HHS Public Access

Author manuscript

J Craniofac Surg. Author manuscript; available in PMC 2024 May 01.

Published in final edited form as:

J Craniofac Surg. 2023 May 01; 34(3): 849–854. doi:10.1097/SCS.0000000000009261.

Nasal construction in congenital arhinia due to novel *SMCHD1* gene variant

Marie Bargiela, MD[1,2,3], **Janina Kueper, AM, MD**[1,2,3], **Arman T. Serebrakian, MD, MS**[1,2,4], **MaKenna R. Browne**[5], **Susan Brogna**[2], **Zachary S. Peacock, MD, DMD**[2,4], **Branko Bojovic, MD**[1,2], **Natalie D. Shaw, MD, MMSc**[5], **Eric C. Liao, MD, PhD**[1,2,4,6]

[1]Division of Plastic and Reconstructive Surgery, Massachusetts General Hospital, Harvard Medical School, Boston

[2]Shriners Hospital for Children, Boston

[3]Institute of Human Genetics, University of Bonn, Bonn

[4]Department of Oral and Maxillofacial Surgery, Massachusetts General Hospital, Harvard Medical School, Boston

[5]Pediatric Neuroendocrinology Group, Clinical Research Branch, National Institute of Environmental Health Sciences, Research Triangle Park, Durham

[6]Center for Craniofacial Innovation, Children's Hospital of Philadelphia, Philadelphia

Background.

Arhinia, or congenital absence of the nose, is an exceedingly rare anomaly caused by pathogenic variants in the gene SMCHD1. Arhinia exhibits unique reconstructive challenges, as the midface is deficient in skeletal and soft tissue structures. We present two related subjects with arhinia who harbour a novel SMCHD1 gene variant and illustrate their surgical midface and nasal construction.

Targeted sequencing was carried out on DNA samples from the two affected subjects, from one anosmic and one healthy parent, to identify variants in exons 3 – 13 of SMCHD1. The affected subjects and anosmic parent, were found to have a novel SMCHD1 gene variant p.E473V.

Corresponding author: Eric C. Liao, MD, PhD, Center for Craniofacial Innovation, Children's Hospital of Philadelphia, 3501 Civic Center Blvd., Philadelphia, PA 19044, liaoce@chop.edu, Tel: 215-590-3096, Fax: 617-643-5967.

Authorship attribution:

MB prepared the manuscript and figures, carried out literature review and reviewed the clinical records of the subjects described.
JK contributed to the manuscript and reviewed the clinical records of the subjects described.
AS prepared and revised the manuscript and reviewed the clinical records of the subjects described.
MRB extracted and Sanger-sequenced the DNA and drew the pedigree.
SB collected clinical data of both patients.
ZP is an oral and maxillofacial surgeon who carried out the planning and execution of the Le Fort II osteotomies and midface distraction; manuscript preparation and editing.
BB is a plastic surgeon who carried out the planning and execution of the nasal construction.
NS supervised the DNA sequencing and reviewed the clinical records.
ECL conceived of the manuscript, prepared the figures and manuscript, supervised the regulatory and compliance of the study, and assembled the clinical and scientific collaborators to carry out this work.

CONFLICTS OF INTEREST

The authors state that they have no conflict of interest with regard to any of the work herein presented.

Financial Disclosures: The authors have no financial interests to declare in relation to the content of this article.

A staged surgical approach was applied. First, both subjects underwent a LeFort II osteotomy and distraction osteogenesis to improve the projection of the midfacial segment, followed by tissue expansion of the forehead, and nasal construction with a forehead flap that was placed over a costochondral framework derived from rib cartilage. The novel gene variant could guide future investigations on genetic pathways and molecular processes that underly the physiologic and pathologic development of the nose. Further investigations on the variable expressivity ranging from anosmia to arrhinia could improve clinical genetic screens for risk stratification of individuals with anosmia on passing on arrhinia to their children.

Due to the exceptional rarity and complexity of congenital arhinia, most surgical approaches are developed on a single-case basis. This case series, albeit limited to 2 cases, is the largest pedigree of such cases in the literature. It highlights key principles of a staged approach to nasal construction in arhinia and discusses nuances and improvements learned between both patients. It subsequently offers an optimized guide to this surgical strategy.

INTRODUCTION

Congenital absence of the nose known as arhinia is exceptionally rare and nasal construction has only been reported a few times in the literature.[1] Arhinia is anatomically defined by the absence of the external nose, nasal cavities, and olfactory apparatus. It is presumed to result from the anomalous development of the nasal placodes or surrounding neural crest cell (NCC)-derived tissues between weeks 3 to 5 of gestation. Pathogenic variants in *SMCHD1* (encoding structural maintenance of chromosomes flexible hinge domain containing 1) have previously been reported as a genetic cause for this rare craniofacial malformation, as well as for its associated reproductive and ocular phenotypes.[1,2]

Surgical approaches to correct congenital arhinia can broadly be divided into the construction of an aesthetic external nose and a functional airway.[3,4] During the neonatal period, arhinia is a potentially life-threatening condition due to respiratory and feeding problems. In such cases, tracheostomy or canalization of the nasal passage, as well as orogastric or gastrostomy tubes can temporarily restore a functional airway passage and help relieve those symptoms. Surgical airway constructions provide a permanent solution to reduce the dependency on mouth breathing or tracheostomy.[4,5]

While techniques for nasal reconstruction for acquired deformities resulting from disease or trauma have been amply described, construction of a nose for arhinia has distinct requirements. Not only are the external structures of the nose absent, the skeletal foundation of the midface is often also uniquely hypoplastic.[6–8]

We present two related subjects with congenital total arhinia, where DNA sequencing identified a shared novel pathogenic variant in the *SMCHD1* gene. Their clinical presentations and nasal construction stages are detailed to highlight the importance of coordinating skeletal and external nasal construction goals.

MATERIALS AND METHODS

Ethical approval

The subjects were consented for all surgical procedures. The collection of human blood and discard specimens were approved by the Institutional Review Board (IRB) of Partners Healthcare (IRB No. 2015P000904) and collection of DNA was approved by the National Institutes of Health IRB (Protocol 12E0049). The subjects agreed with the publication of identifiable photographs of themselves.

Targeted Sanger sequencing and analysis

Targeted Sanger sequencing of exons 3–13 of the *SMCHD1* gene in the affected subjects I and II and both of their mothers was performed and analyzed. Polymorphism Phenotyping v2, Sorting Intolerant from Tolerant, MutationTaster, and Functional Analysis through Hidden Markov Models (v2.3) were used for functional variant consequence prediction.[9–11] The gnomAD platform was used to identify any other missense variants at the location identified in the subjects. [12]

Surgical planning and technique

Surgical plans were made collaboratively between plastic surgeons and maxillofacial surgeons. Both subjects received similar staged procedures. In stage 1, both subjects underwent midface skeletal advancement via Le Fort II osteotomy using a bicoronal and intraoral incisions with placement of a rigid external distraction device. Following 3 weeks of distraction (1 mm/day), the device was used to immobilize the midface for an additional 3 months for consolidation. Stage 2 was then performed where at the time of removing the external fixator hardware, the same bicoronal incision was used to place a tissue expander in the forehead to increase the amount of soft tissue available for nasal construction, and to facilitate forehead closure. After 2–3 months of tissue expansion of the forehead, stage 3 consisted of the removal of the tissue expander and the construction of a nose with a forehead flap. This forehead flap was inset over a costochondral framework to create projection of the nasal dorsum, with a transverse component that simulated the lower lateral cartilages to create nasal width at the lower third of the nose. The costochondral framework was fixated with self-drilling screws at three anchor points: the radix midline, and each side of the nasal base.

RESULTS

Pedigree with congenital arhinia

The two affected subjects come from the same family in central America where we can trace the pedigree over three generations. Two families resulted from relations of the shared grandfather of the two presenting subjects with two different women. Overall, three family members have been affected with congenital arhinia. One of them, born in generation 2 from family II, died. The mother of subject II was born with anosmia. Subjects I (resultant from family I) and II (resultant from family II) were both born with arhinia (Fig. 1).

Phenotype of subject I

Subject I was found to have a very short nasal root with 2 nares ending in blind pouches. Her zygomas and lateral infraorbital rims projected normally. Intraoral examination revealed an omega-shaped maxilla, with significantly reduced vertical, sagittal, and transverse dimensions. She was found to suffer from gingivitis on the facial aspect, likely caused by chronic obligate mouth breathing. On radiographic examination, the subject was found two have a deficient nasal ridge, a complete lack of nasal bones, and hypoplasia of the medial maxilla and nasomaxillary processes (Fig. 2). She was also found to lack the supratrochlear notch on the left, from which the supratrochlear artery usually exits the orbit.

Phenotype of subject II

Subject II was also found to have significant midface deficiency and lack of soft and bony nasal components. She was found to have a short nasal root with one blindending nasal opening on the left side, and diminished projection of the bilateral zygomas. She had an incomplete cleft of the left upper lip, chin point deviation towards the right and approximately 4mm of tooth show at rest. Intraoral examination revealed an asymmetric smile with a canted occlusion up on the right. On radiographic examination, the subject was found to have a lack of nasal bones, hypoplasia of the medial maxilla and nasomaxillary processes, with reasonable projection of the zygomas and lateral infraorbital rims.

Genetic sequencing and identification of pathogenic SMCHD1 variants

DNA sequencing was performed on blood samples collected from subjects I-IV, which corresponded to one parent (mother I) affected by anosmia, one unaffected parent (mother II), and the two affected subjects resulting from two separate relationships of their shared grandfather. A heterozygous missense p.E473V variant (c.1418A>T) was identified on exon 11 of *SMCHD1* which encodes part of the ATPase transducer domain. The identical variant was identified in subjects I and II as well as mother I. A different variant was previously identified at this same amino acid position (p.E473Q) in another patient with arrhinia.[1] The p.E473V variant results in an exchange of glutamic acid to valine, amino acids with substantially different biochemical properties. An identical substitution of glutamic acid with valine results in conformational changes of the protein product of the *HBB* gene which results in sickle cell anemia. The lack of a negative charge of valine as opposed to glutamic acid is predicted to result in severe conformational changes of the *SMCHD1* protein. The identified *SMCHD1* gene variant is predicted to be causative of the phenotypes based on the amino acid position, the prediction of deleterious protein conformational changes, and the previous description of *SMCHD1* gene variants (including p.E473Q) in subjects with congenital arhinia.

The SMCHD1 p.E473V missense variant has not previously been reported in connection with an SMCHD1-related instance of arhinia.[12] The SMCHD1 p.E473V amino acid substitution was absent from the gnomAD Database and was predicted to be damaging and disease causing by *in silico* tools (Sift, Polyphen, muttaster, fathmm). [9,10,13]

Surgical nasal construction

Stage 1: Midface advancement with Le Fort II osteotomy and maxillary distraction.—In stage 1, the goal was to increase the projection of the nasomaxillary segment to improve aesthetic proportions of the face and create the necessary osseous foundation to accommodate a nasal construction. Access to the midface was achieved through a bicoronal flap with extension to the preauricular region bilaterally and an intraoral maxillary vestibular incision. An osetotomy was created from the nasofrontal suture in the midline laterally through the medial orbit behind the lacrimal crest and primitive nasolacrimal duct (ending in a blind pouch). It then extended through the medial orbital rim inferiorly through the anterior maxilla and then posteriorly above the tooth roots below the zygomaticomaxillary buttress. The pterygoid places were separated with an osteotome. An osteotome was carried posterior at the nasofrontal suture to the posterior nasal spine facilitating downfracture and mobilization of the nasomaxillary segment. (Fig. 3, Top) Titanium footplates were attached to the anterior maxilla bilaterally to allow an osseous connection with the distraction devices through external rods curved around the upper lip. Following intraoral and scalp wound closure, a rigid external frame was placed and secured with pins above the top of each ear. Finally, the vertical rod assembly was attached to the external rods that were attached to the bone borne footplate (Fig. 3). After a 1-week latency period, distraction was completed at 1 mm/day over the course of 3 weeks in a sagittal and inferior vector with adjustments to the vertical rod assembly to achieve correction in all 3 planes and relative to the mandible.

Stage 2: Removal of hardware from external distractor, placement of forehead tissue expander.—After distraction, the rigid external distraction device remained for 3 months to allow consolidation of the distraction wound. At the time of external device and anterior maxillary footplate removal, a tissue expander was placed under the skin of the forehead. The postoperative course was uneventful, and the tissue expander was filled 1–2 times a week until a volume of 120 mL was reached (Fig. 4).

Stage 3: Nasal construction with forehead flap and rib cartilage framework.—The tissue expander was removed and a paramedian forehead flap was raised based on the axial supratrochlear artery pedicle. Due to potential aberrant midface anatomy, it is advisable to identify the artery by Doppler or visualize that the foramen is patent from CT (Fig. 5). In subject I, her CT demonstrated patent supratrochlear foramen on the right but not the left, so we elected to base the paramedian forehead flap on the right side (Fig. 4). Since the forehead was expanded, the donor site was closed primarily with minimal tension to achieve a favorable scar. Since the subjects lacked sinuses to create a functional airway, and no baseline functional breathing issues preoperatively, the focus of the nasal construction was to create an aesthetically pleasing shape of the external nose without a patent nasal airway.

Unlike in nasal reconstructions, where there is usually a nasal bone and septum to base a cartilage graft or synthetic support, a stable framework was required to maintain the shape of a nose. A cartilaginous costochondral framework was sculpted from the subjects right floating and conjoined rib. The framework consisted of a piece that provided dorsal

support and projection, and bilateral gullwing pieces to simulate the lower lateral cartilages to provide shape of nares for a nasal base.

For final inset, the de-epithelialized superior two-thirds of the forehead flap was then rotated onto the nasal framework and eventually sutured to the inferior third of the skin containing dimples to simulate the nostrils. The inferior third of the nose used the subjects preexisting nasal dimples to simulate the columella and nasal opening. The dorsal strut was joined with a caudal strut via a dovetail pattern where the cartilages sandwiched each other. Another cartilage was then split along its length to create thinner and more pliable lower lateral nasal cartilages. This part was attached bilaterally to the caudal aspect of the cartilaginous construct (Fig. 4). The superior aspect of the nasal cartilage construct was stabilized using a self-drilling screw at the radix and the inferior aspect of the cartilage was fixated to the anterior nasal spine. Using the weight and contour of the forehead flap, the lower lateral cartilages were curved to provide a stable nasal tip appearance.

Stage 4: Division of pedicle and flap inset.—Two weeks after stage 3 forehead flap turn down, the pedicle of the flap was divided. The flap was then aggressively thinned over the upper half and inset. The lower portion of the donor site was closed to restore the medial eyebrow position (Fig. 6).

Stage 5: Nasal tip reconstruction with bilateral conchal composite grafts—Subject I had two skin folds of atrophic skin with the semblance of nostrils that were blind and did not open into the nasopharynx. The final stage for her consisted of a nasal tip reconstruction and to open up the nostrils using crescentic conchal grafts. For this, the nasal tip was raised as a bipedicle flap and the grafts with the anterior conchal skin attached, were placed with the skin toward the wound bed of the nasal flap to encourage skin graft take through. Lastly, this was inset with a series of transection sutures onto pledgets, to exaggerate the alar contour and supratip break. (Fig. 6). Both subjects recovered from the staged procedures without any postoperative complications and are pleased with their progress so far.

DISCUSSION

Arhinia is an extremely rare congenital condition with fewer than 100 cases reported in the literature worldwide.[1] There are no known multiplex pedigrees of arrhinia prior to the one which is herein described. Our prior work showed that *SMCHD1* is an important genetic determinant for this rare craniofacial malformation and its associated reproductive and olfactory phenotypes.[1,2] We previously analyzed 40 individuals with arhinia and found that 84% of all individuals had missense mutations localized in the early exons (3–13) of *SMCHD1* within the extended ATPase domain.[1] The variant identified in this family is novel but exists at the same amino acid position as another variant previously identified in a patient with arhinia.[14] It lies in the ATPase transducer domain which is believed to be important in N-terminal dimerization in addition to ATP catalysis.[14]

Other *SMCHD1* pathogenic variants also contribute to the oligogenic disorder, facioscapulohumeral muscular dystrophy type 2 (FSHD2, MIM158901). This muscular

dystrophy presents with variable weakness of the facial muscles, the scapular stabilizers, and the dorsiflexors of the foot. The condition is thought to be inherited via heterozygous trans-acting loss-of-function mutations which result in haploinsufficiency and affect the epigenetic function of *SMCHD1*.[15]

Shaw et al. reported that mutations found in subjects with Bosma arrhinia microphthalmia (BAM; MIM603457) and FSHD2 may be identical, yet individuals with FSHD2 exhibit no craniofacial or reproductive abnormalities and individuals with arhinia have no neuromuscular deficits, suggesting that having one condition may be protective from the other. [1,16] Consistent with this idea, neither affected subject with arhinia and an *SMCHD1* missense variant exhibited signs or symptoms of muscular dystrophy in this study.

Sanger sequencing identified a heterozygous missense *SMCHD1* p.E473V variant (c.1418A>T) in the N-terminal region of *SMCHD1* in subjects I and II with arhinia as well as mother I, with isolated anosmia. Such a pattern of variable expressivity, where a parent with anosmia has a child with complete arhinia, for example, has been described in other arhinia pedigrees.[1] This variant results in the mutation of glutamic acid to valine, amino acids with substantially different biochemical properties. The lack of a negative charge of valine as opposed to glutamic acid is predicted to result in severe conformational changes of the SMCHD1 protein. The identified variants are therefore predicted to be causative of the phenotypes based on the known gene function, the prediction of deleterious protein conformational changes, and the previous description of variants of *SMCHD1* in subjects with congenital arhinia. Further research is required to determine if other phenotypes could be associated with this variant and whether isolated anosmia could be used as a predictive clinical screening tool in the future, to guide genetic screens prior to pregnancy.

BAM is the most severe presentation of arhinia. Within this triad, arhinia occurs alongside ocular anomalies as well as hypogonadism.[17] In many cases, arhinia is accompanied by other craniofacial abnormalities, that include but are not limited to a high-arched or cleft palate, absent paranasal sinuses, hypoplastic maxilla, nasolacrimal duct stenosis or atresia and choanal atresia.[1] Additionally, the muscular- and vascular anatomy of the face are often unique and substantially differ from the norm. Altogether, these findings present unique reconstructive challenges and require comprehensive preoperative planning that goes beyond common nasal reconstructions. The feasibility of functional airway construction generally depends on the presence of sinuses and the complexity of the underlying bony hypoplasia. These procedures carry high operative risks due to the technical difficulty from reduced vertical dimensions of the palatal vault and ethmoid, as well as from the proximity of the maxilla and palate to the cranial base. They also bear a high risk of total, or near-total restenosis of the new passage.[18] Consequently, when respiratory issues aren’t the primary concern, it is reasonable to prioritize the aesthetic improvement of the external nose in order to address the social implications of the physical malformation.[19] Our subjects primarily suffered social disruptions from the facial deformity. Both subjects had adapted well to obligatory oral breathing without respiratory insufficiency. We focused our efforts on creating an external nose. Our main objectives when developing the operative plan, were to take an approach that would not only facilitate the nasal construction but also improve aesthetic facial proportions and limit morbidity. Strategies to improve the

cosmetic appearance of the midface and nose, range from the use of autologous cartilaginous grafts to internal and external nasal prosthetics, as well as combinations of either of them.[20,21] One approach proposed by a group in London involved serial staged expansion of midfacial skin with custom implants from childhood to adolescence, with age appropriate nasal construction and gradual expansion of the skin for a definitive reconstruction.[21,22] Historically, the most common method, aims to improve maxillary projection to create a stable foundation for a skeletal nasal framework that is covered by soft tissue, such as from a pedicled forehead flap.[18,19]

We present a detailed report of such a staged approach, in which we learned from the first case, to improve the second case. However, the main steps were consistent in that we improved maxillary projection by midface distraction osteogenesis followed by forehead tissue expansion and lastly nasal construction with a forehead flap on a rib cartilage framework.

Due to the exceptional rarity and complexity of congenital arhinia, most solutions in the literature are developed on a single-case basis. Subsequently, many aspects of the treatment are inconsistent, and a standardized treatment protocol is lacking. The treatment of serial subjects, as presented here, represents a unique and important opportunity to highlight key principles of nasal construction in arhinia. This guide offers and optimized guide to this surgical strategy for improved aesthetic and functional outcomes in these patients.

CONCLUSION

We present two related subjects with congenital arhinia where genetic diagnoses identified a novel pathogenic *SMCHD1* missense variant. This novel gene variant is a fundamental finding for guiding future investigations on genetic pathways and molecular processes, that underly the physiologic and pathologic development of the nose and its functional constituents.

The variable expressivity associated with this variant, that ranges from anosmia to arrhinia in our investigated subjects, requires further investigation with regards to the pathogenetic processes underlying this phenomenon.

Further research is required to determine if other phenotypes could be associated with this variant. This could help develop predictive clinical screening tools, that guide genetic screens prior to pregnancy to stratify the risk of individuals with anosmia or other related presentations, to pass on arrhinia to their children.

We described a staged approach to the construction of a cosmetically acceptable nose based on improving the maxillary foundation and projection prior to the construction of a nose with a forehead flap based on a structural support crafted from the rib cartilage. Le Fort II osteotomy and maxillary distraction osteogenesis not only significantly improves facial proportions but also provides a necessary and durable structural basis to accommodate the external nose. When attempting to create a skeletal framework for the nose, that is covered by soft tissue, we found that using a costochondral graft for the dorsum as well as for the alar is favorable over, as it provides maximal stability and superior contouring. A pedicled

forehead flap is an excellent choice for soft tissue coverage for soft tissue covering. For subjects that present in early childhood, serial expansion of the midfacial skin is also an option to increase the availability of soft tissue coverage.

ACKNOWLEDGMENT

We are grateful for the National Institutes of Health U01DE024443 and Shriners Hospital for Children for funding that supported this work. MB is a recipient of the Shiners Hospital Research Fellowship. ECL is a recipient of the Massachusetts General Laurie and Mason Tenaglia Research Scholar award.

This work was supported, in part, by the Intramural Research Program of the National Institutes of Health, National Institute of Environmental Health Sciences (Z01-ES103315 and 1ZIDES102465-13). NDS is also supported as a Lasker Clinical Research Scholar (1SI2ES025429-01). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center for Research Resources, the National Center for Advancing Translational Science, or the National Institutes of Health.

The authors thank the PI (Dr. Janet Hall) and study staff of NIH Protocol 12E0049 as well as Dr. Kaoru Inoue for assistance with study materials, sample collection, and processing.

REFERENCES

1. Shaw ND, Brand H, Kupchinsky ZA, et al. SMCHD1 mutations associated with a rare muscular dystrophy can also cause isolated arhinia and Bosma arhinia microphthalmia syndrome. Nat Genet. 2017;49(2):238–248. [PubMed: 28067909]
2. Gordon CT, Xue S, Yigit G, et al. De novo mutations in SMCHD1 cause Bosma arhinia microphthalmia syndrome and abrogate nasal development. Nature Genetics. 2017;49(2):249–255. [PubMed: 28067911]
3. Muhlbauer W, Schmidt A, Fairley J. Simultaneous construction of an internal and external nose in an infant with arhinia. Plast Reconstr Surg. 1993;91(4):720–725. [PubMed: 8446727]
4. Cole RR, Myer CM, 3rd, Bratcher GO. Congenital absence of the nose: a case report. Int J Pediatr Otorhinolaryngol. 1989;17(2):171–177. [PubMed: 2759782]
5. Meyer R Total external and internal construction in arhinia. Plast Reconstr Surg. 1997;99(2):534542.
6. Bennett JP. Sir William Fergusson and the Indian Rhinoplasty. Ann R Coll Surg Engl. 1984;66(6):444448.
7. Rana RE, Arora BS. History of plastic surgery in India. J Postgrad Med. 2002;48(1):76–78. [PubMed: 12082339]
8. MILLARD DRJ. Total Reconstructive Rhinoplasty and a Missing Link. Plastic and Reconstructive Surgery. 1966;37(3):167–183. [PubMed: 5326906]
9. Adzhubei IA, Schmidt S, Peshkin L, et al. A method and server for predicting damaging missense mutations. Nat Methods. 2010;7(4):248–249. [PubMed: 20354512]
10. Schwarz JM, Cooper DN, Schuelke M, Seelow D. MutationTaster2: mutation prediction for the deepsequencing age. Nat Methods. 2014;11(4):361–362. [PubMed: 24681721]
11. Shihab HA, Rogers MF, Gough J, et al. An integrative approach to predicting the functional effects of non-coding and coding sequence variation. Bioinformatics. 2015;31(10):1536–1543. [PubMed: 25583119]
12. Karczewski KJ, Francioli LC, Tiao G, et al. The mutational constraint spectrum quantified from variation in 141,456 humans. Nature. 2020;581(7809):434–443. [PubMed: 32461654]
13. Shihab HA, Gough J, Mort M, Cooper DN, Day IN, Gaunt TR. Ranking non-synonymous single nucleotide polymorphisms based on disease concepts. Hum Genomics. 2014;8:11. [PubMed: 24980617]
14. Farzadfard A, Pedersen JN, Meisl G, et al. The C-terminal tail of alpha-synuclein protects against aggregate replication but is critical for oligomerization. Commun Biol. 2022;5(1):123. [PubMed: 35145226]

15. Lemmers RJ, Tawil R, Petek LM, et al. Digenic inheritance of an SMCHD1 mutation and an FSHDpermissive D4Z4 allele causes facioscapulohumeral muscular dystrophy type 2. Nat Genet. 2012;44(12):1370–1374. [PubMed: 23143600]

16. Mul K, Lemmers R, Kriek M, et al. FSHD type 2 and Bosma arhinia microphthalmia syndrome: Two faces of the same mutation. Neurology. 2018;91(6):e562–e570. [PubMed: 29980640]

17. Bosma JF, Henkin RI, Christiansen RL, Herdt JR. Hypoplasia of the nose and eyes, hyposmia, hypogeusia, and hypogonadotrophic hypogonadism in two males. J Craniofac Genet Dev Biol. 1981;1(2):153–184. [PubMed: 6802865]

18. Brusati R, Colletti G. The role of maxillary osteotomy in the treatment of arhinia. J Oral Maxillofac Surg. 2012;70(5):e361–368. [PubMed: 22364860]

19. Feledy JA, Goodman CM, Taylor T, Stal S, Smith B, Hollier L. Vertical facial distraction in the treatment of arhinia. Plast Reconstr Surg. 2004;113(7):2061–2066. [PubMed: 15253197]

20. Harrison LM, Anderson SR, Spiller KE, Pak KY, Schmidt SP, Mancho SN. Reconstruction of Congenital Arhinia With Stereolithographic Modeling: Case Correlate and Literature Review. Cleft Palate Craniofac J. 2021:10556656211012859.

21. Borghi A, Ruggiero F, Tenhagen M, et al. Design and manufacturing of a patient-specific nasal implant for congenital arhinia: Case report. JPRAS Open. 2019;21:28–34. [PubMed: 32158883]

22. Gifford GH Jr., Swanson L, MacCollum DW. Congenital absence of the nose and anterior nasopharynx. Report of two cases. Plast Reconstr Surg. 1972;50(1):5–12. [PubMed: 5032329]

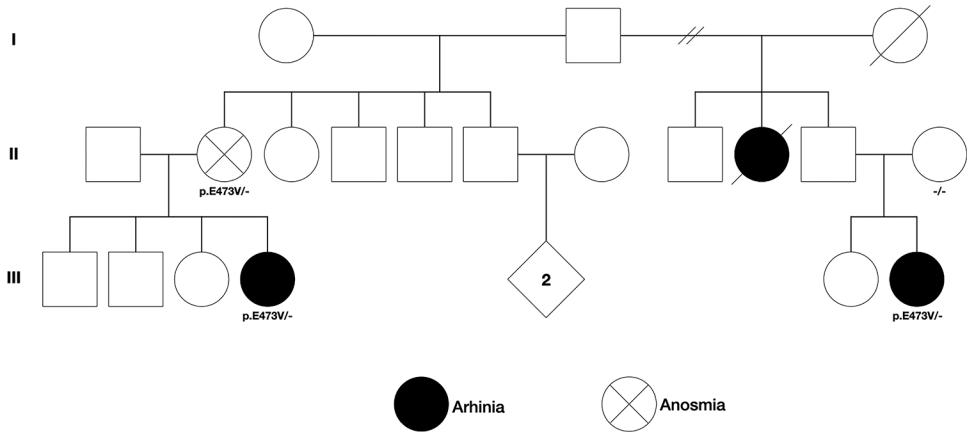

Figure 1.

A three-generation pedigree with three members born with arhinia. Affected individuals are shown as filled circles. The genotypes correspond to the individuals on which DNA sequencing analysis was performed and the *SMCHD1* gene variant was either detected in a heterozygous state (p.E473/−) or not at all (−/−). The diamond with the "2" means there were two healthy children, but gender is unknown. // indicates divorce.

Figure 2.

Preoperative appearance of arhinia in Subject I (top) and Subject II (bottom) in anterior and right lateral view, with typical concave facial profile from pronounced maxillary hypoplasia.

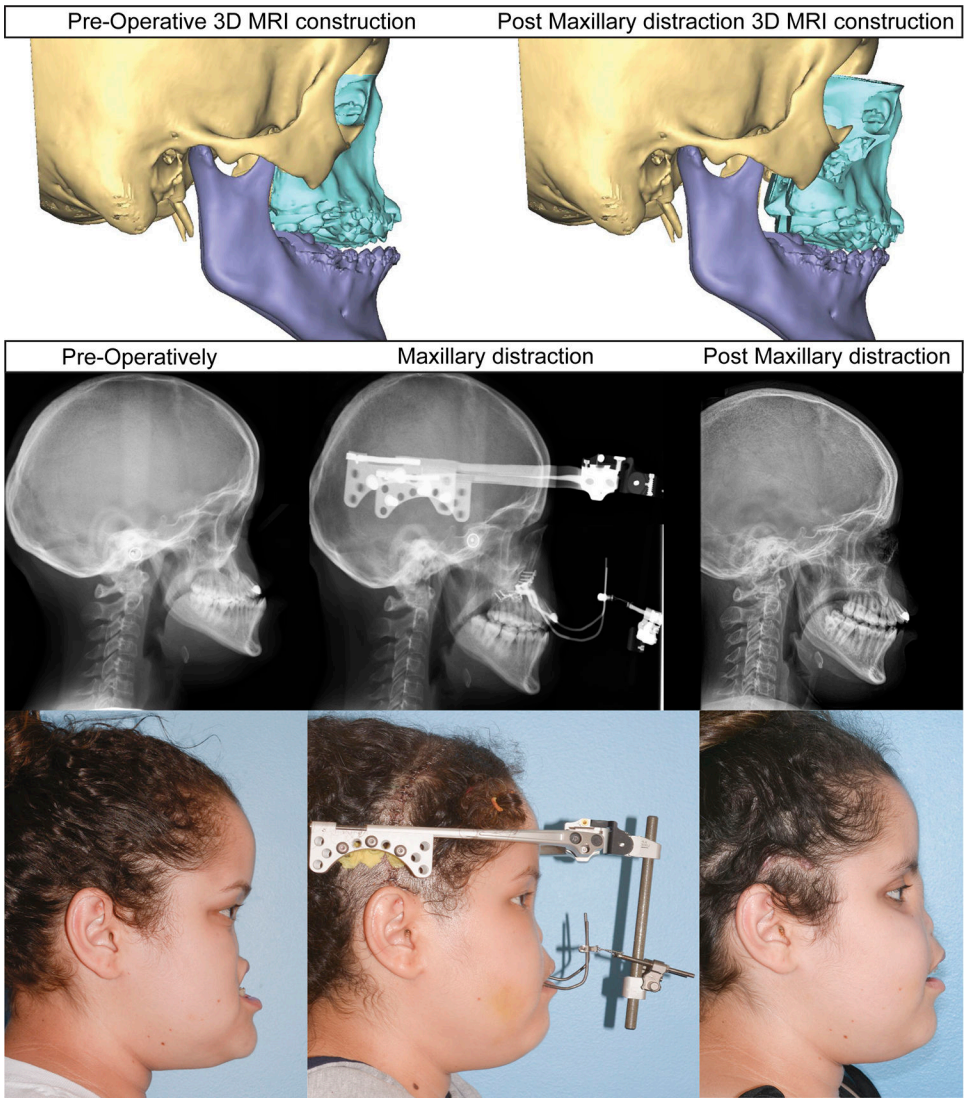

Figure 3.

Le Fort II osteotomy and maxillary distraction Pre-operative 3D computeraided simulation pre- and post- the Le Fort II osteotomy and maxillary distraction with Proplan CMF™ software, based on the subjects 3D magnetic resonance imaging (Top). X-ray images of the skull and (Middle) corresponding photographs of Subject I before, during and after maxillary distraction (Bottom), showing improvement of maxillary projection.

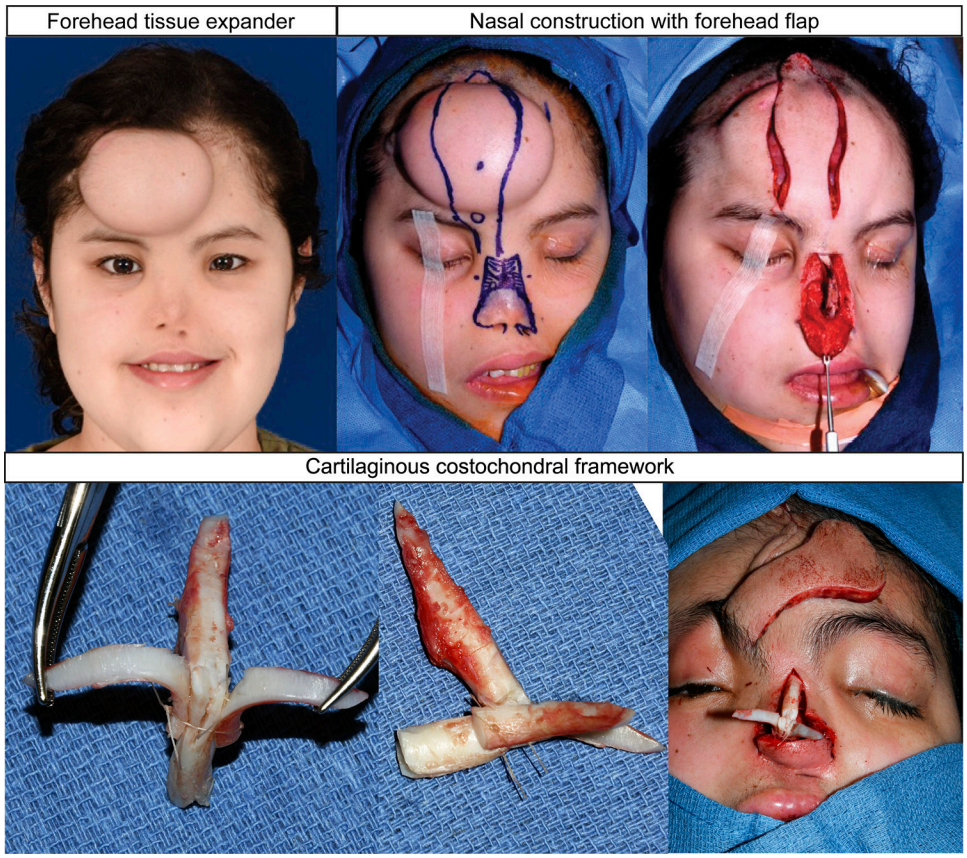

Figure 4.

Nasal construction with forehead flap and rib cartilage structure. Photograph showing Subject I with the forehead tissue expander (top, left). Marks for the forehead flap, after measuring the amount of laxity yielded from the tissue expander, so that the forehead can still close without tension after the forehead flap is harvested (top, middle). Intraoperative view of the pocket created for the nasal construction (top, right). Cartilaginous nasal framework of Subject II. Dorsal strut joined with a caudal strut via a dovetail pattern and attached bilaterally to two thinner and more pliable lower lateral nasal cartilages. (bottom, left and middle). Anterior view of the cartilaginous framework of Subject II before rotation of the de-epithelialized paramedian forehead flap onto the nasal framework (bottom, right).

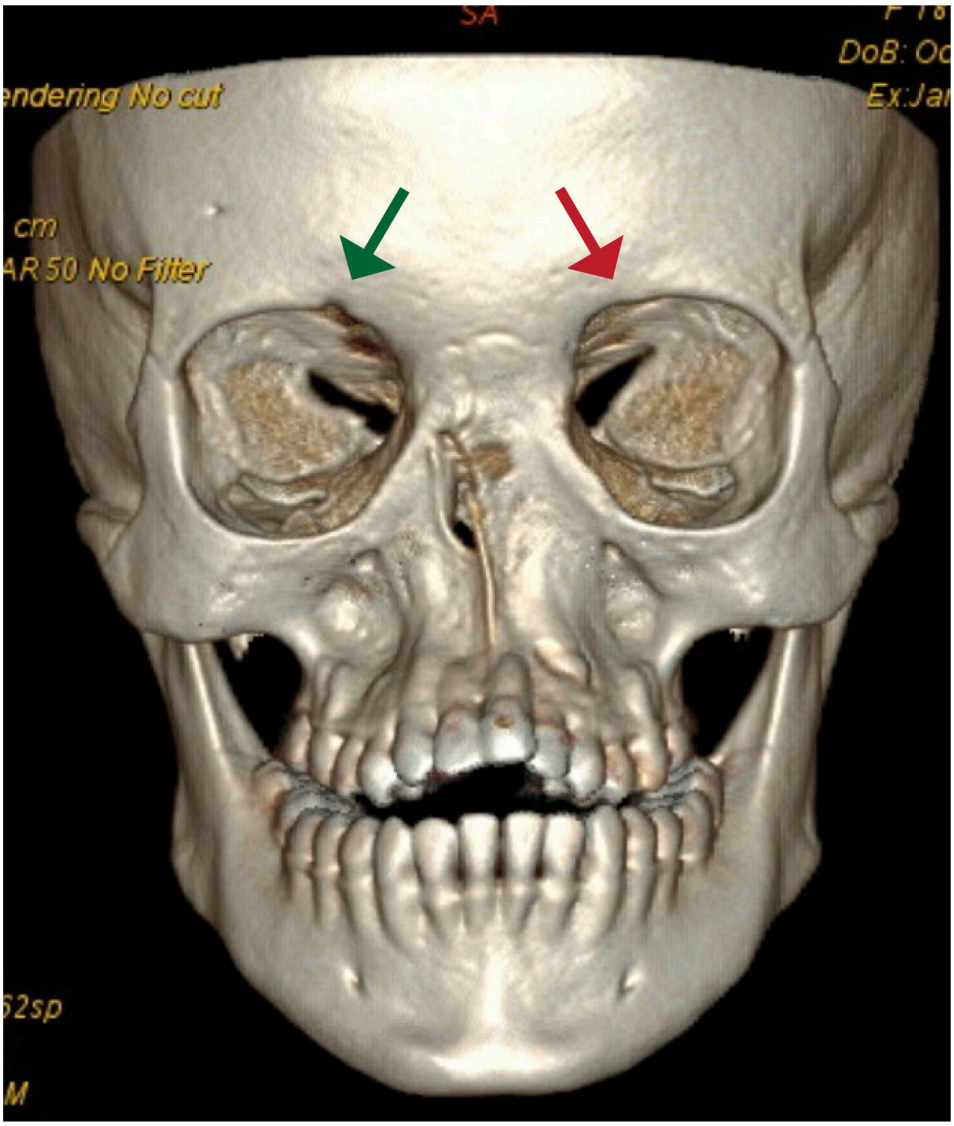

Fig. 5.

Pre-operative CT image of Subject I showing the supratrochlear foramen present on the right (green arrow) and absent on the left side (red arrow).

Figure 6.

Anterior and right lateral view following primary nasal construction with a forehead flap, showing significantly improved midfacial height and the nasal construct with satisfactory alar contour and supratip break, as well as restored medial eyebrow position.