

Cleft Lip: Aetiology, Genetic Basis and Pathological Anatomy

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Abstract:

Background: Cleft lip, with or without cleft palate, is a common congenital craniofacial anomaly arising during early embryological development. Its etiology is complex and multifactorial, involving interactions between genetic susceptibility and environmental exposures. Genetic abnormalities may affect essential processes of midfacial development, including cellular patterning, proliferation, extracellular communication, and differentiation, with several genes implicated in syndromic and non-syndromic forms of clefting. Environmental factors, including certain medications, maternal smoking, alcohol exposure, and folate deficiency, may further increase the risk, particularly in genetically susceptible fetuses. The resulting deformity involves complex alterations of the lip, nose, maxillary skeleton, and associated musculature. In unilateral cleft lip, abnormal insertion and discontinuity of the orbicularis oris muscle produce asymmetric forces that contribute to displacement of the columella, nasal septum, and alar base. The clinical presentation varies considerably in severity, ranging from subtle microform defects to complete clefts involving the lip, alveolus, and palate. A comprehensive understanding of the etiological factors, genetic basis, pathological anatomy, and classification of cleft lip is therefore essential for accurate assessment and appropriate surgical planning.

Keywords: Cleft lip; Cleft lip and palate; Craniofacial anomalies; Genetic factors; Environmental factors; Pathological anatomy; Orbicularis oris; Cleft classification.

Introduction:

Cleft lip etiology and pathogenesis is contributed to two main factors; genetic and environmental factors. However, it is very difficult to recognize specific etiology responsible for these defects because these disorders arise in the early embryological life, therefore these defects are common and unpredictable (1).

Genetic factors:

The process of midface development involves genes which control: cell patterning, cell proliferation, extra-cellular communication and differentiation.

Cleft malformations are linked to gene abnormalities in each of these developmental stages that are critical for midface development. Clefts are generally the result of a complicated genetic event; single genetic disorders linked to clefts are uncommon. While at least one main gene is discovered in half of patients, up to 20 genes are thought to interact to cause facial clefts in the majority of instances. (1).

There are several major categories of genetic defects, either syndromic or isolated non-syndromic (2):

- Patterning defects, e.g. **Dlx gene**.
- Proliferation defects, e.g. **sonic hedgehog gene**.
- Extra-cellular matrix defects, e.g. **TGF-alpha gene**.

- Differentiation defects, e.g. **TGF-beta gene**.
- Interferon regulatory factors, e.g. **IRF-6**.
- Other genes: **MSX-1** (Drosophila msh homeobox homolog-1) and **PAX-9** (Paired box protein) (causing tooth agenesis with or without cleft).
- **TP-63** and **RIPK-4** (causing ectodermal dysplasia, ankyloblepharon and clefting)
- **VAX-1** (ventral anterior homeobox 1) on chromosome 10q25.
- **TBX-22** (T-box transcription factor-22 gene) causing X-Linked cleft palate and ankyloglossia.
- **Chromosomal abnormalities as:** 22q11 deletion syndrome (DiGeorge syndrome).

Dlx gene: The Dlx (Distal Less homeobox) gene family, is a set of six genes that regulate the development of the skeletogenic portion of the mesenchymal elements in the palate. Isolated palatal deficits result from mutations in these genes **(1)**.

Sonic Hedgehog Gene: The secreted sonic hedgehog (SHH) protein mediates ectodermal functions, and mutations of this gene classically produce holoprosencephaly. Multiple lines of evidence support (shh) as an ectodermal signal that shares in regulating the outgrowth and fusion of the facial domains **(1)**.

TGF alpha variant: Transforming Growth Factor alpha is a receptor ligand made in the epithelia. In humans CLP has been accompanied with a variant of TGF-alpha called Tagl, which has been found mostly among individuals with family history of cleft defects. This gene variant appears to have an additional teratogenic role with other agents such as alcohol and cigarette smoking **(1)**.

TGF beta3 gene: It is expressed just before fusion of the palate. In new-born: the lack of this factor results in palatal cleft. Its role likely relates to its ability to cause degradation of the midline epithelial seam, thus allowing complete fusion of palatal shelves. In humans, a rare allele of this gene has been accompanied with CLP particularly among familial cases **(2)**.

IRF 6: is a transcription factor, the specific function of IRF 6 (Interferon Regulatory Factor 6) is unknown. Most IRFs code for DNA binding motifs and as such would be expected to have multiple effects. Mutations in IRF 6 are found in van der Woude syndrome of CLP pits. Several investigators speculate that other alterations of IRF 6 are responsible for a portion of non-syndromic cleft lip/ palate. **(3)**.

MSX1 and PAX-9: Mice lacking a functional Drosophila MSX homeobox homolog-1 (MSX1) gene develop a cleft of the secondary palate and tooth agenesis. In humans, MSX1 mutation was first shown to cause an autosomal dominant form of tooth agenesis. Subsequently, van den **Boogaard et al. in 2000** described a family with a common pattern of tooth agenesis and concomitant presence of cleft lip with or without cleft palate; direct sequencing of MSX1 revealed a disease-causing mutation **(4)**.

VAX-1: (Ventral Anterior Homeobox 1), is a transcriptional regulator containing a DNA-binding homeobox domain. Resequencing of VAX-1 failed to identify an excess of rare variants in NSCL/P. VAX-1 is expressed in several craniofacial structures and mice deficient for VAX-1 develop CP. A homozygous missense mutation was described in a child from a consanguineous family with bilateral microphthalmia, bilateral CLP, and corpus callosum agenesis, mimicking the phenotype of the VAX-1/ mouse **(2)**.

22q11.2 deletion syndrome (22q11.2DS): is the most common chromosomal microdeletion disorder, estimated to result mainly from de novo non-homologous meiotic recombination events occurring in approximately 1 in every 1,000 fetuses. The first description was made in the 1960s in children with DiGeorge syndrome, who presented with the clinical triad of immunodeficiency, hypoparathyroidism and congenital heart disease. The syndrome is now known to have a heterogeneous presentation that includes multiple additional congenital anomalies and later-onset conditions, such as palatal, gastrointestinal and renal abnormalities, autoimmune disease, variable cognitive delays, behavioural phenotypes and psychiatric illness; all far extending the original description of DiGeorge syndrome **(5)**.

Environmental agents

Several substances have been linked to an increased prevalence of midfacial deformity following in-utero exposure. Furthermore, teratogen exposure is a factor in the genetically at-risk fetus. **(3) (Table: 1).**

Table (1): Environmental factors associated with cleft lip **(3)**

Agent	Role
Medications	- Anti-seizure medications: phenytoin and sodium valproate. - Folic acid antagonists like methotrexate. - Corticosteroid. - Glucocorticoids - Diazepam There is a relatively increased risk of orofacial deformities, but low absolute risk for clefts (6).
Cigarette smoking	Cadmium which is a component of tobacco causes hypoxia (6).
Alcohol	The effect of maternal ethanol might be changes in cell membrane fluidity or decreased enzyme activity, such as superoxide dismutase (7).
Folate deficiency	associations are with defects in neural tube and cardiac malformations, but still emerging evidences for a similar association with the development of CL/P (8).

In the unilateral cleft; the normal muscle fibers insertions which cross the embryologic fusion line of the maxillary and nasal processes are disrupted, leading to abnormal muscular forces that exist with the muscle groups in the nasolabial and oral region **(Figure 1).**

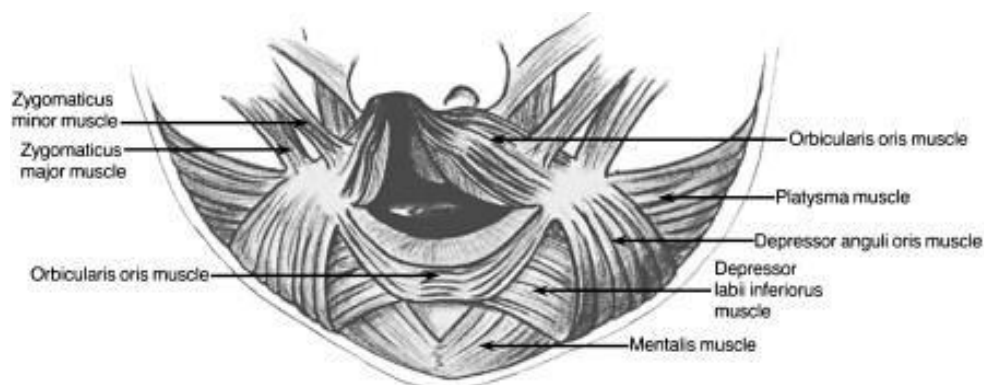
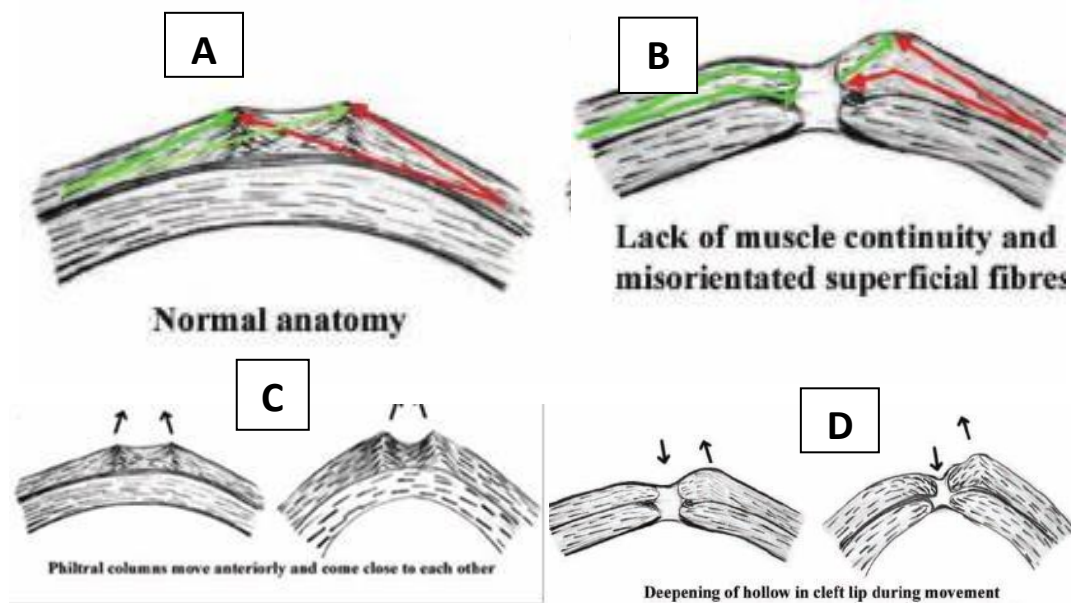


Figure (1): Unilateral cleft lip musculature. **(9)**

The aberrant orbicularis muscle insertion results in an imbalance that is further compounded by the maxillary skeletal hypoplasia. Rather than a horizontal insertion and continuous decussation with the contralateral orbicularis oris seen in the normal lip, the orbicularis oris inserts in a discontinuous manner into the columella on the noncleft side. This creates an unopposed force that pulls the columella and caudal nasal septum to the noncleft side **(10).**

On the cleft side, the orbicularis **(Fig 2)** inserts into the nasal base, retracting it laterally and inferiorly. Additionally, due to poor maxillary skeletal support at the alar base, the ala is further displaced posteriorly **(11).**



Figure(2-A&B): The anatomy of the orbicularis oris muscle and the relation between superficial fibres and philtral columns. **Figure(2-C&D):** Lack of continuity of the muscle and misorientated fibres. Deepening of the hollow as a result, and misorientated superficial fibres while being used. (12).

The asymmetric nasal tip (**Fig, 3**), results from the irregularly formed lower lateral cartilage on the cleft side. Although not universally accepted, the length of the lower lateral cartilage on the cleft side is considered equal to the noncleft side, primarily differing in shape and position (13).

On the cleft side, the medial crus is shorter and the lateral crus longer, with a less defined and wider dome. This results in a poorly defined nasal tip with less projection (14).

Figure 1



Figure (3-A& B): Asymmetry of nasal tip from basal and anterior views (13).

Deviation of the nasal septum is seen both in the cleft and non-cleft nostril. Due to the unopposed pull of the orbicularis oris muscle and the pre-maxillary ligament, the caudal nasal septum is deviated to the non cleft side nostril. This force affects only the caudal septum, allowing for septal bowing in the cleft side nasal airway. Whether alone or in conjunction with hypertrophied nasal turbinates, the aperture of the nasal airway is decreased, resulting in nasal airway obstruction at cleft side (**Fig 4**) (15).

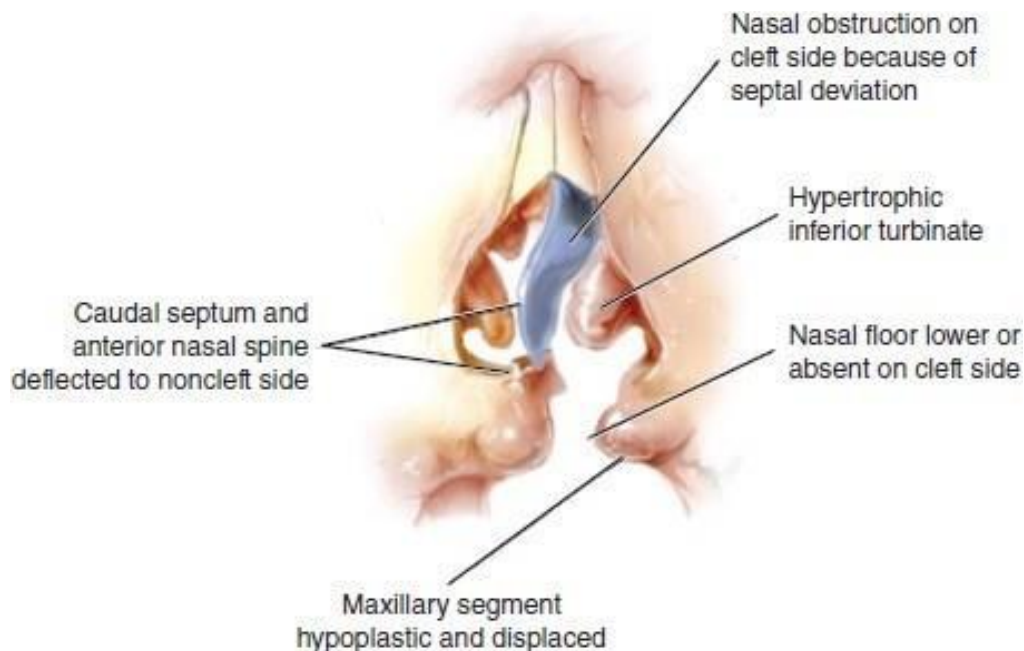


Figure (4): Anatomy of the cleft septum, turbinate, and skeleton (16).

The unilateral cleft lip deformities can be summarized as follows: (Figure 5) (17)

Osseous Deformities:

- The premaxilla is rotated outwards and projected.
- The lateral maxillary element is retro positioned and collapsed medially.

Nasal Deformities:

- The inferior edge of the septum is dislocated from the vomerine groove and presents with the nasal spine in the normal nostril floor.
- There is unilateral shortness in the vertical height of the columella, varying from three fourths to even one-half that of the normal side.
- The lower lateral cartilage is attenuated, its medial crus is shorter and its dome is separated from the opposite one at a lower level. The lateral segment is flattened and stretched across the cleft.
- The alar base is outwardly rotated leading to a flare.
- The vestibular lining is deficient on the cleft side.

Lip Deformities:

- The orbicularis oris muscle in the lateral lip terminates upward at the margin of the cleft to be inserted into the alar wing. In cases of incomplete cleft; the muscle does not, cross the cleft unless the bridge is at least one-third the lip height.
- The philtrum is short.
- The muscles between the midline and the cleft are hypoplastic.
- Two-thirds of the Cupid's bow, one philtral column, and a dimple hollow are preserved (17).

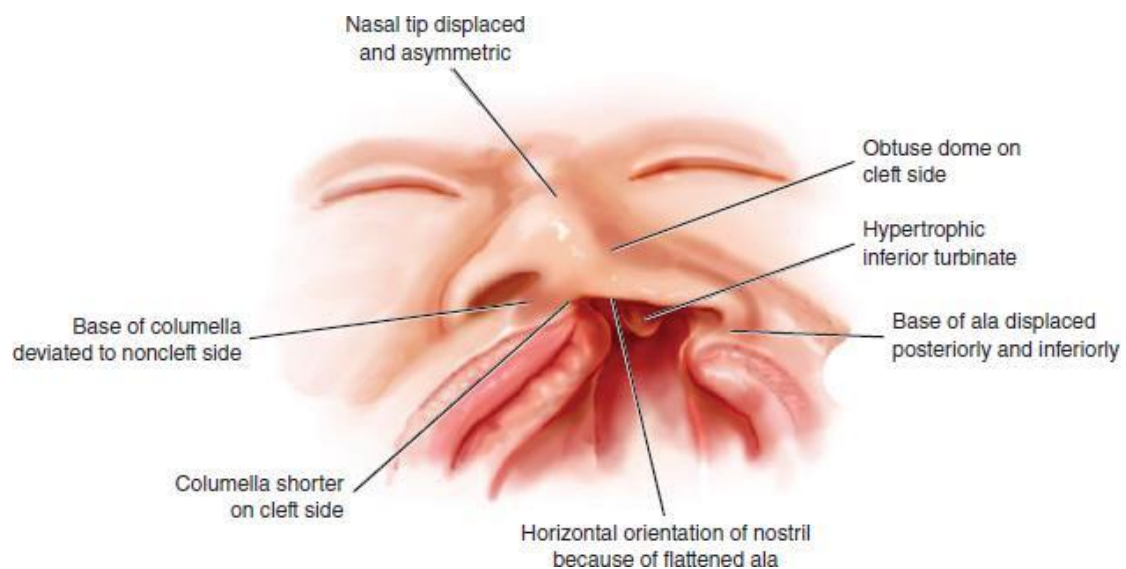


Figure (5): Unilateral cleft deformity. (17)

Clinical Classification:

Cleft lip and palate are traditionally classified by phenotype, which can range from microform to full cleft and can affect the alveolar ridge and palate. (Fig 6) (18).

Simonart's band is a soft tissue bridge that spans the cutaneous lip or alveolus in an incomplete cleft lip and is made up largely of skin with varying quantities of orbicularis oris muscle fibers (18).

Unilateral cleft lip is linked to abnormalities in the premaxilla induced by asymmetric forces during facial development. By applying a restorative force, Simonart's band may help to decrease the amount of facial malformation as a child grows. On the cleft side, there is twisting and distortion of the vermillion, as well as the loss of Cupid's bow and philtral markers. In milder instances, orbicularis oris muscle fibers are orientated asymmetrically along the cleft borders and may be continuous over Simonart's band (19).



Figure (6): Unilateral cleft lip. (A) Microform type, (B) incomplete type, (C) complete type (19).

Subclinical traits are most often seen in the non-syndromic CLP spectrum. Lip abnormalities, dental anomalies, and face morphometric characteristics are examples. Orbicularis oris muscle defects in the absence of a visible cleft are perhaps the most well-studied. These are detected using high-resolution ultrasonography and appear to be more common in close relatives of people with cleft lips. The discovery of subclinical symptoms might help researchers find more genes that are susceptible (19).

Yuzuriha and Mulliken describe lesser form labial clefts (those at the far end of the unilateral incomplete spectrum) as minor form (notched vermillion cutaneous junction extending 3mm or more above the normal Cupid's bow peak), microform (notch less than 3 mm above the normal Cupid's bow peak), or mini-microform (disrupted vermillion cutaneous junction without elevation of Cupid's bow peak). For each, nasal severity reflects that of the lip (Fig.7) (19).

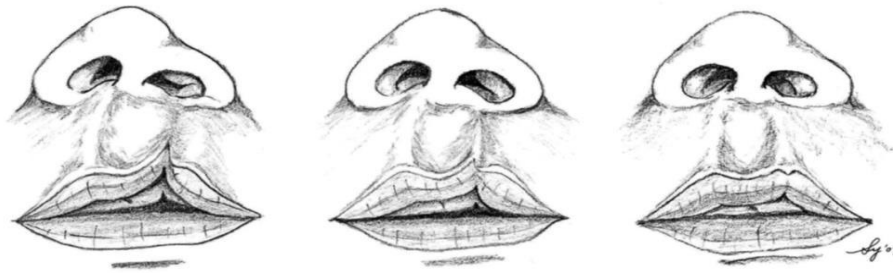


Figure (7): (Left) Minor-form cleft lip. (Center) Microform cleft lip. (Right) Minimicroform cleft lip. (20)

Evolution of cleft classification:

The subcommittee of cleft lip and palate nomenclature of the international confederation for Plastic and Reconstructive Surgery, announced in 1967 Rome Congress; the official Confederation of cleft classification. (Classification based on embryological principles) (21)

Group 1: clefts of anterior primary palate. (a) Lip: right and /or left. (b) Alveolus: right and /or left.

Group 2: clefts of anterior and posterior (primary and secondary) palate. (a) Lip: right and/or left. (b) Alveolus: right and/or left. (c) Hard palate: right and/or left.

Group 3: clefts of posterior secondary palate. (a) Hard palate: right and/or left. (b) Soft palate: medial.

For further subdivisions the terms total and partial should be used (21).

Kernahan (Figure 8) published the Y classification in 1971. The upper limbs represent the lip, the alveolus, and the portion of the hard palate anterior to the incisive foramen on the right and left sides of the main palate, respectively. The hard and soft palate posterior to the incisive foramen are represented by the lower limb. The nasal deformity was not mentioned in this classification, and it did not classify secondary palatal clefts into right or left sides. (22).

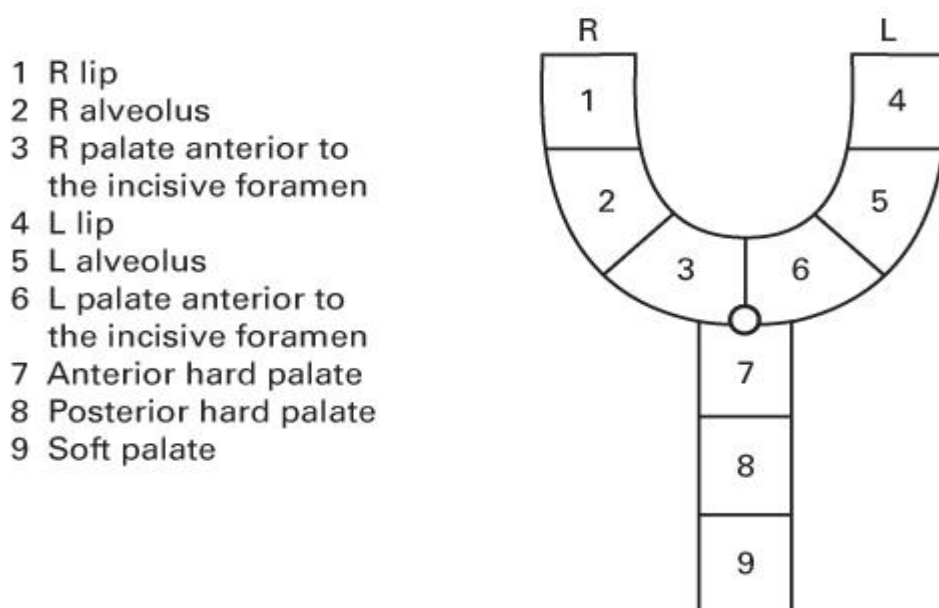


Figure (8): Kernahan Y classification. (23).

Then in 1972 Egyptian **Nabil El-Sahy** offered extensions (**Figure 9**) which deserve consideration, he added triangular peaks (1 and 5) to the ends of the prongs to represent the nasal floor in case of incomplete clefts of the lip. This modification caused shifting of the numbers in the squares with the lip represented by squares (2 and 6) and alveolus by (3 and 7), hard palate anterior to the incisive foramen by (4 and 8) and hard palate by (9 and 10) and soft palate by square (11), he placed circle (12) under the stem of the Y to represent the pharynx. (21).

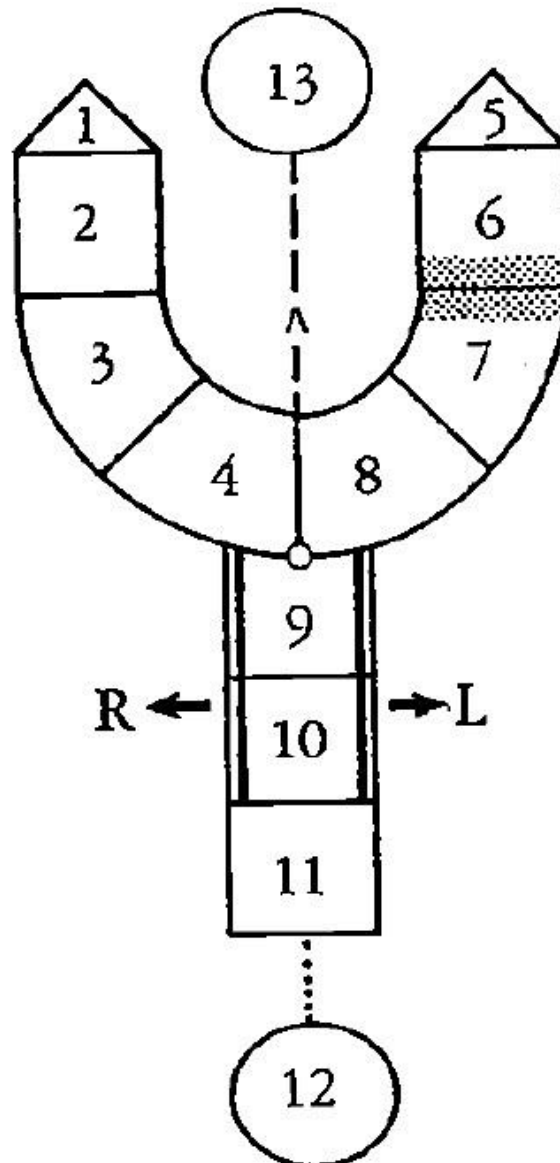


Figure (9): Elsayh modification of stripped Y classification (21).

Then, in 1976, **Millard** added inverted tips to El-triangular Sahy's tips to kernahans prongs, which were then indicated with horizontal lines showing the degree of nasal deformity (**Figure 10**) (21).

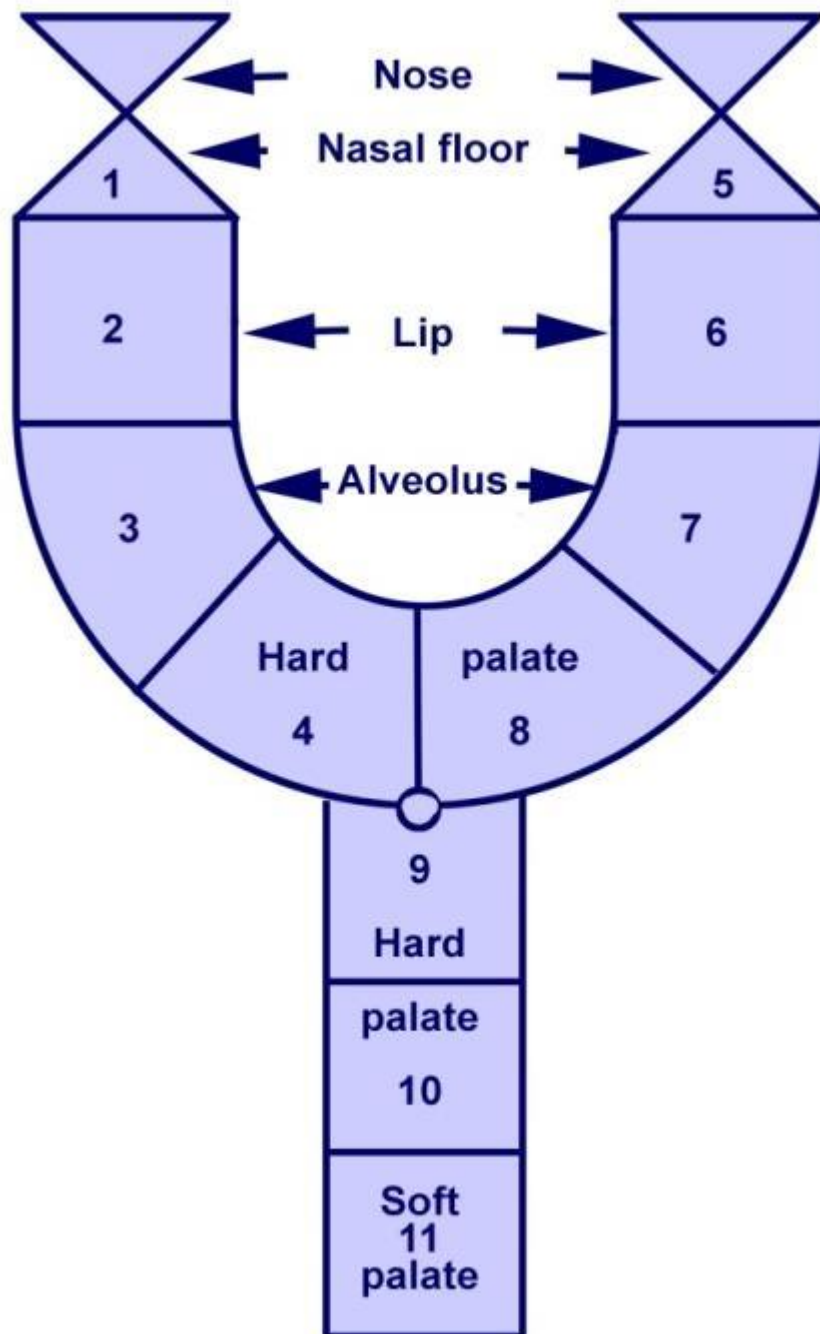


Figure (10): Millard modification of Kernahan striped-Y classification for cleft lip and palate. The small circle indicates the incisive foramen; the triangles indicate the nasal tip and nasal floor (21).

The Y classification was then modified (**Figure 11**) into another numeric system by **Noordhoff and his colleagues** that allowed the classification of the primary and secondary palate into left or right and is easily registered in the computer (24).

In this modified classification, each of the right or the left limb is labelled a number, 1–5 or 11–15, for the primary palate and 6–9 or 16–19, for the secondary palate, and 10 is a submucous cleft palate (22).

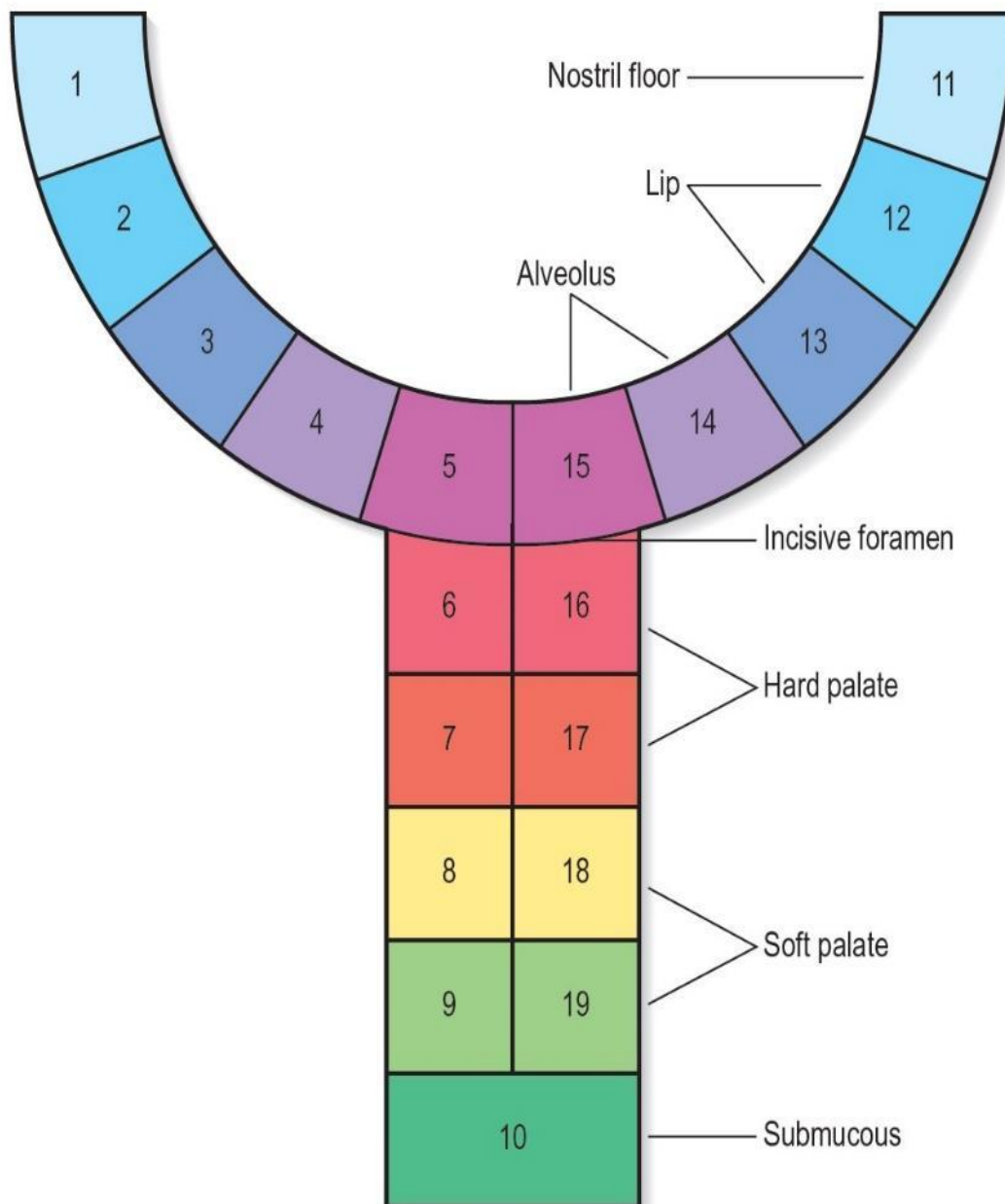


Figure (11): Modified stripped double Y classification (24).

In 2009, **Rossell-Perry** introduced the **Clock Diagram**, a new classification for cleft lip and palate that takes into account the severity of the cleft and describes the components and pathology of the cleft in order to apply it to treatment. When compared to Kernahan's diagram, the clock diagram is more effective in demonstrating a cleft's severity, which has a higher incidence of revision (25). The diagram is a circle divided into four quarters, each representing a cleft component (lip, nose, primary palate and secondary palate). Each section is separated into three sections based on the severity of the condition: mild, moderate, and severe (**Figure 12**).

The cleft code is made up of four digit numbers, one for each segment of the cleft diagram. These four-digit numbers are simple to deduce from the graphic and offer a detailed description of the cleft deformity's severity (25).

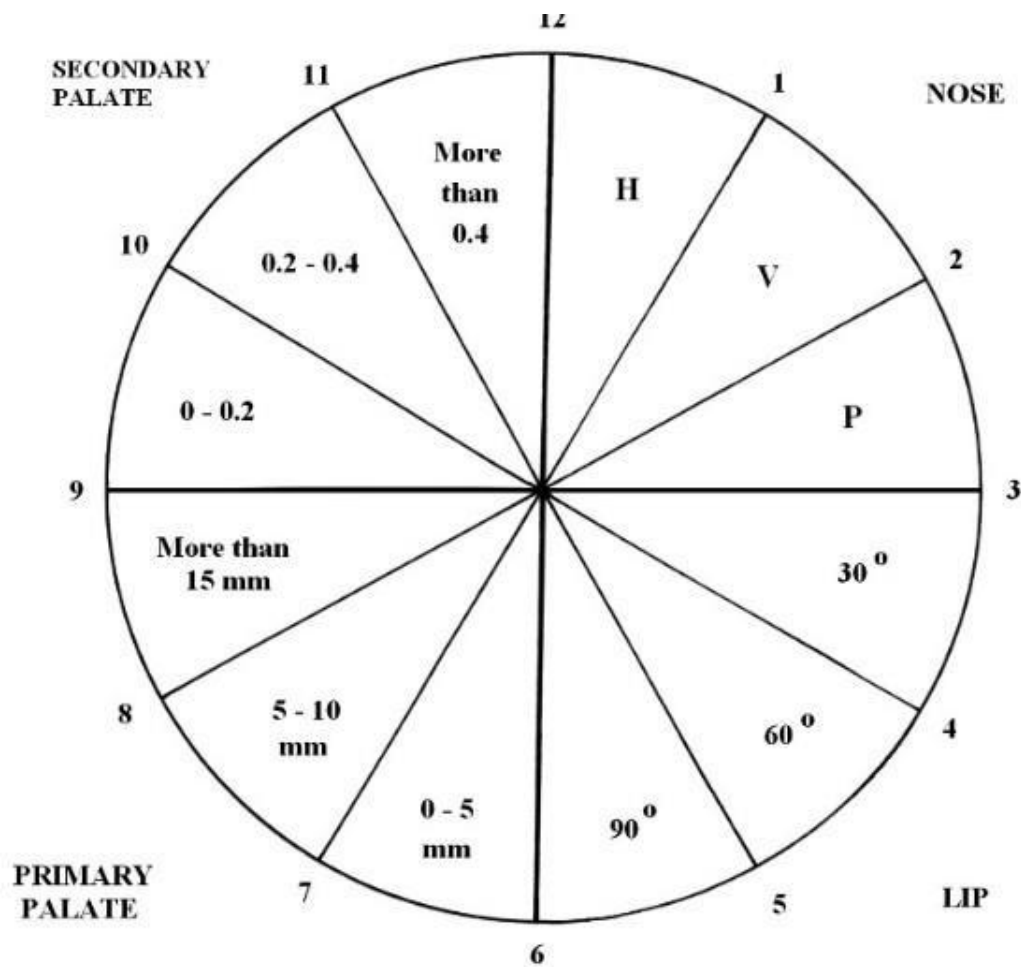


Figure (12): The clock diagram (25).

For nose: we use the letters: H, V and P to refer to horizontal, vertical and posterior displacement of nose.

For lip: we use the degree of cupid bow rotation to determine severity of defect.

For primary palate: we use the defect size in mm.

For secondary palate: we use a ratio between defect width and palatal width at the same level.

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