Gender Links and Non-Syndrome Related Mutations Linking Isolated Cleft Palate and Ankyloglossia in the Fetal Development

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Abstract

AIM: To compare the pathogenesis of ankyloglossia (tongue-tie) with isolated cleft palate only (CPO) by examining the influence of genetic and epigenetic factors.

METHODS: A comprehensive literature review encompassing the years 2012-2017, yielded a substantial body of research linking cleft palate and ankyloglossia. Inclusion criteria comprised randomized controlled clinical trials, both prospective and retrospective; with the exclusion of non-English studies.

RESULTS: The embryonic parallels between CPO and ankyloglossia suggest a phenotypic expression through neural crest cells along the anterior-posterior axis. These developmental pathways persist during palatogenesis, affecting structures such as palatal shelves and the lingual frenum. Significantly, the cranial neural crest derived connective tissue of the lingual frenum demonstrates a functional correlation with the genioglossus muscle. In the context of cleft palate (CP) models, malformation of the genioglossus muscle is associated with micrognathia in extrinsic perspectives, while intrinsic perspectives focus on causal genes affecting palatal shelves. Ankyloglossia is identified as part of an X-linked, gender-specific disease spectrum with various midline-related variations along the anterior-posterior axis.

CONCLUSION: The functional perspective has brought attention to the interplay of structures surrounding the palate in comprehending CP etiology. This approach underscores the importance of tongue position and the attachment of the lingual frenum connective tissue to the genioglossus muscle. Early intervention aimed at reducing the lingual frenum may potentially enhance the form and function of the oral cavity.

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1 Introduction

As this century has brought an outpouring of genome studies, a new perspective has developed on the pathogenesis of CP (Beaty et al., 2016). Numerous genes associated with CP have been identified, as well as complex embryonic pathways and interactions from early embryogenesis (Smith et al., 2012; Zhou et al., 2013; Almaidhan et al., 2014; Parada et al., 2015; Yu et al., 2015). Disruption along the anterior-posterior axis emerges as a recurring theme in various craniofacial anomalies, each with specific genes related to anterior and posterior defects (Smith et al., 2012; Song et al., 2013; Parada et al., 2015; Huang et al., 2016; Kouskoura et al., 2016). Gender related differences manifest as a prevalence of anterior palate defects in males and posterior palate defects in females (Beaty et al., 2016).

Cleft lip and palate (CL/P) affecting primarily the anterior palate and CPO affecting primarily the posterior palate are distinct anomalies (Okano et al., 2014; Beaty et al., 2016). CPO has genetic links to ankyloglossia referred to as X-linked cleft palate (CPX) (Pauws et al., 2013; Jangid et al., 2015). Ankyloglossia is part of this spectrum of diseases that follow an X-linked inheritance pattern (Pauws et al., 2013; Jangid et al., 2015). T-box containing transcription factor 22 (Tbx22) is an X-linked causal cleft palate gene associated with various defects including CPO, ankyloglossia, submucous cleft, partial hard palate cleft, deficient soft palate, and bifid uvula (Pauws et al., 2013; Jangid et al., 2015). The gender specific prevalence of CPX in males contributes to the understanding of X-linked inheritance (Pauws et al., 2013; Fu et al., 2015).

While significant strides have been made in identifying causal genes for CP, the complete pathogenesis of CPO remains elusive (Pauws et al., 2013; Peng et al., 2016). Research highlights that 90% of CPOs result from defects in palatal elevation emphasizing intrinsic and extrinsic pathways concerning the palate (Song et al., 2013; Okano et al., 2014).

Causal genes of CPO gained genome-wide significance through the integration of epigenetic factors which offers a broader perspective on palatogenesis (Beaty et al., 2016). The intricate interplay of craniofacial structures, including the mandible, maxilla, and tongue, influences palatogenesis (Song et al., 2013; Okano et al., 2014; Parada et al., 2015; Huang et al., 2016; Kouskoura et al., 2016). Recent studies in mice reveal complex pathways affecting primarily cranial neural crest (CNC) derived cells focusing on palate closure and its connection to the lingual frenum and genioglossus muscle attachment (Song et al., 2013; Okano et al., 2014; Parada et al., 2015; Kouskoura et al., 2016; Tang et al., 2016).

The maternal desire to breastfeed has heightened interest in diagnosing and treating ankyloglossia which is associated with a deficiency in sagittal development of the jaws such as the Pierre Robin Sequence (PRS) (Song et al., 2013; Parada et al., 2015; Kouskoura et al., 2016). Symptoms linked to ankyloglossia encompass difficulties in breastfeeding, speech articulation issues, swallowing problems, maternal nipple pain, and failure to thrive (Jangid et al., 2015; Ferrés-Amat et al., 2016). Neonatal impairment of tongue protrusion related to ankyloglossia is associated with feeding problems (Ferrés-Amat et al., 2016). Correcting frenum constraints on tongue movement is anticipated to enhance both function, particularly in infant feeding, and form supporting normal development of the anterior-posterior axis (Shen et al., 2014; Ferrés-Amat et al., 2016).

The literature review aims to analyze the current understanding of genetic and epigenetic influences, uncovering common pathways in the pathogenesis of both ankyloglossia and CPO. The objective is to identify embryonic and genetic links to CPO for improved diagnosis and treatment of ankyloglossia.

2 Methods

A comprehensive literature review covering the years 2012-2017 was conducted, focusing on articles with free full-text availability. The search encompassed genetic and epigenetic factors related to early palate development, palatal elevation, tongue malformation, X-linked inheritance, ankyloglossia, orofacial clefts, whole genome sequencing, and risk.

Inclusion criteria comprised randomized controlled clinical trials, both prospective and retrospective, with non-English studies being the only exclusion. The parameters investigated included embryogenesis, palatal shelf closure, and tongue positioning, with an analysis of intrinsic and extrinsic factors as well as epigenetic influences.

The following search combinations were used: early palate AND anterior-posterior axis (3 studies), 1 excluded (non-English); palatal elevation AND tongue malformation (8 studies), none excluded; X-linked AND ankyloglossia AND CP (5 studies), none excluded; genetic factors AND orofacial cleft AND whole genome sequencing AND risk (2 studies), none excluded. The diagnostic and treatment protocols for ankyloglossia were researched with this search combination: ankyloglossia AND treatment AND childhood (2 studies), none excluded.

2.1 Statistics

Descriptive statistics, frequency analysis, and content analysis were employed as part of the qualitative methodology to systematically analyze the textual content of the included studies. It is important to note that, given the narrative nature of this study, regression analysis and meta-analysis techniques were not deemed suitable for the analytical framework.

3 Results

A comprehensive analysis drew upon 19 studies to investigate the potential connections between ankyloglossia and cleft palate (CPO). Eight prospective studies conducted on mice scrutinized gene deletions or exposure to environmental teratogens resulting in CP and/or ankyloglossia (Smith et al., 2012; Song et al., 2013; Zhou et al., 2013; Almaidhan et al., 2014; Kouskoura et al., 2015; Parada et al., 2015; Yu et al., 2015; Tang et al., 2016). These studies were further categorized into intrinsic and extrinsic palatal etiology for CP.

Among these, three prospective studies elucidated intrinsic palatal etiology for CPO in mice studies (Zhou et al., 2013; Almaidhan et al., 2014; Yu et al., 2015), while four prospective studies outlined extrinsic palatal etiology for CPO (Song et al., 2013; Kouskoura et al., 2015; Parada et al., 2015; Huang et al., 2016). Additionally, one prospective study presented a combined intrinsic and extrinsic palatal perspective to explain the etiology of CPO (Tang et al., 2016).

Furthermore, nine retrospective studies delved into genetic networks and causal genes (Jiang et al., 2012; Smith et al., 2012; Pauws et al., 2013; Okano et al., 2014; Fu et al., 2015; Gurramkonda et al., 2015; Jangid et al., 2015; Beaty et al., 2016; Peng et al., 2016). In addition to exploring genetic networks and causal genes, two studies specifically investigated ankyloglossia (Gurramkonda et al., 2015; Jangid et al., 2015) and two studies explored gender-related genetic factors (Okano et al., 2014; Beaty et al., 2016).

3.1 Embryogenesis

Mammalian studies have contributed significantly to the understanding of the complex network of molecular pathways dictating embryogenesis (Smith et al., 2012; Zhou et al., 2013; Parada et al., 2015; Yu et al., 2015; Huang et al., 2016). An anterior-posterior axis of molecular and cellular interaction is established early in neural crest development (Smith et al., 2012; Song et al., 2013; Parada et al., 2015; Huang et al., 2016).

The developmental sequence delineates the progression of structures of the head and face from anterior to posterior, illustrating how anterior development influences posterior structures. The medial nasal prominence and the first pharyngeal arch serve as primary precursors to the oral cavity (Smith et al., 2012; Almaidhan et al., 2014) with the first pharyngeal arch contributing to the formation of the skull, middle ear components, and primary jaw structures (Smith et al., 2012; Almaidhan et al., 2014).The maxillary and medial nasal processes give rise to the anterior (primary) palate and lip, while the secondary palate forms posteriorly from bilateral maxillary processes that develop vertically alongside the tongue (Smith et al., 2012; Almaidhan et al., 2014). Vertical growth of the palatal shelves is a pivotal event in palatogenesis, culminating in oral development through palatal closure (Smith et al., 2012; Almaidhan et al., 2014; Huang et al., 2016).

The vertical elevation of the palatal shelves is subject to intrinsic and extrinsic controls from other developing structures, ultimately positioning them horizontally above the descending tongue for palatal closure (Smith et al., 2012; Almaidhan et al., 2014; Huang et al., 2016). Intrinsic mechanisms, including gene expression, cell density, and cell migration, play an important role in directing palatal elevation (Smith et al., 2012; Pauws et al., 2013; Almaidhan et al., 2014; Fu et al., 2015). Extrinsic mechanisms of palatal elevation involve molecular and functional aspects of the surrounding structures (Song et al., 2013; Parada et al., 2015; Huang et al., 2016; Kouskoura et al., 2016; Tang et al., 2016). Growth factors and bone morphogenetic factors exert influence at every step of palatal development (Smith et al., 2012; Song et al., 2013; Yu et al., 2015).

Growth factors are particularly implicated in maxillary and mandibular growth, pointing to the palatal shelves, the mandible, and the connective tissue of the tongue (Yu et al., 2015). Longitudinal or sagittal growth of the lower jaw is crucial for tongue positioning away from the closing palatal shelves. This growth is secondary to factors including anterior positioning of the genioglossus muscle interrelated ossification and growth of Meckel's cartilage, vertical and anterior positioning of the tongue, anterior-posterior axis alignment of the genioglossus muscle, and morphogenesis of the anterior and posterior palate (Parada et al., 2015; Kouskoura et al., 2016). The morphogenesis of the palatal shelves involves an expansion in the medial walls concurrent with the positional and functional changes in the tongue (Yu et al., 2015). Palatal changes start in the anterior and proceed to the posterior through signaling (Smith et al., 2012). As the palate closes, the cranial base straightens, possibly generating forces in the midline that are transmitted to the sphenoid, and the palatal shelves during elevation (Parada et al., 2015).

3.1.1 Neural crest

The majority of craniofacial structures trace their origins to the early alignment and patterning of the anterior-posterior axis of the neural crest (Smith et al., 2012). Neural crest cell derivatives play a critical role in causing primary malformations of the mandible, tongue, and maxilla, each characterized by distinct mechanisms. Mammalian models have been instrumental in unveiling these upstream influences (Smith et al., 2012; Parada et al., 2015).

Neural crest cell derivatives contribute significantly to primary mandibular development, providing insights that can elucidate conditions like PRS (Parada et al., 2015). Disruption of these cranial neural crest cells can impact other structures, leading to secondary issues such as micrognathia observed in conditions like CP and ankyloglossia (Parada et al., 2015; Huang et al., 2016). The causal gene for CP, Tbx22, is expressed in both the palatal shelves and the frenum area of the tongue (Gurramkonda et al., 2015; Jangid et al., 2015).

3.1.2 Anterior-posterior axis palatal growth

The distinction between anterior and posterior defects is evident in the differentiation between CP, which is mainly in the posterior palate, and CL/P, which is mainly in the anterior palate (Smith et al., 2012; Okano et al., 2014; Beaty et al., 2016). Regional genetic expression along the anterior-posterior axis initiated early in embryogenesis and persisting through development, contributes to critical expansion or limitation of oral structures (Smith et al., 2012). Comprehending this phenotype development aids in understanding the impact of causal genes on the pathogenesis of CP and ankyloglossia (Smith et al., 2012). Notably, the gene expression involved in clefting in the anterior palate differs from that in the posterior palate (Smith et al., 2012; Pauws et al., 2013; Beaty et al., 2016).

The mechanisms governing anterior versus posterior palate development exhibit distinctions (Smith et al., 2012; Zhou et al., 2013; Parada et al., 2015). Emphasis on palatal shelf elevation arises from the fact that approximately ninety percent of CPO results from issues with the elevation of palatal shelves (Song et al., 2013; Okano et al., 2014). Palatal shelves elevate during the process of palatal closure (Kouskoura et al., 2016). Concurrently, with palatal elevation, the cranial base straightens, a crucial event that does not occur without palatal elevation (Parada et al., 2015). Palate closure is also reliant on molecular changes in the midline epithelial seam, progressing from anterior to posterior as the secondary palate closes (Smith et al., 2012; Huang et al., 2016). Fibroblast growth factor 10 (Fgf10) plays a critical role in palatal midline fusion (Smith et al., 2012). Deletion of the Fgf10 gene induces alterations in the shape of the palatal shelves, influencing cell migration (Smith et al., 2012).

Studies on the Gli3 CP causal gene in mice suggest that CPO arises not from intrinsic changes in the palate but from tongue malformation (Smith et al., 2012). The form and function of the tongue are implicated in palatal shelf elevation (Kouskoura et al., 2016).

3.1.3 Tongue function and mandibular growth

Studies in mice reveal the critical role of Meckel's cartilage in influencing tongue positioning, subsequently impacting palatal shelf elevation (Kouskoura et al., 2016). Meckel's cartilage formation precedes palatal shelf elevation (Kouskoura et al., 2016). Bone morphogenetic proteins (BMP), play a critical role in initiating chondrogenesis in the process of mandibular development (Kouskoura et al., 2016). Mesenchymal signaling is vital for the ossification and growth of the mandible (Huang et al., 2016). Deletions of BMP7 result in changes in the normal anterior-posterior position of the genioglossus muscle influencing tongue protrusion and causing micrognathia (Kouskoura et al., 2016). Disruption in the matrix related to the tongue and Meckel's cartilage affects the anterior-posterior axis development (Kouskoura et al., 2016). Whether BMP7 influences a transcription factor related to the genioglossus tendon development, indicating a relationship between the lack of mandibular growth and clefting of the palate, remains to be determined (Kouskoura et al., 2016).

The tongue is comprised of two types of mesenchymal tissue: one derived from mesoderm and one derived from CNC (Song et al., 2013). The connective tissue surrounding the tongue

originates from CNC (Song et al., 2013). Retinoic acid (RA) may increase apoptotic activity at the base of the tongue, hindering tongue positioning and potentially affecting palatal closure (Tang et al., 2016). Excessive RA has been employed to induce CP in laboratory mice (Tang et al., 2016).

Tongue function and genioglossus development play a pivotal role in the elevation of the palatal shelves (Kouskoura et al., 2016). The functional relationship between malformed muscle and clefting of the palate has not been fully established (Kouskoura et al., 2016). In certain mouse studies, cellular changes could not be attributed to the tongue, suggesting that the tongue acts merely as a mechanical development disruptor, with micrognathia being the primary disruptor (Parada et al., 2015).

Palatal development aligns with tongue development and mouth opening reflexes, facilitating tongue repositioning and enabling palatal closure (Smith et al., 2012; Okano et al., 2014; Kouskoura et al., 2016). Fetal swallowing initiates when palatal shelves are closing (Okano et al., 2014). The anterior-posterior growth of the mandible is coordinated with the movement of the tongue away from the elevating palatal shelves and the first swallowing movements (Okano et al., 2014). Lack of mouth movements correlates with craniofacial defects (Okano et al., 2014). Ultimately, the anterior of the secondary palate fuses to the primary palate, and the secondary palate fuses to the nasal septum (Smith et al., 2012). A malformed tongue can lead to a cleft palate (Smith et al., 2012; Kouskoura et al., 2016).

3.1.4 Gender specificity

The developing stomodeum exhibits genetic and gender-specific characteristics in the distinct nature of anterior and posterior tissues (Okano et al., 2014; Beaty et al., 2016). Expression of cleft phenotypes shows discernible differences between anterior and posterior regions, with the anterior palate being male-predominant, and the posterior palate being female-predominant (Okano et al., 2014; Beaty et al., 2016). CL/P, identified as the anterior palate, and CPO, representing the posterior palate, are recognized as separate and distinct anomalies (Okano et al., 2014; Beaty et al., 2016).

CPO is associated with gender-related ankyloglossia, and both anomalies are linked to the X-linked, Tbx22 gene (Pauws et al., 2013). Tbx22 is the X-linked cleft causal gene, presenting with various associated defects, including CPO, ankyloglossia, submucous cleft, partial hard palate cleft, deficient soft palate, and bifid uvula (Pauws et al., 2013). Gender differences are underscored in explaining this X-linked inheritance, with CPO being more prevalent in females, while CL/P exhibits male predominance (Okano et al., 2014; Beaty et al., 2016). In X-linked inheritance, males express one allele while females possess two alleles with one inactivated or expressed in cellular mosaicism.

The CP X-linked genotype may manifest in females without symptoms (Fu et al., 2015). The spectrum of the phenotype expression of Tbx22 mutation includes bifid uvula, soft palate cleft, CPO, ankyloglossia, submucous cleft, and deafness (Pauws et al., 2013; Fu et al., 2015). The closure of the male secondary palate precedes that of the female secondary palate by one week, potentially contributing to the higher incidence of CPO in females. Gender considerations are integral when exploring the pathogenesis of craniofacial anomalies (Beaty et al., 2016).

3.2 Pathogenesis of cleft palate and ankyloglossia

The timing of cellular activity appears to be a contributing factor in the etiology of CPO with delays in cellular activity influencing palatal development (Smith et al., 2012; Almaidhan et

al., 2014). The pathogenesis of CP is intricate and not fully comprehended. Despite the fact that ninety percent of CP cases result from defects in palatal elevation, this critical aspect of palatogenesis remains unclear (Song et al., 2013; Okano et al., 2014).

CPO occurs early in embryogenesis, making intervention challenging, as it is governed by multiple genes and intricate interactions rather than a single gene (Beaty et al., 2016). Genome-wide association studies (GWAS) have identified as many as 18 genes related to non-syndromic cleft, but the genetic causes for non-syndromic cleft have not been conclusively elucidated (Peng et al., 2016). The pathogenesis of ankyloglossia also lacks definitive understanding (Jangid et al., 2015). Ankyloglossia may be inherited through X-linked, autosomal dominant, or autosomal recessive patterns (Jangid et al., 2015). Various theories exist in the literature, some proposing intrinsic mechanisms that control palatal elevation, while others suggest extrinsic controls of palatal elevation (Song et al., 2013; Zhou et al., 2013; Almaidhan et al., 2014; Fu et al., 2015; Kouskoura et al., 2016; Tang et al., 2016).

3.2.1 Intrinsic factors

The palatal shelves consist of mesenchymal tissue derived from neural crest cells along with oral epithelium (Zhou et al., 2013). Phenotypic variations observed along the anterior-posterior axis in palatal shelf elevation can manifest either the mesenchyme or the epithelium (Smith et al., 2012; Zhou et al., 2013). Notably, the deficiency in palatal elevation resulting from the deletion of tissue-specific LIM domain binding protein 1 (Ldb1) in mice was determined to be unrelated to tongue function, as confirmed through the removal of the tongue and mandible for analysis (Almaidhan et al., 2014).

Palatal shelf medial wall protrusion from in vivo observation coordinates mandibular growth and tongue formation from palatal elevation in an intrinsic mechanism. The palatal shelf protrusion of the medial wall initiates tongue and lower jaw movement. This intrinsic protrusion of the shelves is proposed to displace the tongue and mandible (Yu et al., 2015).

3.2.2 Extrinsic factors

Traditionally, PRS has been perceived as mechanically impeding palatal closure and elevation due to tongue crowding secondary to micrognathia (Parada et al., 2015; Huang et al., 2016). Mesenchymal signaling for mandibular ossification plays an important role in mandibular growth, with reduced mesenchymal cell proliferation identified as a cause of micrognathia (Yu et al., 2015).

Transforming growth factor beta (TGFB)/BMP signaling is vital in various aspects of palatal development (Song et al., 2013). The deletion of upstream CNC TGFB-activated kinase 1 (Tak1) gene expression is associated with tongue malformation and CPO (Song et al., 2013). The connective tissue surrounding the tongue, originating from the CNC, exerts functional influence on the muscles of the tongue (Song et al., 2013). Overexpression of Fgf10 has been linked to a defect resembling PRS (Song et al., 2013). However a tissue-specific deletion of the Tak1 gene in palatal tissue did not result in CP (Song et al., 2013).

Initial tongue movements coincide with palatal shelf elevation and fetal swallowing initiates simultaneously with this process (Smith et al., 2012; Okano et al., 2014; Kouskoura et al., 2015). Fetal movement is important for normal development, and a lack of fetal movement increases the risk of craniofacial defects (Okano et al., 2014). Laboratory animals in utero surgery involving the opening of the mouth have been shown to reverse CP (Okano et al., 2014). The position of the genioglossus along the anterior-posterior axis is pivotal to tongue function, which influences palatal shelf elevation (Kouskoura 2015). Palatal elevation

is not solely influenced by the mechanical interference of the tongue but is a result of the changes in overall tongue function and the functional matrix (Song et al., 2013).

3.2.3 Epigenetic factors

The range of manifestations in X-linked CP, including incomplete cleft, with or without ankyloglossia and bifid uvula, goes beyond genetic factors alone, implicating environmental risk factors (Peng et al., 2016). CPO pathogenesis involves a combination of genetic and epigenetic factors (Peng et al., 2016). Epigenetics plays a crucial role in establishing genome significance for the CP phenotype (Beaty et al., 2016). Maternal smoking, alcohol, and retinoic acid have been identified as risk factors for cleft (Okano et al., 2014; Beaty et al., 2016; Peng et al., 2016). Elevated levels of environmental RA are teratogenic and affect the T-box transcription factor 1 (Tbx1) gene, influencing developing tongue size (Okano et al., 2014). The specific epigenetic mechanism through which retinoic acid influences palate closure remains unclear, potentially involving the induction of apoptotic cell activity at the tongue base (Okano et al., 2014; Tang et al., 2016). Future routine risk evaluation for non-syndromic cleft may include genetic profiling of the fetus using plasma from the parents (Peng et al., 2016)

3.3 Diagnosis and treatment of ankyloglossia

The absence of universally accepted criteria for measuring the degree of ankyloglossia has led to variations in diagnosis and treatment protocols. Symptoms associated with ankyloglossia do not align with standardized criteria for treatment contributing to the lack of consistency (Jangid et al., 2015; Ferrés-Amat et al., 2016). The structural defect of ankyloglossia has associations with genetic diseases and deficiencies in craniofacial development (Gurramkonda et al., 2015).

3.3.1 Symptomatology

Ankyloglossia symptoms encompass challenges with breastfeeding, speech vocalization problems, swallowing problems, maternal nipple pain, and failure to thrive guiding the indication for surgical intervention (Shen et al., 2014; Jangid et al., 2015; Ferrés-Amat et al., 2016). Tongue-tie is associated with problems such as improper suckling latch, poor infant weight gain, the inability to clear the mouth with the tongue, and self-confidence issues (Jangid et al., 2015). Ankyloglossia may contribute to an immature swallow development with jaw underdevelopment and dysfunction (Ferrés-Amat et al., 2016). Maternal pain from infant ankyloglossia in the first three weeks poses a risk of discontinuing breastfeeding (Shen et al., 2014).

Speech articulation issues related to tongue-tie are unpredictable and do not consistently correlate with the severity of ankyloglossia; some children with severe ankyloglossia exhibit normal articulation (Shen et al., 2014).

3.3.2 Diagnostic criteria

Ankyloglossia, a prevalent condition with connections to various craniofacial anomalies, plays a role in the diagnosis of X-linked craniofacial anomalies (Jiang et al., 2012; Pauws et al., 2013; Jangid et al., 2015; Gurramkonda et al., 2015; Ferrés-Amat et al., 2016). In the era of widespread genotyping, ankyloglossia reveals clinically significant links (Jiang et al., 2012; Pauws et al., 2013; Gurramkonda et al., 2015; Jangid et al., 2015). Some authors

propose that a thick and short frenum serves as diagnostic criteria for ankyloglossia (Jangid et al., 2015; Ferrés-Amat et al., 2016). Kotlow's (1999) criteria have four to five categories of severity of ankyloglossia based on tongue movement (Jangid et al., 2015; Ferrés-Amat et al., 2016). Hazelbracker (1993) has described an assessment tool for lingual function (Jangid et al., 2015: Ferrés-Amat et al., 2016). Cuestas et al. (2014) base diagnosis on palpation of the frenum and function of the tongue (Ferrés-Amat et al., 2016).

3.3.3 Treatment protocol

Ankyloglossia treatment options include frenectomy or frenotomy with an electrosurgical unit, laser, scissors, or cold blade (**Figure 1**) (Ferrés-Amat et al., 2016). Surgical recommendations encompass z-plasty (4-flap), partial sectioning, and release of the genioglossus muscle, with myofunctional therapy before and after treatment (Ferrés-Amat et al., 2016). Optimal intervention for speech articulation issues is suggested at four or five years of age (Ferrés-Amat et al., 2016). Frenotomy is an effective procedure for addressing a thin frenum associated with ankyloglossia, involving minimal bleeding and rare complications (Shen et al., 2014).

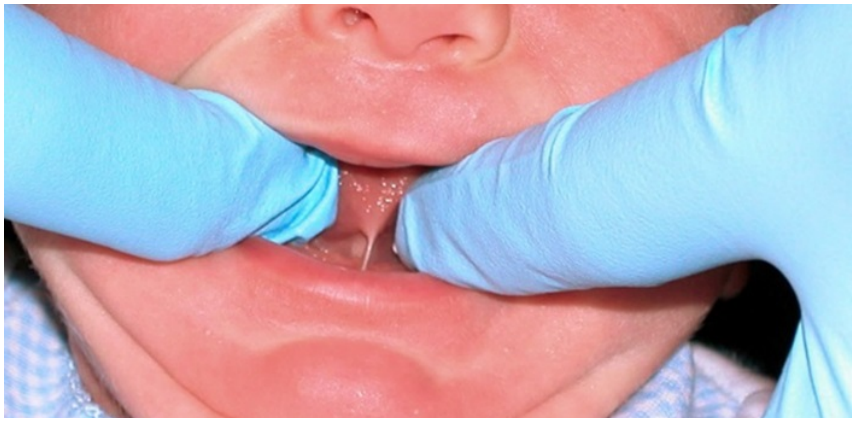

Figure 1. Neonate ankyloglossia.

Frenuloplasty conducted under local or general anesthesia for patients over one year of age, includes suturing of the frenum and, in some cases, z-plasty. Antibiotics are typically unnecessary due to the low risk of infection (Shen et al., 2014). Myotomy of the genioglossus muscle is also recommended by Ferrés-Amat et al., (2016).

4 Discussion

The correlation between ankyloglossia and CPO encounters challenges due to the incomplete understanding of the etiology of both anomalies (Jangid et al., 2015; Fu et al., 2015; Tang et al., 2016). The etiological perspectives of intrinsic CP and extrinsic CP show the complexity (**Table 1**) (Smith et al., 2012; Song et al., 2013; Zhou et al., 2013; Shen et al., 2014; Parada et al., 2015; Tang et al., 2016). The etiology of CPO and CL/P are distinct from an embryonic and genetic viewpoint (Okano et al., 2014; Beaty et al., 2016). Ankyloglossia has links to CPO to the extent that the function of the tongue is considered an etiological factor (Okano et al., 2014; Kouskoura et al., 2016). The extrinsic CP perspective provides some credence to the tongue's role in the etiology of CPO (Okano et al., 2014; Kouskoura et al.,

2016). Causal genes for CPO are notably associated with epigenetic factors, contributing to the understanding of both CPO and ankyloglossia pathogenesis (Gurramkonda et al., 2015; Beaty et al., 2016; Kouskoura et al., 2016).

Table 1. Intrinsic versus extrinsic etiology of cleft palate (CP).

Study	**Etiology**	**Reason for clefting**
Song et al., 2013	Extrinsic	Tongue function
Zhou et al., 2013	Intrinsic	Tissue-specific deletion
Almaidhan et al., 2014	Intrinsic	Tissue-specific deletion
Yu et al., 2015	Intrinsic	Tissue-specific deletion
Kouskoura et al., 2016	Extrinsic	UI influencing the m. genioglossus
Huang et al., 2016	Extrinsic	Primary defect of the mandible from UI
Parada et al., 2015	Extrinsic	Primary defect of the mandible
Tang et al., 2016	Intrinsic	Retinoic acid delays cell development of the palate
Tang et al., 2016	Extrinsic	Tongue function (genioglossus)

UI = upstream inactivation

Genetic and epigenetic factors significantly impact the development of the anterior-posterior axis (Smith et al., 2012; Parada et al., 2015). Neural crest cell-derived tissue influences the anterior-posterior positioning of the palate, tongue, mandible, or genioglossus muscle (Smith et al., 2012; Song et al., 2013; Zhou et al., 2013). Palatal closure correlates with the straightening of the cranial base, indicating a connection between cranial base angle and palatal positioning (Parada et al., 2015).

PRS, characterized by deficient palatal elevation and lack of cranial base straightening, exhibits a lack of sagittal axis growth (Parada et al., 2015). Straightening or flexion of the cranial base angle influences the anterior-posterior axis in development. Tongue function, influencing airway, feeding, swallowing, and speech articulation, plays an important role in craniofacial growth (Shen et al., 2014; Ferrés-Amat et al., 2016). A comprehensive assessment of the entire functional matrix of the craniofacial complex in newborns is essential. The CP-extrinsic perspective provides practical insights into embryogenesis, emphasizing how separate structures impact palatal closure through biochemical changes that affect timing and force distribution in growth. Molecular changes indicating critical tissue alterations in palatal closure underscore the interrelatedness of structures, forces, and timing, particularly involving the tongue.

As demonstrated in this review, the timing and function of tissues are pivotal in craniofacial complex development. Apoptosis of the lingual frenum influences the risk of CPO by affecting tongue protrusion. Evaluating the embryogenesis of the tongue based on the primordial anterior-posterior axis from the neural crest allows for clinical assessment through functional limitations. Symptomatology-based evaluations guide the indication for ankyloglossia treatment (Ferrés-Amat et al., 2016). The sagittal development of the oral cavity serves as an initial assessment of tongue function and genetic mutations contributing to the evaluation of abnormal genioglossus muscle attachment or micrognathia.

Future murine studies focusing on factors related to the rostral attachment of the genioglossus muscle would enhance understanding of palatogenesis and ankyloglossia. CP-induced mice offer a promising model for studying the impact of lingual frenotomy on sagittal or anterior-posterior axis development.

Conclusions

The exploration of CPO pathogenesis unfolds through two lenses: the CPO etiology from the inherited intrinsic mechanism, and the functional extrinsic mechanism (Okano et al., 2014; Beaty et al., 2016). The impact of the genotype on craniofacial development does not mean the genetic information is located solely in the bones, but also in neuromuscular fields, which indirectly influence the bones. Cellular pathways along the anterior-posterior axis signify sagittal development reduction, traceable from early embryonic stages (Smith et al., 2012). The intricate interplay of structures, whether cellular or biomechanical, plays a pivotal role in comprehending the etiology of CP and ankyloglossia (Smith et al., 2012; Song et al., 2013; Okano et al., 2014; Parada et al., 2015; Huang et al., 2016; Kouskoura et al., 2016). Biomechanical alterations can instigate cellular transformations. A diagnostic and treatment perspective for CP and ankyloglossia emerges: addressing increased protrusion of the tongue through frenotomy may aid in reversing anterior-posterior changes linked to cleft palate and the absence of cranial base straightening (Parada et al., 2015). Early release of the anterior functioning of the tongue has potential benefits to overcoming the anterior-posterior developmental delay.

While an intrinsic pattern is discernible in genetic research, the impact of extrinsic biomechanics is increasingly evident. Biomechanical disturbances of palatogenesis are linked to changes in CNC derived tissue in the lingual frenum. Scientific advancements in regenerative medicine are shedding light on mechanotransduction, thus validating this age-old procedure of frenotomy.

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Not applicable.

Ethical approval

No ethical approval was required for this study as it did not involve human participants, animal subjects, or sensitive data. This study falls under the category of data collection without participant identification.

Consent for publication

Not applicable.

Authors' contributions

The author(s) declare that all the criteria for authorship designated by the International Committee of Medical Journal Editors have been met. More specifically, these are: (a) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND (b) Drafting the work or revising it critically for important intellectual content; AND (c) Final approval of the version to be published; AND (d) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Competing interests

The author(s) declare that there are no competing interests related to this work.

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