The Spectrum of Isolated Congenital Nasal Deformities Resembling the Cleft Lip Nasal Morphology

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Objective: To define the intrinsic (hypoplasia) and extrinsic (deformational) contributions to congenital nasal deformities and the potential of a carrier state for orofacial clefting.

Methods: Retrospective case series.

Results: The factors affecting 4 congenital nasal deformities are postulated after contrasting the patient's characteristics.

Conclusions: The spectrum of congenital nasal deformities includes those that resemble the cleft lip nasal deformity, but careful inspection is needed for proper classification. Classifying congenital nasal deformities can be difficult in part due to the highly variable normal range. The most minor form of the typical unilateral cleft lip nasal deformity is the microform cleft. The potential of an isolated cleft lip nasal deformity without obvious cleft lip has been previously suggested to represent a carrier state for orofacial clefting. Definitive genetic studies and continued anthropometric documentation in relatives of patients with orofacial clefts are needed if we are to uncover previously unidentified associations, and a potential carrier state.

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CONGENITAL NASAL DEFORMITIES can occur in a diverse spectrum of severity ranging from minor deformities to severe, atypical craniofacial clefts (eg, Tessier type). The estimated incidence of these deformities ranges from 1 in 20,000 to 1 in 40,000 live births. Losee et al classified congenital nasal deformities into the following (hereinafter, Losee types): type 1, which has hypoplastic nasal structures; type 2, which demonstrates nasal hyperplasia or duplication (eg, polyrhinia); type 3, which involves orofacial clefting; and type 4, in which deformities are neoplastic or vascular malformations of the nose (eg, hemangiommas).1

Of the congenital nasal deformities, the typical cleft lip nasal deformity (CLND) is the most common owing to the relative high incidence of orofacial clefting. The most common congenital craniofacial anomalies are orofacial clefts with an estimated overall incidence that ranges from 1 in 600 to 1 in 750 live births in the United States.2 Orofacial clefts are the fourth most common birth defect after congenital heart deformities, spina bifida, and limb deformities.3

Orofacial clefts can be unilateral or bilateral and exist as complete, incomplete, or microform. Two-thirds of orofacial clefting involve the cleft lip with or without cleft palate (cleft lip/palate), whereas nearly one-third involve the distinctly different, isolated cleft palate only. Cleft lip and cleft palate are most often unilateral (80%), more commonly left-sided, and have an incidence rate in white individuals (1 in 1000 live births) that is distinctly different from incidence rates in other ethnicities. Native Americans (3.6 in 1000 live births) and Japanese (2.1 in 1000 live births) show the highest incidence, while African Americans demonstrate the lowest incidence (0.3 in 1000 live births).3 Although isolated cleft palate is most commonly nonsyndromic (in >90% of cases), at least 300 syndromes have been associated with cleft lip/palate.4

The distinctive characteristics of the CLND (Losee type 3) differ between the type of orofacial clefts and severity of involvement. The severity of the CLND can be highly variable. The nasal deformities associated with the unilateral cleft lip are variably expressed across a spectrum of minor to severe typical abnormalities. The severely wide, unilateral cleft lip and palate often has the most severe nasal deformity. Typical characteristics include (1) an asymmetric nasal tip (owing to lower lateral cartilage dysmorphologic characteristics), (2) caudal septal deflection to the noncleft side, (3) foreshortened columellar skin, (4) alar base malposition (anterior, inferior, and posterior), and (5) splaying of the alar base with smiling ow-
ing to cleft-side orbicularis oris fibers inserting into the piriform aperture and alar base (Figure 1). The typical bilateral CLND exhibits the following characteristics: a short nasal columnella that contributes to bilateral hooding of the ala and alar base widening, along with a wide, bulbous deprojected nasal tip. As outlined by the Kenna-han-Stark striped-Y classification system, the involvement of the lip, nasal sill, alveolus, and palate (primary and secondary) may include a microform cleft on one side and a complete cleft on the contralateral side.

Next along the continuum of severity is the incomplete cleft lip, which is a cleft that extends more than one-fourth of the labial height (from the normal Cupid’s bow peak to the nasal sill). The most diminutive expression of the cleft lip deformity is the “microform cleft,” the definition of which has evolved since first illustrated by Veau in 1938. Other terms for the microform cleft lip and nasal deformity include occult, minor, or forme fruste (aborted form), which was considered to be a cleft that healed prior to birth. The affected lip skin reveals an absence of sweat glands and hair follicles. The characteristics of the microform cleft lip are now considered to include (1) philtral furrowing or groove, (2) notched or indented lip mucosa, (3) a notched vermilion-cutaneous junction with elevated peak of the medial Cupid’s bow, and (4) minor nasal deformity. The microform CLND consists of a depressed nasal sill, alar hooping, and alar base asymmetry (Figure 2).

**METHODS**

**INHERITANCE**

The etiology of orofacial clefts involves the interaction between genetic and environmental factors. Theoretically, genetically susceptible individuals may encounter environmental triggers that progress to a variety of congenital abnormalities. Environmental factors that have been linked to orofacial clefts include maternal exposure to teratogens (eg, phynotoin, alcohol), nutritional deficiencies (eg, folic acid), or tobacco use. The exact interplay between the genetic susceptibilities and environmental assault has not been elucidated, but single gene mutations in candidate genes such as Interferon Regulatory Factor 6, transforming growth factors, TBX22, and MSX1 have demonstrated orofacial clefts in experimental models.

The multiple influences that are involved in orofacial clefting are demonstrated in the variable recurrence rates for parents or relatives of patients with cleft lip/palate. A child with cleft lip/palate will have only a 3% to 5% risk of having a child with cleft lip/palate. Parents without clefts have a 4% recurrence rate in another child after 1 child is affected with orofacial clefting. A parent with a cleft has a 4% risk of having a child with a cleft. The risk increases to 17% for the next child with a cleft after 1 child is born with a cleft. If unaffected parents have 2 affected children, then the risk to a third child rises from 4.4% to 9%. In twin studies, monozygotic twins had a 43% paired concordance, whereas only 5% concordance was seen in dizygotic twins.

**PATHOPHYSIOLOGIC MECHANISMS**

The embryologic development of the upper lip and nose involves a sequence of complex, genetically programmed events. In the third and eighth week of fetal development, the maxillary, median nasal, and lateral nasal prominences converge in a complicated process of epithelial bridging, programmed cell death, and mesenchymal penetration under the epithelium. Cleft lip/palate is likely caused by a defect of epithelial fusion or mesenchymal growth between these prominences that involve a significant number of possible genetic loci or intracellular signaling pathways. The heterogeneity of the phenotypic expression of cleft lip/palate is supported by (1) the complexity of the craniofacial developmental pathway, and (2) the numerous developmental points at which clefting could be induced.

**CARRIER STATE**

Brown first hypothesized that an isolated nasal deformity could occur in the absence of an obvious cleft lip owing to a primary defect of the alar cartilage in 1964. Stenstrom and Thilander observed that the lower lateral cartilages were symmetric and of equal size. The cleft-side lower lateral cartilage had “glided” out of place, and an abnormally lateral incisor was noted. Tulenko, Boo-Chai and Tange, and Cosman and Crkelair considered the unilateral CLND as a finding that is likely associated with the “microform” cleft lip in the 1960s. A carrier state of cleft lip/palate in family members of children with cleft lip/palate has been suggested but is difficult to prove owing to the relatively high frequency of subtle facial asymmetries in the normal population. No orofacial characteristic has been definitively correlated with a carrier state owing in part to normal variations in facial and dental symmetry. Mossey et al postulate that no microform clefting occurs at the dental level and support the assertion by Wolff et al that lateral incisor anomalies occur no more frequently in patients with cleft lip/palate than in the general population.

Support for a possible carrier state was presented in a 2006 meta-analysis of case-controlled studies using cephalomet-
ric data. Unaffected parents of children with cleft lip/palate demonstrated wider intraorbital distance, nasal cavity, and upper facial dimensions than controls. Nasomaxillary asymmetry and nostril asymmetry in parents of children with cleft lip/palate have been reported to be more common than in people without cleft lip/palate. Relatives of patients with isolated cleft palate showed the greatest concordance with nostril asymmetry. Tolarová and Cervenka concluded that congenital nostril asymmetry might represent a microform expression of craniofacial deformities rather than other orofacial clefts.

A recent systematic review of the associations of microform cleft features and possible carrier states for orofacial clefting provided a thorough description of the state of the science and recommendations for future studies. Mossey et al concluded the following: (1) specific craniofacial morphologic differences are noted in children with cleft lip/palate and their parents when compared with the population without cleft lip/palate, but interpretation is difficult owing to the heterogeneity in facial structure; (2) further subclassification of orofacial clefts, including microforms, will allow more accurate comparisons; and (3) intercenter collaborative studies that include genetic predisposition, environmental factors, and facial features representing genetic traits will improve diagnosis, genetic counseling, clinical treatment, and ultimately, prevention of orofacial clefts.

INTRINSIC AND EXTRINSIC THEORY

The etiologies of the classic CLND have been theorized to have intrinsic (deficiency) and extrinsic (force) factors. Intrinsic deficiency implies that the CLND is caused by a hypoplastic or deficient cleft-side lower lateral cartilage. Veau observed that the cleft lip and alveolus demonstrated that posterolateral displacement of the piriform margin and alar base were affected by a deficiency of (1) mesenchyme within the cleft lip and (2) bone in the maxillary piriform aperture. In 1949, Huffman and Lierle proposed that the CLND was solely due to external forces and distortion of the lower lateral cartilage with little contribution from intrinsic factors.

Opposing views have been reported regarding the volume of the lower lateral cartilage on the cleft side. On the one hand, Stark and Kaplan showed a marked difference between the cleft- and the noncleft-side lower lateral cartilage volume. On the other hand, Park et al concluded that the lower lateral cartilage was not hypoplastic in CLND but rather distorted and misplaced. The authors meticulously measured the width, length, and thickness of the lower lateral cartilages during cleft lip rhinoplasty in 35 adult and pediatric patients with cleft lip.

Extrinsic force theory holds that abnormal muscular insertion sites surrounding the cleft create tension that distorts the morphologic characteristics of the nasal soft tissue and cartilage. Fetal and neonatal nasal cartilage is very malleable in the first 6 weeks of life owing to elevated progesterone levels from maternal-to-child transmission. Sadove et al supported the extrinsic theory when they found no histologic difference in the chondrocytes between the cleft-side and noncleft-side medial crural cartilages in 20 patients.

Furthermore, Latham postulated that the principles of extrinsic theory contribute to the deviation of the columella, nasal tip, and caudal septum by attachment between the septo-premaxillary ligament and the anterior septum. The alar base is pulled away from the cleft by the abnormal orbicularis oris muscle insertions.
We present contrasting cases of 3 minor nasal deformities with nostril and nasal tip asymmetry and, for comparison, an adult with unrepaired, unilateral cleft lip and palate. Few cases of isolated CLND have been reported. Most cases have evidence of a concomitant microform cleft lip. Previous authors have hypothesized that an isolated CLND may occur as a minimal genetic expression in parents and siblings of children with cleft lip/palate.16-18 Definitive genetic studies of families with these traits will be necessary to prove this theory. The purpose of this study is to compare and contrast the characteristics, plausible pathogenesis, and surgical treatment of 4 isolated, unilateral congenital nasal deformities.

The study is a retrospective case series of patients with congenital nasal deformities from 4 institutions. Medical chart review consisted of demographic data, differential diagnosis, and surgical technique documentation for each patient. Family history of craniofacial deformities, orofacial clefting, and other congenital birth defects was obtained. In 1 patient, a sonogram of the lip was completed to evaluate for microform cleft lip deformity.

RESULTS

CASE 1

A 25-year-old woman presented with complaints of nasal obstruction and asymmetric nostrils. Nasal airway obstruction was most severe on the left side. The family history revealed that the patient’s mother had an isolated cleft palate. The patient’s nasal architecture demonstrates some findings consistent with a unilateral left-sided CLND. The left alar base was positioned posteriorly, laterally, and inferiorly. Unlike the typical CLND, the ala was retracted and thickened on the base view (Figure 3A), with
Figure 4. Case 2. Preoperative frontal (A), oblique (B, D), lateral (C), and base (E) views are shown. The malpositioned alar base and columellar length asymmetry is noted. An illustration (F) depicts the intraoperative position of the left lower lateral cartilage and foreshortened medial crus. The postoperative views (G-K) demonstrate improved nasal tip and alar base symmetry.
mild alar notching seen on the frontal view (Figure 3B). The maxillary left lateral incisor was laterally malpositioned. The upper lip vertical furrows were mildly asymmetric with lip puckering (Figure 3C). The palate appeared normal, with no bifid uvula or submucosal defect. A cleft lip or vermilion border abnormality was not visible or palpable.

Other authors have found sonograms of the lip to be useful for identifying minor muscular defects. A sonogram was obtained for suspicion of an occult abnormal insertion of the orbicularis oris muscle. An abnormal segment of the orbicularis oris on the affected side of the lip was noted on ultrasonography, demonstrated by hypoechoic notching (Figure 3D).

The patient’s nasal deformity and airway obstruction were approached with an open septorhinoplasty (Figure 3E). Intraoperatively, the left lower lateral cartilage was found to be extremely underdeveloped. The deficient lower lateral crus was reconstructed using a lateral crural strut graft harvested from the septum. The nasal tip was supported with a columellar strut. Nasal tip rhinoplasty was completed with a shield graft and suture refinement using intradomal and interdomal sutures using 5-0 polydioxanone (Figure 3F). The patient was pleased with improved nasal airflow and contour. This patient was unfortunately lost to follow-up despite many contact attempts, and further postoperative photographs could not be obtained.

CASE 2

A 20-year-old woman complained of a nasal deformity and nasal obstruction, primarily on the right side of her nose (Figure 4A-C). She denied previous nasal surgery, trauma, or family history of orofacial clefting. Examination revealed characteristics resembling a unilateral CLND with marked right-sided septal deviation but no obvious cleft lip, palate, or alveolus. Although the lip did not demonstrate clefting, a deficiency of the orbicularis oris muscle could be palpated just lateral to the philtral column inferior to the alar base. At the time of surgery, the left lower lateral cartilage was consistent with the unilateral CLND. The medial crus was foreshortened, resulting in asymmetric dome projection. The left alar margin was pushed downward by the malpositioned left lower lateral crus, creating alar hooding.

Using an open septorhinoplasty approach, the lower lateral crural cartilages were mobilized from the underlying vestibular skin and then repositioned with dome sutures. The nasal tip was reinforced with a shield graft and a columellar strut. The alar base was augmented with a Gore-TEX (W. L. Gore Associates Inc, Flagstaff, Arizona) implant placed in a supraperiosteal plane. Alar base symmetry was achieved with an alar base suture (3-0 polydioxanone) suspended to the nasal spine. Postoperatively, the patient noted aesthetic and functional improvements.

CASE 3

A 47-year-old woman presented with a lifelong history of nasal obstruction, a grossly asymmetric nasal tip, and stenotic left nostril (Figure 5A and B). She denied previous trauma, surgery, or family history of orofacial clefting. Examination revealed an attenuated, left lower lateral cartilage; an asymmetric, small, and excessively circular nostril; and septal deviation. Intraoperative treatment of the absence (or severe hypoplasia) of the left lower lateral cartilage (Figure 5C) included a caudal septal extension graft, lateral crural strut graft, nasal tip shield graft and onlay dome graft (Figure 5D).

CASE 4

A 30-year-old man presented with an unrepaired, left complete unilateral cleft lip and palate. He had developed re-
markable speech and swallowing compensatory techniques. His primary complaint was the appearance of his lip and nose. Findings from a physical examination revealed a narrow (4-mm) left alveolar cleft; wide, complete unilateral cleft palate; and a typical, left unilateral cleft lip with a foreshortened cleft-side vertical lip height (Figure 6).

The cleft-side alar base was inferiorly, laterally, and posteriorly displaced, similar to the typical infant with an unrepaired cleft lip. As observed in this case, 2 of the factors that contribute to the CLND are (1) the intrinsic deficit of maxillary bone in the alveolar cleft and (2) the extrinsic factors of the abnormal orbicularis oris muscle insertions. On smiling, the zygomaticus muscles and others contract and expand the cleft width at the lateral lip edges, alar base, and columnellar base. The nasal tip was deviated along with the septum to the noncleft side. The alar rim demonstrates hooing and flattening of the malpositioned lower lateral cartilage.

**COMMENT**

Careful observation of patterns in congenital nasal deformities can assist in attributing causality. The distinct differences in these 4 cases can be identified by considering both morphologic characteristics and pathophysiologic mechanisms, thus leading to clearer classification. Expanding the taxonomy of these deformities will serve to better understand the complex interplay of genetic and environmental influences on craniofacial embryologic development. The characteristics of the 4 cases are summarized in the Table. The diminutive nasal cartilage and skin changes (intrinsic factors) seen in cases 1 to 3 are likely linked to the Losee type 1 or hypoplastic nasal deformity classification. Extrinsic factors, which predominate in the typical CLND (case 4) and microform cleft lip, are synonymous with the Losee type 3 nasal deformity.

The subtle features that are suggestive of the typical CLND in cases 1 and 2 (orbicularis oris furrow and alar base asymmetry) may be associated with a carrier state for orofacial clefting. Rapidly advancing research into craniofacial developmental biology will assist with further identifying genetic contributions.

After more than 40 years of discussion, CLND occurring either as an isolated phenomenon or associated with microform cleft lip continues to be an enigma. The difficulty in the careful scrutiny and classification of these deformities arises because many normal individuals have been shown to have subtle nasal asymmetries. A microform cleft lip will often be identified in a congenital nasal deformity that mimics a CLND. However, intrinsic factors (Losee type 1) may also play a role and will be further described.

**INTRINSIC AND EXTRINSIC FACTORS**

The atypical congenital nasal deformities presented herein can be analyzed by incorporating the possible intrinsic/

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**Table**  Patient Characteristics With Congenital Nasal Deformities

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Nasal Characteristics</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Left alar retraction with notching</td>
<td>Type 1, hypoplastic</td>
</tr>
<tr>
<td></td>
<td>Hypoplastic lower lateral cartilage</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Caudal septum deviated</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ultrasonographic evidence of orbicularis oris notching</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Left alar base asymmetry</td>
<td>Types 1-3, hypoplastic</td>
</tr>
<tr>
<td></td>
<td>Lower lateral cartilage malpositioned toward alar margin</td>
<td>Has unilateral cleft lip nasal deformity features</td>
</tr>
<tr>
<td></td>
<td>Medial crus foreshortened</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Nostril asymmetry</td>
<td>Type 1, hypoplastic</td>
</tr>
<tr>
<td></td>
<td>Near-total absence of left lower lateral cartilage</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Unilateral cleft lip and palate (unrepaired)</td>
<td>Type 3, orofacial cleft</td>
</tr>
<tr>
<td></td>
<td>Alar base malposition</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Alar hooding</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nasal tip asymmetry</td>
<td></td>
</tr>
</tbody>
</table>

*According to classification system by Losee et al.*

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Figure 6. Case 4. Preoperative (A and B) and postoperative (C) views of a 30-year-old adult with an unrepaired unilateral cleft lip and palate demonstrate the role of the extrinsic theory of the development of the cleft lip nasal deformity. Unlike nasal bases that are repaired in infancy, the nasal base in this patient splays with smiling. The nasal tip and alar malpositioning are also emphasized as the lower lateral cartilages have matured in the abnormal position. Lip repair was performed with no nasal dissection, leaving the stigmata of alar hooing and nasal tip asymmetry, which will be addressed with definitive septorhinoplasty.
extrinsic theories of the typical CLND.\textsuperscript{20,34,35} The intrinsic deficiency and apparently abnormal development of the lower lateral cartilage seem to be the dominate features in case 1, supporting the intrinsic theory. The cartilage was near normal in the affected medial and intermediate crus, but the lateral crus was hypoplastic, partially fibrous, and diminutive at its most lateral aspect.

Microform expressions of cleft deformities are an additional culprit in the spectrum of ambiguous congenital nasal deformities. Most patients with “isolated” CLND do have at least some evidence of microform cleft lip.\textsuperscript{9} Case 2 demonstrates a distinct entity of a microform cleft that does not demonstrate obvious intrinsic nasal cartilage deficiency. A normal-sized but malpositioned lower lateral cartilage formed the affected nasal ala, in keeping with the purely extrinsic theory. Perhaps it is those cases of isolated CLND with minimal lip deformity and no apparent intrinsic deficiency that are the true diminutive expression of CLND, which could be colloquially termed a nanoform cleft.

Extrinsic factors, such as the unopposed action of the right nasalis and orbicularis oris muscles onto the septum, cause caudal deviation to the noncleft side and contribute to the typical adult CLND, as seen in cases 2 and 4. The sonogram of the lip in case 1 suggested abnormal orbicularis insertions on the affected side. Even without definitive radiographic evidence, the hint of an asymmetric pucker is present, but no true microform cleft lip characteristics are seen.

The relevance of the laterally displaced left lateral incisor in case 1 is not clear. Some authors suggest that malpositioned or absent teeth in the general population are too common to be considered a microform of orofacial clefting.\textsuperscript{25} However, multicenter investigations, which provide the appropriate power and diversity of ethnicities and environmental exposures, are needed to assess the potential heritable traits in patients with orofacial clefts. Mosey et al\textsuperscript{26} advocate for research concentrating dental anomalies, microform clefts, and orbicularis oris morphologic characteristics in parents of children with orofacial clefting. They suggest that “altered facial form could be seen as a form fruste of a full-blown cleft”\textsuperscript{22(p30)} and that genetic variations account for the different types of clefts.

Previous studies have looked for lower lateral cartilage deformities in CLND associated with overt cleft lip. One possible explanation is that some cases of isolated CLND are actually an expression of craniofacial abnormalities other than cleft lip, such as microform expressions of an atypical craniofacial cleft as classified by Tessier.\textsuperscript{26} The nostrils’ appearances in cases 1 and 3 were mostly affected by the absence of cartilaginous volume in the lateral crus of the lower lateral cartilage and the associated soft-tissue envelope. Amniotic band syndrome is an additional potential cause of nasal deformities in which intrauterine amnion rupture during development creates a variety of deformational craniofacial and limb defects.\textsuperscript{37}

**CARRIER STATE**

Many authors support continued efforts to examine (both physically and genetically) parents of children with cleft lip/palate to determine if subtle lip and nasal asymmetries reflect a carrier state for cleft lip/palate.\textsuperscript{9,19,26} Conflicting evidence exists for the association between nasal asymmetry and a familial predisposition to cleft lip/palate. As suggested by Tolarová and Cervenka,\textsuperscript{3} the greatest incidence of nostril asymmetry occurs in relatives of patients with isolated cleft palate, which is consistent with the patient described in our case 1 whose mother had an isolated cleft palate. This patient demonstrated both nostril asymmetry and orbicularis oris notchings (seen on ultrasonography); however, the presence of a hypoplastic lower lateral cartilage creates ambiguity. As reported by Martin et al,\textsuperscript{21} the significance of the noted orbicularis oris in parents of children with orofacial clefts is uncertain. Further investigations into lip morphologic inheritance patterns are needed.\textsuperscript{38}

These diverse cases illustrate the challenge of classifying craniofacial “deformities” when the normal range is highly variable even within our own species. Human facial characteristics are at once highly conserved between individuals and within vertebrate species and inexplicably different enough to allow identification of one another. Exciting research into the molecular patterns that contribute to species-specific facial characteristics provides a framework for understanding mechanisms for craniofacial deformities. Craniofacial diversity and, thus, deformities will be more clearly understood by identifying the effects of genetic patterns on “molecular, cellular, and tissue interactions.”\textsuperscript{39(p2529)} Recent advances into understanding how genes govern the skin, neural crest cells, and ectoderm derivatives have led to a field studying gene regulatory networks.\textsuperscript{30,31} The translation of this basic science research into clinical practice may improve genetic counseling and potential gene therapy options.

In conclusion, symmetric congenital nasal deformities can resemble the CLND. Proper classification involves careful scrutiny of facial characteristics for intrinsic deficiencies and/or extrinsic deformations, such as seen in microform clefts. Further understanding of the presence of a carrier state in relatives of patients with orofacial clefts will require additional studies that document anthropometric craniofacial measurements and genetic associations in family members.

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