Clinical and Genetic Characterization of Frontorhiny

Report of 3 Novel Cases and Discussion of the Surgical Management

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Objectives: To (1) define the nasal, columellar, and lip deformities of 3 patients with characteristics consistent with frontorhiny; (2) illustrate the embryologic correlation of the oronasal findings to the development of the median nasal prominence; (3) report the clinical manifestation in 3 patients from 2 unrelated families; (4) report a novel Y214X mutation in \textit{ALX3}; and (5) describe the surgical reconstruction.

Methods: In this case series, we report 3 novel cases of frontorhiny from 2 different families. The surgical reconstruction technique is reviewed. Extension of the columellar medial crural cartilage into the upper lip cleft is examined histologically. Signed consent was granted for all patient photographs and specimens, and the study was approved by the institutional review committee of the University of California Davis. The genetic sequencing of the \textit{ALX3} homeobox gene was performed in 2 of our 3 cases using standard commercially available sequencing kits. The genetic material in our third case was not available for analysis.

Results: Patients 1 and 2 were brothers from the same family. Both exhibited bifidity of their columella, a widened philtrum, poor nasal tip development, and low hairlines. Genetic sequencing in the 2 brothers confirmed the presence of a novel \textit{ALX3} homeobox mutation at the second exon (mutation Y214X). Patient 3 was a 4-year-old girl. She presented with an underdeveloped, widened nasal tip and a bifid columella. Her philtrum was widened and had a left-sided cartilaginous prominence. She also had a widened nasal root. Family history revealed no family members with the same features.

Conclusions: Frontorhiny represents a new syndromic frontonasal malformation with consistent characteristic features. The genetic abnormality has now been found in 14 different patients. Careful scrutiny and classification of frontonasal deformities will expand our understanding of causes, genetic susceptibility, and treatment options.

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MBRYOLOGY IS A HIGHLY CHO- 
reographed dance in which multiple parts must embrace, move, and grow in perfect synchrony. The tissues that move most closely together, that respond and react to the same stimuli, are embryonic subunits called developmental fields. Any misstep in embryogenesis, therefore, results in a chain reaction that affects the entire developmental field in predictable patterns.

One such pattern is a series of anomalies called \textit{frontonasal malformations}, rare craniofacial defects thought to arise from the abnormal development of the frontonasal prominence. As described by Sedano and Gorlin,\textsuperscript{1} \textit{frontonasal malformation} describes a type of developmental field defect in which the root cause is believed to be abnormal development of the frontonasal prominence in craniofacial embryogenesis. The features that are used to define frontonasal malformation include at least 2 of the following characteristics: hypertelorism, broad nasal root, median facial clefting, nasal alar clefting, malformed nasal tip, anterior cranium bifidum occultum or a V-shaped hair pattern on the forehead (Figure 1).

Median oronasal clefts are rare deformities that likely arise from the incomplete fusion of the paired median nasal prominences during embryologic development. When they are less severe, these clefts are often seen in conjunction with hypertelorism and normal brain development. Meanwhile, the other end of the spectrum includes the various forms of holoprosencephaly (the most severe being cyclopia with hypotelorism). Many classification systems have been proposed, including that of DeMyer,\textsuperscript{2} who proposed the term \textit{holoprosencephaly} in 1967. In addition, these deformities have been classified as Tessier type 0 and type 14.

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The terms frontonasal dysplasia and frontonasal malformation were introduced by Sedano and Gorlin\(^1\) to emphasize that the continuum of median facial deformities represents a developmental field defect. Most of the various median facial deformities are sporadic and have multiple etiologic factors; however, familial cases and syndromic associations have also been reported. In the case of frontonasal malformations, the persistence of the frontonasal process in its embryogenic position keeps the orbits from reaching their normal position. This is thought to cause the distinct hypertelorism and midline abnormalities such as clefting of the lip and nose.\(^1\) Embryologic development of the face is also closely related to forebrain development through the frontonasal prominence, which gives rise to the paired medial nasal prominences as shown in Figure 2.

The 5 facial primordia are formed by the proliferation of neural crest cells. During the fourth week of development, these cells migrate ventrolaterally from their initial dorsal location to populate mesenchyme of the facial primordia (The 5 facial prominences are organized around the primitive mouth—the stomodeum (Figure 2). They consist of a single frontonasal prominence and paired maxillary and mandibular prominences. The frontonasal prominence surrounds the ventrolateral part of the forebrain and forms the upper border of the stomodeum.\(^4\) The maxillary and mandibular prominences are derived from the first pair of pharyngeal arches and form the lateral and caudal borders of the stomodeum, respectively. Midline merging of the medial nasal prominences leads to formation of the upper lip tubercle and philtrum, the nasal tip, primary palate, and premaxilla.\(^3\) The lateral portions of the upper lip, the bulk of the maxilla, and the secondary palate are formed by the maxillary prominences. Lateral unions of the maxillary and mandibular prominences create the oral commissures.\(^2\)

Twigg et al\(^6\) and Lees et al\(^7\) have described a unique frontonasal malformation they termed frontorhiny, a new autosomal recessive syndrome characterized as a distinctive disease entity falling within the spectrum of frontonasal malformations. Twigg et al\(^6\) reported 3 cases presenting with the classic features. In the same study, a causative ALX3 homeobox gene (OMIM 136760) for frontorhiny was identified. Lees et al\(^7\) described 2 additional patients with the same clinical features and the same genetic mutation. The syndrome was described in 11 different patients from 7 families, and is characterized by hypertelorism, wide nasal bridge, bifid nasal tip, broad columella, widely separated narrow nares, long philtrum, and bilateral nasal swellings. In addition, a genetic study of the 11 patients with the clinical features of frontorhiny revealed 7 distinct gene mutations in the same ALX3 homeobox gene.\(^6,7\)

In the present study, we describe 3 patients with clinical findings consistent with the distinct features of frontorhiny. The purpose of this study is to present the characteristics of our 3 patients with this unique frontonasal malformation and the techniques used for surgical reconstruction.

### METHODS

Herein, we report 3 novel cases of frontorhiny occurring in patients from 2 different families. The surgical reconstruction technique is reviewed. Histologic analysis of soft-tissue extension of the columellar medial crural cartilage into the upper lip is examined.

Sequencing of the ALX3 homeobox gene was performed in 2 of our 3 cases. All patient photographs and specimens were obtained only after signed consents, and the study was approved by the institutional review committee of University of California, Davis. The DNA of our third case was not available for analysis.

Total lymphocyte DNA from the affected brothers and their parents was extracted and purified using a standard DNA extraction kit (Qiagen Inc, Valencia, California) in accordance with the manufacturer’s instructions. Primer sequences based on GenBank accession code NG_012039.1 were designed to amplify the complete coding region of ALX3, including the 5‘- and 3‘- untranslated regions. Direct forward and reverse sequencing was carried out by the deoxy chain termination method with the Sequenase, version 2.0, DNA sequencing kit (US Biochemical, Cleveland, Ohio) with a relevant primer. A custom

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**Figure 1.** Photograph of a child with typical features of frontonasal malformation (not frontorhiny), as defined by Sedano and Gorlin,\(^1\) including at least 2 of the following: true ocular hypertelorism, broadening of nasal root, median facial cleft, lack of formation of nasal tip, cranium bifidum occultum, V-shaped frontal hairline, and/or alar cleft.

**Figure 2.** Color-coded developmental fields. A, In week 6 of embryogenesis, yellow indicates the frontonasal prominence; brown, maxillary processes; blue, the mandibular arch; green, median nasal processes; and purple, lateral nasal processes. B, Color-coded illustration of patient 1 shows the embryologic derivation of his facial structures.
TaqMan assay (Applied Biosystems, Carlsbad, California) for the mutation was designed, and 186 control individuals were tested. All sequences were reviewed by at least 2 independent investigators. Polymerase chain reaction conditions and primer sequences are available from the authors on request.

RESULTS

GENETICS

Patients 1 and 2 were brothers from a nonconsanguineous relationship and of South American descent. Both exhibited the typical features noted by Twigg et al.\(^6\) and Lees et al.\(^7\) Genetic analysis revealed a previously unreported mutation in exon 2 (mutation Y214X) of the ALX3 gene with the substitution of tyrosine by a stop codon. This leads to premature mRNA termination and results in the loss of the functional protein.

CASE 1

Patient 1 was the younger sibling. He began walking at age 15 months and performed normally in school. His workup included renal ultrasonographic analysis and cardiac evaluation, both of which demonstrated no abnormalities. Figure 3A shows a wide nasal bridge. His nasal tip was underdeveloped. The tip was bulbous in appearance and extended up to the nasal dorsum, nearly to the nasion. Inferiorly, his philtrum showed an abnormal length. Where the philtrum met the nasal sill, he possessed the very distinctive nasal swellings and bifid columella. In the base view of the nose (Figure 3B) the underdevelopment of the tip, wide columella, and the slit-like nares can be seen.

CASE 2

Patient 2 was the older sibling, age 15 years at the time of this study (Figure 4). Given that he had undergone puberty at the time of this study, his nose showed more definition than that of his younger sibling. His nasal bridge was taller, and his nares were wider. Nonetheless, Figure 4 illustrates that all of the characteristic features are present.

CASE 3

Patient 3 was a 4-year-old girl of African descent. She was born at term and of normal intelligence. A frontal view (Figure 5A) reveals a widened nasal bridge. A more pronounced bifidity is present in the columella, resulting in a large pit, giving almost the appearance of a third nostril. In addition, in the nasal base view (Figure 5B), she does not appear to have narrowed nares, as were seen in patients 1 and 2. This difference may be a byproduct of ethnically inherent differences in alar base and nostril size.\(^8\)

ANATOMIC ASSESSMENT

A preoperative computed tomographic scan of patient 1 revealed several distinct features (Figure 6). There was a central maxillary diastema. At the nasal-orbital-ethmoid region, the underlying widening of the nasal and ethmoid bone was apparent along with widening at the junction of the nasal prominence of the frontal bone and frontal prominence of the maxillary bone.
SURGICAL RECONSTRUCTION TECHNIQUE

All 3 patients were treated with a reconstructive open rhinoplasty approach with attention to columnar contouring, eradicating bifidity, columnar lengthening with V-Y closure, and enhancing tip projection. Techniques to repair a shortened or widened columella have been described previously, including performing V-Y columellar advancement, creating forked flaps from the lip, skin grafting, or recruiting columellar skin from the lobule with rim incisions.

The incision was marked out with a modified transcolumellar approach. We marked out a trapezoidal area of skin resection below the columella to reduce the philtral length.

Meticulous dissection of the skin soft-tissue envelope from the lower lateral cartilages revealed medial crura that seemed to extend into the soft tissue of the upper lip. The splayed medial crural footpods were freed from the intracrural fibrofatty tissue, which was reduced, and the remnant was repositioned superiorly. The interdomal angle was set with a 5-0 polydioxanone absorbable suture in a horizontal mattress fashion. The lateral crural dome-binding sutures were placed with emphasis on lateral crural steal (to enhance tip projection). Septal cartilage was not incised or exposed so as to preserve growth and vascularity. The soft tissue extending into the fibers of orbicularis oris muscle was dissected free, and in 1 case was sent for histologic examination (Figure 7).

The orbicularis oris pars peripheralis muscle was then reapproximated with 2 sutures using absorbable 4-0 Vicryl (Ethicon Inc, Somerville, New Jersey) at the midline to create a concentric perioral muscle. The excess width of the columellar skin was reduced with lateral skin excision, which in the brothers included abnormal atrophic mucosal rests. The skin and soft-tissue envelope were then closed with a V-Y advancement using 5-0 chromic suture for the lateral incisions and 6-0 fast-absorbing gut and 6-0 nylon sutures. Standard nasal taping was completed postoperatively.

In patient 3, an excision of a triangular portion of columellar skin allowed for the simultaneous shortening and narrowing of the columella.

The 1-year postoperative results are shown for case 1 (Figure 8) and case 2 (Figure 9). In case 3, the postoperative photograph was taken 1 week after surgery and 2 years after surgery, with fullness remaining in the left upper lip (Figure 10).

COMMENT

Frontorhiny is a genetically distinct syndrome that gives rise to a characteristic pattern. The identifying features are telecanthus, a broad nasal root, bifid nasal tip, broad columella, philtral swellings, and a midline notch of the upper alveolus. Our experience sheds light on the bony and soft-tissue abnormalities that lead to the overall appearance. Computed tomographic imaging reveals the widening of the nasal bones and the nasofrontal junction at the radix, with the widened area extending down to the nasal dorsum.

The primary aesthetic challenges presented by frontorhiny are (1) telecanthus, (2) widened nasal root and dorsum, (3) broad alar base and underprojected nasal tip, (4) columellar widening and bifidity, and (5) wide philtrum with increased philtral height.

In our patients, the severity of the telecanthus was relatively mild, with the intercanthal distance approximating the intracanthal distance in each patient. Orbital repositioning would be a surgical option in cases of severe telecanthus but was not considered in our patients.

Addressing the nasal dorsum and underdeveloped nasal tip presents a unique clinical challenge. Although the deformities were clearly present, treatment was complicated by our patients’ ages. In our oldest patient, the nasal dorsum and root were surprisingly well developed, obviating the need for treatment. In our 2 younger patients, addressing this area was deferred until after ado-
lescence. Staged, definitive rhinoplasty will be performed after full facial growth and subsequent orthognathic treatment of dental-facial malocclusion.

The malformations readily amenable to treatment in early childhood are the columellar widening and bifidity, reducing the philtral swellings, and reducing philtral height. We have been able to show that the underlying cause of the bifidity is the lateralized location of the medial alar cartilages. The modified V-Y advancement can be used to narrow the columella as well as reduce the philtral height.

The oronasal characteristics that are associated with the cases that we present seem to be related to the embryologic development of the globular process of the median nasal prominence. The globular process is the rounded mass of tissue at the inferior margin of each median nasal prominence. As development progresses, the nasal pits grow inward and expand into nasal sacs, eventually terminating at the nasal choana. While the nasal sacs are being transformed into the nasal cavities, the globular processes give rise to the nasal laminae, which later fuse to form nasal septum. The globular processes also form the premaxilla and prolabium.

Intraoperative examination of the medial crura suggest a cartilage extension into the lateral bulges of the upper lip, but the high-magnification histologic review did not show cartilage remnants. In Figure 7, the finding of somewhat disorganized muscle fibers amidst a fibrofatty substrate is consistent with histologic findings in other embryologic orofacial clefts.

The bifidity is due to flaring of the medial crural footpods and associated excessive soft-tissue envelope of the columella.

Analysis of a profile photograph (Figure 11) suggests that a long upper lip and lack of adequate tip projection remain even after reconstruction. Long philtral height is not a distinguishing characteristic of every patient, but of course the nasolabial angle is greatly affected by lip length and tip projection. If the nose is underprojected, then the lip will appear long in relation. There are a variety of measures of adequate tip projection in adults, but these do not correlate well to children owing to infantile nasal tip development. The Simmons method suggests a 1:1 ratio of the length of the subnasale to the tip-defining point (pronasale) and from the subnasale to the vermilion cutaneous junction of the upper lip.

In the studies by Twigg et al and Lees et al, objective analysis of facial features was performed using dense surface modeling and revealed deficiencies in tissue in the midface, nose, and philtrum; the authors concluded that the findings were "consistent with embryonic tissue disturbance predominantly affecting the frontonasal and medial nasal prominences." Interestingly, their patient pool exhibited several unique characteristics that are predictable, given the cause of frontorhiny, but that were not seen in our patients. Among them were dermoid cysts, eyelid ptosis, and a bifid tongue.
Molecular genetic analysis identified a previously unreported mutation in exon 2 of ALX3 where tyrosine was substituted by a stop codon, leading to premature termination of the mRNA and lack of functional protein. The mutation was absolutely conserved among 8 different species (Figure 12) and was inherited from the clinically unaffected father. The figure chromatogram and Clustal analysis (Science Foundation Ireland, University College Dublin) were not able to identify the maternal mutation in the coding and 5'- and 3'- untranslated regions. The TaqMan assay did not identify the mutation in a total of 372 control human chromosomes. Considering the reported autosomal recessive inheritance, most likely the maternal mutation is within the region regulating the expression of ALX3. Because no cell lines were available from the probands or their parents, we were not able to carry out functional experiments, such as quantitative real-time polymerase chain reaction analysis. Twigg et al identified 7 different homozygous mutations in 7 unrelated families, and we report herein the eighth mutation, Y214X in ALX3.

In conclusion, frontorhiny is a recently characterized autosomal recessive syndrome falling within the spectrum of frontonasal malformations that presents a surgical reconstructive challenge. Additional case studies will assist in classifying the congenital craniofacial anomalies and identifying associated genetic mutations.

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