Growth and Craniofacial Anomalies

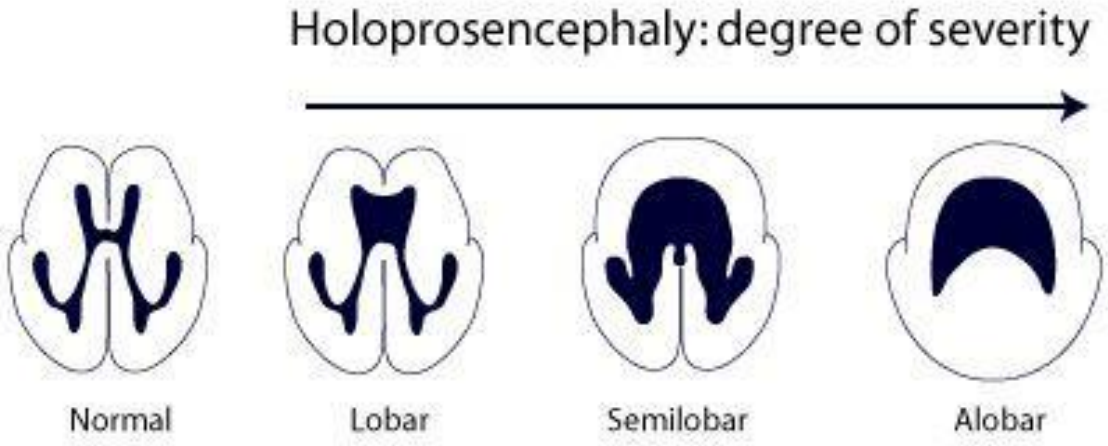
DR SHAHBAA ABDULGHAFOOR

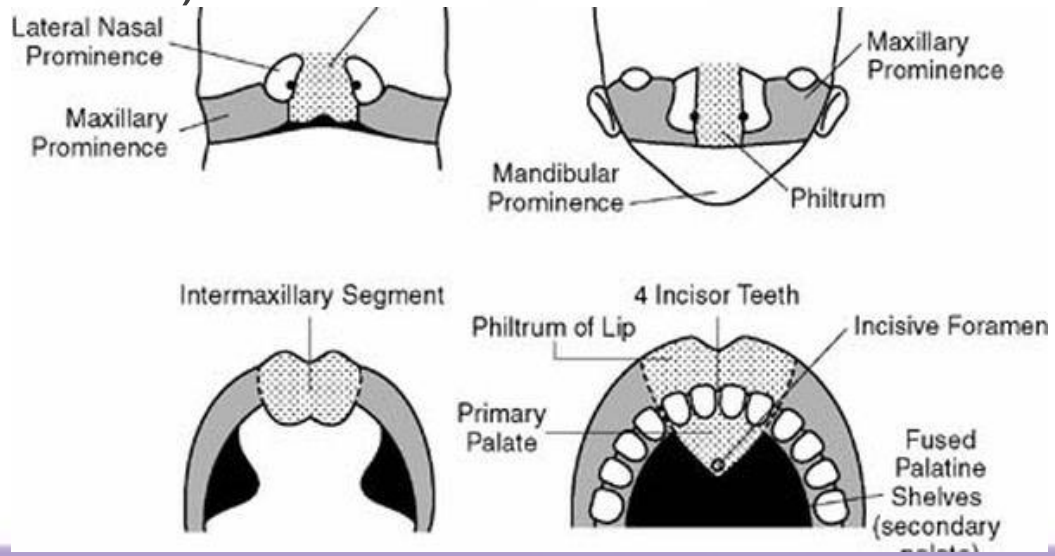
DEVELOPMENTAL ANOMALIES

Abnormalities of Neural Crest Cell Origin and Migration

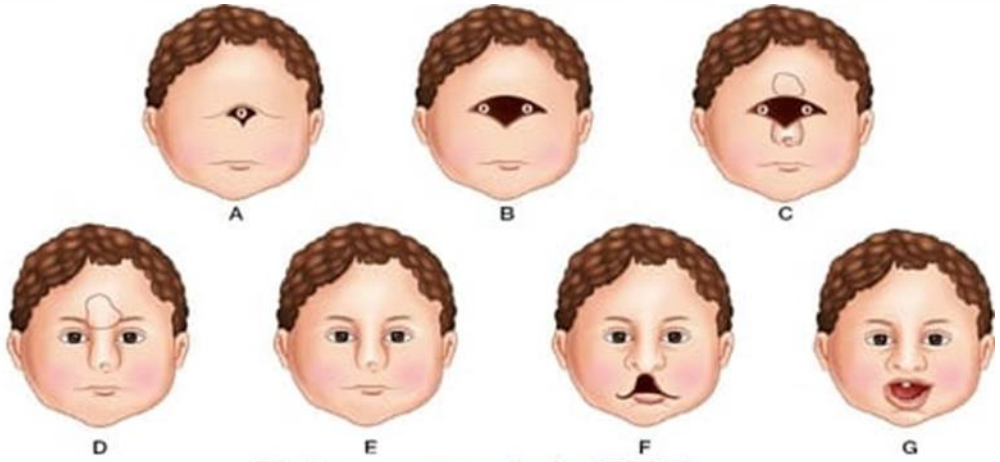
1. Holoprosencephaly and Fetal Alcohol Syndrome (FAS)

- It is characterized by decreased forebrain and increased tendency for the three ventricles to form a single cavity.
- The main defect is **reduced midline components**.
- Facial defects include **defects of medial nasal prominence**.
- **Philtrum** and portions of maxilla (**premaxilla**) are deficient.





- Contact of olfactory placodes in the midline results in failure of the medial nasal prominences to develop and leads to **arrhinencephaly**.
- Increasing deficiency leads to progressively **smaller eyes** which may unite to form one median eye or remain as two small eyes close to the midline.



Holoprosencephaly (HPE)

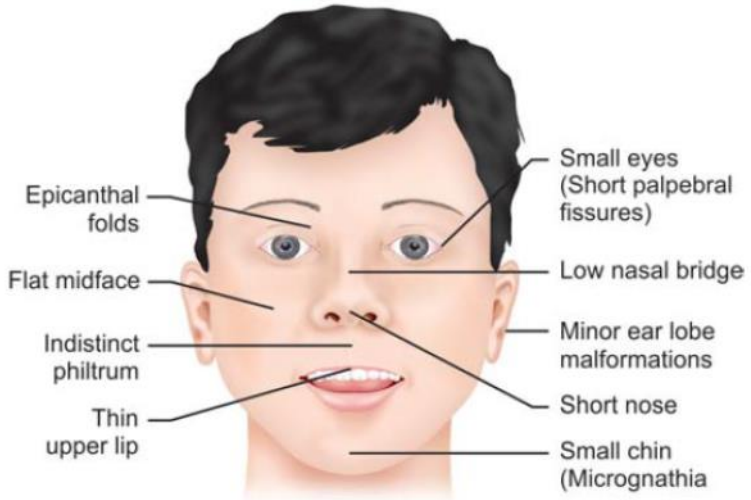


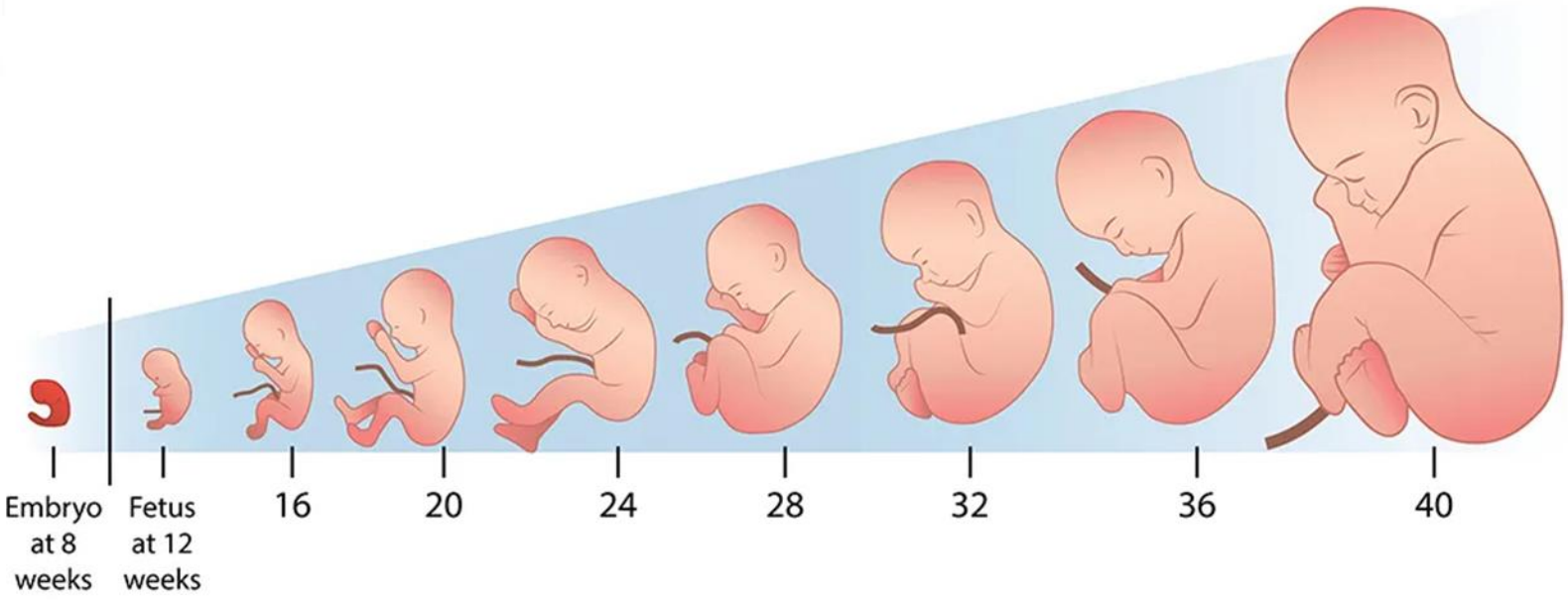
Fig. 15.6: Features of fetal alcohol syndrome

- Exposure to **high levels of ethanol** at early stages of fetal development produces fetal alcohol syndrome (FAS) which now is recognized as one of the holoprosencephalies.

Box 15.1: Stages of development and related abnormalities

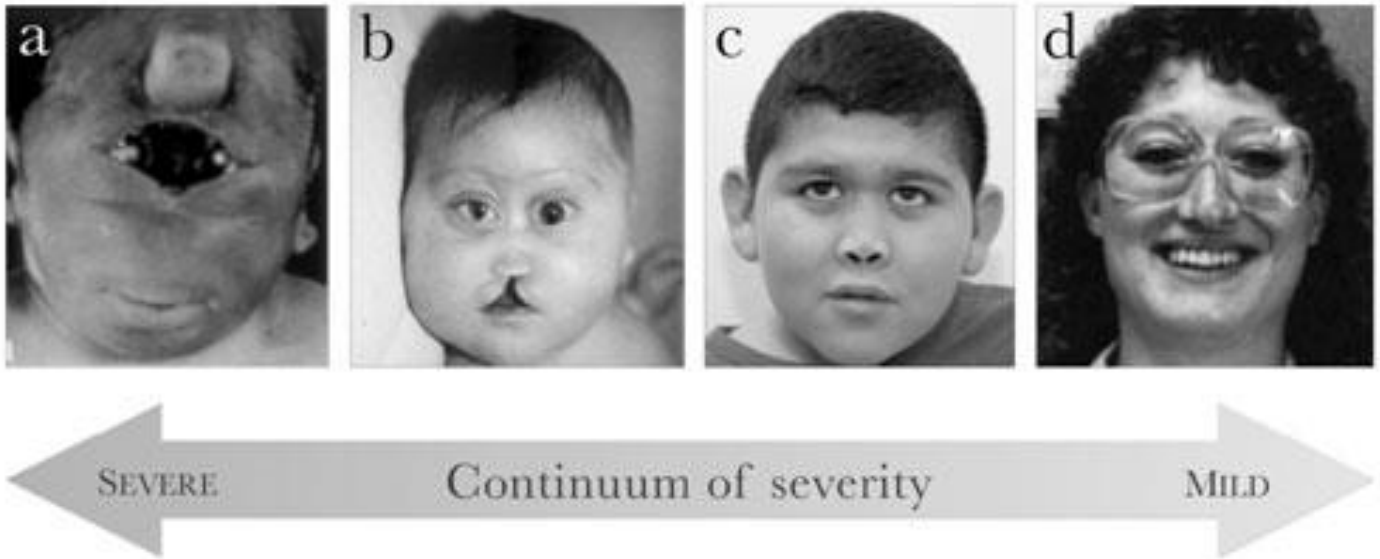
Stage	*Time (humans) postfertilization*	*Related syndromes*
Germ layer formation and initial organization of structures	Day 17	Fetal alcohol syndrome
Neural tube formation	Days 18-23	Anencephaly
Origin migration and interaction of cell populations, formation of organ systems	Day 19-28	Hemifacial microsomia Mandibulofacial dysostosis Limb abnormalities
Primary palate	Days 28-38	Cleft lip or palate, other facial clefts
Secondary palate	Days 42-55	Cleft palate
Final differentiation of tissues	Day 50-birth	Achondroplasia, synostosis syndromes

- **Ethanol** has direct effects on neural plate or the mesoderm. This results in **considerable cell death in anterior neural plate.**
- **Normal programmed cell death** is required for normal sculpting of the embryo.



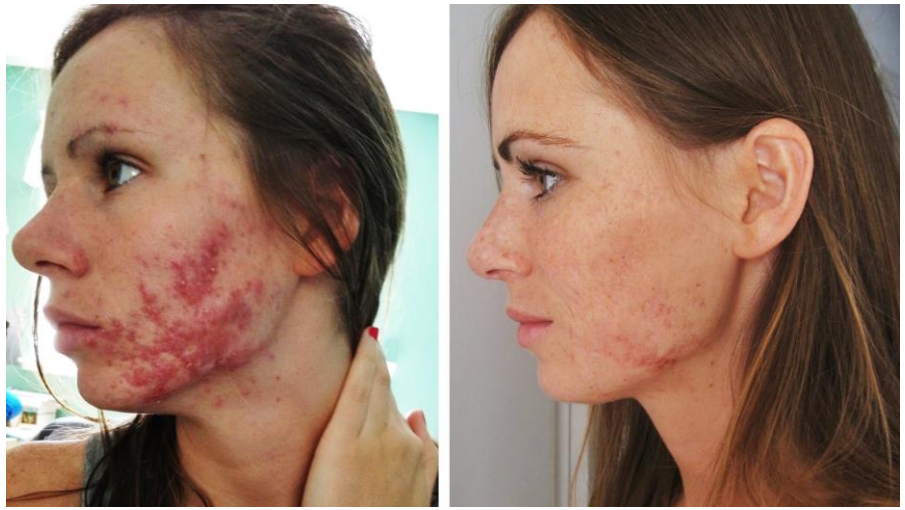
(Premkumar, 2011)

- If apoptosis becomes excessive, the embryo's ability to process the debris becomes overwhelmed and leads to abnormal development.
- The homeobox gene MSX1 and MSX2 are essential for the normal regulation of apoptosis.



2. Retinoic Acid Syndrome

- This syndrome appeared after the introduction of the acne drug ***Acutane*** **in 1982**. Retinoic acid contains 13- cis-retinoic acid (**Isotretinoin**). The severity of the anomaly depends on **degree of metabolism of the drug**.
- The main target of retinoic acid is the **neural crest cells.**



- The neural crest cells are killed before leaving the neural plate which occurs at a later period.
- retinoic acid increases the expression of the **MSX2** and causes upregulation of **retinoic acid receptor** β (RARβ), which in turn causes increased **affinity** for retinoic acid and further increased MSX2 expression causes **excessive apoptosis** which causes loss in neural crest cells.

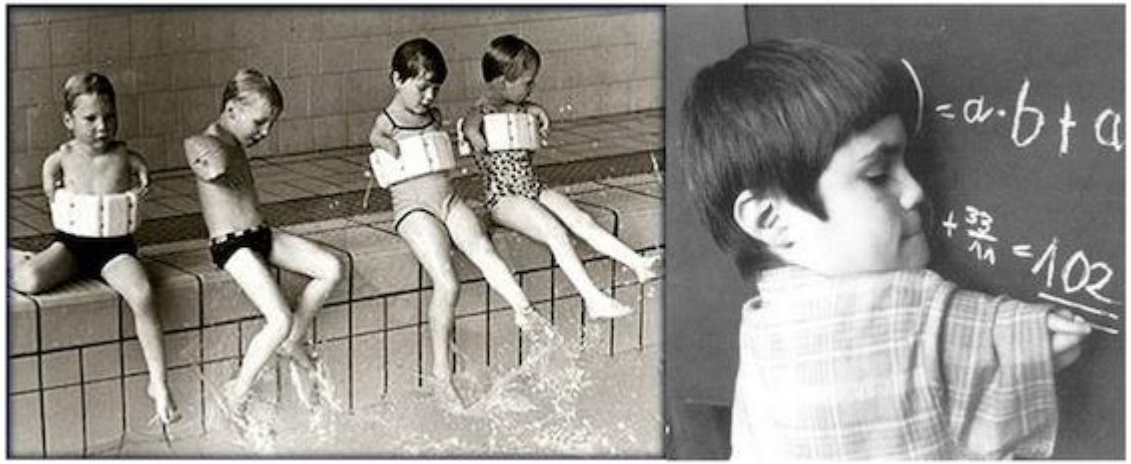
The clinical features of retinoic acid syndrome are:

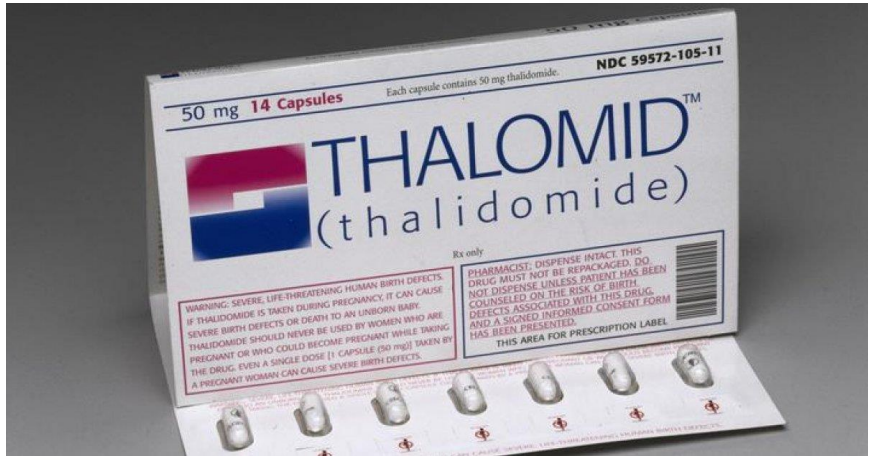
- Microtia.
- Facial bone and calvarial abnormalities.
- Micrognathia.
- Cleft palate.
- Congenital heart disease.
- Aortic arch abnormalities.
- Cerebellar hypoplasia and vermis agenesis.
- Microcephaly.
- Limb abnormalities

(Premkumar, 2011)

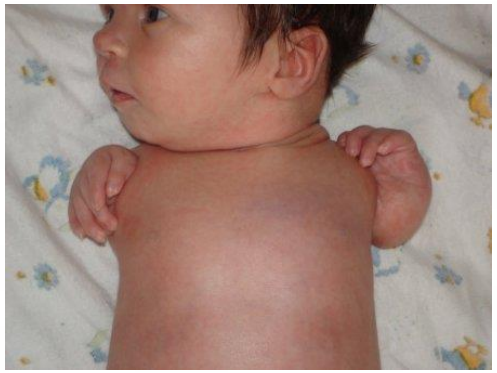
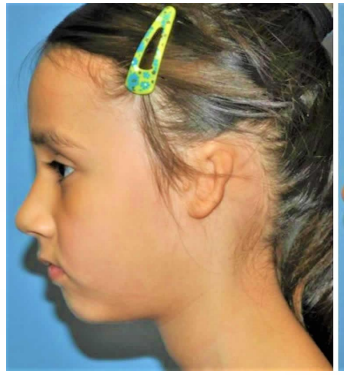
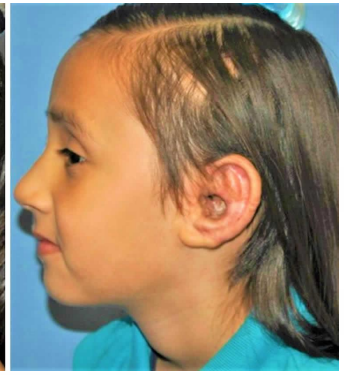
3. Thalidomide Related Craniofacial Abnormalities

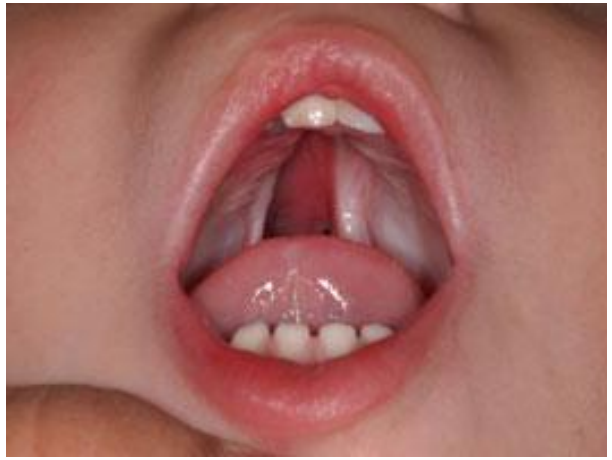
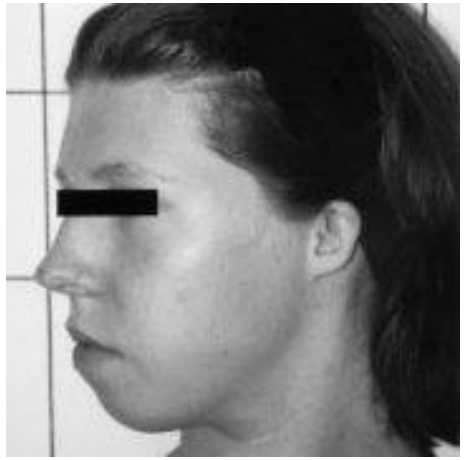
- Thalidomide was a drug sold in Germany extensively as an over-the-counter tranquilizer. Many of the early exposures produced craniofacial and cardiovascular malformations similar to retinoic acid.





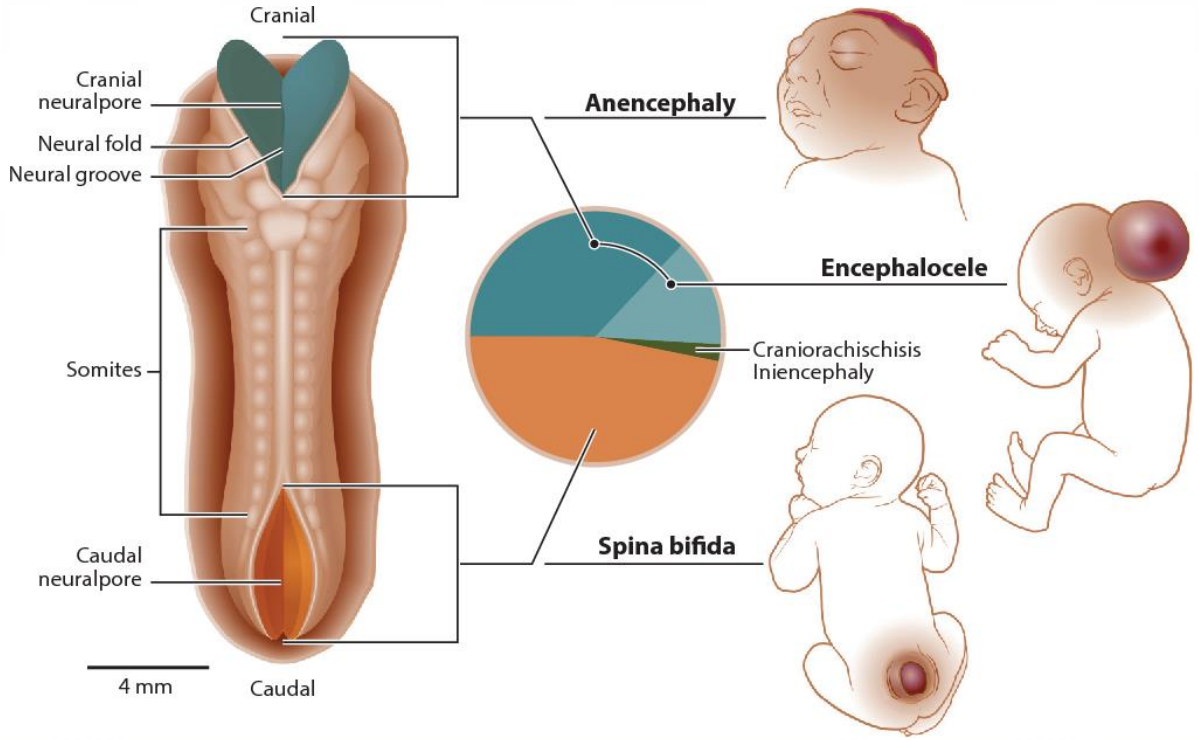
- Depending on the **time of exposure**, it produced malformations similar **to retinoic acid syndrome (exposure on 19-23 days)** and related syndromes.

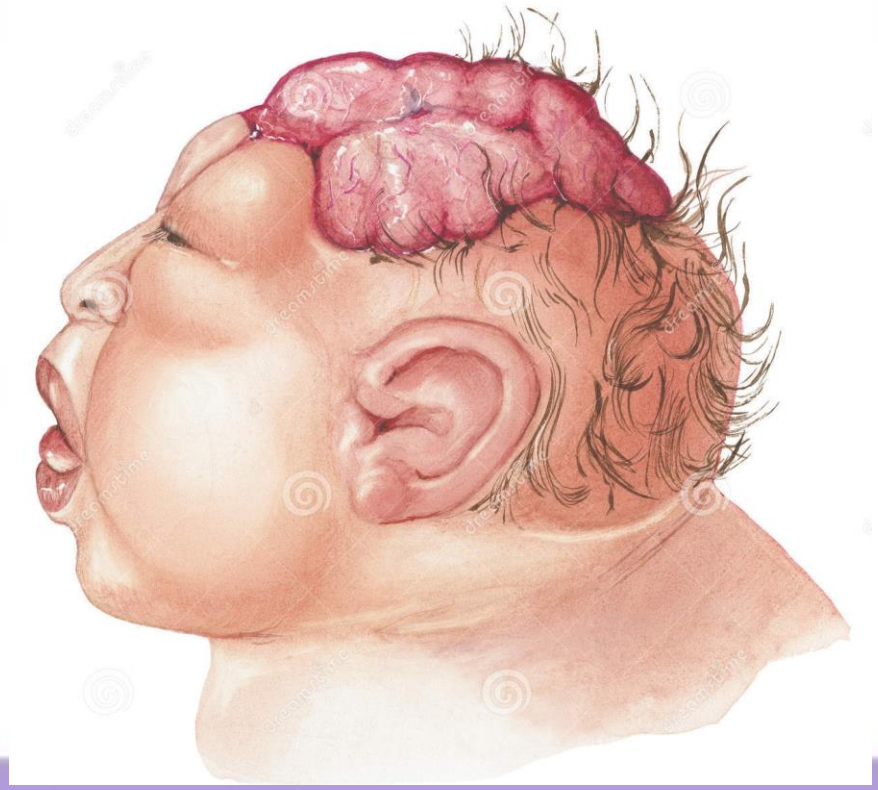



4. Neural Tube Defects (NTD)

- NTDs are defined as a group of defects in which the neural tube has failed to complete neurulation and one or more of the neural tube coverings are incomplete.



- In most cases this failure leads to **exposure of a portion of the neural tube at the body surface.** The problems are related to neural tube closure, principally neural fold elevation and contact.



- Neural tube defects are those involving the brain (**anencephaly**) and the spinal cord.
- Anencephalies are usually lethal. There are secondary facial abnormalities, of which occasional cleft palate (CP) is severe.

- It is one of the five most common human malformations. Over the past few decades there has been a worldwide decline in the number, mainly due to;
  - **Therapeutic termination of pregnancies.**
  - Primary prevention **folic acid supplementation**.

- **Causes** include
  - Chromosome abnormalities,
  - Single mutant genes, teratogens,
  - Maternal predisposing factors (diabetes, insulin and drugs)
  - Multifactorial inheritance socioeconomic status,
  - Nutritional deficiency.
  - Several lines of evidence suggest a **genetic basis** in the majority of human ntds.

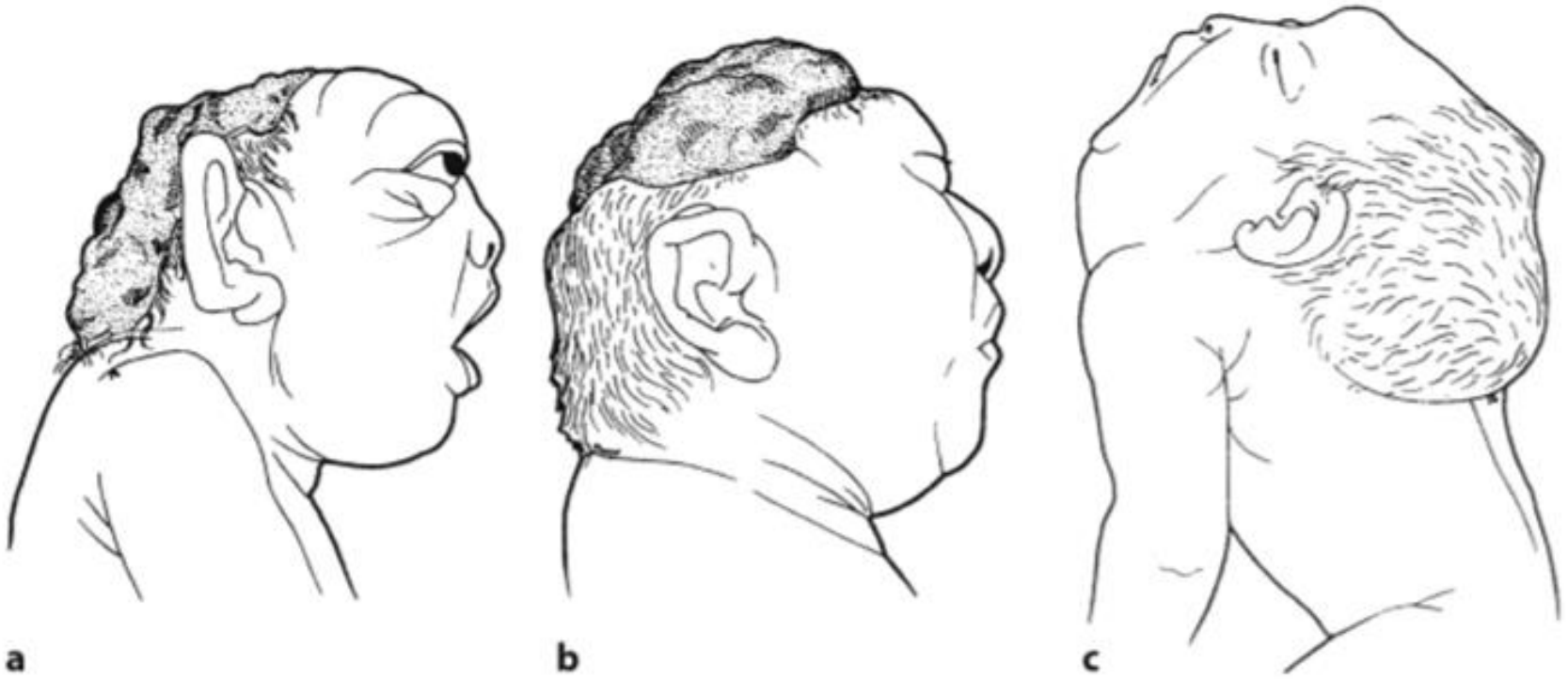
- **Anencephaly** is the most severe, usually **lethal** type of cerebral dysgraphia. Data suggest that anencephaly in man arises in three stages

A. **Cerebral dysgraphia**, beginning before or during Carnegie stage 11 (approximately 23–25 days)

B. **Exposure** of the resulting exencephalic but well-differentiated brain during the remainder of the embryonic period.

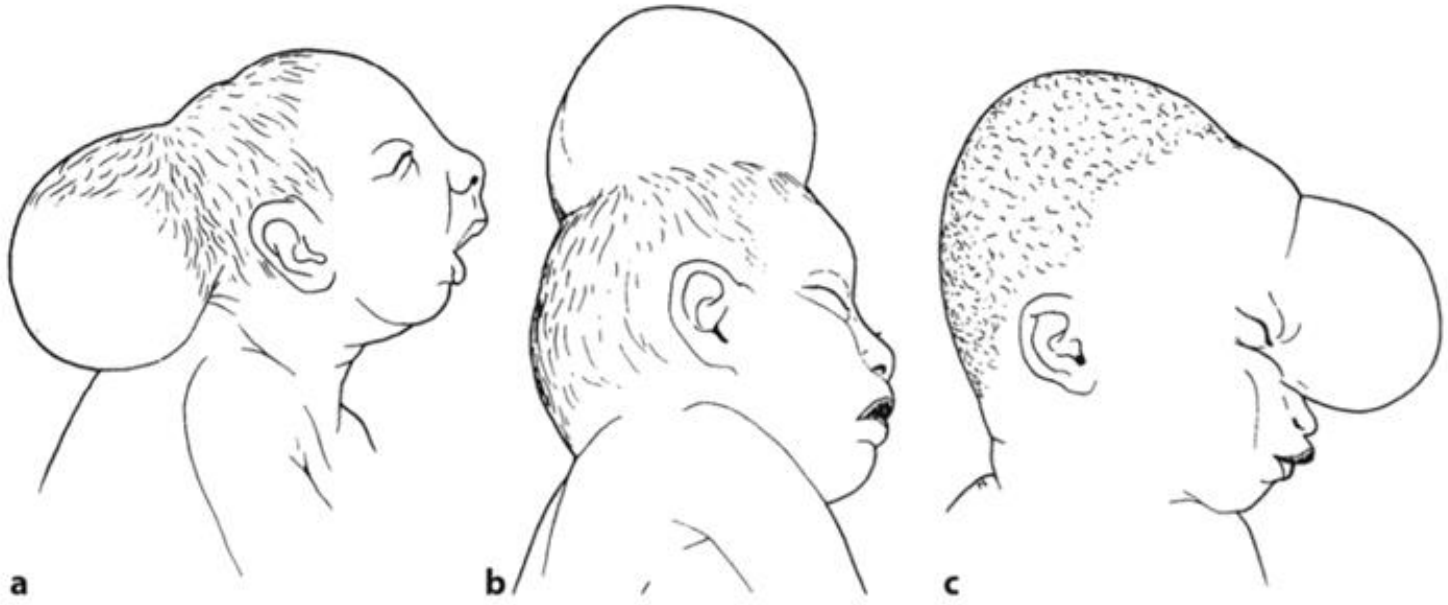
C. **Degeneration** of the exposed brain during the fetal period.

Anencephaly



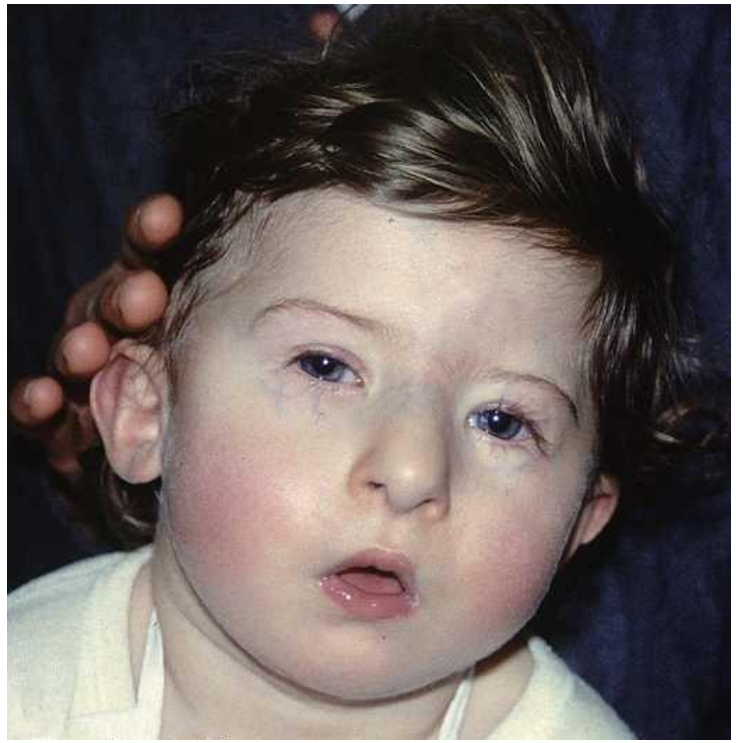
Encephaloceles

Encephalomeningoceles or encephaloceles are **protrusions of brain** and meninges through an abnormal opening in the skull most commonly in either the **occipital** or the **frontal** region.

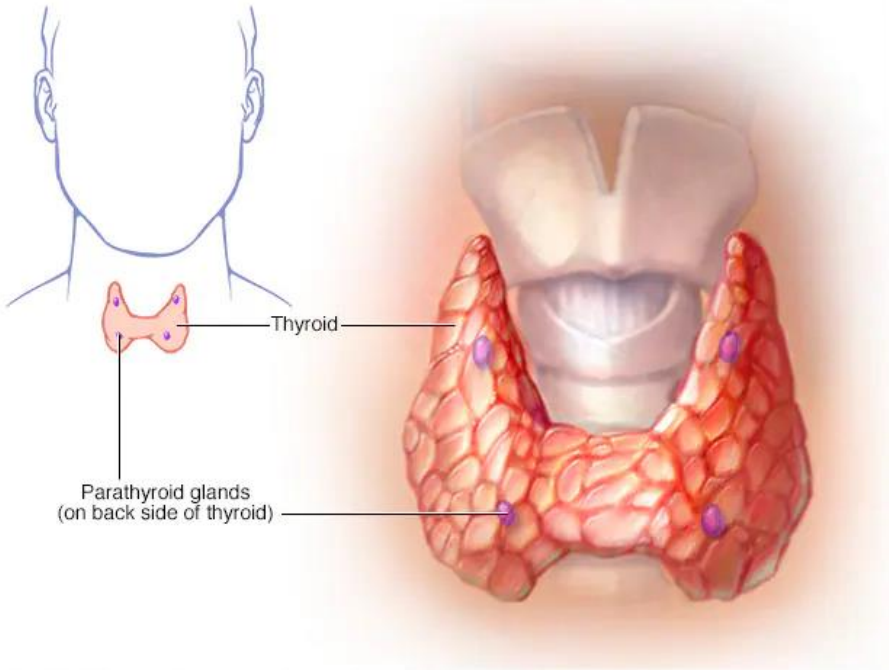


5. DiGeorge Syndrome

- This syndrome is related to maternal alcoholism. The manifestations are **similar to retinoic acid** syndrome except for the **short upper lip** which is not seen in retinoic acid syndrome.

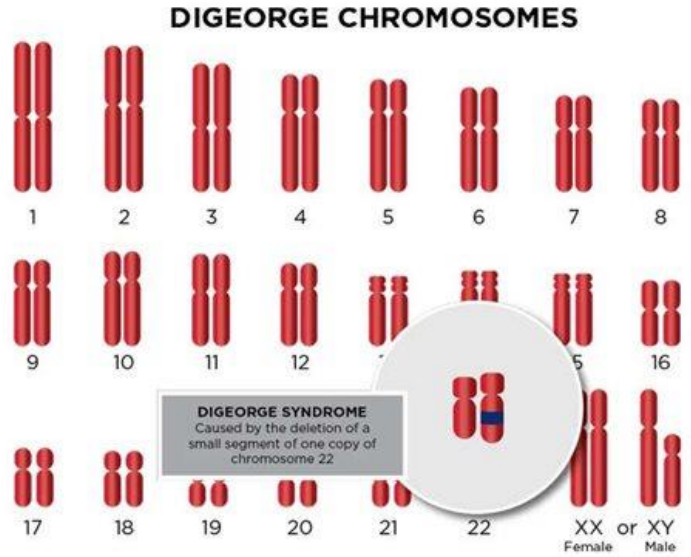


- A unique feature of this syndrome is the occurrence of **pharyngeal gland problems** (thyroid and parathyroid deficiencies).



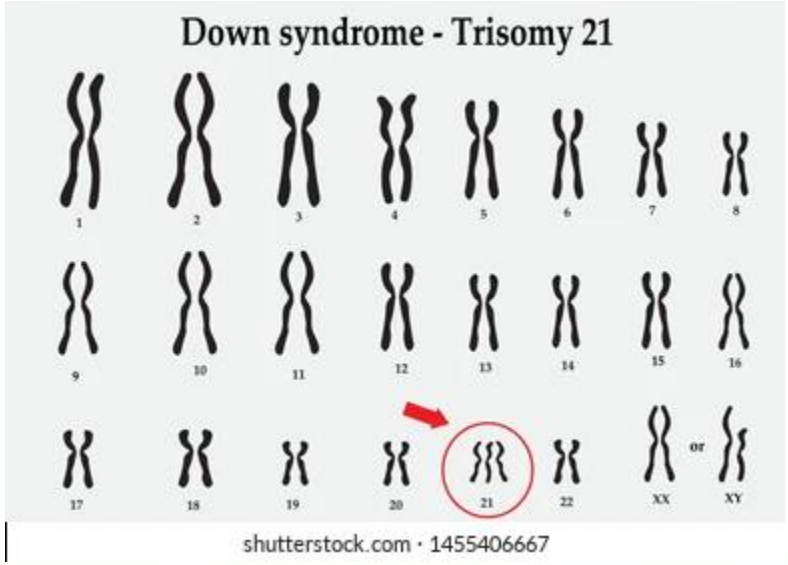
- **The main etiological** agent is **ethanol** which is lethal for migrating neural crest cells.
- This syndrome is frequently associated with **chromosomal deletion 22**. Cardiac defects, abnormal facies, thymic hypoplasia, cleft palate and hypocalcemia are the other clinical features.

(Hans, et al., 2006)



6. Down's Syndrome

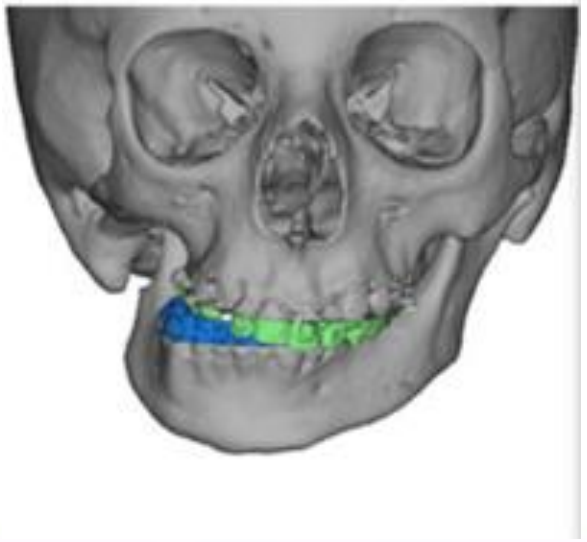
- It is a **chromosomal disorder** that occurs mainly due to **trisomy 21**.
- It can also occur due to **translocation** in which extrachromosomal material is translocated to chromosome **G or D** group and rarely due to **chromosomal mosaicism**.



- Clinical features of Down's syndrome are
  - Flat face
  - Larger anterior fontanelle, with open sutures,
  - Small slanting eyes with epicanthal folds,
  - Open mouth, frequent prognathism,
  - Sexual underdevelopment,
  - Cardiac abnormalities,
  - Hypermobility of the joints.
  - Short upper lip in the midline, and a
  - Lop-ear are similar to those seen in DiGeorge syndrome.(Premkumar, 2011)

7. Hemifacial Microsomia

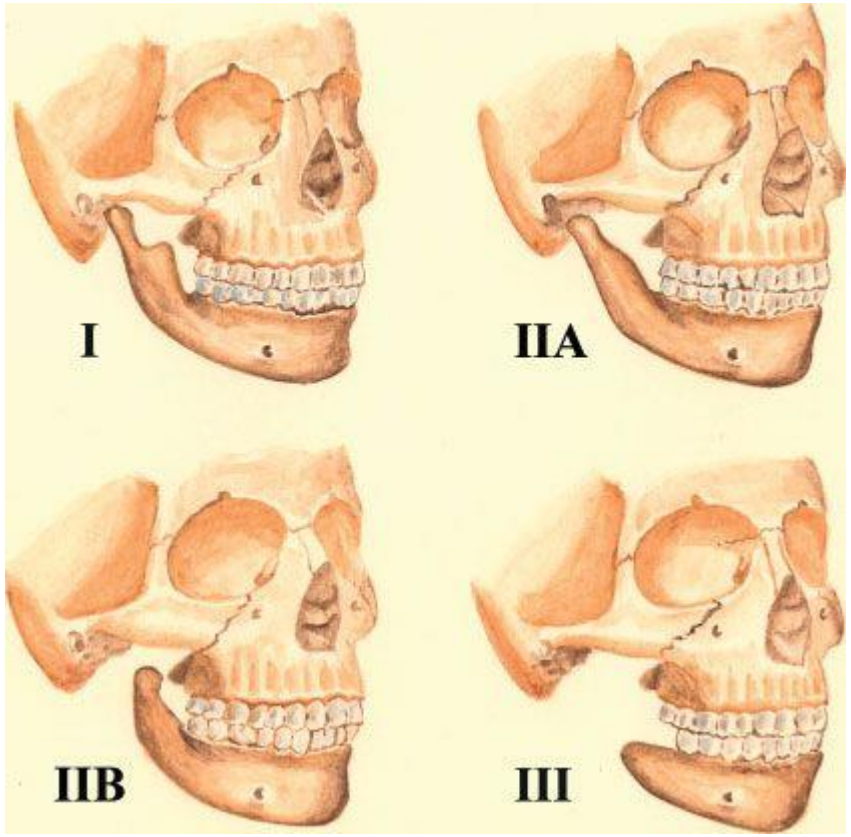
- It occurs in 1:4000 livebirths. It is a common **otofacial** malformation.
- It is frequently associated with **conotruncal** and **vertebral** abnormalities.
- There are no clear environmental associations. In most or all cases neural involvement is seen.



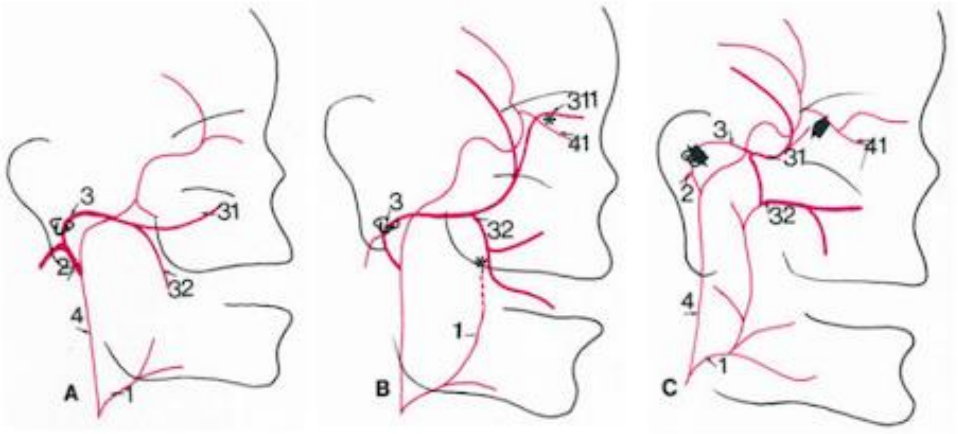
- It is characterized by a lack of tissue on the affected side of the face, usually in the area of the mandibular ramus and external ear.

Table 1 New Classification

Type I	Hypoplastic temporomandibular joint
Type II	IIa—hypoplastic and abnormal shape of mandibular ramus, condyle, and temporomandibular joint
	IIb—mandibular ramus is hypoplastic and markedly abnormal in form and location, being medial and anterior
Type III	Absence of the mandibular ramus
Type IV	Mandibular body hypoplasia



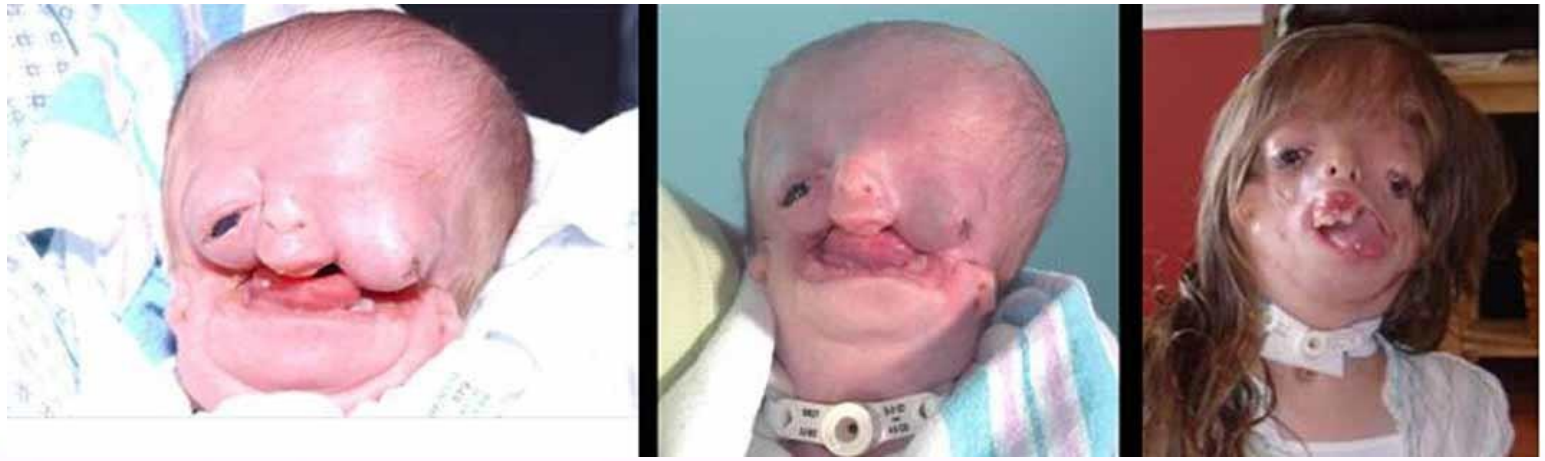
- Poswillo in the 1970s suggested that **hemorrhage from stapedial artery** and tissue necrosis might be involved in the development of hemifacial microsomia.
- Stapedial artery forms the temporary blood supply to the area of developing ear and mandibular ramus between 33rd and 40th day of gestation, which is later taken over by maxillary artery.



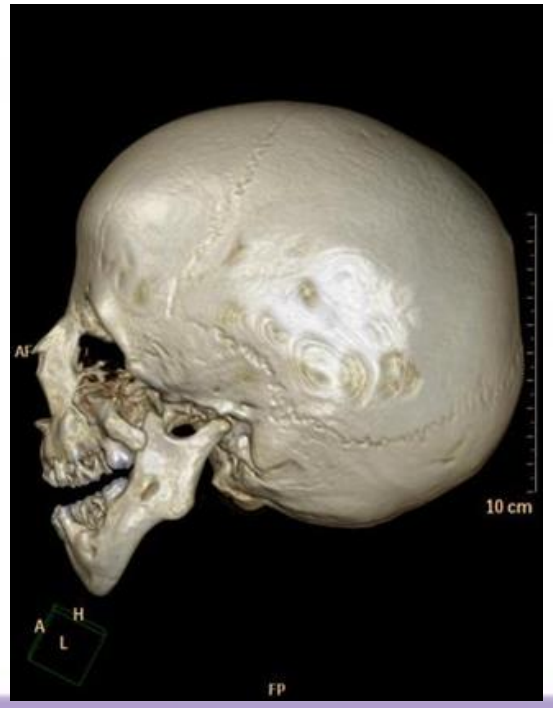
- It was also found that hemifacial microsomia was associated with many defects resembling those arising from neural crest cell loss. **(Thalidomide)**
- hemifacial microsomia result from **differing expressions** of the same basic defect, **early loss of neural crest cells**.
- The main etiology is the death of **neural crest cells with the longest circuitous migration path**→ lower areas of the face are most affected, whereas those going to the central face tend to complete their migratory movement. This explains why midline facial defects including clefts are rarely part of the syndrome.

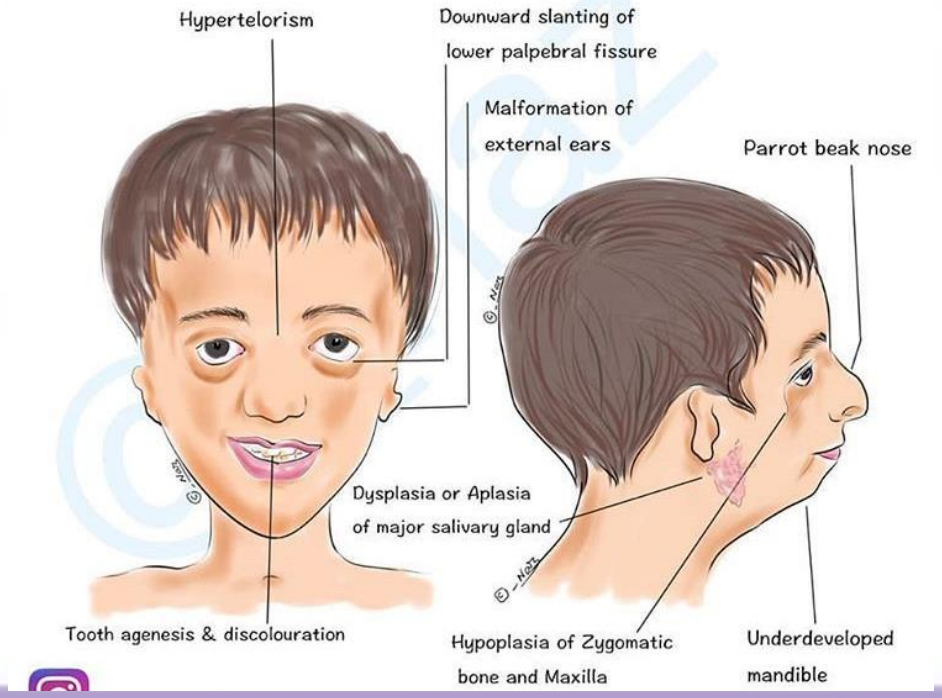
8. Treacher-Collins Syndrome

- Treacher Collins syndrome, or **mandibulofacial dysostosis**, is an **autosomal dominant condition** with variable expressivity. It is generally characterized by **bilaterally symmetrical abnormalities** of the structures within the **first and second branchial arches**.



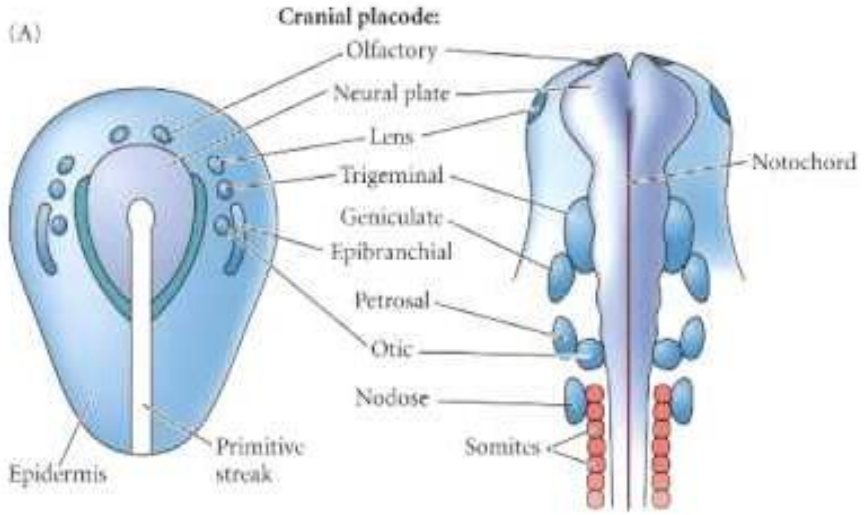
- It is characterized by malar hypoplasia, mandibular hypoplasia, downward palpebral fissures and coloboma of lower eye lid and malformed external ears.





- The main problem is due to the **massive cell death** in the trigeminal ganglionic placode, which alters the further development of the placodal cells, ultimately resulting in **secondary defects in neural crest cell derivatives.**

Cranial Placodes



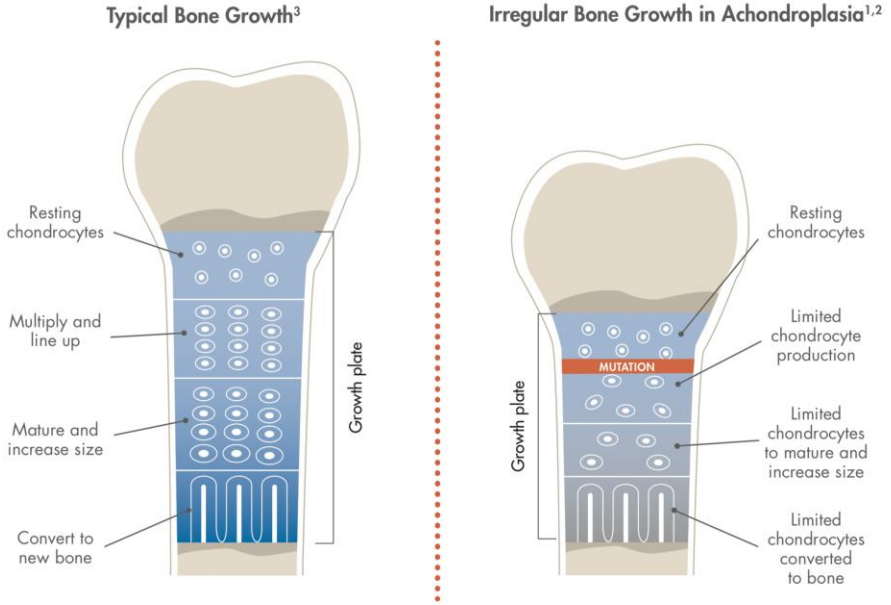
Genetic etiology:

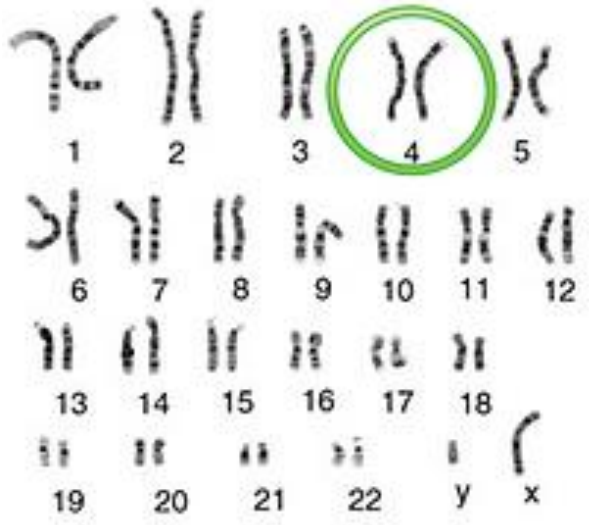
- The gene for Treacher Collins syndrome has been mapped to **chromosome 5q31.3-q33.3**.
- Theories of pathogenesis include the **failure of differentiation** of the branchial arch mesoderm, defective facial bone ossification, and **tissue ischemia** resulting from stapedial artery hypoplasia.
- **Variability** in the extent of the deformities is due to the influence of "**strong" or "weak" gene acting at an earlier or later period of the embryo's development**.

9. Achondroplasia

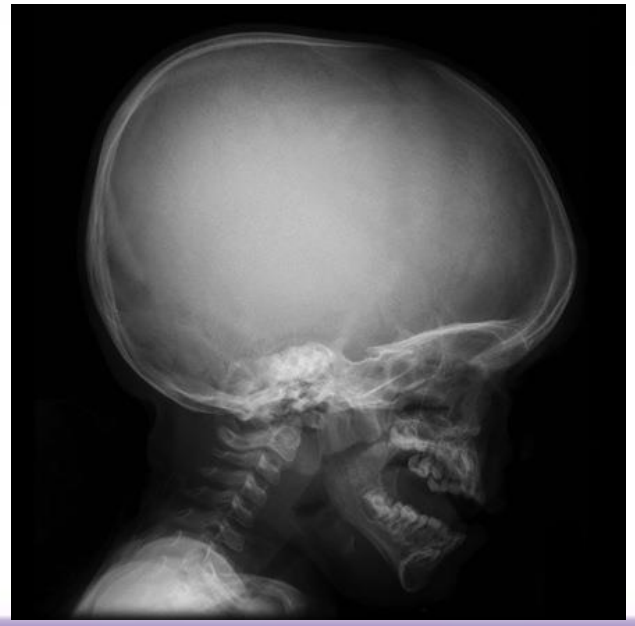
- Achondroplasia is the most common form of short-limb dwarfism, occurring in 1 of 25,000 births. It is inherited as an autosomal dominant trait.

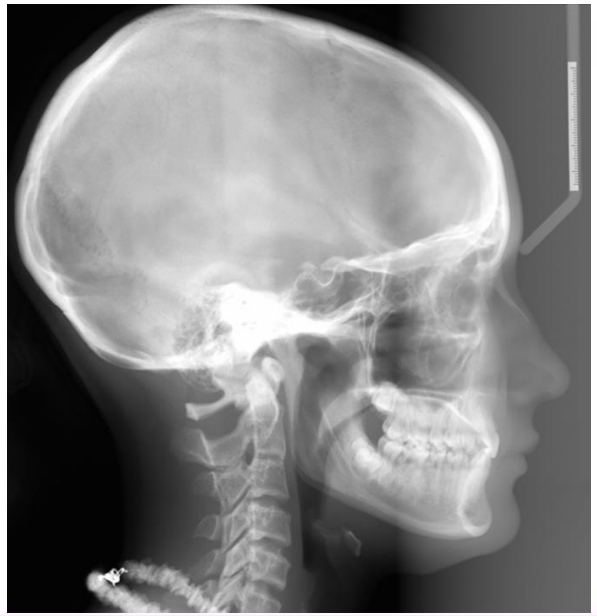
- Achondroplasia is caused by **mutation** in **fibroblast growth factor 3** (FGFR3) on **chromosome 4,** causing a **defect in the maturation of chondrocytes** in the cartilage growth plate which enables abnormal cartilage growth-plate differentiation and insufficient bony development.



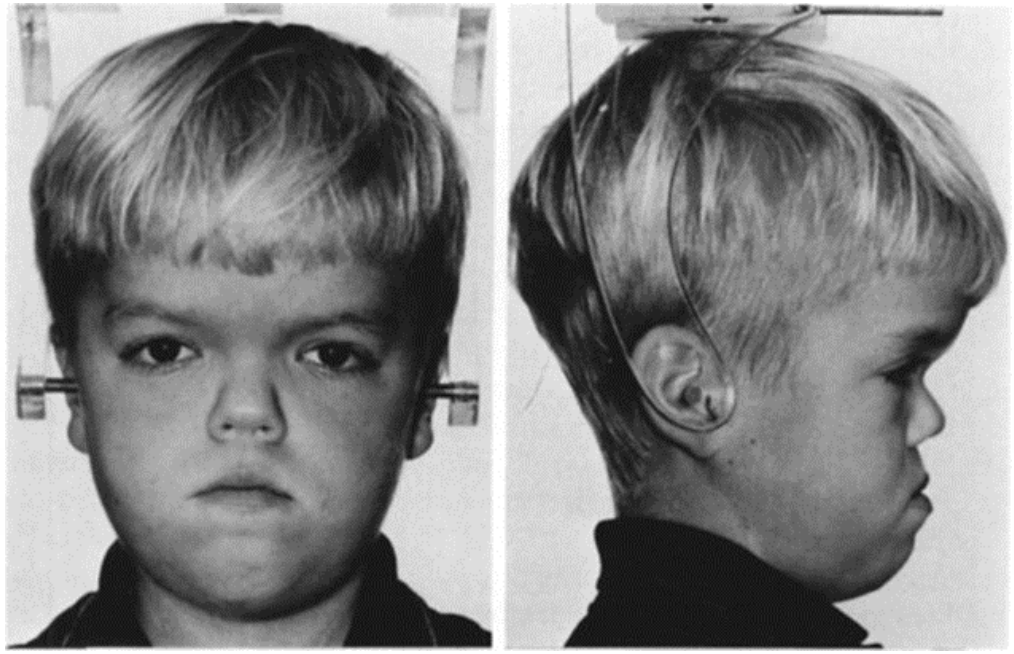


- Forward growth of the mid face is produced by the **normal lengthening of the anterior cranial base**, which in turn is dependent on the growth at sphenoccipital, intersphenoidal and spheno-ethmoidal synchondroses. **In achondroplasia**, **growth is diminished at these synchondroses.**





- Craniofacial characteristic of this disorder include
  - Macrocephaly,
  - Prominent forehead,
  - Depressed nasal bridge,
  - Maxillary hypoplasia.
  - Foramen magnum stenosis.

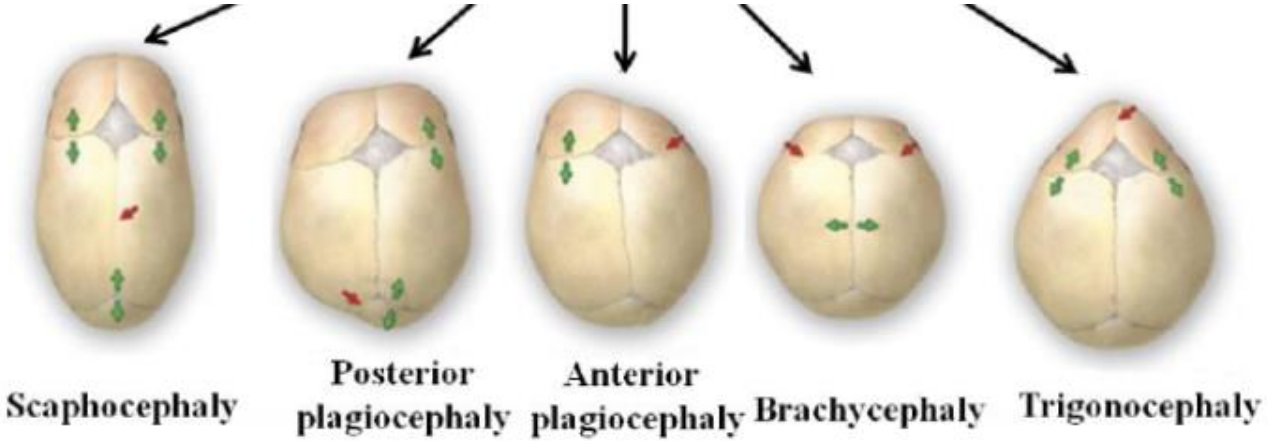


- These characteristics may lead to number of complications including **hydrocephalus**, **apnea**, **upper-airway obstruction**, **otitis media**, **sinusitis and malocclusion**. Others, obesity and diabetes

- There is **no cure for this disease**, however,
  - **Extended limb lengthening** has been used to improve stature.
  - **Growth hormone** therapy may result in a transient increase in growth rate but not effective in significantly increasing stature.
- Most individuals with achondroplasia are of **normal intelligence** and are able to lead independent and productive lives

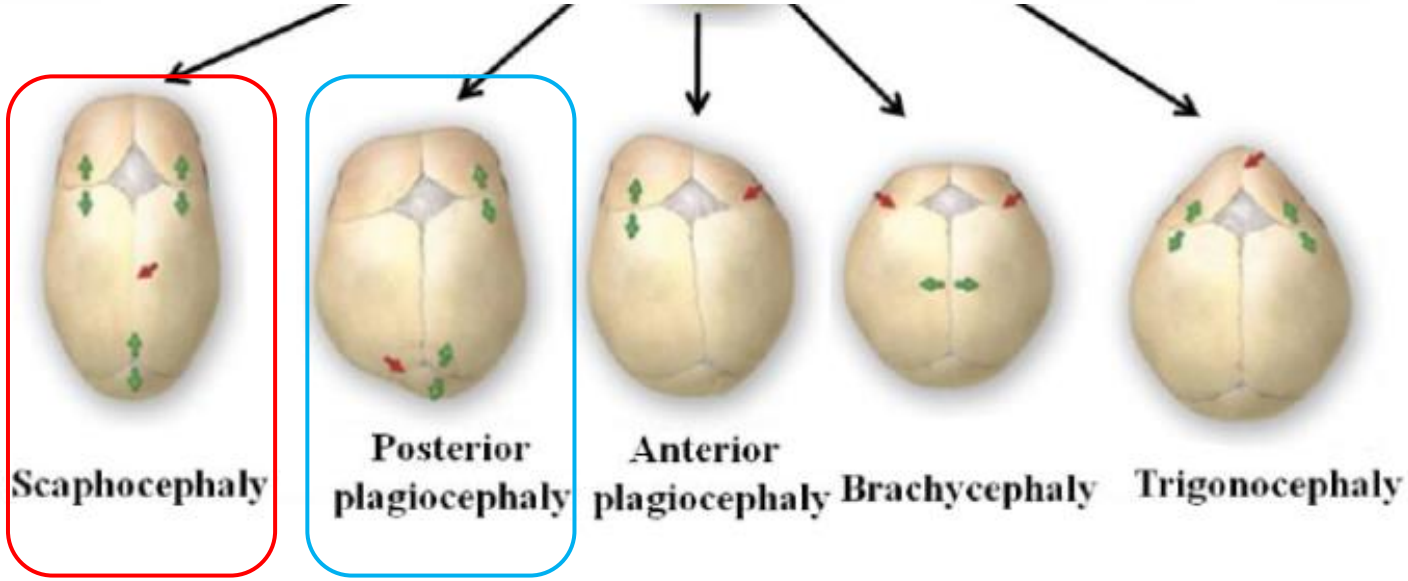
Premature Closure of Cranial and Facial Sutures
Craniosynostosis

- Premature fusion of the **midsagittal** or **posterior** cranial sutures can produce deformities of head **without affecting the face**, e.g. Scaphocephaly.
- **Unilateral** fusion along the **coronal suture ring** (plagiocephaly) has the potential to **produce facial as well as cranial asymmetry**.
- Premature fusion of sutures may cause secondary problems in the cranial base.

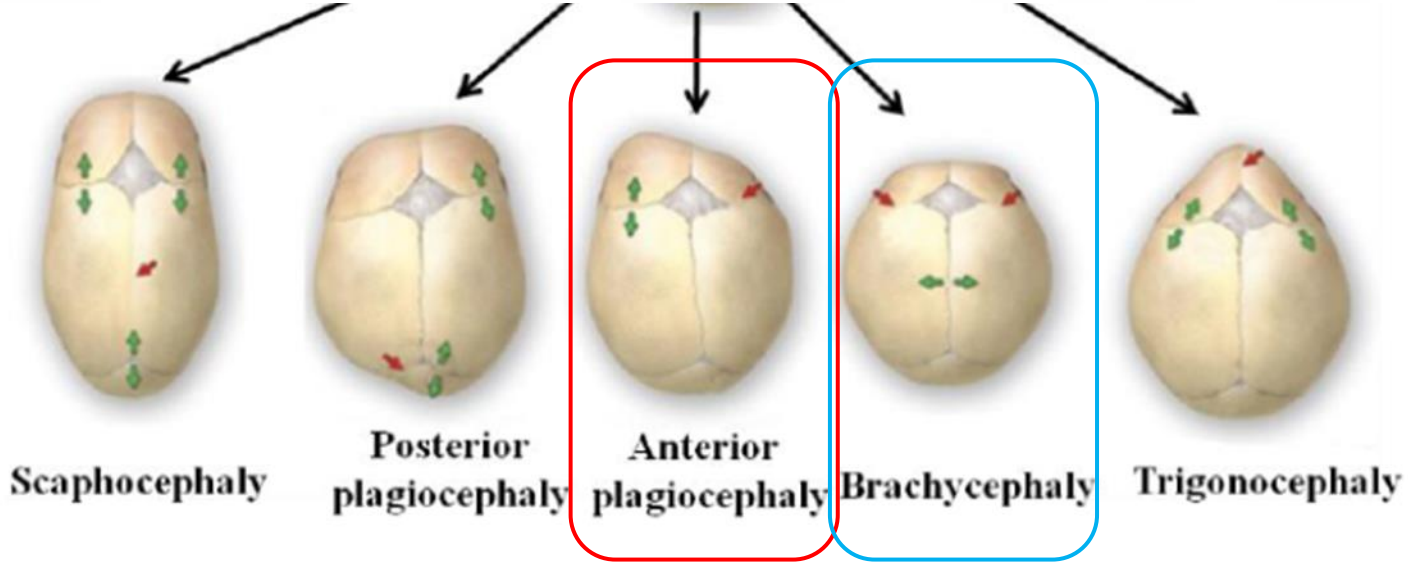


- Premature obliteration of sutures leads to **abnormal compensatory morphogenesis** throughout the head.
- **Several growth factors** are **found in the suture** and the underlying dura mater.
- **Over expression** of transcription factors RUNX2 and MSX2 induces suture obliteration.
- **Mutations** in genes for fibroblast growth factor receptors 1, 2, and 3 (FGFR1, FGFR2, and FGFR3) and MSX2 and TWIST genes are associated with craniosynostosis in humans.

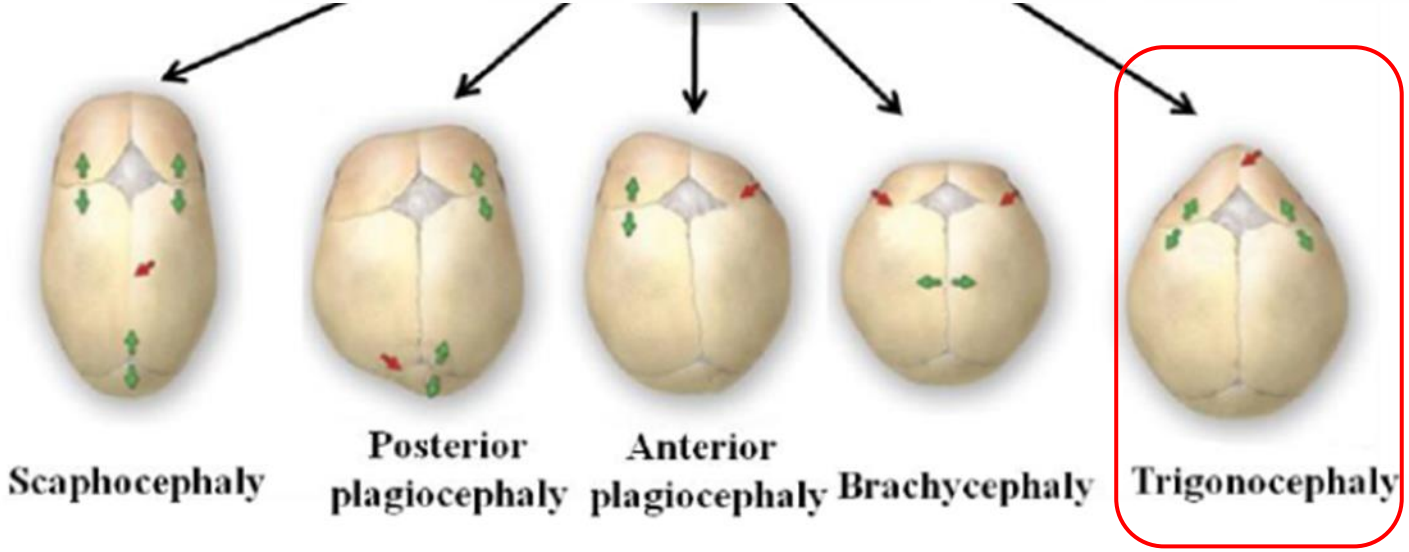
- **Scaphocephaly**: It is a type of cephalic disorder which occurs when there is a premature fusion of the **sagittal suture**, it is the **most common** craniosynostosis condition characterized by **long narrow head**
- **Posterior plagiocephaly**: (**unilateral lambdoid synostosis**) results in flattening of the back of the head on the affected side This leads to a characteristic and **unique "tilt" in the cranial base.**



- **Anterior plagiocephaly**: It is the Premature fusion of a **single coronal suture** leads to a restricted anterior growth of the skull,
- **Brachycephaly**: It is caused by **symmetrical flattening of the occipital bone area at the back**, lower part of the skull. These infants have **little or no rounding on the back of the head** and a disproportionately **wide head when viewed from the front**.



- **Trigonocephaly**: It's a congenital condition of premature fusion of the **metopic suture** (forehead), leading to a **triangular forehead**.
- When the suture fuses prematurely the frontal bone and forehead cannot grow in response to the growth of the brain.

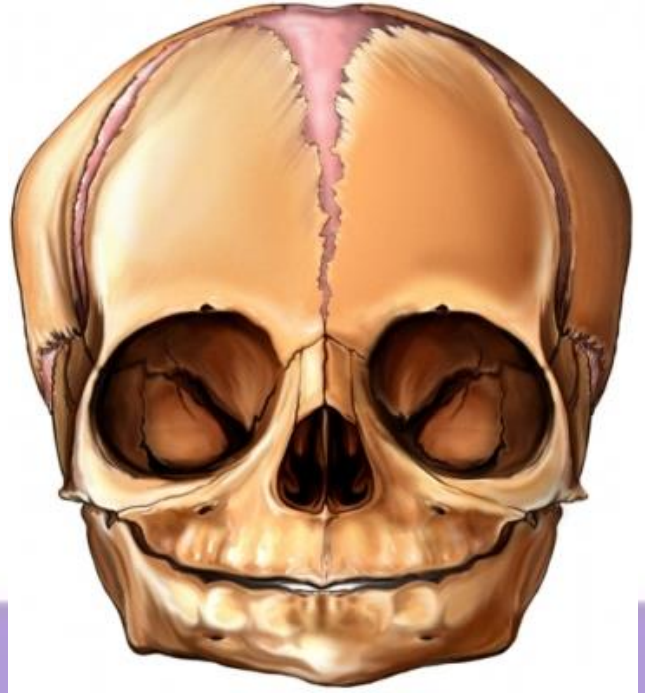


Treatment:

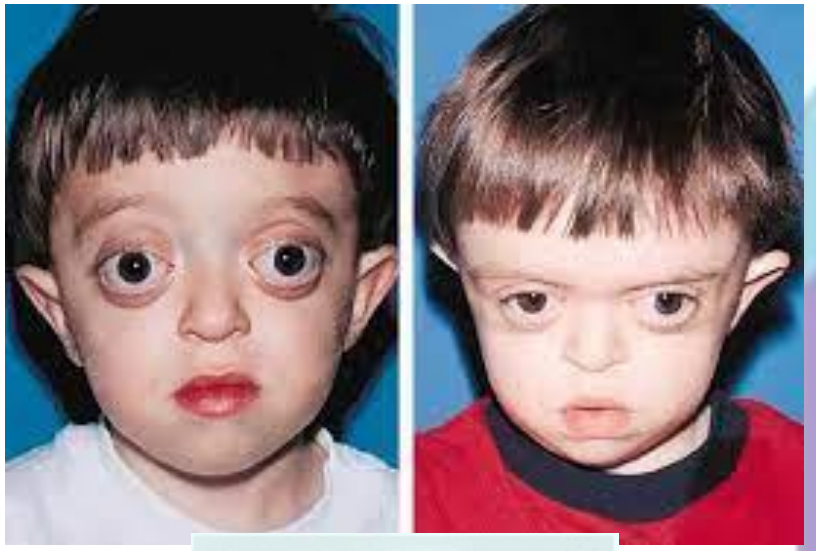
- Surgery is not performed in patients without **increase ICP (Intra Cranial Pressure)** until the shape of head does not improve by age, 2-4 months; it is unlikely to resolve with age.
- **Cosmetic surgery** is performed in infants **aged 3-6 months**.

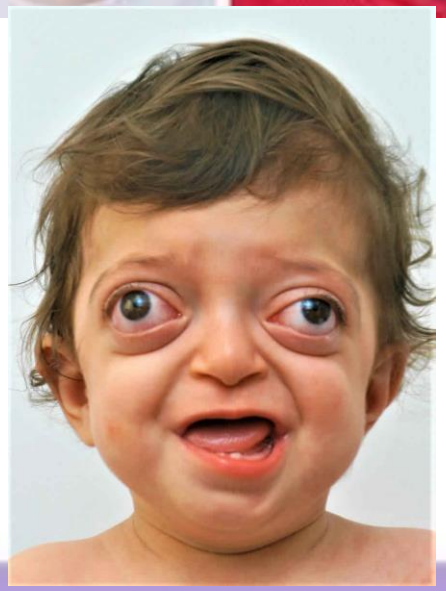
11. Crouzon's syndrome

- Results from the **premature fusion** of the **posterior and superior sutures of the maxilla** along the walls of the orbit with cranial base involvement. It is characterized by symmetric maxillary deficiency that affects the infraorbital area. It is also characterized by shallow orbits resulting in protruding eye balls

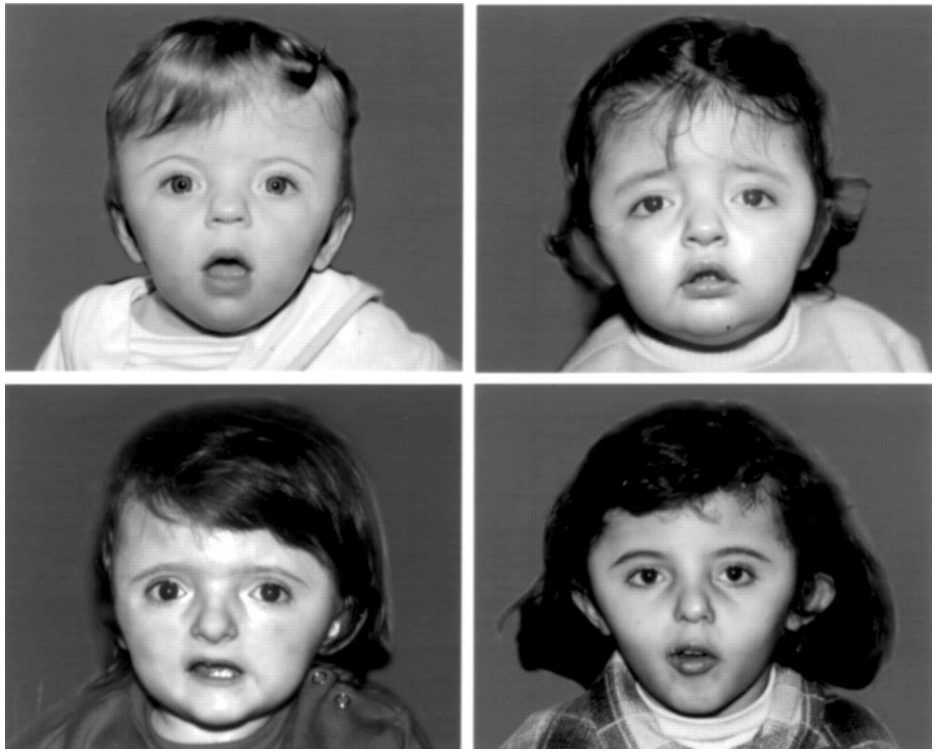


- Characteristic **premature synostosis of both coronal sutures** results, with a resultant
  - **Brachycephalic** shape to the skull
  - Midface hypoplasia with **class III** malocclusion,
  - **Hypoplastic orbits** with a **proptosis**,
  - **Parrot beak nose** and short anterior cranial base.





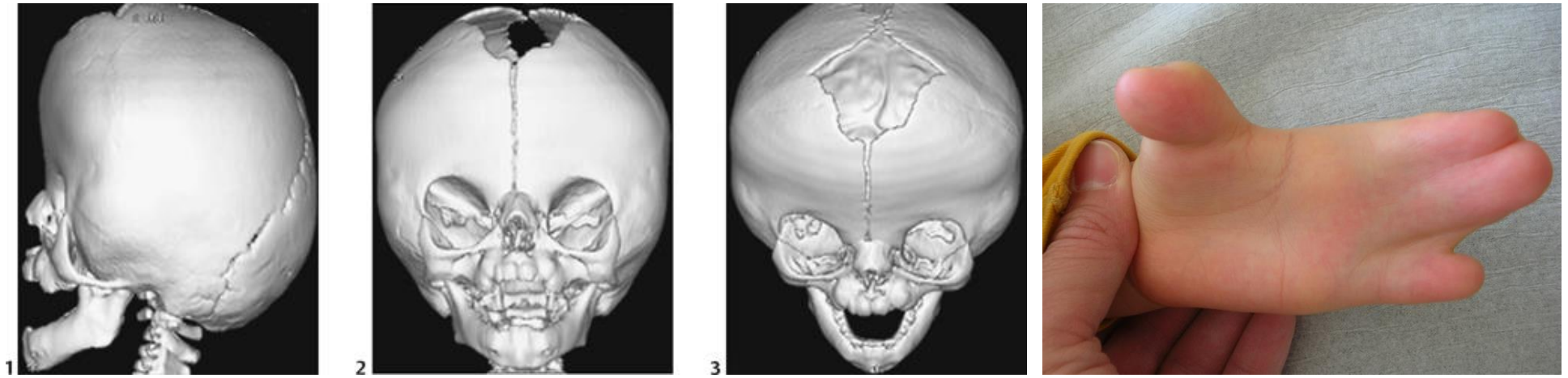
- **Genetic etiology**: It is caused by **multiple mutations** in the fibroblast growth factor receptor2 gene **(FGFR2)** and tyrosine kinase receptor.
- Mutation in FGFR3 result in syndrome called **FGFR3 syndrome** and the associated coronal synostosis syndrome may present as **bilateral coronal synostosis** with **minimal midface involvement**.



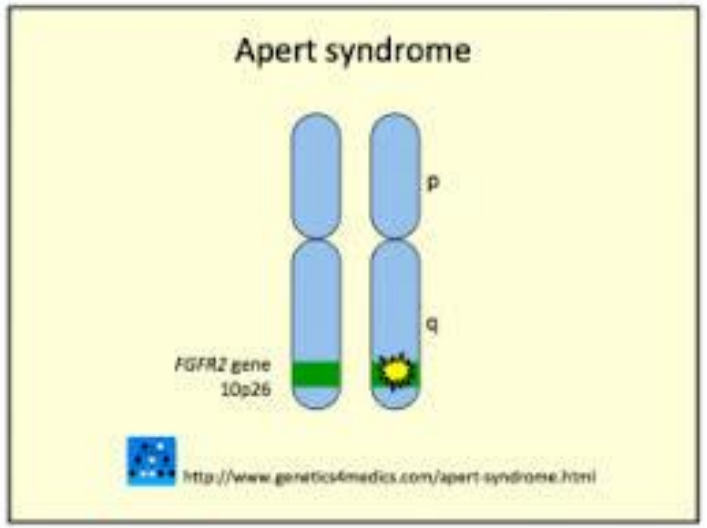
(Freudlsperger & Engel, 2021)

12. Apert's syndrome

- Also known as **Apert-Crouzon disease**, is characterized by **fusion of multiple facial and cranial sutures** and **synchondroses** of the cranial base.
- Appearance similar to Crouzon's syndrome and have **syndactyly** as an additional feature.
- Metopic suture and **anterior fontanelle are open** at birth and during infancy in these patients, leading to pronounced **frontal bossing** and a high steep forehead.



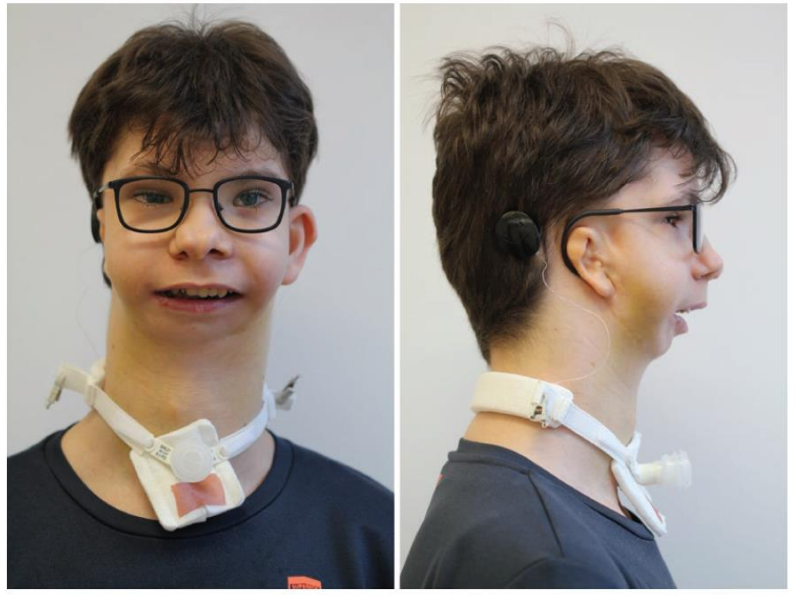
- **Genetic etiology**: At the molecular level, one of the two fibroblast growth factors 2 **gene (FGFR2) mutations** involving amino acids (ser 252 trp and pro 253 Arg) are found to cause Apert's syndrome. Tyrosine kinase receptor is affected at the extracellular IgII–IgIII domain



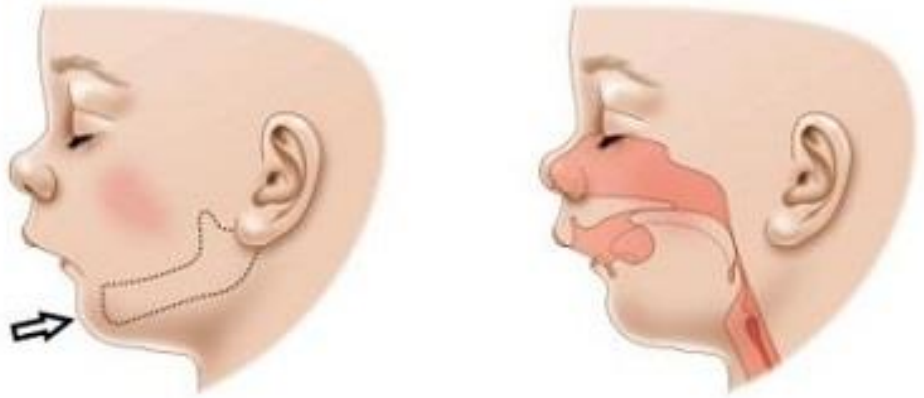
(Freudlsperger & Engel, 2021)

13. Pierre Robin Sequence

- In 1923, Pierre Robin, documented a disorder which now bears his namesake. Pierre Robin sequence (PRS) was originally described as consisting of micrognathia (“**mandibular hypotrophy**”), **glossoptosis** which result in **airway obstruction** and **feeding difficulties**.



- The small mandible is thought to be due to an **inherent genetic** problem or a **deformational problem** where intrauterine growth is restricted or mandibular positioning is altered. **Rather than a syndrome**, which is defined as multiple anomalies **arising from a single underlying pathogenesis.**



Genetic Basis

- Pierre Robin sequence occurs in 1/8500 to 1/14,000 births. This phenotype is due to several causes and can be seen in isolation or in conjunction with a syndromic presentation. **Support for a genetic basis** is evidenced by a high incidence of **twins with PRS**.
- Moreover, family members of PRS infants have a **higher incidence of cleft lip and palate.**

(Gangopadhyay, et al., 2012)

Thank you