Learning Objectives: After studying this article, the participant should be able to: 1. Describe the differing types of congenital clefting defects that extend outward from the perioral region. 2. Define the sites of anatomical disruption and deformities that these types of facial clefts cause. 3. Describe the cause and incidence, if known, of orofacial clefts and their inheritance/transmission risks.

**Background:** Clefts of the orofacial region are among the most common congenital facial defects. The clinical presentation is usually that of a lateral cleft of the lip through the philtrum with or without extension through the palatal shelves. However, atypical forms of clefts with lip involvement also occur in a variety of patterns, some of which are embryologically predictable; others are not.

**Methods:** An overview of the embryology, cause, and incidence of this diverse and interesting group of congenital orofacial clefts is presented.

**Results:** Clefts involving the lateral upper lip; median upper lip; and oblique facial, lateral facial, and median mandibular regions are reviewed.

**Conclusions:** This review of orofacial malformations describes clefting anomalies that emanate from the mouth and lips. As the causes of orofacial clefts are better understood, it is becoming clear that a complex interplay between genetic and environmental variables causes these clefts. Future study of orofacial clefts will require increasingly sophisticated methods of elucidating these subtle interactions. (Plast. Reconstr. Surg. 115: 101e, 2005.)

Orofacial clefting is a failure in developing embryonic facial and palatal processes to either completely merge or fuse, which results in a predictable series of postnatal deformities. What is frequently not appreciated is that these congenital anomalies show a wide variety of anatomical disruptions extending outward from the oral cavity with varying frequencies and association with other congenital malformations. As such, the term *cleft lip–cleft palate* should be restricted to those clefts involving the embryonic primary and secondary palate. The variability of expression and decreased frequency of the more unusual orofacial clefts represent a set of more complex and etiologically distinct developmental problems.

**Classification**

A universally accepted classification scheme that fully encompasses, accurately describes, and integrates all the various types of orofacial and craniofacial clefts does not exist. Van der Meulen’s classification has an embryologic basis and Tessier’s classification has an anatomical basis (Fig. 1). Tessier’s classification system is commonly used by surgeons because it is purely descriptive and makes no pretense at causation and developmental relationships. There is also an ease of correlation between the anatomical defect and the required reconstructive surgery. The Tessier classification includes numbered clefts from 0 (midline cleft of the lip and nose) to 30 (a mandibular cleft). Cleft nos. 1, 2, and 3 are through the lateral margin of Cupid’s bow (corresponding with
the more commonly seen cleft lip–cleft palate deformities). Tessier cleft nos. 4, 5, and 6 are oro-ocular clefts; however, cleft no. 6 does not emanate from the oral cavity. Cleft nos. 7, 8, and 9 are lateral facial clefts; among these clefts, only cleft no. 7 emanates from the oral cavity. The remaining clefts are above the palpebral fissure (Figs. 2 and 3). Although this classification system is of value for most craniofacial clefting problems, it is inadequate for the commonly seen cleft lip–cleft palate deformity (the typical cleft lip corresponds in part to Tessier cleft nos. 1, 2, and 3).

A purely descriptive classification scheme is used for this review of orofacial clefts and includes only those clefts that have an oral component. In circumoral fashion, these clefts include the median cleft lip (Tessier cleft no. 0), unilateral and bilateral cleft lip (primary palate; Tessier cleft nos. 1, 2, and 3), oblique facial cleft (Tessier cleft nos. 4 and 5), lateral facial cleft (Tessier cleft no. 7), and the median mandibular cleft (Tessier cleft no. 30).

INCIDENCE

According to recent studies, the frequency of orofacial clefting is on the rise.²,³ In a study of clefting frequency in spontaneously aborted and stillborn fetuses, the incidence of facial...
malformations was 4.25 percent. With the remarkable improvements in perinatal care and prenatal medical technology, it seems likely that more of these fetuses will survive to term and require treatment. In a recent population-based sample from California, the birth prevalence of all orofacial clefts was 0.17 percent, with isolated clefting constituting roughly two-thirds of these patients; the remainder were a mixture of sequences, chromosomal aberrations, associations, and unknown causes. An increased awareness and understanding of these unique facial clefting anomalies is particularly pertinent to the plastic surgeon.

**EMBRYOLOGY**

Virtually all cases of cleft lip–cleft palate are attributable to the failure of the medial nasal process to either contact or maintain contact with the lateral nasal and maxillary processes. The embryologic pattern of neural crest cell migration and subsequent merging is now appreciated to be a complex interplay of movements initiated when the inferior edge of the medial nasal process joins the maxillary process at approximately day 30 in the human embryo. A significant morphogenetic movement of the nasal placode (rotation and advancement) then permits its lateral nasal process to sweep over the maxillary process a few days later to join with the medial nasal process to collectively form the upper lip-nasal unit. A cellular deficiency or failure of contact maintenance in one or several components of this six-piece midfacial convergence results in the variations in clinical presentations that are commonly seen (Figs. 2 and 3). Simonart’s band, which can be seen at the posterosuperior aspect of some lip clefts (Fig. 4, left), may well illustrate a rupture of contact (lack of contact maintenance) rather than failure to make contact between the processes and may be the primary developmental problem in many clefts. This residual fibrous band is found in the approximate location of the embryonic union of the maxillary and median nasal processes that constitute the primary palate and is often associated with a narrower cleft defect than those clefts in which it is not found. Various other webs or synechiae can occasionally be seen attached to the cleft, indicating inadvertent adhesion of structures from surrounding facial processes (Fig. 4, right).

In addition to the importance of merging and fusion, the size of the facial processes affects facial morphology and cleft susceptibility. An inherently smaller median nasal process, as would be suspected in Asians because of their smaller midfaces, tendency for class III occlusal relationships, and flatter nasal structures, may partially account for their relatively high rates of clefting. Conversely, some African Americans have broad, larger noses, increased facial widths, and a tendency for maxillary dentoalveolar protrusion, all of which indicate the
presence of well-developed median nasal processes and a decreased clefting frequency.

The cause of cleft lip–cleft palate is complex and multifactorial, involving both genetic and environmental factors (Tables I through IV). Transmission of the cleft phenotype in a simple mendelian fashion, as is seen in many other hereditary disorders, rarely occurs. This is supported by studies of cleft monozygotic twins that show a 30 to 60 percent concordance rate. When compared with the 1.0 to 4.7 percent concordance rate for dizygotic twins, these results favor an important but not exclusive role for genetics in the development of cleft lip–cleft palate. In a family with a cleft lip–cleft palate child, the chance that a second child will be born with a similar defect is 3 to 4 percent; if two children have the defect, the chance of a third child being born with the defect is 9 percent. In addition to genetics, environmental factors (Table III), such as smoke exposure and use of steroids, phenytoin, and retinoids, have also been implicated in the development of cleft lip–cleft palate. More recently, a complex interplay between genetic and environmental factors has been unfolding.

### TABLE I
Genetic Links to Syndromic Orofacial Clefts*

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Location</th>
<th>Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van der Woude</td>
<td>1q32–41</td>
<td></td>
</tr>
<tr>
<td>Ectrodactyly ectodermal dysplasia</td>
<td>3q27</td>
<td>P63</td>
</tr>
<tr>
<td>Margarita Island ectodermal dysplasia</td>
<td>11q23</td>
<td></td>
</tr>
<tr>
<td>Aicardi</td>
<td>Xp22</td>
<td></td>
</tr>
<tr>
<td>Craniofrontonasal dysplasia</td>
<td>Xq22</td>
<td></td>
</tr>
<tr>
<td>Hypertelorism-microtia-clefting</td>
<td>1q, 7p</td>
<td></td>
</tr>
<tr>
<td>Kallman</td>
<td>Xp22</td>
<td>KAL1</td>
</tr>
<tr>
<td>Gorlin</td>
<td>9q22–31</td>
<td>LMX1B</td>
</tr>
<tr>
<td>Velo-cardio-facial</td>
<td>22q11</td>
<td></td>
</tr>
</tbody>
</table>


### TABLE II
Genetic Links to Nonsyndromic Orofacial Clefts*

<table>
<thead>
<tr>
<th>Gene</th>
<th>Locus</th>
</tr>
</thead>
<tbody>
<tr>
<td>SKI/MTHFR</td>
<td>1p36</td>
</tr>
<tr>
<td>TGFβ2</td>
<td>1q11</td>
</tr>
<tr>
<td>TGFα</td>
<td>2p13</td>
</tr>
<tr>
<td>MSX1</td>
<td>4p16, 1q31, 6p23</td>
</tr>
<tr>
<td>PRL1</td>
<td>11q23</td>
</tr>
<tr>
<td>TGFβ3</td>
<td>14q24</td>
</tr>
<tr>
<td>GABBR3</td>
<td>15q11</td>
</tr>
<tr>
<td>RARα</td>
<td>17q21</td>
</tr>
<tr>
<td>BCL3</td>
<td>19q13</td>
</tr>
</tbody>
</table>


### GENETIC FACTORS

Cleft lip is a feature in 171 syndromes (15 percent of cleft lip–cleft palate cases are syndromic) (Table I). Sixty-four are autosomal recessive, 35 are autosomal dominant, and six are X-linked recessive. In a series examining the association of malformations with clefting, 13.6 percent of patients with cleft lip, 36.8 percent of patients with both cleft lip and cleft palate, and 46.7 percent of patients...
with cleft palate alone had associated malformations.22

Nonsyndromic cleft lip–cleft palate is a heterogeneous disease entity with candidate clefting loci on chromosomes 1, 2, 4, 6, 11, 14, 17, and 19 (Table II). Chromosome 1 is associated with nonsyndromic orofacial clefting by means of a mutation in methylenetetrahydrofolate reductase on 1q36.24 The short arm of chromosome 2 has a susceptibility gene in the 2p13 region found to be associated with cleft lip–cleft palate.25 Studies have disagreed about whether this site involves transforming growth factor alpha26 or not.27 MSX1 located on chromosome 4 (4q25) has been associated with increased risk of cleft lip–cleft palate.28 Chromosome 6 contains a likely gene responsible for cleft lip–cleft palate at 6p23.29 Other chromosomes with possible clefting loci include chromosome 11, the transforming growth factor beta locus on chromosome 14, the retinoic acid receptor-α gene on chromosome 17, the BCL3, and the transforming growth factor beta locus on chromosome 19.30,31

ENVIRONMENTAL FACTORS

The list of environmental factors associated with orofacial clefting is growing (Table III). Any maternal alcohol consumption during pregnancy increases the incidence of orofacial clefting.32 Increased alcohol consumption results in further increases in the incidence of developing both syndromic and nonsyndromic clefts.33 An association between maternal cigarette smoking and orofacial clefting is well established,30 resulting in at least a doubling of the incidence of cleft lip–cleft palate compared with nonsmoking mothers. Furthermore, increased maternal smoking further increases the odds of having a child with cleft lip–cleft palate.54 The effect of maternal smoking appears to be related to increased serum carbon monoxide levels,15–17 which exert their effect on cytochrome oxidase.7

Multiple studies have shown that folate deficiency is associated with cleft lip–cleft palate.19,20 Prenatal folic acid supplementation has been shown to decrease this risk35; high pharmacologic doses (6 mg/day) are required for the protective effect.36 At present, folic acid supplementation is the only empiric preventative treatment shown to decrease the incidence of facial clefting. Conversely, folic acid antagonists increase the incidence of orofacial clefting.18 These findings highlight the (as yet incompletely understood) role of poor nutrition in the development of orofacial clefts, and suggest the reason for a link between increased risk of orofacial clefting and low socioeconomic status and the higher incidence of unusual orofacial clefts found in developing countries.

Maternal corticosteroid use causes a 3.4-fold increase in orofacial clefting.37 The increase has been corroborated by other investigators in nonsyndromic cleft lip–cleft palate.14 Anticonvulsants, including phenytoin, oxazolidinediones, and valproic acid, also cause cleft lip–cleft palate. Phenytoin causes a nearly 10-fold increase in the incidence of facial clefting11 and exerts its effect by inhibiting enzymes in the NADH dehydrogenase electron transport chain.7 Other pharmacologic agents, including retinoic acid, have also been implicated in orofacial clefting, but the exact mechanism of action remains to be determined.18

GENETIC-ENVIRONMENTAL INTERACTIONS

Much of the literature on facial clefting has examined environmental and genetic factors in isolation. More recent work indicates that there is a complex interplay between the two.10,30 Smoking, for example, is known to increase the incidence of orofacial clefting; however, infants with the transforming growth factor alpha genotype (also previously known

<table>
<thead>
<tr>
<th>Gene</th>
<th>Chromosome Map Location</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHH</td>
<td>7q36</td>
<td>60</td>
</tr>
<tr>
<td>TGFB</td>
<td>18p11</td>
<td>61</td>
</tr>
<tr>
<td>SIX3</td>
<td>2p21</td>
<td>62</td>
</tr>
<tr>
<td>ZIC2</td>
<td>13q22</td>
<td>63</td>
</tr>
<tr>
<td>PTCH</td>
<td>9q22</td>
<td>64</td>
</tr>
</tbody>
</table>


---

TABLE III

Environmental Causes of Orofacial Clefts*

<table>
<thead>
<tr>
<th>Teratogen</th>
<th>Cleft Type</th>
<th>Genetic Link</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>Cleft lip–cleft palate</td>
<td>MSX1, TGFb3</td>
</tr>
<tr>
<td>Cigarette smoke</td>
<td>Cleft lip–cleft palate</td>
<td>TGFa</td>
</tr>
<tr>
<td>Folic acid</td>
<td>Cleft lip–cleft palate</td>
<td>TGFa, MTHFR</td>
</tr>
<tr>
<td>Steroids</td>
<td>Cleft lip–cleft palate</td>
<td>TGFb</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Cleft lip–cleft palate</td>
<td>GABA receptor b3</td>
</tr>
<tr>
<td>Altitude</td>
<td>Cleft lip</td>
<td>TGFa/b, transforming growth factor alpha/beta.</td>
</tr>
</tbody>
</table>

to be associated with orofacial clefting) have a sixfold increase in orofacial clefting when combined with maternal smoking. Maternal cigarette smoking also interacts with an allelic variation of MSX1 that further increases the incidence of orofacial clefting. Infants with allelic variants at the MSX1 site born to mothers who have more than four drinks per month also show a higher incidence of clefting.

Maternal folic acid deficiency has been associated with orofacial clefting. This finding may be explained by a variant in the maternal 5,10-methylene-tetrahydrofolate reductase enzyme, making the enzyme less efficient. Additional work suggests that maternal genotype may also play a role in fetal folate status. With increased understanding about the causes of cleft lip–cleft palate, it is becoming more apparent that subtle interactions between the environment and genetic background make infants susceptible to clefting.

UNILATERAL AND BILATERAL CLEFT LIP–CLEFT PALATE

Clefts of the embryonic primary (cleft lip) and secondary palate (cleft palate) are overwhelmingly the most frequently encountered congenital facial defects, constituting nearly two-thirds of major facial malformation and nearly 80 percent of all orofacial cleft types (Figs. 2 and 3). Differences in racial susceptibility are well documented and are the result of racial variations in the timing and coordination of cellular morphologic patterns, particularly the development of the median nasal process. As such, the frequency may range from an incidence of one in 400 to 500 live births in Asians and American Indians to one in 1500 to 2000 live births in African Americans. Caucasian susceptibility is intermediate at one in 750 to 900 live births. The left side of the primary palate, for reasons as yet unclear (fetal position and circulatory and neural anatomy have all been implicated), is more often cleft than the right.

MEDIAN CLEFT LIP

In contrast to clefts of the lateral lip, median lip clefts are relatively rare. They are found in less than one in 100 cases of cleft lip–cleft palate, with a reported incidence of between 0.43 and 0.73 percent of cleft lip–cleft palate cases. Median cleft lips occur in less than 0.0001 percent of all births. Racial and sex differences have not been established.

Like all cleft lip processes, a graded spectrum of deformity occurs and is the result of failure of the two medial nasal processes to meet in the midline and fuse. However, median lip clefting raises concerns about the underlying face and brain not seen in the more common lateral lip clefts. An incomplete median cleft (vermilion notch) may occur as an isolated entity (Fig. 5) or as part of such syndromes as orofacial-digital syndrome (Fig. 6), which represents a spectrum of anomalies of the face, head, hands, and feet (types I to VI). More complete median cleft defects

FIG. 5. Incomplete median cleft lips. (Left) Vermilion notch, presence of central maxillary skeletal diastema, and double frenulum; (right) wider median cleft lip extending through the alveolus to the palate.
are syndromic and present as two separate entities: the median cleft lip with hypotelorism (holoprosencephaly) and median cleft lip with hypertelorism (median cleft face syndrome). When medial cleft lip occurs without holoprosencephaly, head circumference is within two standard deviations of the mean and normotelorism is usual.31

Holoprosencephaly (cyclopia-rhinencephaly) results from deficient anterior neural plate development. If the original holospheric telencephalon fails to develop lateral evaginations, the cerebrum remains singular rather than hemispheric. Therefore, the prosencephalic cavity remains as a monoventricle.49 The associated median facial abnormalities occur because of the sharing of embryologic cellular tissue (mesenchymal primordium) and the prechordal mesoderm (mesoderm between the prosencephalon and stomodeum) in conjunction with migrating neural crest cells.50 The frontonasal prominence of the prosencephalon then produces the median craniofacial skeleton (crista galli, ethmoid, vomer, nasal, and premaxillary bones) and the cartilaginous septum. The overlying soft tissues (forehead, nose, and prolabium) likewise arise from these embryonic tissues. Unlike lateral lip clefts, which represent a problem of merging and fusion, the holoprosencephalic median lip clefts are caused by a failure of development. The lateral aspects of the face are produced separately by the brachial arches and, as a result, are normal. Although the facies of holoprosencephaly are different and parallel that of brain development (cyclopia, type I; ethmocephaly, type II; and cebocephaly, type III),51,52 the median cleft lip with hypotelorism (type IV) is characterized by absence of the crista galli, nasal and premaxillary bones, and nasal septum. The hypoplastic ethmoids accompany but are not the cause of the orbital hypotelorism, which is primarily a brain defect (Fig. 7). It is important to note that other forms of median cleft lip exist that appear very similar to holoprosencephaly but without cere-
bral involvement, and that have varying degrees of vomero-septal-prolabial hypoplasia. An intact ethmoid, nasal bone, and crista galli appear to represent the key anatomical differences in these patients as compared with classic holoprosencephaly (Fig. 8).

A group of “syndromic”-appearing patients who have traditionally been assigned a place on the “normal” end of the holoprosencephaly spectrum has recently been described by Mulliken et al. These patients have nasomaxillary hypoplasia, orbital hypotelorism, and an associated unilateral and bilateral cleft lip–cleft palate. Because these patients have normal head circumference and intelligence, they cannot belong on a continuum with holoprosencephaly. To differentiate these patients from those with holoprosencephaly, authors have historically labeled these patients as “false” or “pseudomedian” cleft lips. Other authors have denoted this entity as a Binder anomaly, which is associated with chondrodysplasia punctata, cervical spine anomalies, and fetal exposure to warfarin. The patients in the study by Mulliken et al. did not have any of these characteristic findings or exposures and therefore cannot be classified as having Binder anomalies. Mulliken et al. prefer to refer to these patients as binderoid.

The median cleft face syndrome or frontonasal dysplasia appears to be the result of incomplete midline merging of the facial processes, with varying degrees of lateralization of their contents. Forebrain morphogenesis is rarely involved, and subsequent brain development is usually normal. Thus, frontonasal dysplasia is strikingly different from holoprosencephaly and presents in its extreme with a median cleft lip and palate, bifid nose, orbital hypertelorism, inferiorly displaced V-shaped frontal hairline, and cranium bifidum occultum (Fig. 9). Unlike holoprosencephaly, the premaxillary segment is usually present, although it is clefted and maxillary incisor eruption can be expected.

Mutations in several genes have been linked to holoprosencephaly. These include sonic hedgehog (SHH), TGIF, SIX3, ZIC2, and PTCH (Table IV). The only comparable animal model for holoprosencephaly (cyclopia) occurs in the offspring of sheep that ingest plant alkaloid. This finding is unique because of the specificity and reproducibility of the defect by this teratogen. Although nonspecific craniofacial malformations, including median cleft lip, have been produced by numerous other agents in animals, specific teratogenic sources for median defects in humans have not been reported. Alcohol—specifically, fetal alcohol syndrome—has been associated with midline developmental defects, including the median facial cleft in rare cases.

OBLIQUE FACIAL CLEFTS

The term oblique facial cleft, occurring in a variety of manifestations from the lip to the orbit, is a vague designation. The cleft has also been described by other equally nondescript names, including meloschisis and vertical facial and orbitalfacial clefting. It really represents a group of lateral midfacial dysplasias that consist of distinct malformations involving differing points of origin from the lip and superior extensions into the orbit. These clefts correspond to the Tessier cleft nos. 3, 4, and 5; the use of this nomenclature is of particular help in this area (Figs. 2 and 3). Because of their rarity (less than 0.25 percent among all facial clefts) and incomplete case descriptions in the literature, the actual incidence of these clefts as a group and individually is not known. All known cases are sporadic, with no syndromic association or sex predilection.

The oblique clefts, as indicated by Tessier cleft nos. 3 through 5, occur in slightly different regions of the lateral midface (cleft nos. 1 and 2 are best described as paramedian or
vertical facial clefts and are excluded from this discussion). The most medial variety (cleft no. 3, also known as a naso-ocular or nasomaxillary cleft) extends from the philtrum of the lip, as occurs in the more common lateral cleft of the lip, to the medial canthus of the eye, with foreshortening of this distance. As a result, a bony cleft occurs at the lateral incisor/canine area of the alveolus, extending through the frontal process of the maxilla to the lacrimal groove of the medial orbit. Soft-tissue defects, including colobomas of the nasal ala and lower eyelid and an inferiorly displaced medial canthus and globe, are characteristic. Concurrent absence or dysfunction of the nasolacrimal system is predictably high (Fig. 10). More laterally, the cleft no. 4 (also known as an oro-ocular cleft) spares the nose and extends toward a more centric orbital position. The lip origin of this cleft deviates from common lip clefts and does not violate the philtral ridge. At a point between the philtrum and commissure, the cleft extends superiorly through the nasolabial fold and passes into the orbit just medial to the infraorbital foramen (Fig. 11). As such, the medial canthal tendon and nasolacrimal duct are usually intact. However, a marked coloboma of the lower eyelid is present, and in some cases, varying degrees of anophthalmos are present. The no. 5 cleft is primarily distinguished from the more medially positioned cleft no. 4 by passing lateral to the infraorbital foramen (Fig. 12). This skeletal pathway difference has long been recognized and has historically (pre-Tessier) been subdivided into type I (no. 4) and type II (no. 5) forms of oro-ocular clefting. The lateralization of this cleft is also distinctly different at the alveolar level by originating posterior to the canine. The ocular findings, however, including a severe lower eyelid coloboma, inferior displacement, and partial prolapse of the orbital contents into the sinus and anophthalmos, are not unlike findings in a no. 4 cleft.
The embryology of the oblique facial clefts is difficult to explain by the known facial processes of merging and fusion. The no. 3 cleft occurs along the naso-optic groove, formed by the confluence of the lateral aspects of the olfactory placode and frontonasal process and the medial edge of the maxillary process, and as such the associated abnormalities are completely predictable. Cleft nos. 4 and 5, however, correspond to no known embryologic grooves or plane of mesenchymally supported epithelium, and their origin currently remains speculative. The cause of these clefts has loosely been ascribed to a primary arrest of development, neurovascular insufficiency or necrosis, or a result of tears in the developing maxillary process. More recent experimental work suggests that these malformations are caused by a combination of directly tethered tissue migration (such as from amniotic bands) and increased local pressure that produces cellular ischemia. As a result, such clefting may occur later in fetal development rather than during primary facial morphogenesis.

LATERAL FACIAL CLEFTS

Lateral facial clefts, or commissural clefts, are best thought of as a variable finding within the broader congenital condition of hemifacial microsomia (Tessier cleft no. 7). They are the second most common orofacial cleft (second to the common cleft lip), with an incidence less than that of hemifacial microsomia (one in 3500 to 5000 live births) because of an inconsistent occurrence within the syndrome. Although commissure clefts are not seen in every case of hemifacial microsomia, their occurrence should initiate a search for involvement of the ipsilateral ear, mandible, and facial nerve and overlying facial soft-tissue deficiencies. These clefts also occur in the oculoauriculovertebral spectrum (historically referred to as Goldenhar syndrome), which has the additional features of epibulbar dermoids, vertebral anomalies, and central nervous system and cardiopulmonary defects.

The clinical findings of the lateral oral cleft variably extend along a line from the commissure to the tragus. Most commonly, a 1- to 3-cm-long cleft is present, with disruption of the orbicularis and buccinator muscles and with the cleft edges lined by vermilion. Only rarely does a complete cleft extend posterior to or beyond the anterior border of the masseter muscle, although a groove or skin depression continuing along the cleft line to the ear may occasionally be seen (Fig. 13). Because of the association between lateral oral clefts and hemifacial microsomia, underlying deformities of the mandible are well appreciated. Less appreciated but equally common, particularly in severe expressions of the syndrome, is the zygomatico-orbital dysplasia, marked by a disruption of the zygomatic arch and inferior displacement of the lateral canthus caused by variable amounts of accompanying zygomatic hypoplasia and resultant orbital dystopia.

Lateral facial clefts are easy to understand embryologically, as the commissure represents the most anterior point of mesodermal merg-
ing of the maxillary and mandibular processes. Should the fusion process remain incomplete, a variable spectrum from furrowing of the tissues to complete anatomical separation persists. The pathogenesis of the lateral facial cleft appears to be heterogeneous. A vascular cause, attributable to embryonic hematoma formation from disruption of the stapedial artery stem, is one proposed mechanism.\textsuperscript{77} The severity of the condition subsequently depends on the size of the hematoma and its time course of resolution as brachial arch development occurs.\textsuperscript{78} The cause of this embryonic hemorrhage has been speculated to range from vascular flow anomalies, such as hypertension and hypoxia, to pharmacologic agents, such as salicylates and anticonvulsants.\textsuperscript{79} Intrauterine compression secondary to oligohydramnios in the embryonic head region has also been suggested and may account for some cases of hemifacial microsomia that occur with other anomalies, such as limb reduction defects.\textsuperscript{80}

\textbf{MEDIAN MANDIBULAR CLEFTS}

Clefting of the lower face (Tessier cleft no. 30) (Fig. 1) almost universally occurs through the midline of the lip and mandible. Although paramedian lower lip/mandibular clefting has been reported, there are fewer than 70 reported cases in the literature, appearing with less frequency than the oblique facial clefts.\textsuperscript{11,81,82} Sex and racial predilections remain indeterminate.

A range of inferior clefting has been reported that extends from mild notching of the lower lip and mandibular alveolus (Fig. 14) to complete cleavage of the mandible, extending into inferior neck structures.\textsuperscript{81–85} Tongue involvement is typical though variable in expression, ranging from a bifid anterior tip with ankyloglossia to the bony cleft margins, to marked lingual hypoplasia. Inferior cervical defects (midline separation, hypoplasia, and agenesis) of the epiglottis, strap muscles, hyoid bone, thyroid cartilage, and sternum may also be present, particularly when the cuta-
neous cleft passes caudal to the gnathion point on the chin.

The embryologic basis of median mandibular clefts lies in the failure of coaptation of the free ends of the first visceral arches in the midline. Once the arches are formed through neural crest cell migration, vascularization, and mesodermal myoblastic ingrowth, growth centers are organized at their tips that are responsible for closing the final gap and coalescing the two sides. As the incisor teeth are frequently missing along the medial mandibular margins, this suggests that partial or complete failure of growth center differentiation and development is responsible for such defects rather than a simple merging and contact maintenance. Because no animal models exist for study of the median cleft lip, the cellular basis for this defect may remain unknown for some time. Presumably, however, more inferior cervical defects would be caused by similar mechanisms in the second and third visceral arches. The occasional association of a superior midline defect (cleft palate) with a median mandibular cleft is interesting because it suggests that a broader defect in epithelial mesenchymal merging and fusion is occurring or that the tongue abnormality affects palatal shelf closure in utero in these patients.

**SUMMARY**

This review of orofacial malformations describes clefting anomalies that emanate from the mouth and lips—the most common cleft structure of the face. Some of these clefts are relatively common, including the typical cleft lip with or without cleft palate; others are extremely rare. As the causes of orofacial clefts are better understood, it is becoming clear that a complex interplay between genetic and environmental variables causes these clefts. Future study of orofacial clefts will require increasingly sophisticated methods of elucidating these subtle interactions. Orofacial clefts are of particular relevance to plastic surgeons, who set the world’s standard for care and reconstruction of such facial congenital deformities.

Barry L. Eppley, M.D., D.M.D.
Division of Plastic Surgery
Craniofacial Program
Indiana University School of Medicine
702 Barnhill Drive, Suite 3540
Indianapolis, Ind. 46202
beppley@iupui.edu

**REFERENCES**


