Genetics

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Pediatrics

Chromosomal Abnormalities

- Chromosomal abnormalities are either numerical or structural.
- Chromosomal abnormalities occur in approximately 8% of fertilized ova but only in 0.6% of liveborn infants.
- 50% of spontaneous abortuses have chromosomal abnormalities.
- In newborns and older children, many features suggest the presence of a chromosome anomaly, including LBW (SGA), FTT, developmental delay, and the presence of three or more congenital malformations.
- Acquired chromosomal changes play a significant role in carcinogenesis and tumour progression.
- The diagnosis is confirmed by chromosome analysis

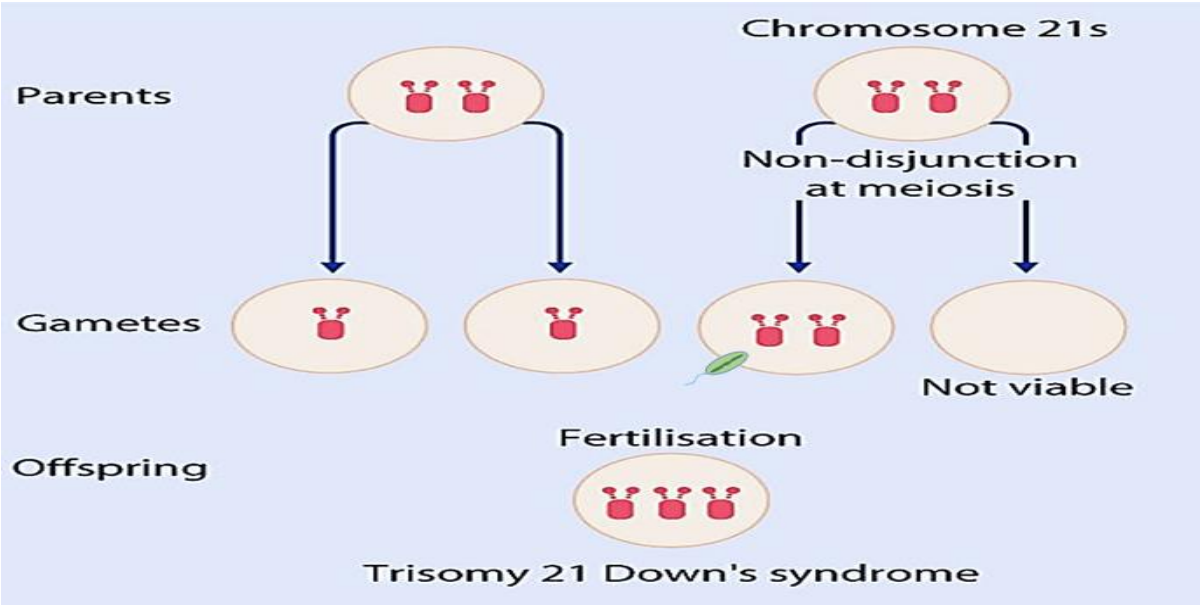
TRISOMY

Down Syndrome (trisomy 21)

- DS is the most common abnormality of chromosomal number. It occurs in 1 of every 1000 births.
- DS considered most common genetic cause of moderate intellectual disability and characteristic dysmorphic features.
- Cytogenetics: the extra chromosome 21 may result from:
    - Nondisjunction.
    - Translocation.
    - Mosaicism.

Non-disjunction (94%):

- Most cases result from an error at meiosis, the pair of chromosome 21s fails to separate, so that one gamete has two chromosome 21s and one has none.
- Fertilisation of the gamete with two chromosome 21s gives rise to a zygote with trisomy 21.
- Parental chromosomes do not need to be examined.



Clinical Features:

- Down's syndrome is usually suspected at birth because of the baby's facial appearance.

Typical craniofacial appearance

- Brachycephaly with flat occiput and third fontanelle
- Round face and flat nasal bridge.
- Upslanted palpebral fissures.
- Epicanthic folds (a fold of skin running across the inner edge of the palpebral fissure).
- Brushfield spots in iris (pigmented spots).
- Small mouth and protruding tongue.
- Small ears.

Other Anomalies

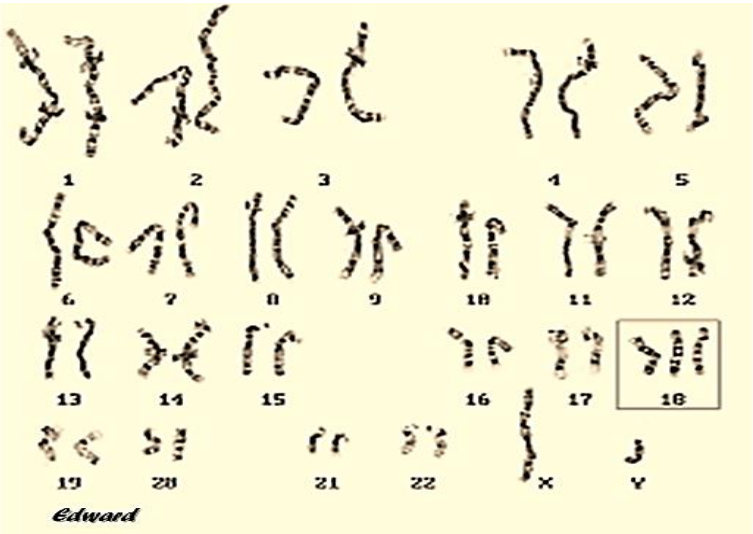
- Normal BW & length, but hypotonic.
- Short neck
- Short broad hand with single palmar creases, incurved fifth finger.
- Wide 'sandal' gap between 1^{st} & 2^{nd} toes.
- Congenital heart defects (40%)
- Duodenal atresia
- Annular pancreas
- Imperforated anus.
- Hirschsprung's disease

Later Medical Problems:

- Delayed motor milestones.
- Moderate to severe learning difficulties.
- Increased susceptibility to infections.
- Hearing impairment from secretory otitis media.
- Visual impairment from cataracts, squints, myopia.
- Increased risk of leukaemia and solid tumours.
- Risk of atlantoaxial instability.
- Hypothyroidism and DM.
- coeliac disease
- Epilepsy
- Alzheimer's disease

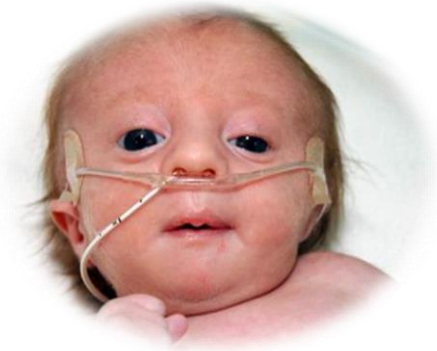
Edwards' syndrome (trisomy 18)

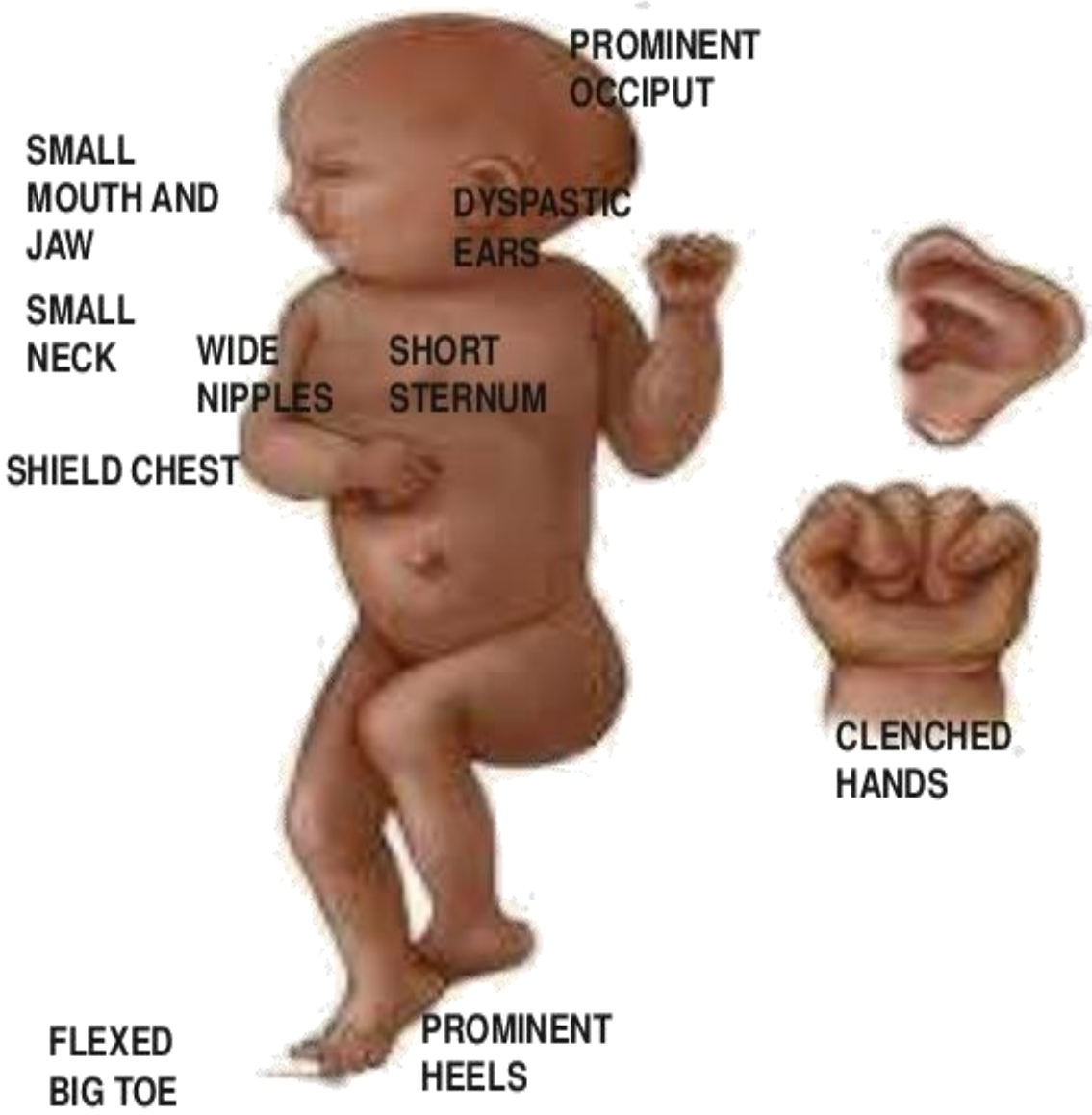
- It is the second most common autosomal trisomy, occurring in approximately 1 in 7500 live births.
- Greater than 95% of conceptuses with trisomy 18 are spontaneously aborted in the first trimester.
- Trisomy 18 is usually lethal; less than 10% of affected infants survive until their first birthday.
- The diagnosis is confirmed by chromosome analysis



Clinical Features:

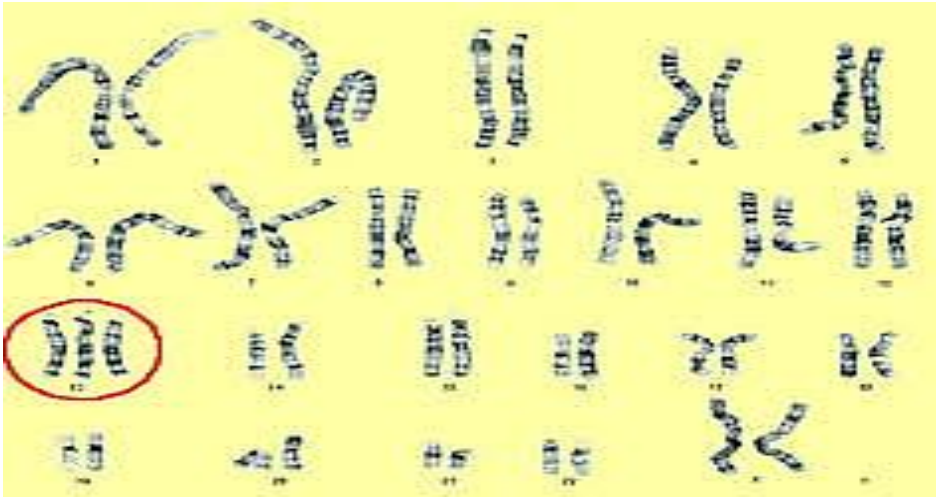
- Low birth weight
- Prominent occiput
- Small mouth and chin
- Cleft lip or palate
- Low set & malformed ears
- Short sternum
- Flexed, overlapping fingers
- Rocker-bottom feet
- Cardiac and renal malformations
- Severe developmental delays



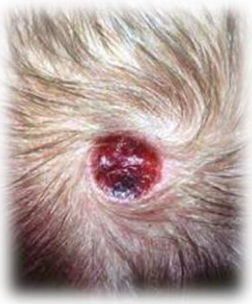


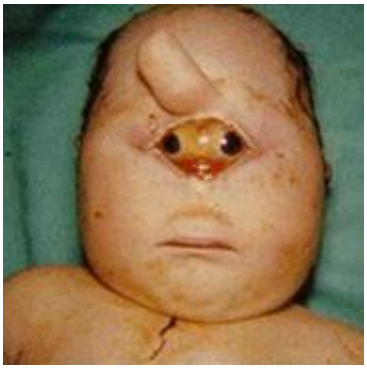
Patau's Syndrome (trisomy 13)

- trisomy 13 third of the common trisomies, occurs in 1 in 12,000 live births. It is usually fatal in the first year of life.

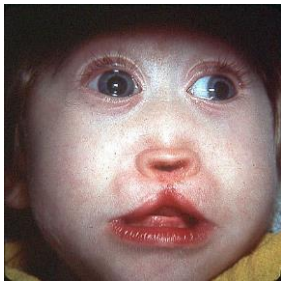


Clinical Features:

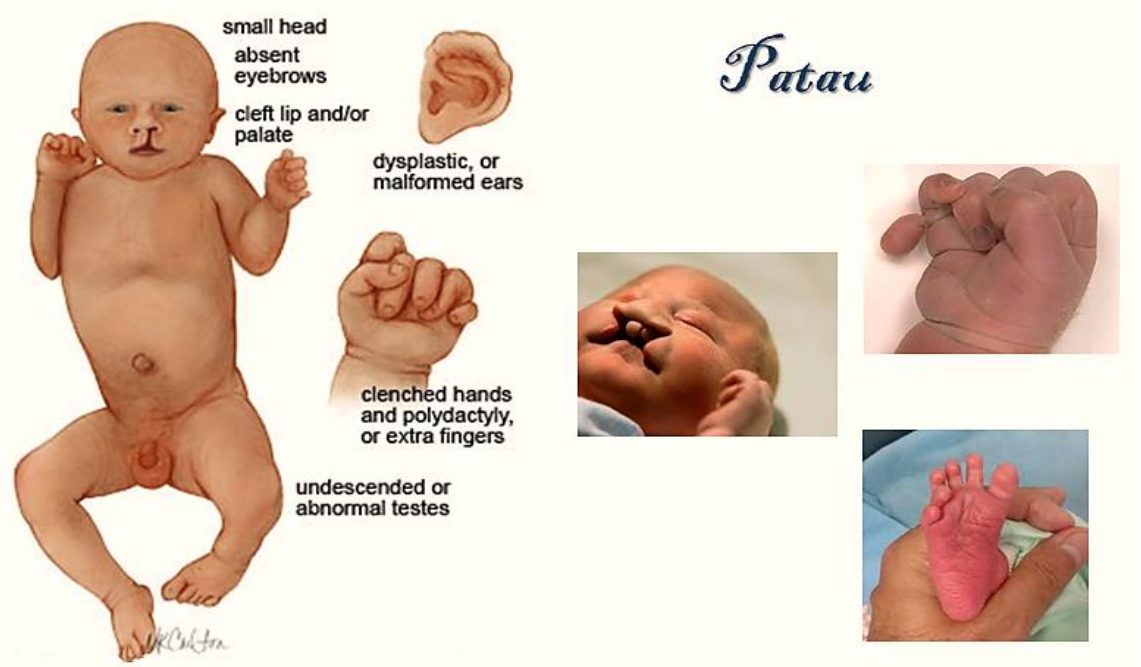




- SGA
- Structural defect of brain
- Scalp defect
- Microcephaly
- Microphthalmia



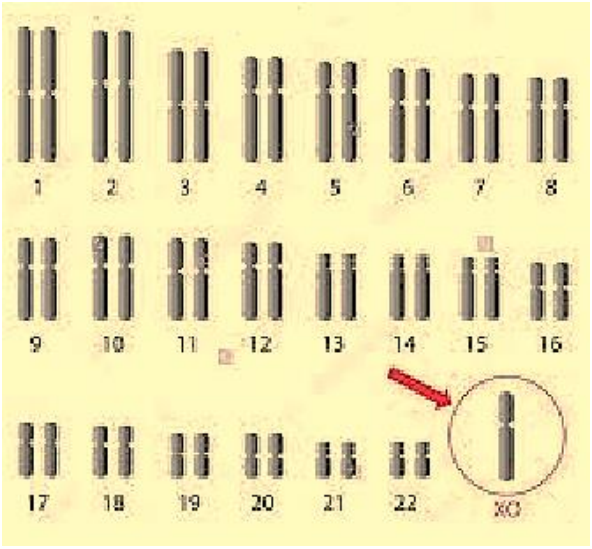
- Midline facial defects as single orbit, single nostril
- Cleft lip and palate
- Polydactyly
- Cardiac and renal malformations



MONOSOMY

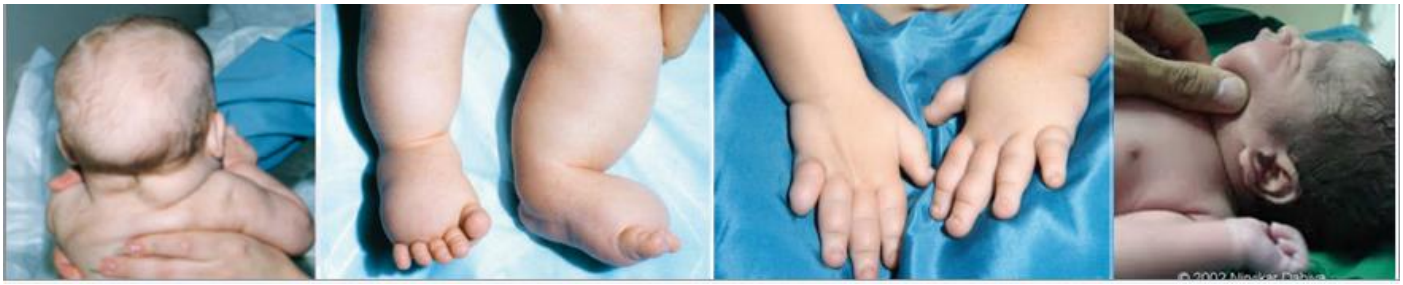
Turner's syndrome (45, X)

- ❑ TS is the only condition in which a monosomic conceptus survives to term; however, 95-99% of embryos with 45,X are spontaneously aborted.
- ❑ TS occurs in approximately 1 in 5,000 female live births.



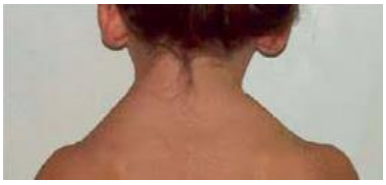
Clinical Features:

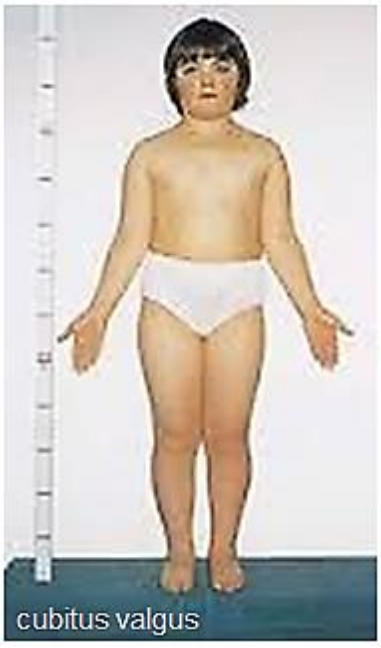
- ❑ <u>In the newborns</u> can include: SGA, webbing of the neck, protruding malformed ears, and lymphedema of the hands and feet, although many newborns are phenotypically normal.



- ❑ <u>Older children and adults:</u>
  - Short stature - cardinal feature (SS may be the only clinical abnormality in children).
  - Neck webbing or thick neck
  - Wide carrying angle (cubitus valgus)
  - Widely spaced nipples
  - Congenital heart defects (particularly coarctation of the aorta)

- Delayed puberty
- Ovarian dysgenesis resulting in infertility, although pregnancy may be possible with in-vitro fertilisation (IVF) with donated ova.
- Hypothyroidism
- Renal anomalies
- Pigmented moles
- Recurrent otitis media
- Most patients tend to be of normal intelligence, but intellectual disability is seen in up to 6% of affected children.



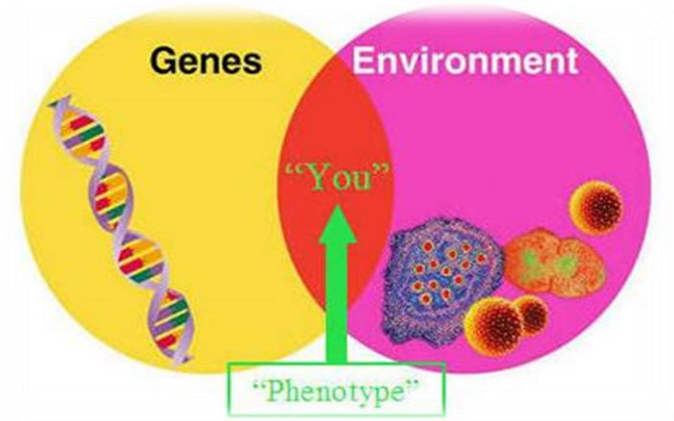


Treatment:

- Growth hormone therapy.
- Oestrogen replacement for development of secondary sexual characteristics at the time of puberty (but infertility persists).

Multifactorial Inheritance

- Result from the interplay of genetic and environmental factors.
- The disorders occur more often in first- and second-degree relatives than would be expected by chance.



Characteristics of Multifactorial Inheritance:

- The risk of recurrence is related to the incidence of the disease.
- Some disorders have a sex predilection. E.g. pyloric stenosis is more common in males, whereas congenital dislocation of the hips is more common in females.
- The likelihood that both identical twins will be affected with the same malformation is less than 100% but much greater than the chance that both members of a nonidentical twin pair will be affected. This is in contrast with the pattern seen in mendelian inheritance, in which identical twins almost always share fully penetrant genetic disorders.
- The risk of recurrence is increased when multiple family members are affected. E.g. the risk of recurrence for unilateral cleft lip and palate is 4% for a couple with 1 affected child and increases to 9% with 2 affected children.
- The risk of recurrence may be greater when the disorder is more severe. E.g. an infant who has long-segment Hirschsprung disease has a greater chance of having an affected sibling than the infant who has short-segment Hirschsprung disease.

Conditions with multifactorial inheritance:

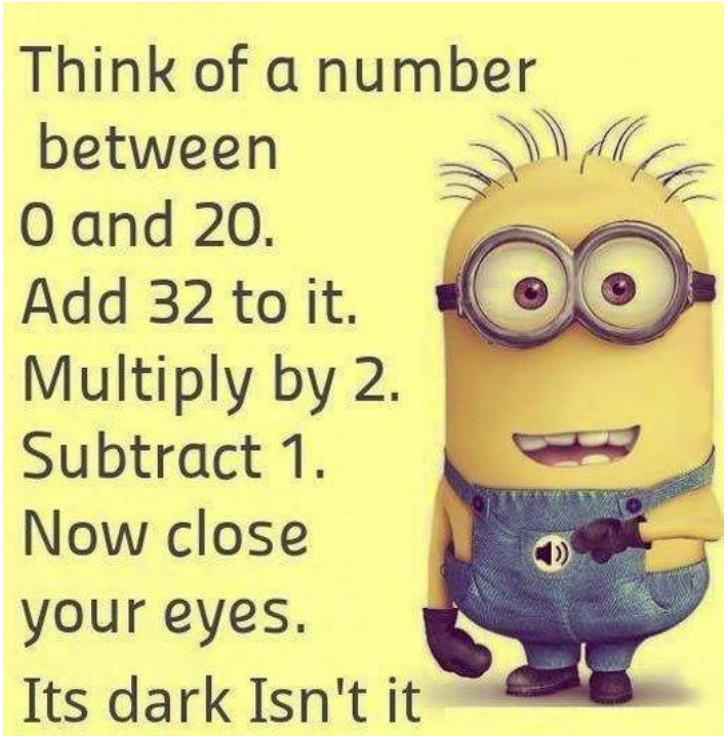
⇨ **Congenital Malformations**

- Neural tube defects
- Congenital heart disease
- Cleft lip and palate
- Pyloric stenosis
- CDH

- Talipes
- Hypospadias

⇨ **Adult Life**

- Atherosclerosis and coronary heart disease
- Obesity
- Diabetes mellitus
- Asthma
- Epilepsy
- Hypertension
- cancer



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