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BRIEF REPORT

Duplicated, Translocated Upper Lip and Maxilla: An Extremely Rare Congenital Craniofacial Anomaly With Novel Genetic Findings

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ABSTRACT

Importance: Diprosopus is an exceedingly rare craniomaxillofacial dysmorphosis that is considered a subgroup of conjoined twins. This phenotype encompasses a broad spectrum of duplications ranging from partial structures to complete dicephalus. The embryogenesis and mechanism of disease are not well understood. The objective of this investigation was to describe a case of partial dentofacial duplication and to discuss the possible etiology with novel genetic insights thereof.

Observations: A newborn Kazakh boy was referred to the First Affiliated Hospital of Xinjiang Medical University because of a maxillary mass detected on prenatal imaging. Physical examination revealed a unilateral cleft lip and a soft lump around 2.5 cm in diameter with the appearance of an accessory upper lip. He underwent two surgical procedures at 11 months and 4 years of age for definitive treatment. He demonstrated favorable recovery outcomes, maintaining normal speech and oral intake capabilities during long-term follow-up.

Conclusions and Relevance: Our preliminary findings and comprehensive literature review suggest that mutations in the *PAX7* gene could contribute to the pathogenesis of craniofacial duplication. This hypothesis establishes a previously unrecognized association between specific genetic alterations and the clinical manifestations of this condition, potentially offering a molecular foundation for prenatal diagnostic approaches. The present case provides more profound insights into the disease mechanisms compared to prior reports. Further validation through basic scientific investigations and clinical studies, incorporating comprehensive genetic analyses, will be essential to substantiate this proposed mechanism.

1 | Introduction

Diprosopus, which includes the duplication of stomatodeal structures, is extremely rare, with fewer than 40 cases worldwide since this birth defect was first reported in 1948 [1]. Its phenotypes range from isolated duplication of cranial or facial structures to a variety of combinations. In cases of partial craniofacial duplication, the most commonly affected

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regions are the mandible, maxilla, and oral cavity. Cerebral involvement may also occur, with the mildest form being pituitary gland duplication [2]. Common comorbidities related to craniofacial duplication include macrosomia, orbital hypertelorism, cleft lip and palate, accessory tongue, Pierre Robin sequence, and Klippel–Feil syndrome. However, isolated oral and maxilla/mandible duplication without associated syndromes has been described only a handful of times [2–4]. This condition is more frequently reported in the mandible than the maxilla; in addition, it has a greater incidence in females, but its contributing factors have yet to be elucidated. Maxillary duplication cases often present with concomitant facial clefts, requiring comprehensive surgical planning for both the bony and soft tissue components [5]. Here we give this brief report based on an individual patient with partial craniofacial duplication involving the maxilla and upper lip, and discuss the possible etiology and diagnostic marker, including a candidate genetic variant.

2 | Case Presentation

A newborn Kazak boy was referred to the otolaryngology service after prenatal ultrasonography detected a maxillary mass during the third trimester of pregnancy. The initial differential diagnosis included teratoma, ectopic sinus, congenital cyst, foregut duplication, or fibrous dysplasia. The infant was delivered by cesarean section at 38 weeks' gestation. Birth weight was 2956 g, and Apgar scores were 7 and 8 at 1 and 5 min after delivery, respectively. No respiratory distress was present at birth. His mother was Kazak, 32 years old, and healthy (Gravid 2, Para 1). There was no history of exposure to teratogens in utero, preeclampsia, or polyhydramnios. There was no family history of congenital defects. After delivery, the physical examination revealed a 2.5–3.0 cm mass on the upper gingiva, protruding into the lip, and featured a small sinus tract in its center. It resembled the upper vermilion and appeared innervated and moved in conjunction with oral movements (Figure S1). Imaging after

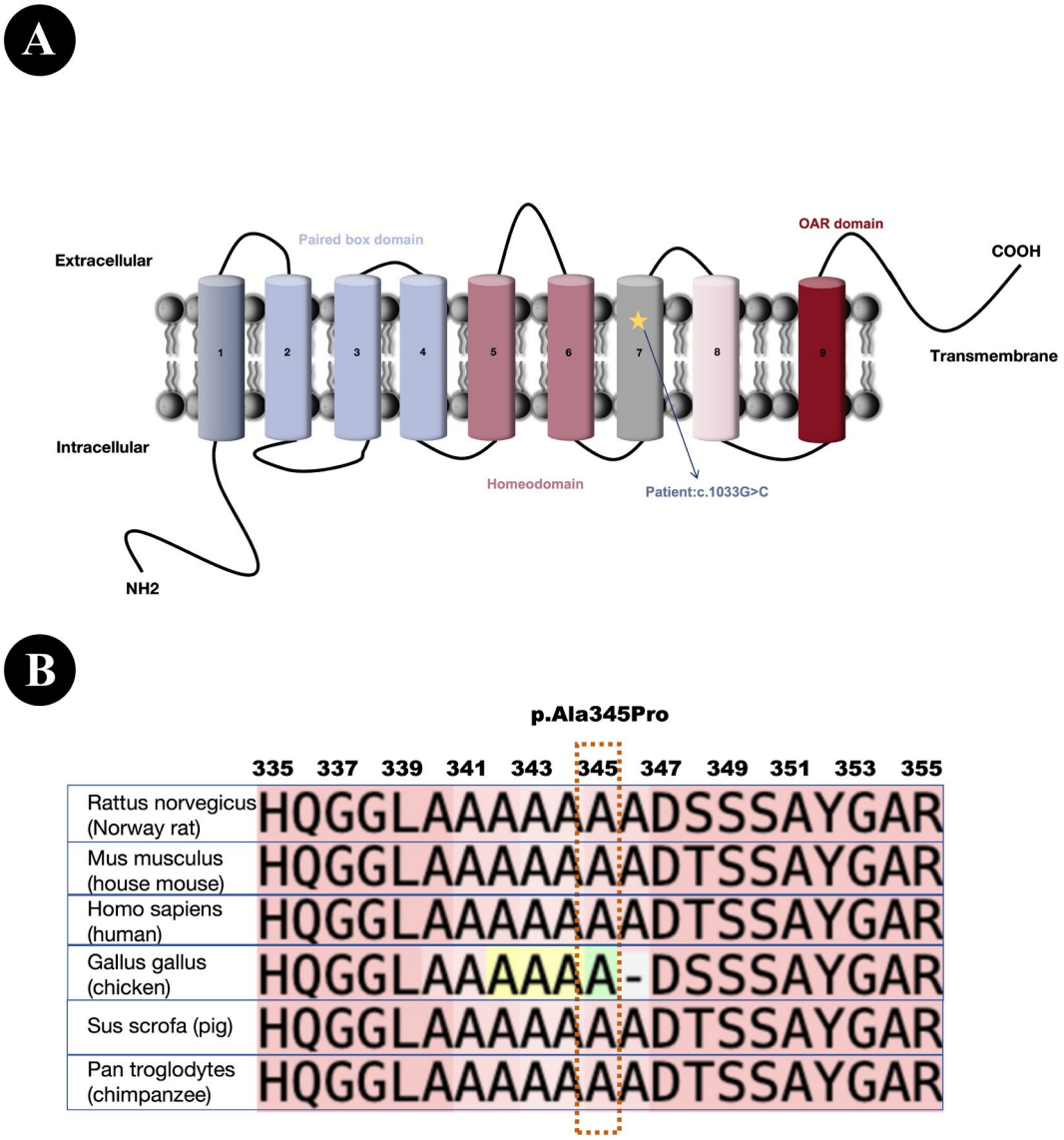

FIGURE 1 | (A) Topological representation of the PAX7 protein showing the nine transmembrane segments and the three different cytosolic domains, which are indicated in blue (paired box domain), purple (homeodomain), and red (OAR domain). The dotted line indicates the location of the patients' variant investigated. (B) Sequence conservation analysis of *PAX7* missense variant. Conservation of the altered amino acid was shown in the T-COFFEE alignment.

birth revealed an abnormally broadened nasal bone, a left complete unilateral cleft lip, an irregularly shaped soft tissue deriving from the ipsilateral upper lip, and a duplicated, translocated maxilla intersected in the midline. The coexistence of maxillary duplication with cleft lip in our patient is consistent with previously reported cases, where facial clefts represent a common associated feature of craniofacial duplication [6]. There were no aggressive osseous features or evidence of periosteal reaction (Figures S2 and S3). Based on CT data performed using the DICOM format, were processed utilizing Mimics software version 19.0 (Materialise Inc., Leuven, Belgium) to reorient every plane, set the grayscale thresholds (226–3071 HU), and determine and perform the three-dimensional reconstruction for subsequent customized surgical guides (Videos S1 and S2). He was taken to the operating room for mass excision (at 11 months of age, Stage I) and maxillofacial reconstruction (at 4 years of age, Stage II). Postoperatively, he healed well and was feeding and speaking without any issues until now (Figure S4). The patient has been followed for 2 years with regular assessments at 3-month intervals during the first year, then annually. At the most recent follow-up visit, the patient demonstrated normal oral intake without difficulty, age-appropriate speech development with clear articulation, symmetric facial growth with satisfactory aesthetic appearance, and without infection, dehiscence, or need for revision surgery. Consequently, based on patient history and clinical findings, his final diagnosis was confirmed as partial craniofacial duplication (Type II) [7, 8] (Table S1).

Samples from the patient and his mother were evaluated using scalable whole-exome sequencing (WES) of cell-free DNA. Paternal samples were not available as the biological father was deceased at the time of genetic testing. The average sequencing depths of WES were 100 ± 20, with a coverage of over 95%. The obtained sequencing results were aligned to the Genome Reference Consortium *Homo sapiens* (human) genome assembly GRCh37 (GRCh37/hg19). Variant calling was performed using GATK (Genome Analysis Toolkit), and variants were filtered based on the following criteria: read depth $\geq 10\times$, quality score ≥ 30, and minor allele frequency < 0.01 in population databases. Variant annotation was conducted using ANNOVAR software, with reference to gnomAD (Genome Aggregation Database), ClinVar, OMIM (Online Mendelian Inheritance in Man), and HGMD (Human Gene Mutation Database). Pathogenicity prediction utilized

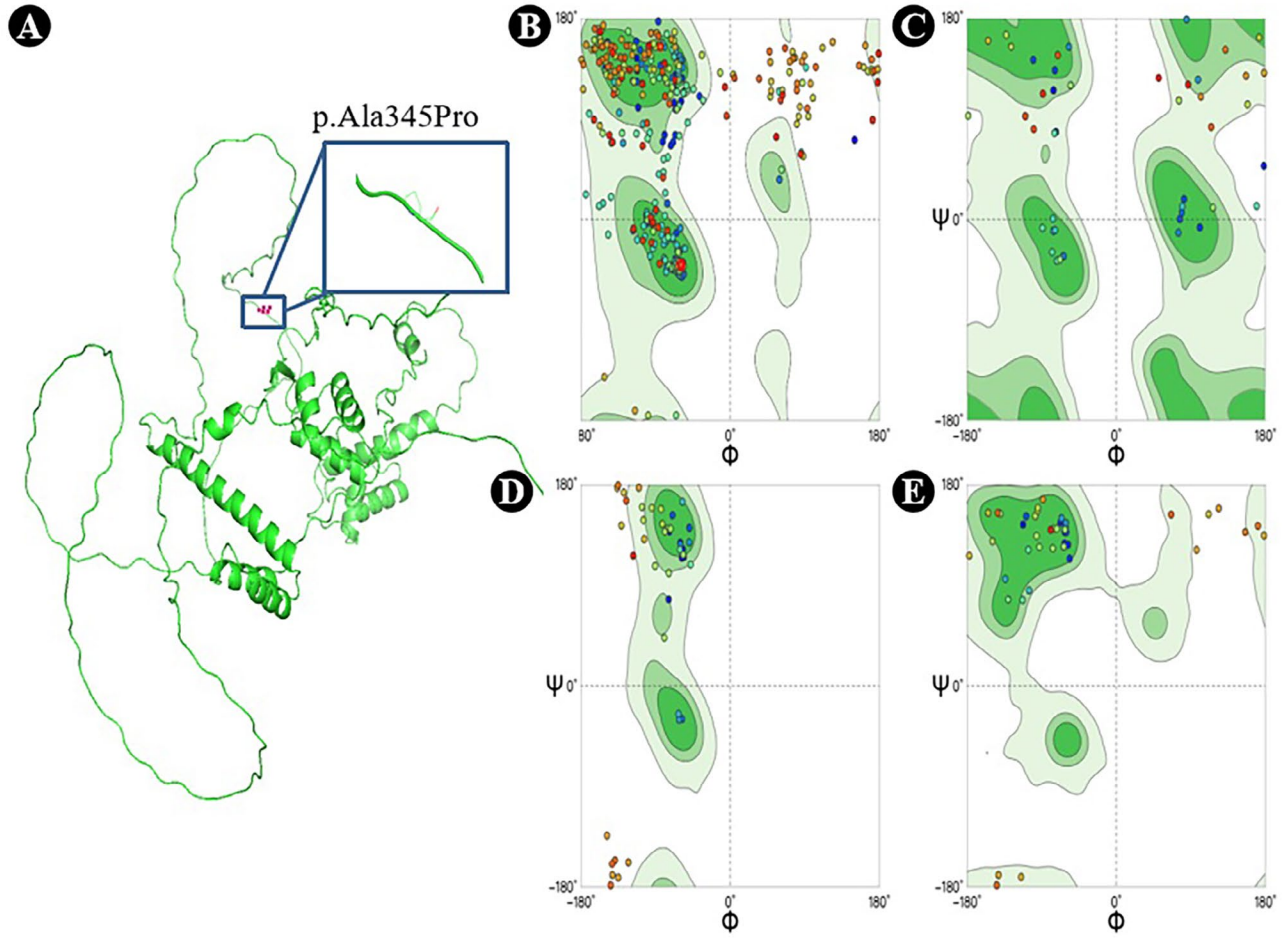

FIGURE 2 | Molecular analysis of *PAX7* protein structure and protein structural alterations (p.Ala345Pro). A. PAX7_HUMAN predicted in the SWISS-MODEL (https://swissmodel.expasy.org/interactive/rfrgfe/models/). The box shows the functional region alterations in the protein structure of the mutant (p.Ala345Pro) (B–E). Ramachandran plots showed the values of the φ (phi) and ψ (psi) dihedral angles for each amino acid (B, general; C, glycine; D, proline E, pre-proline) residue within the protein. The φ angle represents the angle between the α carbon atom of an amino acid and the carbon atom of its neighboring nitrogen atom, while the ψ angle represents the angle between the α carbon atom of an amino acid and the nitrogen atom of its neighboring carbon atom.

multiple in silico tools, including SIFT, PolyPhen-2, and MutationTaster. In our sequencing analysis, we focused on genes with enriched and specific expression patterns associated with craniofacial abnormalities [9]. Our findings revealed a missense mutation c.1033G>C (p.Ala345Pro) in the *PAX7* gene (NM_001135254.1) identified in both the affected child and the mother (gnomAD allele frequency: not reported; predicted damaging by SIFT and PolyPhen-2) (Figure 1A). We also performed a conservation analysis showing high sequence conservation at the protein-coding levels (Figure 1B) and conducted predictive analyses on the protein structural changes at the mutated site (Figure 2).

3 | Discussion

The pathogenesis of craniofacial duplication remains controversial and is yet to be fully understood. Many hypotheses exist to explain the initiating event, but most scholars agree that the notochord that induces neurulation is the kernel of the problem. Duplication of cells at the anterior termination of the notochordal process may initiate duplication of facial–oral elements (Figure 3). In addition, in partial diprosopus, only certain craniofacial components or elements of the first branchial arch are duplicated (especially the mandible and lower lip duplication) [10, 11]. In recent years, the scalable WES cell-free DNA technique, which could enable comprehensive profiling of conditions from peripheral blood, has been increasingly utilized for more precisely defining genetic disorders or rare diseases. Furthermore, with the advances in molecular genetics, an increasing number of gene mutations have been found to be associated with craniofacial duplication or anomalies derived from syndromes lately. The major disease-causing genes include *SHH*, *TWIST1*, *ZIC2*, *GLI3*, *FOXC1*, and *EFNB1* [12]. By analyzing gene expression data of human craniofacial tissues and integrating thousands of gene expression profiles from adult tissues, Yankee et al. revealed 539 previously unappreciated genes with craniofacial bias expression and identified 34 genes. These genes, including *PAX7*, exhibited the highest Gini index in craniofacial tissues [9]. *PAX7* is a member of the paired box gene family, encoding an important transcription factor. The *PAX7* gene plays a fundamental role in multiple aspects of craniofacial development, including neural crest cell regulation, cranial bone and facial muscle development, and overall craniofacial structure patterning. *PAX7* is expressed in neural crest cells beginning at the early somite stages and plays a critical role in their specification and migration [13]. During craniofacial development (weeks 4–8 in humans), *PAX7*-expressing cranial neural crest cells migrate from the dorsal neural tube to populate the first branchial arch, giving rise to maxillary and mandibular structures [14]. *PAX7* regulates the balance between neural crest cell proliferation, survival, and differentiation. Disruption of *PAX7* function could theoretically alter neural crest migration patterns or cell fate decisions during notochord-dependent facial patterning [15]. If *PAX7* dysfunction occurs during the critical period when the notochord signals midline facial development, aberrant neural crest behavior might contribute to duplication of facial primordia rather than typical fusion defects like clefts.

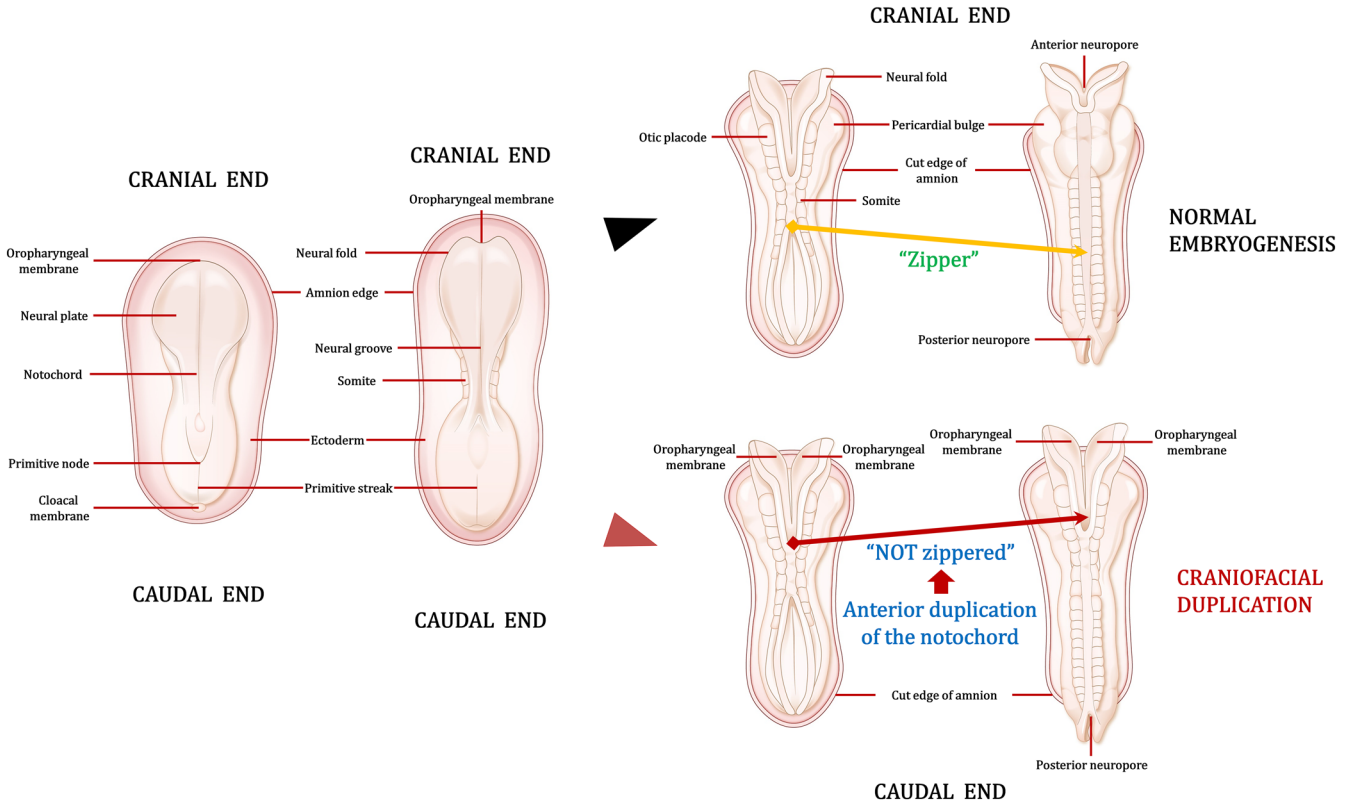

FIGURE 3 | Dorsal views of a normal embryonic development with a single notochord and a human embryo showing bifurcation of the cranial portion of the notochord. This figure was created using Figdraw 2.0 online platform (https://www.home-for-researchers.com).

To our knowledge, this is the first report of a *PAX7* variant in diprosopus, precluding direct genotype–phenotype comparison with previous cases. While *PAX7* mutations have been associated with other craniofacial anomalies, including cleft palate and midfacial hypoplasia in syndromic conditions, craniofacial duplication has not been previously reported [16]. The extreme rarity of diprosopus (<40 cases since 1948) and the absence of comprehensive genetic characterization in most historical cases limit comparative analysis. Future international case registries with systematic genetic screening are needed to establish genotype–phenotype correlations. In the case of *PAX7*, this may impact its function as a transcription factor, potentially leading to craniofacial developmental abnormalities. However, the presence of this mutation in the phenotypically normal mother suggests incomplete penetrance, variable expressivity, or the involvement of additional genetic or environmental factors. In vitro assays (e.g., luciferase reporter assays, DNA-binding studies) and in vivo animal models (e.g., zebrafish or mouse models) are needed to confirm pathogenicity.

4 | Limitations

Our genetic testing identified a missense mutation in the *PAX7* gene in both the patient and the patient's mother. While missense mutations can alter encoded amino acids and potentially affect protein function, this finding represents an association rather than proof of causation. The pathogenic significance of this specific variant remains uncertain based on a single case and the absence of functional studies. While bioinformatic analysis suggests potential functional impact, this variant should be classified as of uncertain significance pending functional validation. The presence of this mutation in the phenotypically normal mother indicates incomplete penetrance or involvement of additional factors. Without paternal genetic data, we cannot determine if the variant is de novo in the mother or represents a familial variant with reduced penetrance. The lack of paternal information also limits our ability to provide accurate recurrence risk counseling for future pregnancies.

5 | Conclusion

Collectively, this investigation reports a *PAX7* variant associated with craniofacial duplication for the first time, providing preliminary data suggesting a potential association that warrants further investigation. Establishing a causal relationship will require functional validation studies and replication in additional cases. As multiple gene mutations may be involved, comprehensive genomic screening is necessary. Future priorities include establishing international case registries, performing functional validation studies, expanding genetic screening in additional cases, and investigating embryological mechanisms. Multicenter collaboration is essential to validate our findings and improve molecular diagnosis and genetic counseling for this rare condition.

Author Contributions

C.-X.L. made substantial contributions to the acquisition, analysis, and interpretation of data, drafted the article, approved the final version to be published, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of all parts of the work are appropriately investigated and resolved. D.-S.H. and Z.-C.G. made substantial contributions to the conception and design, reviewed the article critically for important intellectual content, approved the final version to be published, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of all parts of the work are appropriately investigated and resolved.

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Ethics Statement

The present study was approved by the Ethics Committee at the First Affiliated Hospital of Xinjiang Medical University (approval no. K20240919-06). Procedures operated in this research were completed in keeping with the standards set out in the Announcement of Helsinki and laboratory guidelines of research in China.

Consent

Written informed consent to participate in this study was provided by the participants or their legal guardian/next of kin.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Data S1:** Supplemental references. **Video S1** and **S2**. Preoperative videos depicting the craniofacial reconstruction containing the maxillary duplication using digital technique. High-resolution CT images were imported into Mimics software (version 19.0, Materialise) for segmentation and 3D reconstruction. Threshold-based segmentation was performed using Hounsfield Unit (HU) ranges of [226–3071] for bone and soft tissue, with manual corrections to refine boundaries. To ensure reproducibility, segmentations were independently verified by three trained operators, and interobserver variability was assessed using intraclass correlation coefficient (ICC) as well as Dice similarity coefficient (DSC), demonstrating excellent agreement (ICC > 0.9, DSC > 0.85). Reconstructed models were validated against anatomical landmarks and clinical imaging to confirm anatomical accuracy. The imaging protocol on segmentation reproducibility and validation can be found in our previous work (supplemental references [1–6]). **Table S1:** Classification of stomatodeal structure duplications, adapted and modified from Chen and Noordhoff. **Figure S1:** Panel A exhibits absent anterior nasal spine, wider alar base root width, short columella, flattened nose and broader nostril floor width on the cleft side, acute nasolabial angle, and a flat frontonasal angle. In addition, orbital hypertelorism, the interocular distance, is clinically informative and in extremes is considered a minor physical anomaly. Panel B shows nasomaxillary disharmony, with gingival thickening around the upper deciduous incisor teeth with partial eruption. Overgrowth can be observed in the anterior maxilla covered by duplicated and malformed upper lip, with possibility of two shortened dental arches. **Figure S2:** Complete duplication of maxillary dental arch indicated through preoperative dynamic contrast-enhanced CT images. The duplicated primary dentitions with partial permanent tooth germs were overlapped in the midline area that are displayed in each slice of axial planes scanned using high-resolution CT scanner (Siemens Healthineers, Erlangen, Germany). **Figure S3:** A three-dimensional dataset was acquired with a Volume Zoom CT scanner (Siemens Healthineers, Erlangen, Germany) with a section thickness of 1 mm. Panel A provides a gross view showing left complete unilateral cleft lip and duplicated, translocated maxilla intersected at the upper deciduous incisor teeth. Panel B shows three-dimensional CT reconstruction indicating an ossified and soft tissue mass of the maxillary body containing teeth. There was a soft tissue component along the surface of the bony compartment and no aggressive osseous features or evidence of periosteal reaction. **Figure S4:** Intraoral postoperative documentation at (A) 1-week and (B) 3-month follow-up.