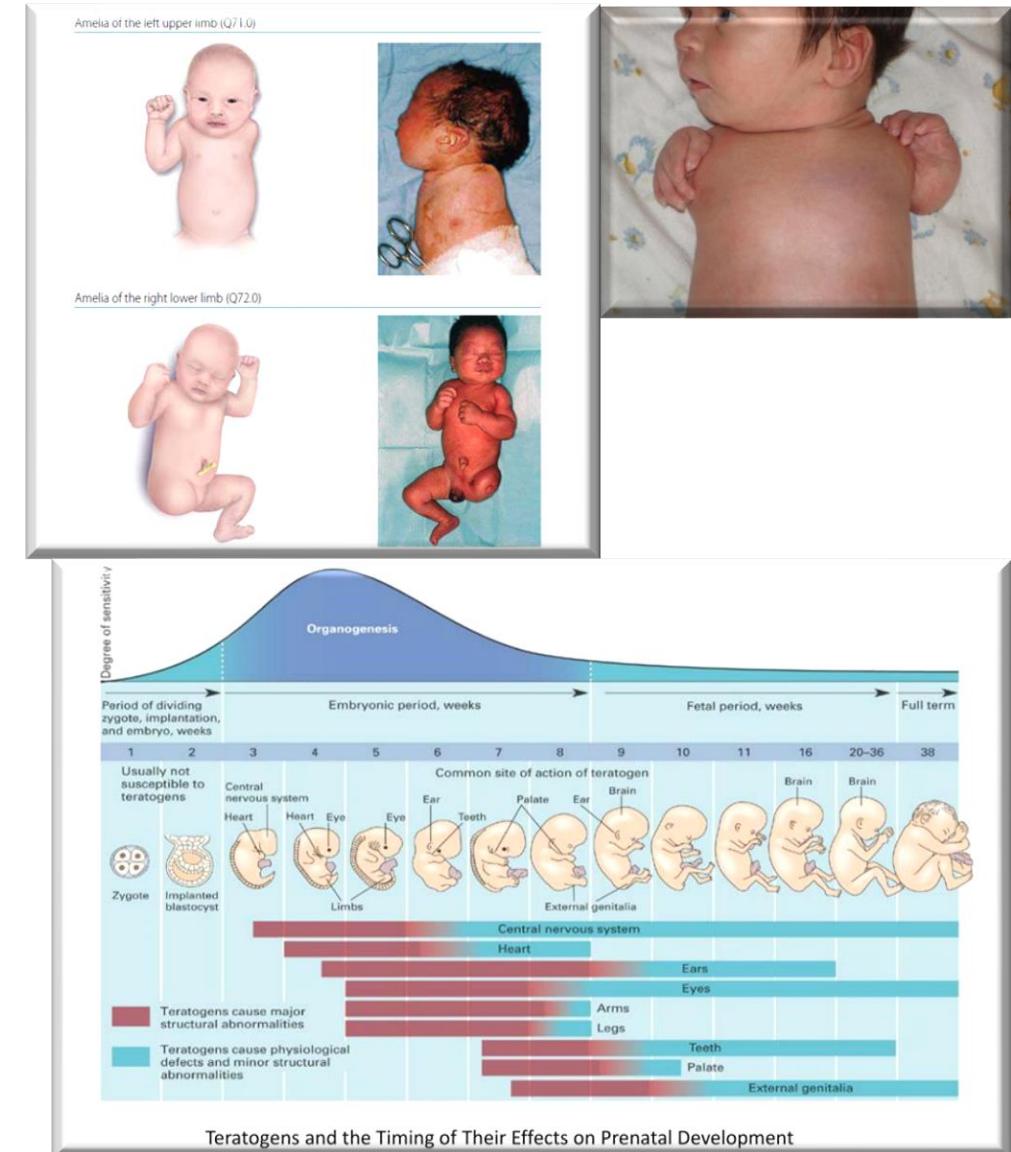


- The **route** and **timing of exposure** are also critical factors in determining the teratogenicity of a drug.
- The timing of exposure influences what structures or organ systems are most likely to be affected during development, along with the severity of the malformations.
- Reducing or eliminating exposures during the most sensitive windows of development** is one way of lowering teratogenic risks.



# DRUGS-THALIDOMIDE

- **Anti-nausea and sleeping pill (Tranquilizer)**
- Characteristic birth defect feature: Meromelia.  
Ranges from Amelia, Micromelia and Phocomelia.
- Other associated defects: intestinal atresia, Cardiac abnormalities
- Other factors: Country of residence – Thalidomide induced congenital malformations seen more in West Germany (from 1961) and Australia, but not USA due to FDA restriction of this drug.



Defect window for thalidomide inducing limb defects: 1<sup>st</sup> trimester.

# DRUGS

- **Anticoagulants (e.g. Warfarin)**

- May cause haemorrhage in embryo/fetus
- Defect window: 2<sup>nd</sup> and 3<sup>rd</sup> trimester
  - CNS defects - mental deficiency and optic nerve atrophy
- Heparin does not cross placental barrier, therefore drug of choice for pregnant women needing anticoagulant therapy.

# DRUGS

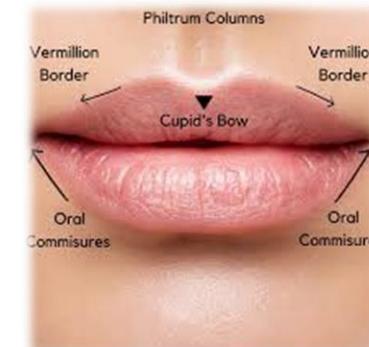
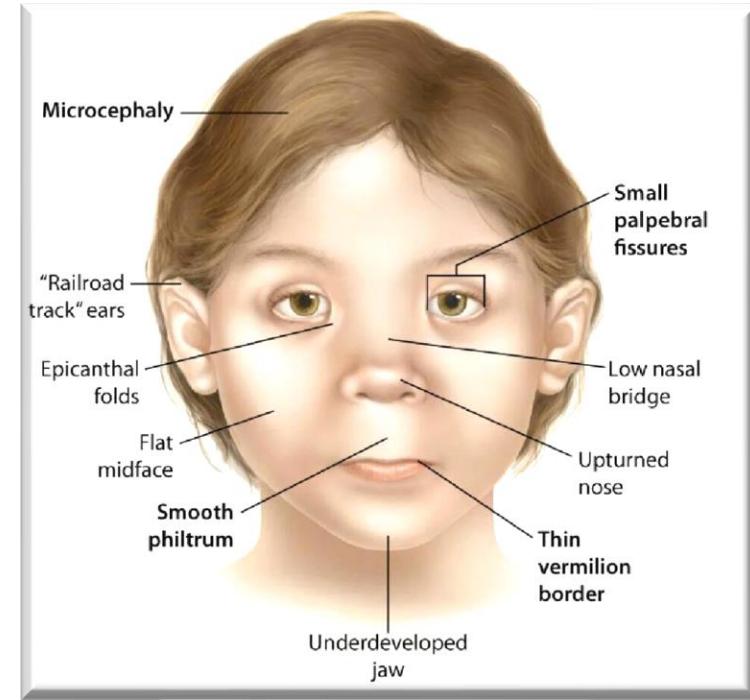
- **Isotretinoin Analogue of Vitamin A or Retanoic Acids.**

- Prescribed for cystic acne and other chronic dermatoses
- Highly teratogenic- no dose is safe
  - Reduced and abnormal ear
  - Craniofacial malformations- cleft palate, small jaw
  - Hydrocephaly
  - Neural tube
  - Heart anomalies

# ALCOHOL

- **Fetal Alcohol Syndrome (FAS)**

- Specific pattern of defects (10% cases)
- Identified in 1970s
- **Sentinel facial features**
  - Craniofacial abnormalities - short palpebral fissure
  - Hypoplasia of the maxilla
  - Low birthweight
- Limb deformities
  - Altered joint mobility and position
- Cardiovascular defects
  - Ventricular septal defects
- Microcephaly
- **Learning difficulties – low IQ**
- **Cognitive and behavioural problems**



# ALCOHOL

- **Fetal Alcohol Spectrum Disorder (FASD)**

- Wider range of disorder (90% cases) includes **Alcohol-related neurodevelopmental disorder (ARND)** and **Neurobehavioral disorder associated with prenatal alcohol exposure (NDPAE)**
- **No craniofacial abnormalities**
- May have some physical problems
- **Average IQ range**
- **Cognitive and behavioural problems**

# SMOKING

- Cigarettes have toxic chemicals such as **nicotine, carbon monoxide and tar.**



- Can cause:

- **CO- reduced oxygen for fetus from maternal blood → IUGR**
- **Nicotine- constricts uterine vessels → reduced uterine blood flow and lowers oxygen supply → IUGR**
- **premature delivery**
- **Placenta abnormalities: placenta previa and abruption**
- Cardiac septal defects
- Cleft lip and palate
- Sudden infant death syndrome (SIDS)
- Some evidence that it causes behavioural disturbances

HYPOXIA



# OTHER ILLICIT DRUGS

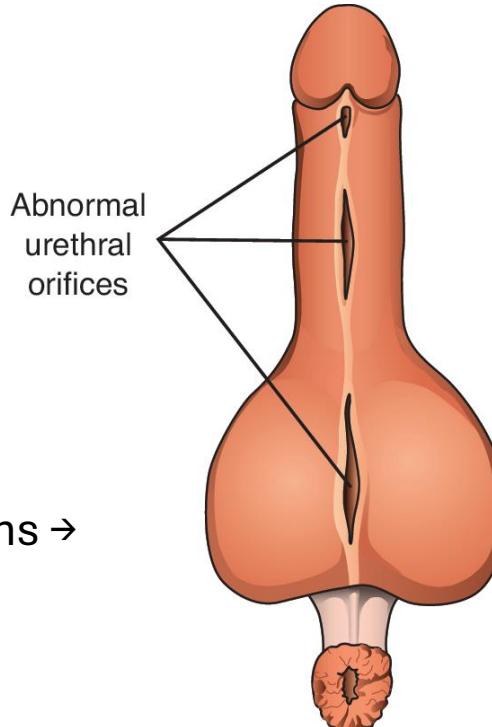
- Alcohol
- Amphetamines (ADHD treatment, but also widely misuse)
- Methadone
- Cocaine

**Key concept:** Not everything that is familial is genetic. Could be due to **shared environmental exposures or behaviours among family members.** E.g. **lifestyle choices**

# HORMONES

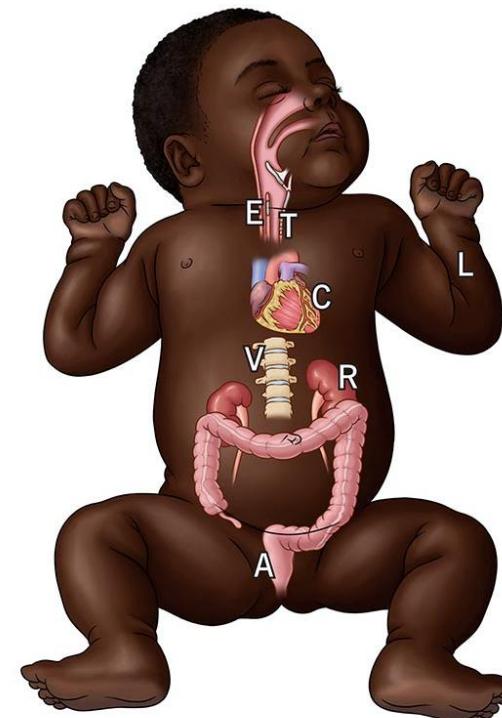
- **Androgenic effects:**

- Synthetic progestins or excessive androgens →  
**Masculinization of external genitalia in females; increase risk of hypospadias in males.**



- **Oral contraceptives**

- Progestogen-estrogen contraceptive pill →  
**VACTERL association (Vertebral, anal, cardiac, tracheal, oesophageal and limb anomalies).**



V - Vertebrae  
A - Anus  
C - Cardiac (heart)  
T - Trachea  
E - Esophagus  
R - Renal (kidneys & urinary tract)  
L - Limb & radius

# MATERNAL DISEASE

- **Disturbances in CHO metabolism (diabetic mothers):**
  - High incidence of stillbirth, neonatal deaths
  - **Macrosomia- abnormally large infants**
  - Congenital malformations- 3-4 times increased risk:
    - CNS-Holoprosencephaly, Meroencephaly
    - Caudal dysgenesis-Sacral agenesis, hindlimb hypoplasia
    - Congenital heart defects

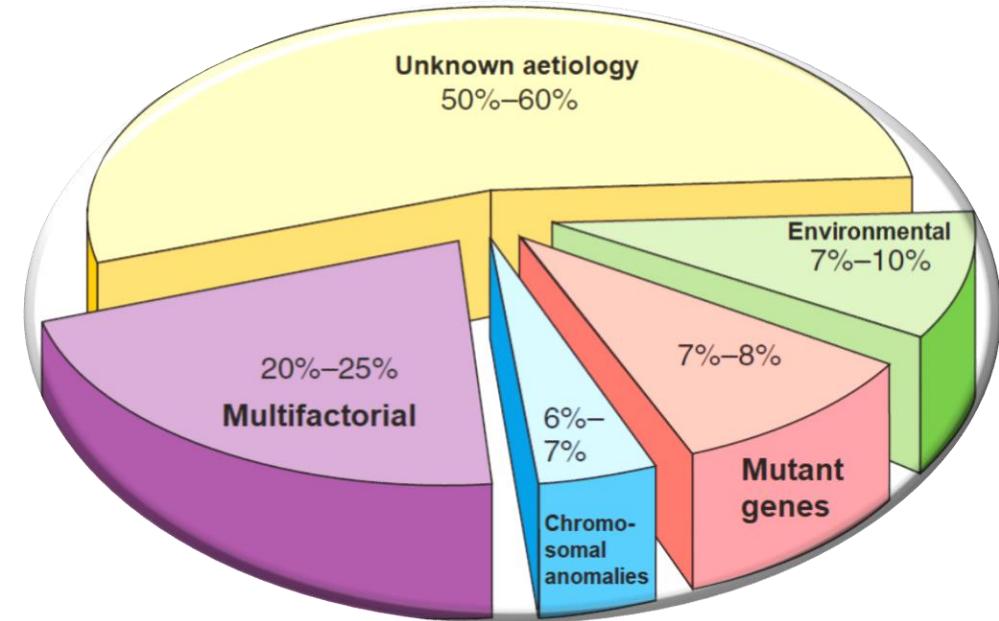


Normal

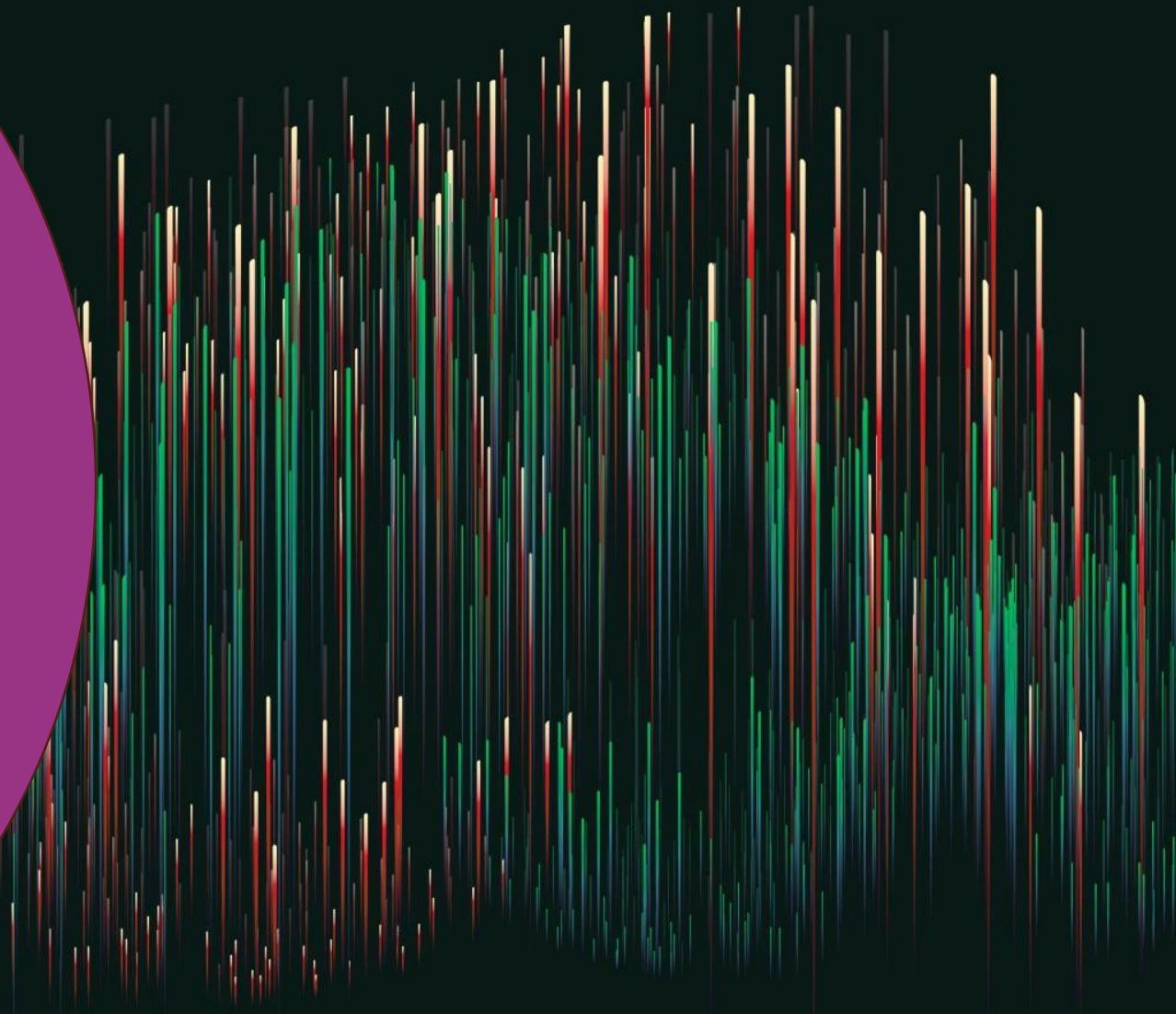
Macrosomia baby

# MULTIFACTORIAL

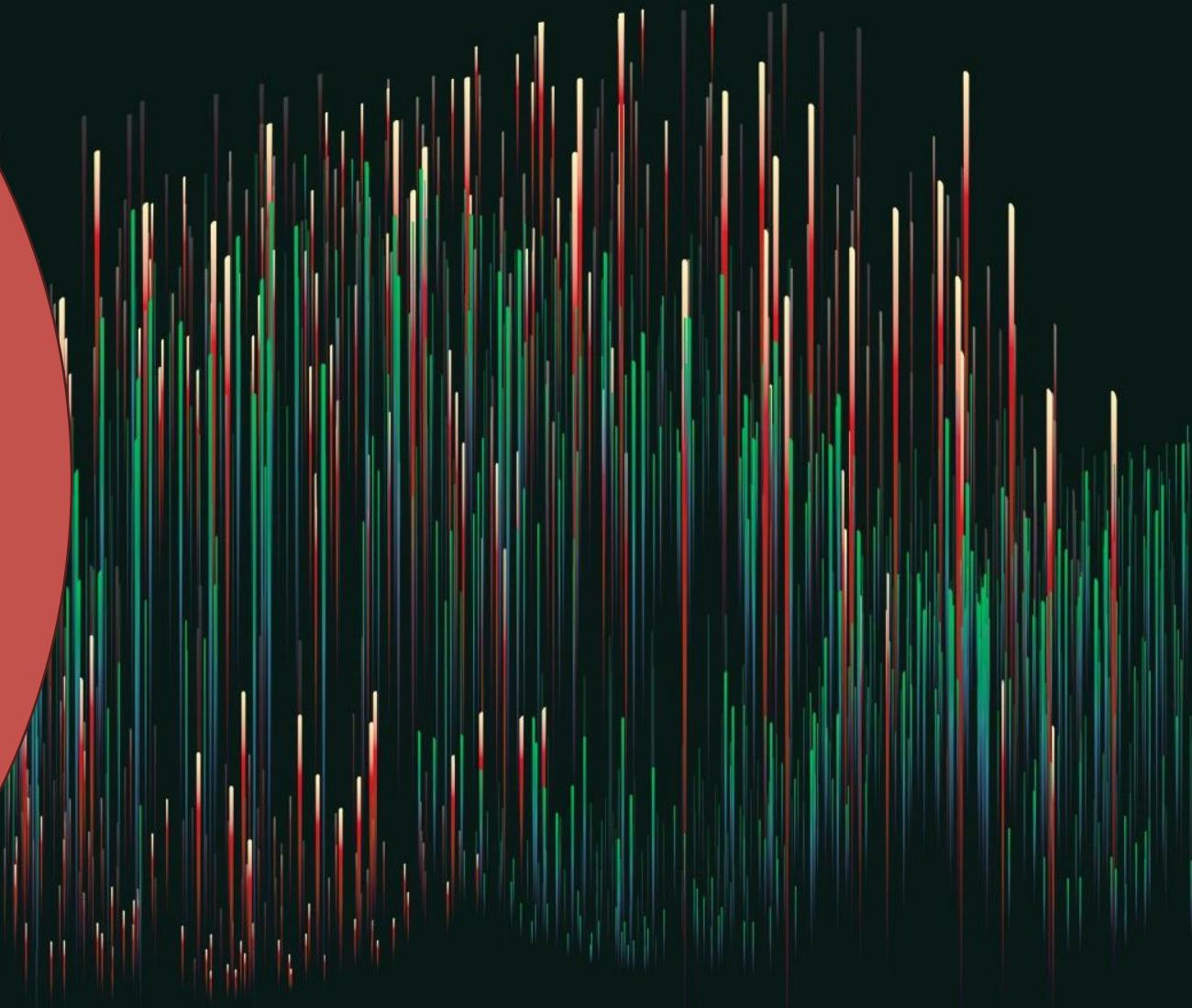
- Multifactorial inheritance: liability for developmental disorder is a continuous variable determined by combination of GENETIC and ENVIRONMENTAL factors .
- Often seen as **single major defects**:
  - Neural tube defects
  - Cleft lip +/- palate
  - Congenital heart disease
- E.g. Epigenetics: Dutch Famine data (1944) has shown a multigenerational effect on postnatal health, associated with timing of nutrient restriction in utero.
  - Low birth weight babies for successive generations.
  - Correlation with Type 2 Diabetes and cardiovascular disease.



# PART 2



# CLASSIFICATION OF BIRTH DEFECTS



# TYPES/CLASSES

- 4 clinically significant types of mechanism of birth defects:
  1. Malformation
  2. Disruption
  3. Deformation
  4. Dysplasia

# TYPES/CLASSES

## Malformation

- Structural defect that occurs during early stages of organ or tissue formation (**organogenesis**).
- Abnormal developmental effects that are **DIRECTLY** involved in the development of that organ or body part, usually caused by genetic or environmental factors.
- E.g. Neural tube defects, Syndactyly, Tera-amelia



## Disruption

- Structural defects caused by the breakdown or destruction of a previously normal tissue or structure.
- Due to an **extrinsic disturbance** or interference with normal development such as physical injury, lack of blood supply, or infection.
- E.g. Amniotic band disrupt growing limb or digit- results in missing hands and feet or fingers or toes



# TYPES/CLASSES

## Deformations

- **Mechanical forces during fetal development causes an abnormal shape or position of a part of the body.**
- Usually arise later in pregnancy and are often related to external factors such as a lack of amniotic fluid (oligohydrominos) causing less uterine space and hence compression against the uterine wall-results in flattened face or club foot.



## Dysplasia

- **Abnormal organisation or development of cells into tissue(s) or organ(s), leading to loss in cellular architectural orientation of the cells in a tissue-dyshistogenesis**
- Often results from a genetic defect affecting the formation and growth of specific types of tissue.
- E.g. Ectodermal dysplasia. Achondroplasia



# OTHER IMPORTANT CONCEPTS

- Syndrome, Association and Sequence are terms used to describe pattern of multiple congenital anomalies that occur together.
- Refers to different ways in which a combination of anomalies can be grouped or related based on their causes or how they develop in relation to each other

## Syndrome

- A collection of a major and minor anomalies that occur together in a predictable fashion presumably due to a specific common identifiable cause which may be monogenic, chromosomal, or teratogenic in origin.
- E.g. Down syndrome (Trisomy 21), Turner syndrome, Marfan syndrome

## Association

- A group of anomalies that occur more frequently together than would be expected by chance alone.
- No specific common single cause identified
- E.g. VACTERL association

# Sequence

- A series of related anomalies that arise from single initial defect or event that triggers a cascade of secondary and tertiary anomalies during development.
- E.g. Potters sequence

## POTTER

P-Pulmonary hypoplasia

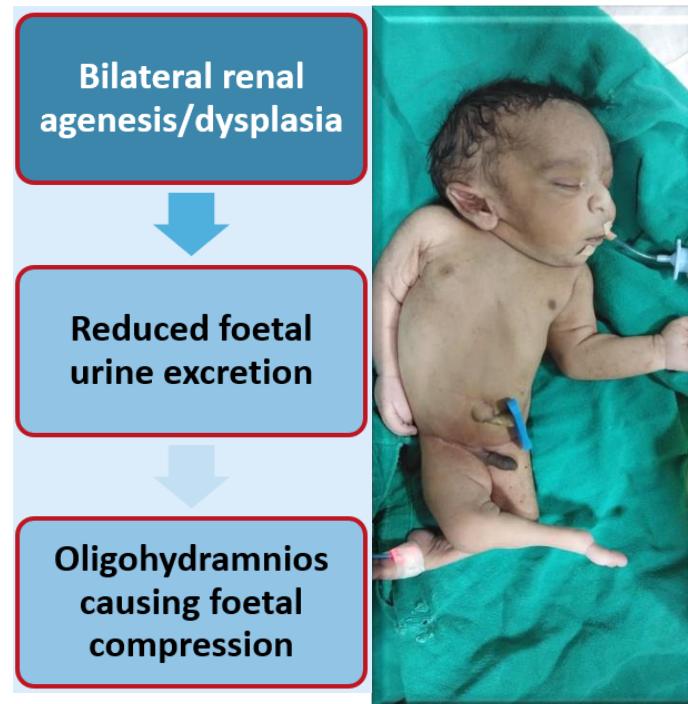
O-Oligohydramnios

T-Twisted skin (wrinkly skin)

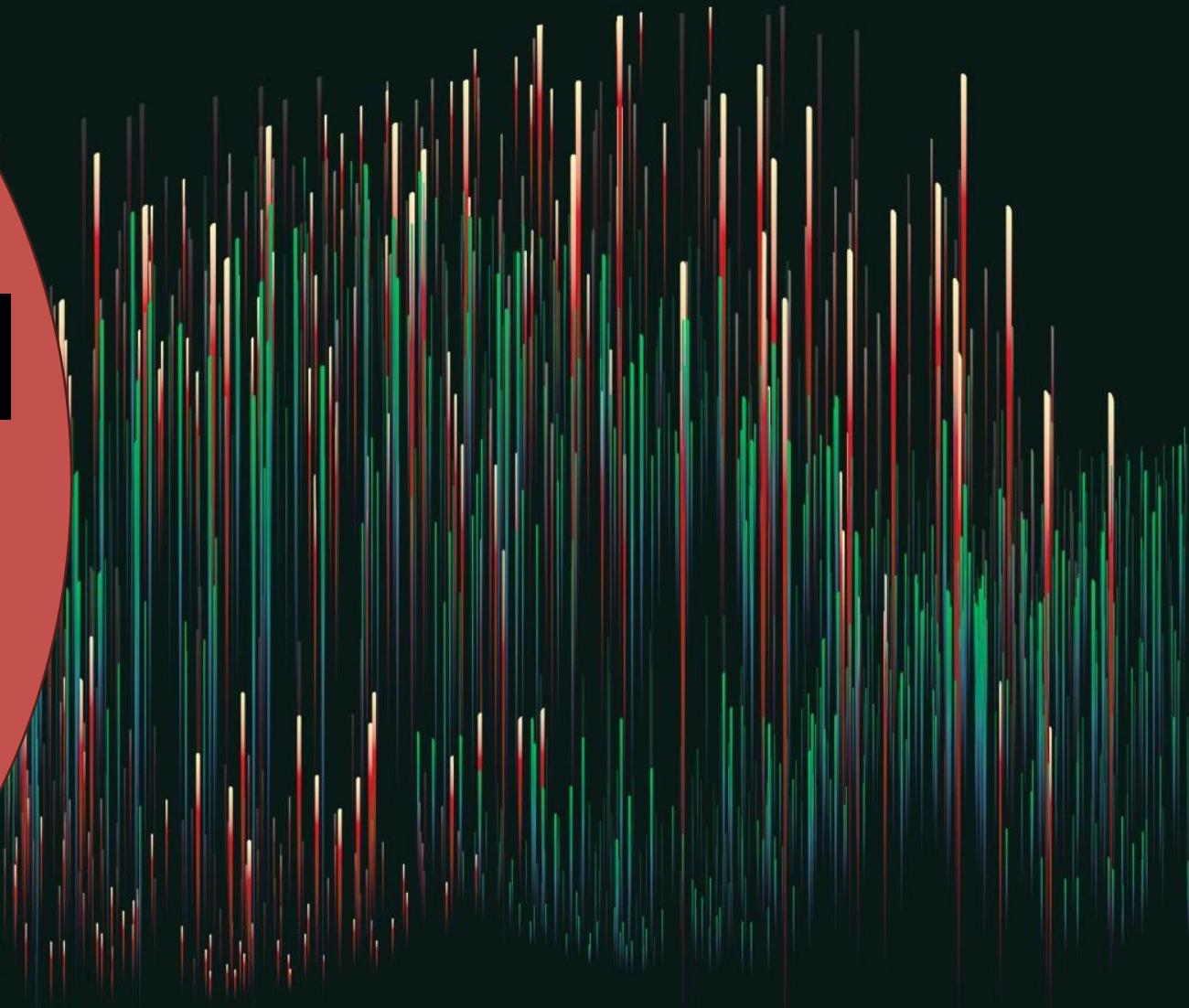
T-Twisted face (potter facies )

E-Extremities defect

R-Renal agenesis

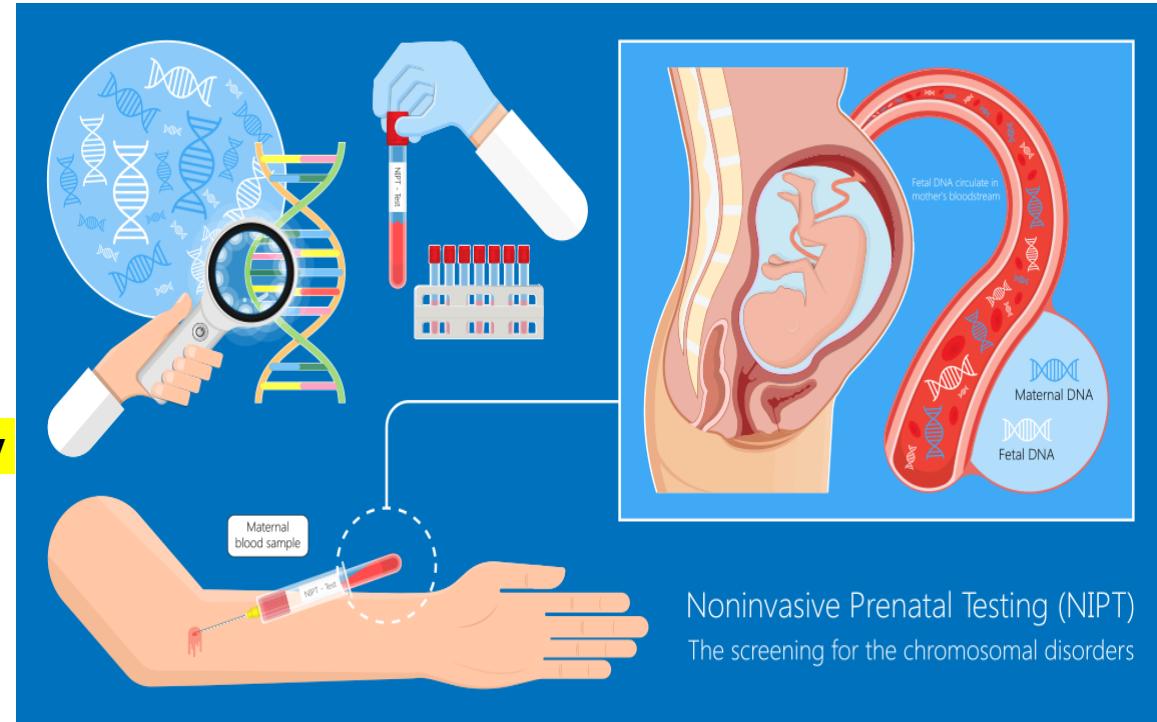


# PRENATAL TESTING & PREVENTION OF BIRTH DEFECTS



# IDENTIFYING BIRTH DEFECTS

- **1<sup>st</sup> Trimester Screening**
  - Maternal Blood Screen for general health screening e.g. anemia or chronic diseases, risk for pre-eclampsia
  - Ultrasound
- **2<sup>nd</sup> Trimester Screening**
  - Maternal Serum Screen (MSS) for markers of trisomy or neural tube defects
  - Fetal Echocardiogram
  - Anomaly Ultrasound
- **Diagnostic Tests**
  - High-res ultrasound
  - Chorionic villus sampling (CVS)
  - Amniocentesis



Noninvasive Prenatal Testing (NIPT)  
The screening for the chromosomal disorders

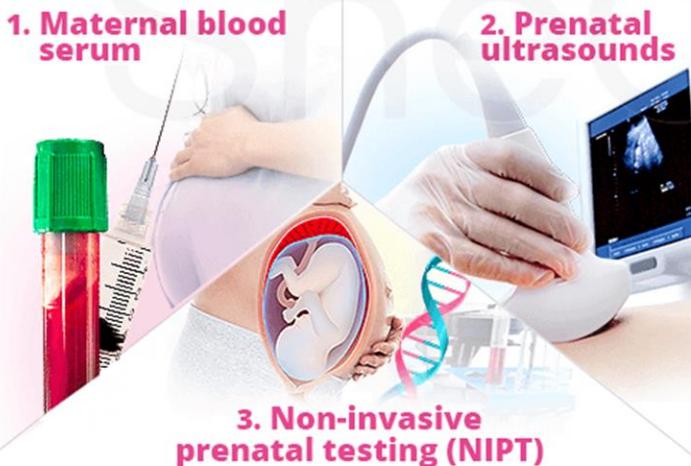
# IDENTIFYING BIRTH DEFECTS

## Prenatal Genetic Testing

There are **five types** of prenatal genetic tests, which can be used for screening the risk of the baby having a genetic disorder or for diagnosing such abnormalities.

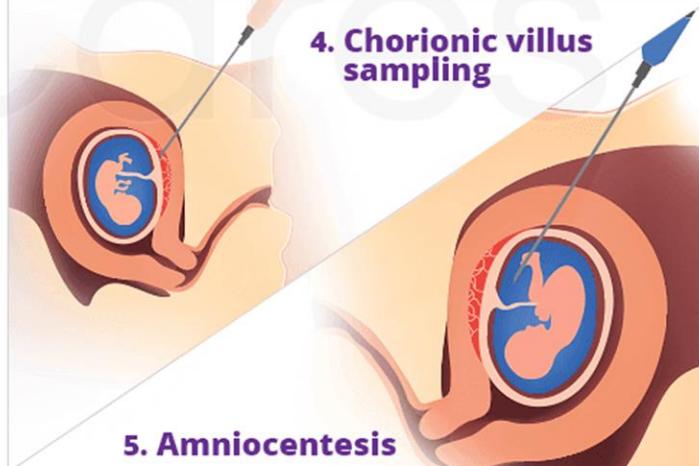
### FOR SCREENING

- Evaluate the risk of genetic problems
- Non-invasive
- Offered to all women



### FOR DIAGNOSING

- Confirm or rule out genetic problems
- Invasive
- Offered after abnormal screening tests or known risks factors



**Prenatal Testing (NIPT)** is a

more accurate and

comprehensive screening

method that analyses fetal

DNA from the mother's

bloodstream.

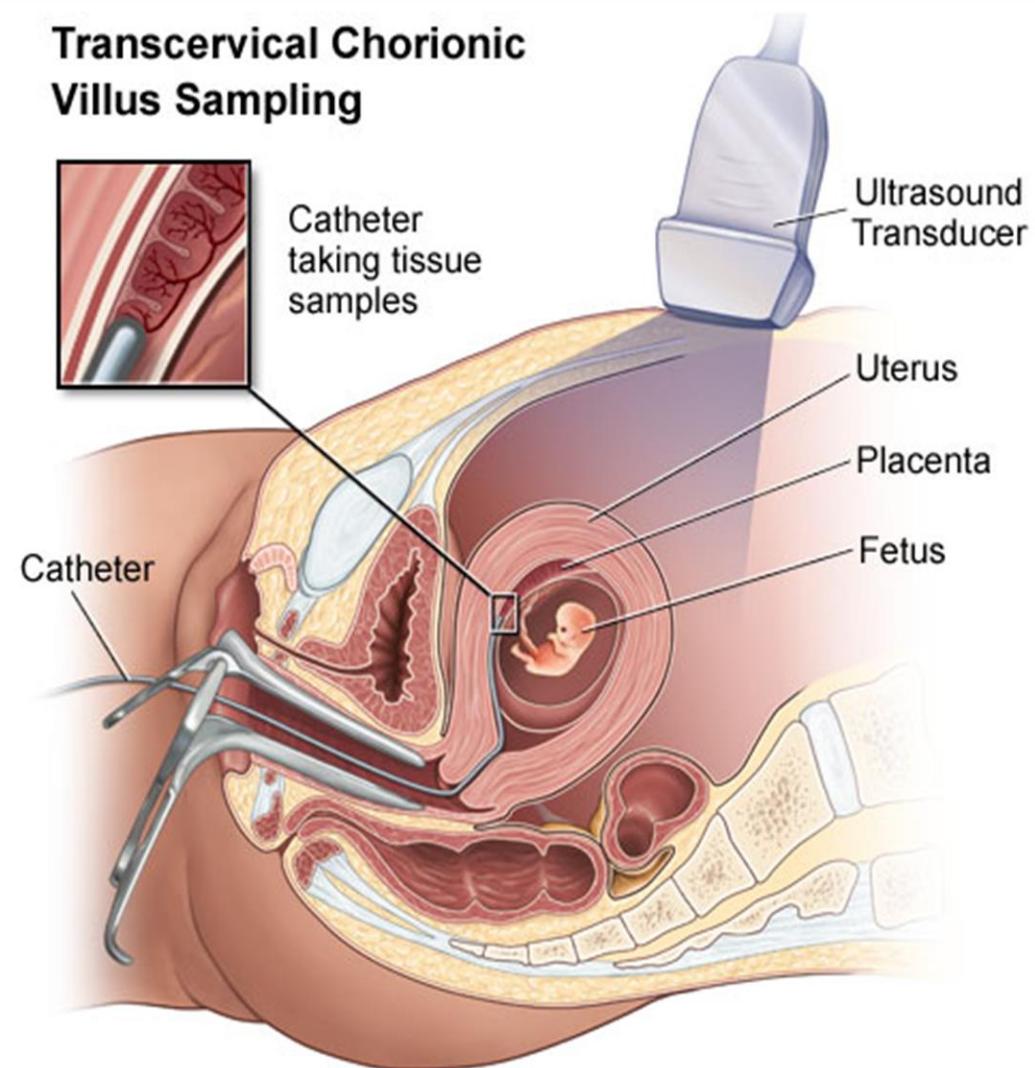
- Can be performed earlier at week 10 GA for wider range of conditions.
- Primarily for **Trisomy syndromes**.

# IDENTIFYING BIRTH DEFECTS

- **Diagnostic Tests**

- High-res ultrasound
- **Chorionic villus sampling (CVS)**
- Amniocentesis

## Transcervical Chorionic Villus Sampling



# RISK OF CHORIONIC VILLUS SAMPLING (CVS)

**Miscarriage:** 1 in 100 pregnancies

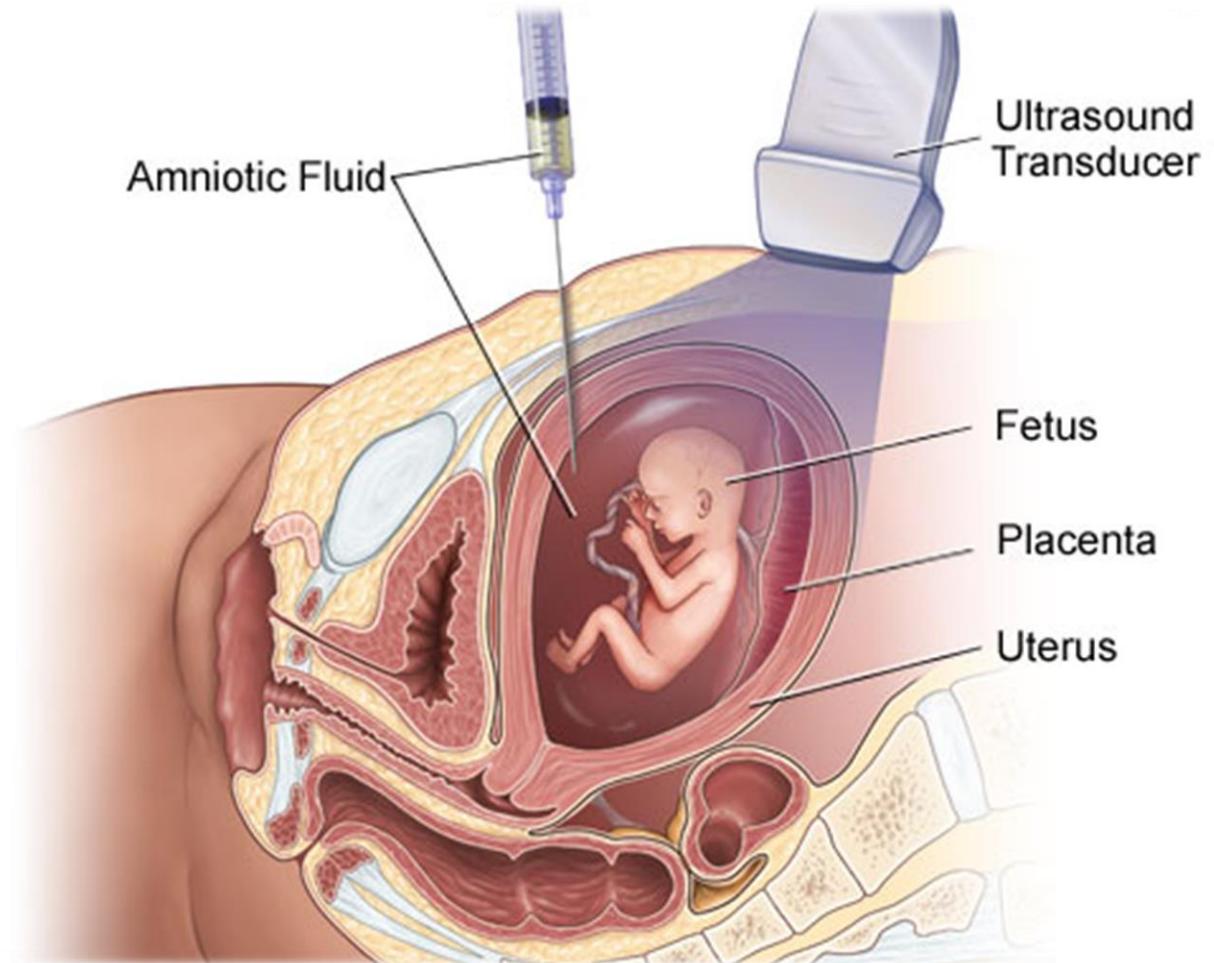
Rare or mild side effects:

- Dizziness
- Infection
- Abdominal cramps
- Rh incompatibility



# IDENTIFYING BIRTH DEFECTS

- Diagnostic Tests
  - High-res ultrasound
  - Chorionic villus sampling (CVS)
  - **Amniocentesis**



# RISK OF AMNIOCENTESIS

## AMNIOCENTESIS RISKS & COMPLICATIONS

Though generally safe, it is an **invasive procedure**.

Possible, but **rare** risks and complications include:

- Miscarriage
- Amniotic fluid leakage
- Infection
- Injury to the baby



# PRENATAL THERAPIES

Interventions aimed at improving the health of both fetus and the pregnant mother.

1. **Nutritional and Lifestyle**
2. Pharmacological
3. Fetal surgery
4. Genetic therapy
5. Immunological therapy

- 
- **Folic acid supplement:** Daily folic acid 0.4mg-0.8mg. Prevents neural tube defects (e.g. spina bifida)
  - **Iron supplement:** Prevent or treat anemia
  - **Iodine supplement:** Reduce risk of mental retardation and bone deformities
  - **Lifestyle changes:** Cessation of smoking and any illicit drug use

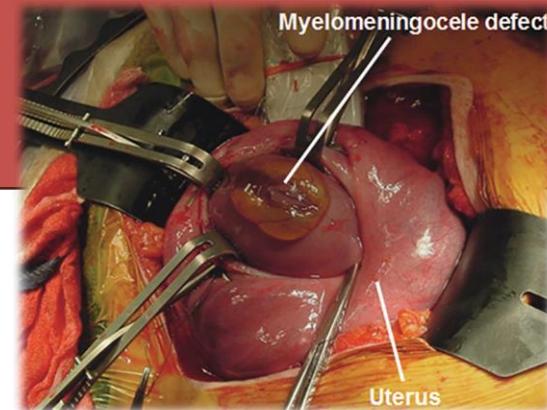
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## Surgery in womb

- **Fetal Shunt Placement:** Fetal hydrocephalus to drain excess CSF in brain or congenital hernia
- **Laser Therapy for Twin-to-Twin Transfusion Syndrome (TTTS):** Ablation of placental vessels is to correct imbalance in blood flow between twins
- **Spina Bifida Repair-**



# PRENATAL THERAPIES

Interventions aimed at improving the health of both fetus and the pregnant mother.

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- 
- **In utero gene therapy (IUGT)** still in research phase
  - Gene modification therapies for hereditary diseases in fetus e.g. Cystic fibrosis, Sickle cell anaemia

# PRENATAL THERAPIES: GENETIC THERAPY



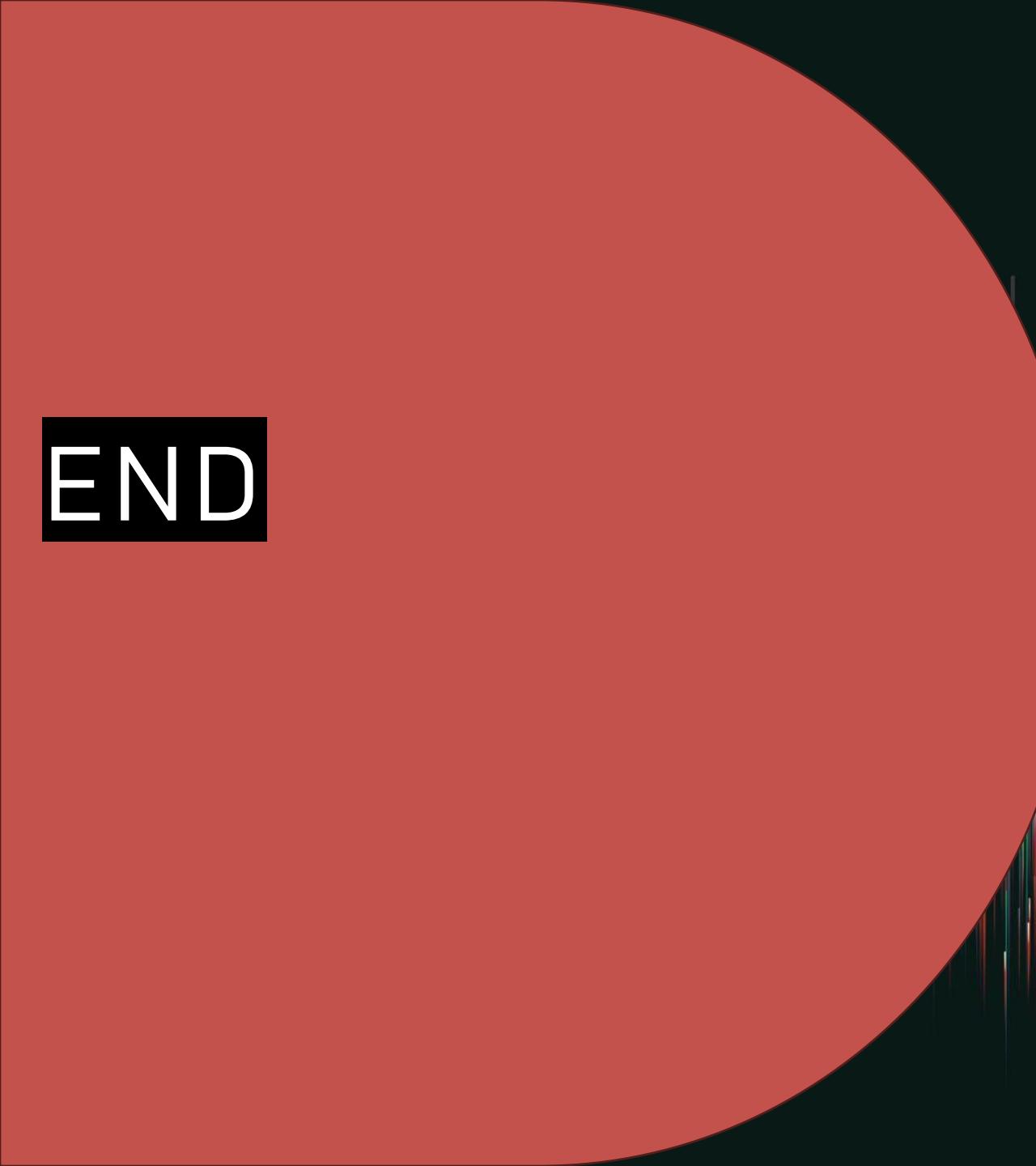
# PRENATAL THERAPIES

Interventions aimed at improving the health of both fetus and the pregnant mother.

1. Nutritional and Lifestyle
2. Pharmacological
3. Fetal surgery
4. Genetic therapy
5. Immunological therapy



- **Fetal transfusion:** Fetal anemia-Rh incompatibility-corrects severe anemia and prevent heart failure (hydrops fetalis-presence of extracellular fluid in body compartments e.g. pericardial effusion)
- **Corticosteroids:** Administered to mothers at risk of preterm birth to accelerate fetal lung maturation-reduces risk of neonatal respiratory distress.



END

