Medical State University of Medicine and Farmacy ”N. Testemițanu”
Republic Moldova

Stomatological facultet
Maxillo-facial surgery department for children

Congenital malformations. Congenital syndrome

Face Embryology. Human eyes are highly sensitive in discerning minimal differences in the structure of human faces and in distinguishing persons. Discerning eyes can also detect many facial anomalies associated with systemic congenital anomalies. A classification of these facial anomalies based on embryological bases is helpful for understanding the morphogenesis of each anomaly.

F*acial morphogenesis.* Craniofacial development is an extraordinarily complex process that requires the orchestrated integration of multiple specialized tissues, such as the surface ectoderm, neural crest, mesoderm, and pharyngeal endoderm, in order to generate the central and peripheral nervous systems, axial skeleton, musculature, and connective tissues of the head and face.

The head and neck region development occurs during 4th and 8th weeks of embryonic life. The facial primordia begin to appear early in the fourth week around the large stomodeum. The face is formed by the fusion of five swellings [primordia], i.e., an unpaired frontonasal process, a pair of maxillary processes and a pair of mandibular processes. The Pharyngeal Apparatus contributes extensively to the formation of the face, nasal cavities, mouth, larynx, pharynx and neck. Much of the human face and neck is derived from the ancient gill apparatus.

Branchial arches form on either side of the foregut and correspond to the primitive branchial arches. The pharyngeal arch consists of a core of mesenchyme covered externally by ectoderm and covered internally by endoderm. The ectoderm is well around the stomodeum by the fourth week of embryonic development and contributes to the formation of the face and the nasal and oral cavities.

The mesenchyme that fills the pharyngeal arches is derived from the following 3 origins: the paraxial mesoderm, the lateral plate mesoderm, and the neural crest cells. Although paraxial mesoderm and lateral plate mesoderm contribute to the musculature that develops in each particular arch, neural crest cells contribute to the skeletal portion of each arch.

At the early stages of embryonic development, the vertebrate face has a common plan. A series of small buds of tissue called the facial primordia forms around the stomodeum, which forms the primitive mouth. The facial primordia are made up mainly of neural crest cells that have migrated from the cranial crest and settled.

The upper jaw develops from the following 5 main buds of tissue: a single median frontonasal mass (sometimes present as the median nasal processes or frontonasal prominences), the 2 lateral nasal prominences on both sides, and, flanking these, the 2 maxillae (maxillary prominences). The lower jaw develops from the paired mandibular primordia (mandibular prominences). Paired maxillary and mandibular prominences are derivatives of the first pair of branchial, or pharyngeal, arches. All of these prominences are produced by the

proliferation of the neural crest cells that migrate into the arches from the neural crest during the fourth week of gestation.

The neural crest cells give rise to the connective tissue components, including cartilage, bone, and ligaments in the facial and oral regions. The myogenic cells of the muscles constitute a separate cell lineage. These cells originate from the paraxial mesoderm and migrate into the facial primordia. Prior to emigration, the neural crest cells in the head are formed according to which facial primordium they belong.

The individual facial primordia are populated by neural crest cell populations that arise in different regions of the head neural folds. The neural crest cells that settle to form the frontonasal mass first migrate from the prosencephalic region (forebrain) and are later joined by other migrating cells, mainly from the anterior mesencephalic region (midbrain). The cells of the maxillae come from the posterior mesencephalic region, whereas the cells of the mandibular primordia come mainly from the region of the anterior rhombencephalon (hindbrain). In the trunk, exchanges between different regions of the neural crest almost invariably lead to normal development.

The frontonasal prominence surrounds the ventrolateral part of the forebrain, which gives rise to the optic vesicles. These vesicles project from the sides of the forebrain into the mesenchyme and form the eyes. The frontal portion of the frontonasal prominence forms the forehead, whereas the nasal part of the frontonasal prominence forms the rostral boundary of the stomodeum and nose. A summary of the derivatives of the prominences is as follows: 1. Frontonasal prominence - Forehead and the dorsum apex of the nose. 2. Lateral nasal prominences - Sides (alae) of the nose. 3. Medial nasal prominences - Nasal septum. 4. Maxillary prominences - Upper cheek region and most of the upper lip. 5. Mandibular prominences - Chin, lower lip, and lower cheek regions. 6. Mesenchyme in the facial prominences - Fleshy derivatives and various bones.

A summary of the derivatives of the first and second pharyngeal (ie, branchial) arches is as follows:

- Pharyngeal arch I
  -
    - Cranial nerve - Maxillary and mandibular division of the trigeminal nerve (cranial nerve V)
    -
    - Artery - Maxillary (terminal branch)
    -
    - Muscles - Muscles of mastication (ie, temporalis, masseter, pterygoids), mylohyoid, anterior belly of digastric, tensor tympani, and tensor veli palatini
    -

    - Skeleton - Maxillary cartilage (incus, alisphenoid), mandibular or Meckel cartilage (malleus), and arch dermal mesenchyme (maxilla, zygomatic, squamous portion of temporal bone, mandible)
-
- Pharyngeal arch II (hyoid)
    - Facial nerve - Cranial nerve VII
    -
    - Artery - Stapedial
    -
    - Muscles - Muscles of facial expression (ie, orbicularis oculi, orbicularis oris, risorius, buccinator, platysma, auricularis, frontalis), stapedius muscle, posterior belly of digastric, and stylohyoid muscle
    -
    - Skeleton - Stapes, styloid process, stylohyoid ligament, lesser cornu of hyoid, and the upper part of the body of the hyoid bone

Early development of the face. Facial development occurs mainly between the fourth and eighth weeks of gestation.

- Fourth week of development (stage 12 and 13)
    -
    - Primordia of the face appear at the cephalic end of the embryo.
    -
    - Two nasal placodes cap the bulbous frontal prominence.
    -
    - The optic discs appear posterolateral to the frontal prominence.
    -
    - Three paired branchial arches have formed.
    -
    - The first arches split into maxillary and mandibular prominences. The hyoid arches are the second pair.
    -
    - Between the first arches and frontal prominence, the buccopharyngeal membrane becomes fenestrated.
-
- Fifth week of development (stage 14 and 15)
    -
    - Nasal pits develop in the nasal placodes, and the rims of the placodes differentiate into medial and lateral nasal prominences.
    -
    - The lens vesicles invaginate and close within the optic discs.
    -

    - The mesenchyme of the mandibular arch fills in across the midline.
    -
    - The caudal end of the medial nasal prominences begins to fuse with the maxillary prominences.
-
- At the beginning of the sixth week of development (stage 16)
    -
    - The nasals have shifted to a more ventral, central position.
    -
    - Growing and shifting subectodermal mesenchyme smooths out the furrows between prominences and arches, and the second arch becomes more massive.
    -
    - Six auricular hillocks, which will become the pinna of the ears, form on the mandibular and hyoid arches.
- By the end of the sixth week of development (stage 17)
    -
    - Medial and lateral nasal prominences fuse.
    -
    - Maxillary prominences begin the formation of the upper jaw.
    -
    - The midline approximation of the medial nasal prominences forms the nasal septum.
-
-
- At the beginning of the seventh week of development (stage 18)
    -
    - The tip of the nose is elevated between the medial nasal prominences and is visible in profile.
    -
    - Eyelids become prominent.
    -
    - The pinna of the ear takes shape.
-
- End of the seventh week of development (stage 18)
    -
    - The pattern of facial features has taken on a human appearance. However, facial proportions develop during the fetal period.
    -
    - The fusion of the medial nasal prominences, which forms the central axis of the nose and the philtrum of the lip, is complete.

Final development of the face. From the beginning of the eighth week of development to birth, the final facial development occurs slowly and consists mainly of changes in the proportion and relative positions of the facial components.

During the early fetal period, the nose is flat and the mandible is underdeveloped. They obtain their characteristic form while facial development is being completed. As the brain enlarges, it creates a prominent forehead, the eyes move medially, and the external ears rise.

The prenatal face is small because of (1) the rudimentary upper and lower jaws, (2) the unerupted primary teeth, and (3) the small size of the nasal cavities and maxillary sinuses.

Most congenital anomalies in oro maxillo facial region originate during transformation of the pharyngeal apparatus into its adult derivatives. During the fifth week, the second pharyngeal arch enlarges and overgrows the third and fourth arches, forming an ectodermal depression - the cervical sinus. The pharyngeal grooves disappear except for the first pair, which persist as the external acoustic meatus. The pharyngeal membranes also disappear, except for the first pair, which become the tympanic membranes. The Branchial anomalies result from persistence of parts of the pharyngeal apparatus that normally disappear. The Branchial cleft anomalies include branchiogenic sinuses, cartilaginous rests, fistulae and cervical cysts. There are four Branchial cleft anomalies described. The First Branchial cleft anomalies are above the level of hyoid and the external orifice is near the auricle or beneath the mandibular ramus. The Second Branchial cleft anomalies are the most common. The external opening is near the junction of the middle and lower thirds of the sternocleidomastoid muscle. The Third branchial cleft anomalies are rare. The external orifice may be located in a similar manner as that of the Second Branchial cleft fistulae, along the anterior border of the lower half of the sternocleidomastoid muscle. The Fourth Branchial cleft anomalies are rare. The internal openings of all the above four Branchial Cleft anomalies open in the tonsillar fossa and piriform sinus.

The thyroid gland develops from the thyroglossal duct, extending from the foramen cecum in the posterior midline of the tongue through the hyoid bone to the midline of the lower neck. The Thyroglossal duct cysts and sinuses may form anywhere along the course followed by the thyroglossal duct during descent of the thyroid gland from the tongue. Normally the thyroglossal duct atrophies and disappears, but remnants of it may persist and form a cyst in the tongue or in the anterior part of the neck, usually below the hyoid bone. The thyroglossal sinus opens in the median plane of the neck, usually below the hyoid bone. The thyroglossal sinus opens in the median plane of the neck. Incomplete fusion of the distal tongue buds results in a deep median sulcus or cleft in the tongue [glossoschisis].

Conclusion. The development of the vertebrate face is a dynamic

multistep process that starts with the formation of neural crest cells in the developing brain and their subsequent migration to form, together with mesodermal cells, the facial primordia. Patterning and morphogenesis of neural crest–derived tissues within a developing vertebrate embryo rely on a complex balance between signals acquired by neural crest cells in the neuroepithelium during their formation and signals from the tissues that the neural crest cells contact during their migration. Neural crest cells carry information that directs the axial pattern and species-specific morphology of the head and face. Signaling interactions coordinate the outgrowth of the facial primordia from buds of undifferentiated mesenchyme into the intricate series of bones and cartilage structures that, together with muscle and other tissues, form the adult face.

Some of the molecules thought to be involved have been identified through the use of mouse mutants, data from human craniofacial syndromes, and expression studies of signaling molecules during facial development. However, the way in which these molecules control the epithelial-mesenchymal interactions, which mediate facial outgrowth and morphogenesis, is unclear.

The role of neural crest cells in these processes has yet to be well defined. Similarly, the complex interaction of all these processes during face development and the candidate signaling molecules and their possible target genes have not been clearly defined.

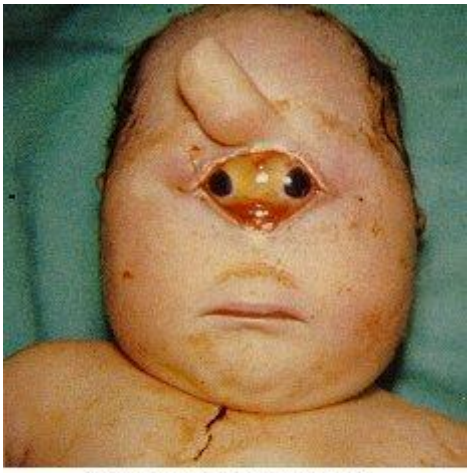
Classifying the rare craniofacial cleft. Midline deformities can be subdevided into 1. Those involving a deficiency in tissue and 2. those in which there is either an excess or a near normal amount of intervening tissue.

Tissue-dificient median cerebrofacial dysmorphogenesis (holoprosencephaly). These cases can be grated to the degee of severity as to lobar, semilobar and alobar holoprozencephaly. The varios degree of facial dysmorphism associated with the severity of holoprosencephaly have been grouped into five major types: cyclopia, ethmocephaly, cebocephaly, hypoteleorbitism with median cleft lip, and hipoteleobitism with bilateral cleft lip.

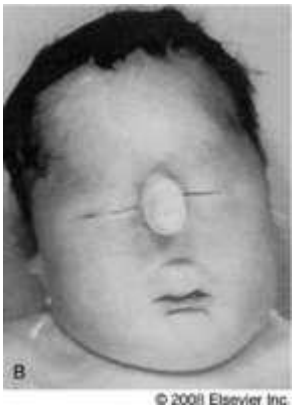
Tissue exess and near- normal median cerebrofacial dysmorphogenesis(frontonazal dysplasia. Characteristic features of the syndrom include: 1) orbital hipertelorism; 2) V-shaped frontal hear-line; 3) bifid cranium; 4) median cleft of the upper lip; 5) median cleft of the premaxilla; 6) median cleft of the palate; and 7) primary telecanthus.

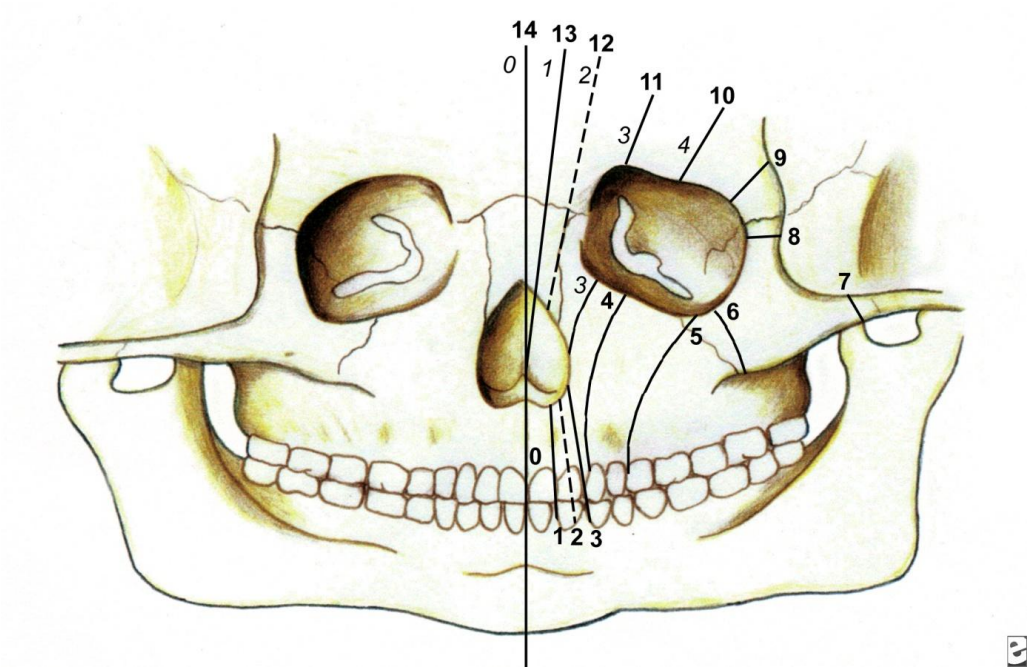
Tessier classification In 1994 at the Interdisciplinary Workshop Conference in Chicago on Craniofacial surgery, Tessier prezented a comprehensive classification scheme of craniofacial cleft base on personal experience with 336 . The important landmarks through wich the lines cross are mouth, nose, orbit and cranium and found that 15 distinct location of the clefts can be differentiated. The clefts are numbered from 0 to 14, in a counterclock wise fashion,

circumferentially around the orbit. The orbit was selected as the point of reference because it belongs to both the cranium and the face.

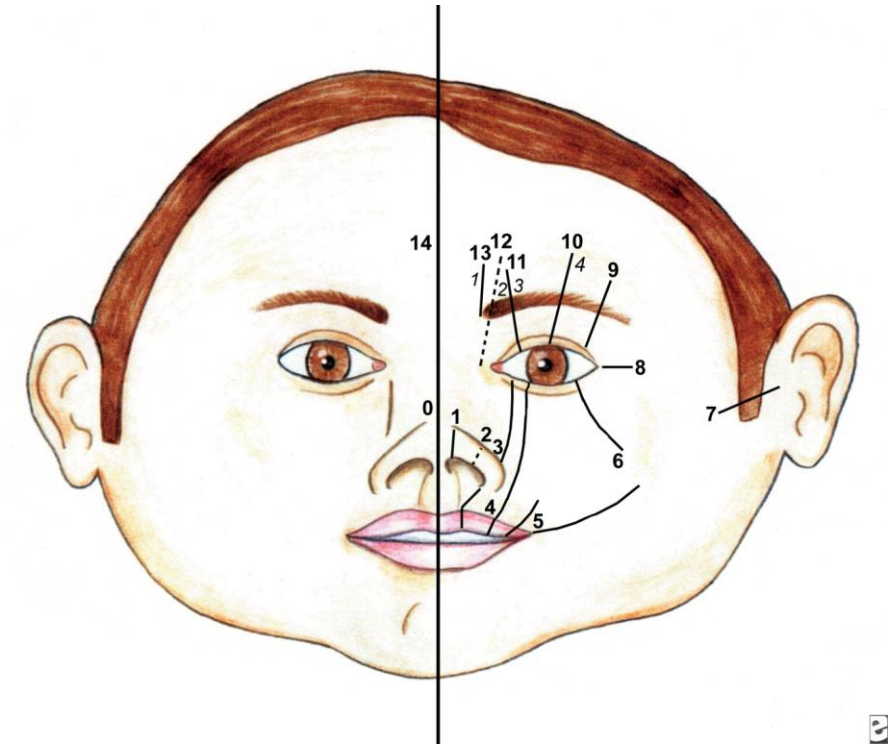


Cyclopia. S.S. Gellis and M. Feingold. Atlas of Mental Retardation Syndromes. 1968.





This drawing shows bone clefts in the Tessier classification system.



This drawing shows soft tissue clefts in the Tessier classification system.

Number I is the upper median facio cranial cleft. The soft tissue cleft starts from the oral cavity, runs in an upward and median plane involving the upper lip, nose [Rhinoschisis], naso frontal. The cleft may involve all of the above soft tissue structures [S] as an isolated cleft or may involve all of the above tissue structures. The Skeletal Cleft [Sk] starts from the oral cavity, runs through the maxilla, nasal, ethmoid, vomer, sphenoid and frontal bones in the midline. The cleft may involve one of the above cranial bones as isolated cranial bony cleft or may involve all the above cranial bones. The cleft may occur as an isolated soft tissue or as an isolated skeletal or in combination of both structures.

Number II is the Oblique facio cranial cleft. The soft tissue cleft runs in the upward and oblique direction from the oral cavity, involving the medial one third of the upper lip, nose [Rhinoschisis] and forehead. The cleft may involve one of the above soft tissue structure [S] as an isolated cleft or may involve all of the above soft tissue structures. The Skeletal cleft [Sk] starts from the oral cavity runs in upwards and oblique direction, involving the medial aspect of maxilla, nasal, ethmoid, lacrimal, palatine, sphenoid and frontal bones. The cleft may involve one of the above cranial bones as an isolated cleft or may involve all of the above cranial bones. The cleft may occur as an isolated soft tissue or skeletal or in combination of both structures. The cleft may be unilateral or as bilateral.

Number III is the Oblique facio cranial cleft. The soft tissue cleft [S] runs in the upward and oblique direction from the oral cavity, involving the medial one third of upper lip [lateral to Number II], in the junction of middle and lateral third of nose [Rhinoschisis], medial third of lower and upper eyelids [Blepharoschisis] and in the medial third of forehead. The cleft may involve one of the above soft tissues as an isolated cleft or may involve all of the above soft tissue structures. The skeletal cleft [Sk] starts from the oral cavity runs in an upward and oblique direction, involving maxilla, lateral aspect of nasal, lacrimal, palatine, sphenoid and frontal bones. The cleft may involve one of the above cranial bones as an isolated cleft or may involve all the above cranial bones. The cleft may occur as an isolated soft tissue or skeletal cleft or as a combination of both structures. The cleft may be unilateral or bilateral.

Number IV is the oblique facio cranial cleft. The soft tissue cleft [S] runs in the upward and oblique direction from the oral cavity, involving the junction of the medial and middle third of the upper lip, face [Meloschisis] at alar groove, middle third of the lower and upper eyelids [Blepharoschisis] and in the junction of medial and middle third of forehead. The cleft may involve one of the above

soft tissue structures as a partial cleft or may involve all of the above soft tissue structures. The skeletal cleft [Sk] starts from the oral cavity runs in an upwards and oblique direction, involving the lateral aspect of maxilla, sphenoid, zygoma and frontal [middle third] bones. The cleft may involve one of above cranial bones as isolated cleft or involve all bones or in combination of both soft tissue and skeletal structures. The cleft may be unilateral or bilateral.

Number V is the oblique facio cranial cleft. The soft tissue cleft [S] runs in the upward and oblique direction from the oral cavity, involving the upper lip at the junction of middle and lateral third, face [Meloschisis] lateral to the nasolabial groove, middle third of lower and upper eyelids [Blepharoschisis or Colomba eyelids] and in the middle third of forehead. The cleft may involve one of the above soft tissue structures as a partial cleft or may involve all of the above soft tissue structures as complete cleft. The skeletal cleft [Sk] starts from the oral cavity, runs in upward and oblique direction, involving lateral aspect of maxilla, sphenoid, zygoma and frontal and parietal bones. The cleft may involve one of the above cranial bones as a partial cleft or all of the bones or in combination of both soft tissue and skeletal structures. The cleft may be unilateral or bilateral.

Number VI is the oblique facio cranial cleft. The soft tissue cleft [S] runs in the upward and oblique direction, involving the lateral third of the upper lip, face [Meloschisis], lateral third of lower and upper eyelids [Blepharoschisis] and in the lateral third of the fronto parietal regions. The cleft may involve one of the above structures as a partial cleft or may involve all of the above soft tissue structures as a complete cleft. The skeletal cleft [Sk] starts from the oral cavity runs in an upward and oblique direction, involving the zygoma, temporal and parietal bones. The cleft may involve one of the above cranial bones as a partial or complete cleft of all bones or in combination with both soft tissue and skeletal structures. The cleft may be unilateral or bilateral.

Number VII is the oblique facio cranial cleft. The soft tissue cleft [S] runs in the upward and oblique direction, involving the lateral third of upper lip, face [Meloschisis], lateral to the lateral canthal region, and temporo parietal region. The cleft may involve one of the above structures as an isolated cleft or may involve all of the above soft tissue structures. The skeletal cleft [Sk] starts from the oral cavity runs in an upward and oblique direction, involving the zygoma, temporal and parietal bones. The cleft may involve one of the above cranial bones or in combination with both soft tissue and skeletal structures, the cleft may be unilateral or bilateral.

Number VIII is the oblique facio cranial cleft. The soft tissue cleft [S] runs in an upward and oblique direction, involving commissure, face [Meloschisis] and external ear [auricle]. The cleft may extend from the commissure to the external ear cartilages. The cleft in the upper three fourths of the ear occurs in soft tissue and auricular cartilages. In the middle, it may pass through the external auditory canal involving both soft tissue and cartilage. On the lower level it may pass through soft tissue only i.e. lobule. The cleft may involve one of the above soft tissues as an isolated cleft or all the above structures. The cleft in the upper three fourth of the External ear occurs together in soft tissue and skeletal [Auricular cartilage] structures [S-Sk]. The external auditory canal cleft involves both soft tissues and cartilage, and the cleft in the lower one fourth of the external ear is the only soft tissue ear lobe cleft. The skeletal cleft [Sk] runs in upward and oblique direction, involving ramus of the mandible. The cleft may occur as an isolated cleft in the commissure and face as macrostomia, or may involve in a combination of commissure, face and external ear. The cleft may occur one side or on both sides. Clinically unilateral or bilateral cleft through commissure may be seen as macrostomia.

Number IX is the Transverse medial ocular facio cranial cleft. The soft tissue cleft [S] runs in the transverse direction from the medial canthal region towards the median plane, involving the soft tissue in between the eyelids in the medial canthal region and the nose. The skeletal transverse cleft [Sk] runs in the transverse direction in the medial canthal region towards the midline, involving the nasal, ethmoid and lacrimal bones. The cleft may involve only the soft tissue structure or may involve both soft tissue and skeletal structures. The cleft may be unilateral or bilateral.

Number X is the lateral ocular Transverse facio cranial cleft. The soft tissue cleft [S] runs in the transverse direction from the lateral canthal region towards the temporal region, involving the soft tissue in between the eyelid in the lateral canthal region and temporal region. The skeletal transverse lateral ocular cranial cleft [Sk] runs in the transverse direction in the lateral canthal region towards temporal region, involving fronto zygomatic and temporal bones. The cleft may involve only the soft tissue structure or may involve both soft tissue and skeletal structures. The cleft may be unilateral or bilateral.

Number XI is the First Branchial Cleft Anomalies. The external opening of this cleft is below the external auditory canal in the anterior border of the sternocleidomastriod muscle. The internal opening is in the Tonsillar sinus or near the palatopharyngeal arch. In this Branchial cleft anomaly there may be

only soft tissue involvement or a combination with cartilage clinically recognized as Branchial vestige. The cleft may be unilateral or bilateral.

Number XII is the Second Branchial Cleft Anomaly. The external opening of this cleft anomaly is at the junction of the upper two thirds and lower one third in the anterior border of the sternocleidomastriod muscle. The internal opening is in the Tonsillar sinus or near the palatopharyngeal arch. This is a common variety of cleft anomaly. The cleft may be unilateral or bilateral.

Number XIII is the Third Branchial Cleft Anomaly. The external opening of this cleft anomaly is just below the external opening of the Number XII [Second branchial cleft anomaly], in the anterior border of sternocleidomastriod muscle. The internal opening is in the Tonssillar sinus or near the palatopharyngeal arch. The cleft may be unilateral or bilateral.

Number XIV is the Fourth Branchial Cleft Anomaly. The external opening of this cleft is in the anterior border of the sternocleidomastriod muscle near the sternoclavicular joint. The internal opening of this cleft is in the Tonsillar sinus or near the palatopharyngeal arch. This cleft anomaly may occur as a unilateral or bilateral cleft. According to Converse Plastic Surgery, Volume 5, the Fourth Branchial cleft anomalies have not been clinically demonstrated, despite a theoretical basis for their existence

Number XIV cleft [Fourth Branchial Cleft anomaly] has been documented.

Number XV is the Lower median facio cervical and tongue cleft [Glossoschisis]. The cleft may be seen as a soft tissue cleft of the lower lip and tongue in the midline. The cleft may be seen in the skeletal structure i.e. mandible or cartilaginous structures like hyoid, thyroid, cricoid and trachea in the midline. The soft tissue cleft starts from the oral cavity in the midline of the lower lip, and runs in the downward direction in the neck, some time upto the sternal notch. The cleft may involve these soft tissues in varying degrees. The external opening of this cleft is in the midline of the neck and the internal opening is in the tongue. The median cervical cleft, represents remnants of the thyroglossal duct with external opening in the midline of the neck . The internal opening is in the foramen cecum of the tongue. The skeletal bony cleft occurs in the medium plane of the body of mandible. The skeletal cartilaginous cleft occurs in the median plane through Hyoid, Cricoid, Thyroid and Trachea.